The Disaster of Water Pollution by Heavy Metals: A New Perspective on the Risks, and Unique and Sustainable Remedial Techniques

Chapter · August 2023

6 authors, including:

Dwaipayan Sinha
GOVERNMENT GENERAL DEGREE COLLEGE, MOHANPUR, PASCHIM MEDINIPUR W…

Somnath Kar
Tripura University

Sharmistha Ganguly
Central Ayurveda Research Institute

Shahana Chowdhury
German University Bangladesh

Chapter 10

The Disaster of Water Pollution by Heavy Metals: A New Perspective on the Risks, Unique and Sustainable Remedial Techniques

Dwaipayan Sinha[1,*]
Shilpa Chatterjee[2]
Somnath Kar[3]
Sharmistha Ganguly[4]
Shilpi Sharma[5]
and Shahana Chowdhury[6]
[1]Department of Botany, Government General Degree College, Mohanpur, Paschim Medinipur, West Bengal, India
[2]Newcastle University, Newcastle upon Tyne, United Kingdom
[3]Department of Botany, Holy Cross College, Agartala, Tripura University
[4] Department of Botany, Ranchi University, Ranchi, Jharkhand, India
[5]Department of Botany, University of Delhi, Delhi, India
[6]Department of Biotechnology, German University, Gazipur, Bangladesh

Abstract

Introduction: Water pollution is one of the major concerns faced by society in the twenty-first century, intending to improve water quality and reduce human and environmental impacts. Water contaminants are produced as a result of industrialization, climate change, and urbanization. The main source of the increased levels of heavy metals in

* Corresponding Author's Email: dwaipayansinha@hotmail.com.

In: Sustainable Disaster Management and Human Health
Editors: Sandeep Poddar, Debajyoti Bose and Najma Memon
ISBN: 979-8-89113-127-9

aquatic ecosystems has been recognized as a result of anthropogenic activity. The chapter is a comprehensive review of the contamination of water bodies by heavy metals leading to disastrous consequences.

Methods: This review is the result of a collaborative effort to inform readers and pass on knowledge about a serious issue facing humanity today by detailing its origins, effects on the environment and human health, and possible solutions. Google Scholar, Scopus, PubMed, and PubMed Central are used to conduct a comprehensive literature search on the internet. Work was done to organize the data so that it was most relevant to the topic of the search. Most recent data was compiled and obsolete sources were removed.

Results: In this article, the most current and significant results related to heavy metal leakage, as well as the potential consequences to human health and the environment have been discussed. Some of the health risks associated with prolonged exposure to heavy metal residues, such as lead, cadmium, mercury, and arsenic, are discussed. This article also highlights the possible sustainable ways to reduce the menace of heavy metals, with a major focus on bioremediation techniques. The mechanisms at the cellular level, involved in the process of bioremediation, have also been taken into consideration.

Keywords: phytoremediation, pollution, phytoextraction, sustainable, toxicity

Introduction

For the survival of humans, easy access to potable water is crucial. World Water Development Report published by UNESCO in 2021 states that freshwater consumption has increased by around 1% per year since the 1980s (a six-fold rise during the past century) (Vanham et al., et al., 2021). The primary issues resulting from increased water consumption are its quality and quantity. The effects of industry, agricultural productivity, and urbanization have caused environmental deterioration and pollution. Water pollution is one of the deadly consequences of these anthropogenic activities, which in turn is harming human health and long-term social development (Lin et al., 2022). The amount of industrial and community sewage deposited into the atmosphere without any preliminary treatment is estimated to exceed 80% worldwide (The world bank, 2020), which harms ecosystems and human health. Due to a lack of wastewater treatment infrastructure and sanitation, this percentage is significantly greater in the poorest countries. (Lin et al., 2022). Industrialization (Rajput et al., 2017), agricultural practices (Kumar et al., 2021), inadequate water supply, and inefficient sewage treatment facilities (Bekturganov et al., 2021) are the chief reasons for water contamination. Primarily, the industry is the major contributor to water pollutants (Ilyas et al., 2019; Zhang et al., 2021), including tannery (Asaduzzaman et al., 2016), pulp and paper (Singh and Chandra, 2019), textile (Kumar et al., 2021), iron and steel (Tong et al., 2018), nuclear (Miao et al., 2013), and distillery industries (Mikucka & Zielińska, 2020). In the process of industrial manufacture, a variety of dangerous chemicals are released. These waste products consequently cause water pollution, if introduced into aquatic habitats untreated (Chowdhary et al., 2020). Heavy metals (HMs) like arsenic (As), cadmium(Cd), lead (Pb), and chromium (Cr) that are discharged into the water come from industries, which adds meaningfully to water contamination (Ngoc et al., 2020; Du et al., 2020). Industrial wastewater generation has gradually increased as a result of accelerated urbanization (Wu et al., 2020). Human health, aquatic life, and agriculture are seriously threatened by several harmful pollutants present in wastewater produced by many industrial sectors. Heavy metals namely Cr, zinc (Zn), Pb, copper (Cu), iron (Fe), Cd, nickel (Ni), As, and mercury (Hg) are examples of such contaminants. The manufacturing of paint and dyes, textiles, pharmaceuticals, paper, and fine chemicals are the industries that release the majority of these HMs (Ahmed et al., 2021). Consuming contaminated water is the major reason for heavy metal (HM) exposure to humans. As a result, people experience kidney and cardiovascular problems, neurological damage, and an increased risk of cancer and diabetes Reactive oxygen species production is recognized as the primary mechanism underlying HM-induced toxicity, which results in oxidative damage and adverse health effects. Thus, the use of HM-contaminated water contributes to high rates of sickness and mortality all around the world (Rehman et al., 2018) and has taken the form of a disaster. With the lack of treatment facilities, this disaster seems to aggravate with time. A summary of the disastrous effects of HM pollution on humans is provided in this chapter. Efforts have been made to illustrate possible ways to remediate HMs using microbes and plants.

Methodology

Sources of Heavy Metal Contamination in Water

Natural metallic elements with high density and atomic weight are known as heavy metals. (Li et al., 2019). They are pervasive throughout the environment and have a plethora of applications including industrial, domestic, agricultural, medical as well as technological (Edelstein & Ben-Hur, 2018). However, the major concern is their potential adverse effects on human health. Their toxicity can be attributed to several factors. These factors include the dose, the route of exposure, the chemical nature of the species, the age, the gender, the nutritional status, or any other genetic predisposition (Liu et al., 2018).

The HMs of main concern are As, Cd, Pb, and Hg (Bi et al., 2020). These are the HMs having a great impact on public health. They are considered systemic toxicants, capable of causing damage including multiple organ failures even at very small doses of exposure (Zeng et al., 2020). This is the case with metalloid As, which is recognized to be hazardous even at very low exposure levels or doses (Zeng et al., 2020).

The routes of exposure to HMs include ingestion (involving the oral route), inhalation, dermal or skin contact, and the parenteral route (Zwolak et al., 2019). Heavy metals are also referred to as chemical carcinogens for their potential of causing cancer in human beings (Jin et al., 2019). The public health concern related to these HMs has been exacerbated in recent years (Wu et al., 2018). Due to the increasing rise in the usage of HMs in industry, agricultural, residential, and technological applications, humans are becoming more susceptible to such HM exposure (Men et al., 2018).

Natural Source

The main sources of HM contamination in water are natural and manmade. Numerous studies have examined different natural processes that might lead to the contamination of soil with HMs. These include volcanic eruptions (Bazzi et al., 2020), sea-salt sprays (Gaur et al., 2021), forest fires (Srivastava et al., 2017), rock weathering (Chheang et al., 2021), and wind-borne-soil particles (Liang et al., 2017; Shirani et al., 2020). They are typically liberated from their endemic spheres by natural weathering processes. Additionally, organic compounds, hydroxides, oxides, sulfides, sulfates, phosphates, silicates, and HMs can also be detected (Sharma et al., 2021).

Anthropogenic Source

When it comes to the serious effects of HM contamination in water, anthropogenic sources play a crucial role. It includes mining operations (Piñeiro et al., 2021), indoor dust from leather industries (Junaid et al., 2017), fertilizer manufacture (Alengebawy et al., 2021), coal combustion (Jaishankar et al., 2014), pharmaceutical industry (Nessa et al., 2016), and electronic waste recycling activities (Houessionon et al., 2021). The anthropogenic sources often lead to disastrous consequences in society. Heavy metal contamination is primarily caused by the discharge of wastewater, with no appropriate treatment, into groundwater and surface waters (Astatkie et al., 2021; Shimod et al., 2022). Most HMs and their compounds are discovered in streams as sediments. Because they are non-biodegradable, HMs are harmful to the environment and people's health (Kapahi and Sachdeva, 2019). An alarming rate of growth in the amount of HM contamination in groundwater has been observed, mainly from anthropogenic sources including coal-fired power stations (Verma et al., 2016), smelting (Camacho et al., 2011), and other industrial performances (Karthikeyan et al., 2021). Cadmium contamination in the water is exacerbated by the effluents from manufacturing sectors such as batteries (Ni-Cd) (Idrees et al., 2018), paints (Apanpa-Qasim et al., 2016), plastic, and electroplating (Kobya et al., 2010). On the other hand, agricultural sources like phosphate fertilizers with Cd are also contributing to the Cd poisoning of water resources (Bandara et al., 2011). Today, Pb contamination of groundwater is a burdensome and intimidating issue for society. Lead pollution in groundwater is a consequence of battery manufacturing facilities (Van der Kuijp et al., 2013). Lead pollution in water is directly being added by old, used pipes that contain Pb (Jarvis et al., 2018). Lead pollution in water is also caused by industrial sources and auto emissions (Karrari et al., 2012; Wani et al., 2015). The extensive use of Cr in the chemical sector, the fabrication of dyes, the storage of wood, the tanning of leather, the chrome plating of metals, the development of various alloys, etc. causes environmental pollution in a variety of ways (Zhitkovich, 2011).

Industrialization and technological development have caused a significant amount of hazardous waste, HMs, and organic toxins to be released into the environment, which has caused significant harm to the ecosystem (Mahey et al., 2020). Due to its toxicity, HMs in water bodies have an impact on the biota. They can also bioaccumulate, which has an impact farther up the food chain. Biomagnification is the process by which a contaminant, such as a metal, gradually increases in concentration as it moves up the food chain (Mahey et al., 2020).

Waters become contaminated with heavy metals due to human and natural activities, particularly those related to industrialization. Heavy metal contamination of wastewater results in severe environmental pollution that endangers both human health and the ecosystem. The treatment of wastewater, particularly that coming from the metal sector, has been one of the biggest issues in recent years, according to (Lellis et al., 2019). Heavy metal concentrations are high in these types of effluents. Zn, Pb, Cr, Ni, Cu, Mn, Co, Al, and other metals are examples of those that can be found in these effluents and are mostly produced by various businesses (Lellis et al., 2019). Due to drip irrigation, sludge applications, solid waste management, automotive emissions, and commercial disposal of wastes, HM pollution has posed a major risk to the ecosystem. Multiple studies have shown that industrial wastewater contains HMs in amounts that are higher than those allowed for drinking water or surface/irrigation water (Arregui, et al., 2019). In certain regions of India, farms are irrigated with wastewater that contains excessive quantities of HMs (Arora, 2018). Heavy metals have bioaccumulated in crops and related food chains as a result of the application of HM-contaminated water in agricultural areas. Rainwater and contaminated surface or groundwater cause indirect HM pollution. One of the most crucial sources of fresh water is rivers, which are significantly impacted by sources of pollution (Arora, 2018). Figure 1 schematically illustrates the different sources of HM pollution in the atmosphere.

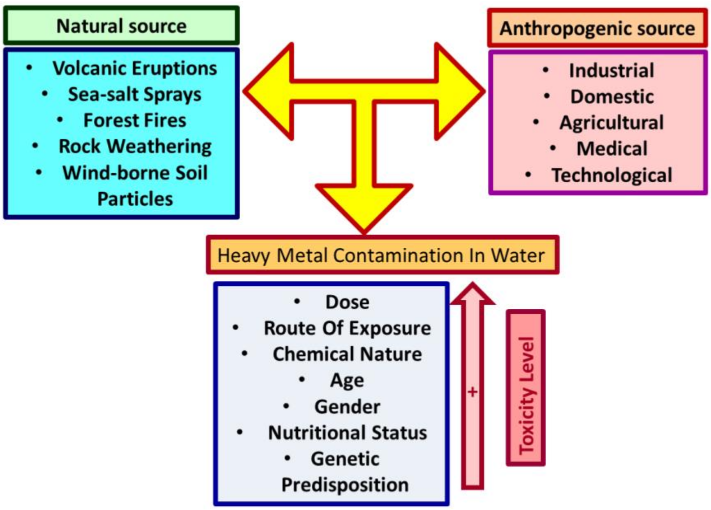


Figure 1. Various sources of heavy metals.

Result

Toxicological Effects of Heavy Metals

There have been numerous toxicological reactions linked to heavy metal exposure in both humans and animals. With the onset of the "itai-itai" disease in Toyama Prefecture, Japan, following World War II (1950), the first case of Cd poisoning ever recorded, the general public became more aware of cadmium's disastrous consequences. Consuming runoff water carrying Cd from adjacent mountain mining operations caused the Itai-Itai, or "ouch-ouch," sickness. The disease's moniker comes from the painful cries brought on by excruciating pain in the spine and joints. Bioassays carried out in the middle of the 1960s, utilizing the injection method of exposure, were the first investigations demonstrating Cd to be a carcinogen (Huff et al., 2012). The International Agency for Research on Cancer (IARC, 2012) has classed Cd as carcinogenic (Group 1) because of its demonstrated positive relationships with kidney and lung malignancies, as well as potential relationships with prostate and breast cancers (Filippini et al., 2022). An international problem, Cd pollution of water and soil significantly affects food and drinking water supplies in Asia and Africa. To reduce anthropogenic Cd output, additional efforts should be prioritized to clean up wastewater, prevent the leaching of contaminated material, such as in landfills and mines, and cut back on the usage of phosphate fertilizers polluted with Cd (Kubier et al., 2019). The risk of various chronic ailments, particularly kidney disease, has also been linked to high levels of Cd (Madrigal et al., 2019), bone (Li et al., 2021), and cardiovascular problems (Borné et al., 2015). Atherosclerosis (Barregard et al., 2021), hypertension (Lee et al., 2016), and metabolic syndrome (Ayoub et al., 2021), which cause cardiovascular disorders, have also been linked to even modest levels of Cd exposure (Jeong et al., 2020; Lin et al., 2021). Apart from humans, there are several reports of adverse effects of Cd in animals. The selected studies about the effects of Cd on various organs of rats and mice have been illustrated in Table 1 while Figure 2 illustrates the harmful effects of HMs in humans and animals,

Chromium is a potentially harmful metal that can be encountered in surface and groundwater due to anthropogenic and natural activities. Chromium's oxidation state has a significant impact on its biological effects.

Table 1. Effects of cadmium in rats and mice

S. No.	Affected animal	Organ affected	Adverse effects	Reference
1.	Rats	Kidney	1. Swelling of glomeruli, severe damage of renal tubules, rupture of the capillary network, necrosis of the epithelial cells, gathering of cells in the lumen, serious renal interstitial congestion, and seeping of inflammatory cells into the interstitium. 2. Abnormalities in the mitochondrial ridge, vacuoles, and swelling and distortion of the mitochondria.	Liu et al., 2019
2.	Male Sprague-Dawley rats	Kidney	1. Swelling of glomeruli and narrowing of capsular space. 2. Cytoplasmic degeneration of epithelial cells of renal tubules in the cortex. 3. Occurrence of pycnotic nuclei with condensed chromatin in the epithelial cells of proximal convoluted tubules and collecting ducts. 4. Increase in malondialdehyde (MDA) content in the kidney. 5. Reduced renal glutathione (GSH) levels and antioxidant enzyme activity, including catalase (CAT) and superoxide dismutase (SOD).	Fang et al., 2021
3.	Male Wistar rats	Kidney	1. Diffuse disintegration of renal tubules and glomerulus. 2. Severe renal cortex congestion, glomerulus collapse, and necrosis.	Abarikwu et al., 2017
4.	Sprague Dawley (SD) rats	Testes	1. Various magnitudes of spermatogenic epithelial anomalies namely shedding of cells, abnormal nuclear division, pyknosis of the nucleus, and occurrence of vacuoles. 2. Spermatogenic epithelium separation from the basal membrane. 3. Atrophy of tubules characterized by necrosis. 4. Reduced spermatogenesis and deformation of spermatogenic epithelium. 5. Increased level of MDA and reduced actions of GSH, CAT, and SOD.	Chen et al., 2022
5.	Sprague Dawley (SD) rats	Testes	1. Reduction in weight of testes. 2. Reduction in sperm count, sperm motility, and sperm viability. 3. Shrinkage of spermatogenic cells in seminiferous tubules of testes. 4. Reduction in the density of spermatozoa and number of interstitial cells in the center of seminiferous tubules. 5. Reduction in GSH content. 6. Increase in MDA and hydrogen peroxide content.	Wang et al., 2021
6.	Male Wistar Rats	Liver	1. Slight hydropic degeneration of hepatocytes.	Abarikwu et al., 2017

S. No.	Affected animal	Organ affected	Adverse effects	Reference
7.	Male albino Wistar rats	Liver	1. Microvesicular steatosis hepatocytes with ballooning of hepatocytes and pericellular fibrosis. 2. An increase in the enzyme levels for alanine, aspartate, alkaline phosphatase, and lactate dehydrogenase. 3. Decrease in activities of antioxidant enzymes namely SOD, GPx, and CAT.	Al-Baqami and Hamza, 2021
8.	Male Swiss albino mice	Brain	1. Vacuolation, crowding, hyperemia, lymphocytic permeation, and edema in the brain. 2. Significant decrease in acetylcholine esterase activity. 3. Significant decline in the content of glycogen.	Vijaya et al., 2020
9.	Male Wistar rats	Pancreas	1. Significant pancreatic degeneration, scattered islets of Langerhans, hyalinized interstitial connective tissue (HICT), and lymphocyte (L) replacing the islet cells	Aja et al., 2020
10.	Female Wistar rats	Ovary	1. Severe corrosion of ovarian follicles and poor vascularization. 2. Reduction in red blood cells. 3. Reduction in FSH and LH in serum.	Oyewopo et al., 2020
11.	Female Wistar rats	Uterus and Ovaries	1. Significantly thickened endometrium. 2. Degeneration of corpora luteum and damage of oocytes.	Nasiadek et al., 2018

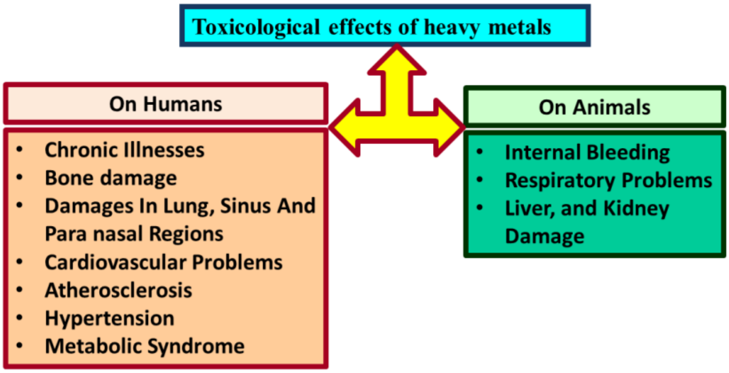


Figure 2. Toxicological effects of heavy metals

Nutritionally, the important trace element Cr (III) is nontoxic and poorly absorbed. The most toxic form of Cr is Cr(VI) which causes internal bleeding, respiratory problems, liver, and kidney damage. It has been categorized by the International Agency for Research on Cancer as Group I human carcinogen (Tumolo et al., 2020) and has disastrous consequences on human health. When breathed, hexavalent chromium [Cr(VI)] is known to cause cancer. However, only a tiny part of the population is affected by inhalational exposure to Cr(VI), primarily due to industrial exposures. However, oral exposure to Cr(VI) is frequent and has a significant worldwide impact(Sun et al., 2015). Additionally, sufficient evidence connects Cr(VI) to lung, sinus, and paranasal regions cancers. (Deng et al., 2019). According to research, serum Cr levels and lung cancer incidence are connected (Baszuk et al., 2021). Another study confirmed the association of exposure to Cr with the occurrence of sinonasal epithelial cancers (d'Errico et al., 2020). Hexavalent Cr is testified to induce extrinsic apoptosis in human renal epithelial cells. In a study, it was reported that after 24 and 48 hours of incubation, exposure to Cr(VI) dramatically reduced the viability of HK2 cells and increased intracellular ROS production. In HK2 cells treated with $K_2Cr_2O_7$, the expression of apoptotic pathway indicators such as cleaved caspase 3 and poly (ADP-ribose) polymerase rose significantly. HK2 cells treated with $K_2Cr_2O_7$ also showed the activation of intrinsic and extrinsic apoptotic markers (Wu et al., 2019). In numerous investigations, the toxicity of Cr to animals has been documented. A recent report states the alteration of the diversity of gut microbiota in chickens. It was shown that Cr exposure reduced the variety of bacteria in the stomach and caused dysbiosis (Li et al., 2021). The hepatotoxic effects of Cr(VI) of *Ctenopharyngodon idellus* were also evaluated in a recent study. According to the study's findings, hexavalent Cr exposure caused intercellular vacuolation, sinusoidal dilation, hemorrhage, peripheral nuclei, cytoplasmic vacuolation, nuclear pleomorphism, lymphocyte infiltration, hyperplasia, pyknotic nuclei, karyolysis, nuclear vacuolation, and necrosis in the liver tissues of fish. In addition, there was an increased MDA content and increased activity of antioxidant enzymes (Handa and Zindal, 2021). Another study found that Channa asiatica exposed to hexavalent Cr had impaired digestion and immunity, increased oxidative stress, and increased levels of genes related to apoptosis and inflammation (Yu et al., 2021). In *Chana punctatus*, exposure to hexavalent Cr resulted in a significant increase in the activities of antioxidant enzymes such as SOD and CAT. *In vivo* studies indicated a significant upsurge in the generation of micronuclei along with transcriptional responses of target genes linked to antioxidant enzymes, DNA damage, and apoptosis (Awasthi et al., 2018). In Zebrafish, hexavalent Cr induces DNA damage through the apoptotic pathway. It was observed that there was a transcriptional up-regulation of p53, Bax, Caspase 9, and Caspase 3 and down-regulation of the Bcl2 gene, thereby, affirming the onset of apoptosis(Shaw et al., 2022). In *Sousa chinensis* lowered the viability of fibroblasts of skin cells through induction of apoptotic pathway accompanied by onset of oxidative stress. Moreover, there was an upsurge in the percentage of cells arrested in the G2/M transition along with the upregulation of p53 and increased expression of caspase 3. Alteration of mitochondrial membrane potential and altered expression of Bcl-2/Bax was also noted upon exposure to Cr (Yu et al., 2018).

Numerous incidences of Hg poisoning have also been documented throughout the world, and each year, many people pass away as a result. Three major Hg poisoning cases were documented in the 20th century. The first was the Minamata disease, which occurred in Kyushu, Japan, and poisoned 2200 individuals when they consumed Hg-tainted fish and shellfish. Secondly, there were 700 victims of Hg poisoning documented in Niigata (the main island of Honshu, Japan) between the 1950s and 1960s (Maruyama et al., 2012; Rafati-Rahimzadeh et al., 2014; Yorifuji et al., 2020). The third pandemic of Hg poisoning occurred in Iraq between the 15th of September and the first week of December 1971. In that period, 73000 tons of wheat and 22000 tons of barley, treated with organomercury compounds were distributed for planting purpose but was somehow consumed which resulted in a toxic response, attracting investigation at international levels (Skerfving and Copplestone, 1976). In Bolivia, Hg pollution has also caused a significant issue. Northwest of *La Paz*, Bolivia, in the Apolobamba gold mining region, high Hg levels were discovered. According to reports, the sediments from the *Sunchull-Viscachani* Lake and river have Hg concentrations of 102, 12.3, and 11.7 mg per kg, respectively (Acosta et al., 2011). Additionally, residents around the lower Beni River, where gold mining was most prevalent, were reported to have greater Hg levels in their hair than the unexposed population (Barbieri et al., 2009). Additionally, it was asserted that Titicaca's mercury levels were 3–10 times lower than those in Uru Uru Lake (Guédron et al., 2017). Another occurrence connected to Hg pollution is the catastrophe at the Schweizerhalle. In Switzerland, Schweizerhalle is an industrial area close to Basel. Environmental contamination occurred as a result of a fire at the Sandoz Limited warehouse on November 1st, 1986. According to estimates, the fire destroyed over 1250 tonnes of chemicals kept in the building. The majority of these chemicals were then released into the nearby Rhine River after being driven off into the environment by firefighter water. Highly dangerous Hg compounds were contained in the stored materials and were identified by the luminous red dye rhodamine B, which upon contamination caused the Rhine River to become red. The catastrophe caused changes to the rhine river's aquatic flora and wildlife (Giger, 2009). According to a recent analysis, Hg as a pollutant is found in the sediments and water of Lake Baikal and the nearby Selenga delta (Roberts et al., 2020). Since inorganic Hg can be changed into the hazardous form of methyl Hg in aquatic ecosystems and elemental Hg is reemitted globally into freshwater settings, aquatic ecosystems are a crucial part of the biogeochemical cycle of Hg (rivers and lakes) (Kocman et al., 2017). Potential environmental changes were found to have a significant impact on the Mississippi River deltaic freshwater marsh soil's capacity to absorb Hg, indicating that these aspects should be taken into account when mitigating the impact linked with Hg in freshwater wetlands to be ready for potential future climate change scenarios (Park et al., 2018). Mercury has negatively affected all biotic components of the ecosystem. Table 2 illustrates the effect of Hg on selected organisms.

Owing to its physiochemical properties, Pb is a HM that has been extensively used in a variety of industrial and home settings. Depending on the degree and length of exposure, Pb exposure in humans can have various biological impacts, including detrimental impacts on the hematological, cardiovascular, neurological, and reproductive domains (Fenga et al., 2017).

Table 2. Toxic effects of mercury on selected organisms and humans

S. No.	Study System	Target Tissue/ Parameter	Study Location	Source	Toxic Effect	Reference
1.	*Acanthopagrus latus*	Hematological parameters	Creeks of Malashar Region, Iran	Hg in creek water	1. Significant increase in values of differential neutrophils and monocytes than the control. 2. Significant decrease in hemoglobin, hematocrit, leukocyte count, and differential eosinophil, lymphocyte, and mean corpuscular hemoglobin concentration than the control. 3. Significant depletion in total protein concentration while increase in glucose concentration.	Hedayati et al., 2012
2.	Harbour seals	Hematological and molecular parameters	Seal Station, Friedrichskoog, Germany	Hg of marine water/ Exposed to methyl Hg	1. A significant drop in the proportion of lymphocyte proliferation when exposed to methyl Hg. 2. A decrease in DNA, RNA, and protein synthesis. 3. Reduced cytokine indexes	Das et al., 2008
3.	*Pseudosciaena crocea*	Larva & Embryo	Laboratory experiment	Methyl Hg	1. Increase in mortality of larva and embryo. 2. Decrease in hatching rate. 3. Significant decrease in yolk absorption. 4. Deformity in the spine, tail curl, degeneration of the tail, pericardial edema, and erosion of the fin of the larva.	Yu et al., 2019

Table 2. Toxic effects of mercury on selected organisms and humans

S. No.	Study System	Target Tissue/ Parameter	Study Location	Source	Toxic Effect	Reference
4.	*Betta splendens*	Fish	Laboratory experiment using neurological parameters of fish	Mercuric chloride	1. Decrease in motor activity. 2. Impairment of partner selection, territoriality, reproductive behavior, avoidance of predators, and eating behavior.	Mansur et al., 2012
5.	*Heteropneustes fossilis*	Fish	Laboratory experiments using hematological and behavioral parameters	Mercuric chloride	1. Increase in lymphocytes and basophils. 2. Decrease in counts of Eosinophil, Neutrophil, and Monocytes. 3. Behavioral changes namely restlessness, abnormal swimming, jerks, loss of balance, and secretion of mucus observed.	Das et al., 2020
6.	Human	Children	An epidemiologic cohort study in an Italian coastal area	Methyl Hg	1. Relationship between maternal fish diet and methyl Hg exposure during pregnancy and children's development of fine motor abilities	Barbone et al., 2020

Additionally, the International Agency for Research on Cancer has recognized inorganic compounds as possible human carcinogens (category 2A) (Rousseau et al., 2005). In a variety of human groups, Pb exposure has been linked to an amplified possibility of the bladder (Golabek et al., 2009), gastrointestinal (Sohrabi et al., 2019), and lung cancer (Wynant et al., 2013). Major macromolecules, as well as the liver (hepatotoxicity), nervous system (neurotoxicity), kidneys (nephrotoxicity), and DNA (genotoxicity), are the main targets of Pb toxicity. Lead cytotoxicity is largely related to the activation of the c-Jun NH2-terminal kinase, phosphoinositide 3-kinase, or Akt and p38 mitogen-activated protein kinase signaling pathways. Lead greatly reduces cell differentiation and maturation and increases apoptosis via a signaling cascade and related components. Lead also has a significant impact on metabolic processes including heme production, which causes anemia in Pb-exposed individuals (Singh et al., 2018). Pb exposure resulted in 900 000 deaths and 21.7 million years of lost healthy life, or DALYs, globally in 2019, as per the estimations from the Institute for Health Metrics and Evaluation. The burden was greatest in low- and middle-income nations. According to IHME's estimates, Pb exposure was also responsible for 6.25 percent of the world's burden of developmental intellectual disability with an unknown cause, 8.2 percent of the world's burden of hypertension, 7.20 percent of the world's load of ischaemic heart disease, and 5.65 percent of stroke in 2019 (World health organization, a). Although Pb levels in source water are typically low, components of water distribution systems that contain Pb, such as Pb service lines and Pb pipes, solders, and faucets, can leak Pb into the water. The presence of Pb in the distribution or plumbing system, the age of the plumbing system, the water chemistry, and water consumption modes are some of the elements that affect Pb release. Lead components may also be found in water coolers and fountains (Levallois et al., 2018). In Benin, a study reported high blood Pb levels in mothers due to the consumption of piped water (Bodeau-Livinec et al., 2016). In another investigation on children, it was reported that the developmental quotients of adaptive behavior, fine motor skills, language improvement, and individual social conduct were all significantly negatively correlated with blood Pb levels. More children with Pb poisoning exhibited deviant behaviors than children who were healthy, particularly social isolation, despair, odd body motions, anger, and destruction (Hou et al., 2013). Lead toxicity also has an impact on animals. Studies have been undertaken to ascertain the effects of Pb on the animal system. One of the studies on *Heteropneustes fossilis* indicated a decrease in levels of plasma calcium and phosphate upon exposure to inorganic Pb (Srivastav et al., 2013).

In another study on the same species, it was found that exposure to Pb resulted in a decrease in the gonado-somatic index, the content of total protein, glucose, and nucleic acids. In addition, there was also an expression of metallothionein. At the histological level degeneration of spermatogonia was observed with the aggregation of spermatogonial cells and degeneration of interlobular tissue. Prolonged exposure to Pb resulted in dead sperms, vacant seminiferous tubules, and degeneration of spermatocytes (Choubey et al., 2015). The effect of Pb and Cd was studied on African Catfish (*Clarias gariepinus*). The result of the study indicated that individual exposure to Pb and Cd resulted in decreased activities of lactate dehydrogenase and SOD. In addition, Pb significantly increased the levels of glyceraldehyde-3-phosphate dehydrogenase and decreased the levels of the reduced GSH in the gills. Cadmium elevated the levels of CAT in the kidney and liver and also induced lipid peroxidation as evidenced by an upsurge in MDA levels (Elarabany and Bahnasawy, 2019). Exposure to sub-lethal concentrations of Pb in *Labaeo rohita* resulted in increased expression of cytochrome P450 1 A (CYP1A) and cytochrome P450 3 A (CYP3A). In addition, there was an upregulation of heat shock proteins (Hsp60 & Hsp70) and metallothionein. Both the number of red blood cells and the serum levels of the liver-marker enzymes alanine transaminase and aspartate transaminase decreased (Pandi Prabha et al., 2022).

In more than 50 countries, spanning several continents, As contact is one of the biggest disasters to community health. With the identification of more recent sites and a rising prevalence of affected individuals, the global situation regarding As pollution has been evolving (Sanyal et al., 2020). As contamination of drinking water is significant in several locations, and As groundwater contamination is pervasive. As levels over the WHO's interim recommendation limit of 10 g/L have been detected in at least 140 million people in 50 different countries. (World health organization, b). Around the world, 500 million people are thought to be affected by groundwater poisoning by As (Shaji et al., 2021). Continuous contact with high As water damages the liver (Yao et al., 2021), kidney (Zhao et al., 2021), heart (Al-Forkan et al., 2021), and lungs (Signes-Pastor et al., 2021) in addition to causing pigmentation, hyperkeratosis (Kaur and Budhwar, 2021), and skin cancer (Mayer and Goldman, 2016). The International Agency for Research on Cancer (IARC) has designated as a class I human carcinogen, indicating that there is sufficient evidence of its carcinogenicity to humans. (Martinez et al., 2011). It has been stated that the presence of As in drinking water is negatively associated with the occurrence of lymphoma and leukemia in both men and women (Lin et al., 2022). In a study done in the state of Bihar in India, it was shown that the population residing in places with proximity to the Ganges has a greater risk of developing cancers. The study also states that compared to sarcomas, lymphomas, and leukemias, carcinomas have a higher prevalence of cancer disease burden, which is associated with As exposure. According to the study, people who live in the Gangetic basin continue to be exposed to hazardous levels of As, which can cause a variety of malignancies (Kumar et al., 2021a). In a related study conducted in the Bihar village of Chapar, it was shown that 52 percent of the entire groundwater samples had an As concentration that was higher than the WHO-permitted standard, which is 10 g/L. The health study of the locals reveals that exposure to As has caused serious health risks among the exposed population, including prominent skin expressions, appetite loss, anemia, constipation, diarrhea, generalized body weakness, higher blood pressure, breathing difficulty, diabetes, cognitive impairments, lumps, and a small number of cancer incidences. The hair of the locals had As which was higher than the permissible limit set by WHO. Arsenic was also detected in the urine samples of the locals (Kumar et al., 2022). In another study performed at the Shahpur block of Bhojpur district in the Indian state of Bihar, it was found that 21.1 percent of the tubewells had an As concentration above 10 and 50 μg/L, respectively. Skin lesions were observed among the local population while hair, nails, and urine had As above normal levels. Arsenical neuropathy was also observed and the pregnancy of the women was adversely affected along with the development of skin lesions (Chakraborti et al., 2016). A study reported As content in the water of the handpump of Khap Tola, West Champaran in the Indian state of Bihar. It was also calculated that children in the age group of 5-10 years possess a high risk of developing cancer (Bhatia et al., 2014). In Sabalpur village of Saran district in Bihar, the groundwater was reported to contain As above the permissible limit of WHO. The hair samples of the people living in the region also had As above the permissible limit. The health survey study's findings revealed that the exposed population had a high illness burden with symptoms like asthma, anemia, hepatomegaly, diabetes, heart issues, fungal infections of the skin, shortness of breath, and mental impairment. A few cases of kidney, skin, breast, and cervix cancer were also discovered among this village's unprotected residents (Kumar et al., 2021b). In another study done at Simri village in Bihar, it was found that the drinking water contained As above the permissible limit. There was also a high concentration of As in the blood of the residents accompanied by symptoms like hyperkeratosis, hyperpigmentation, etc. (Rahman et al., 2019). According to estimates, 50 million people in Bangladesh could get As exposed by consuming water from tainted tubewells. Arsenicosis is brought on by long-term exposure to As and may entail several organ diseases. In Bangladesh, many of the negative health impacts of chronic poisoning are visible (Ahmad et al., 2018). A study performed in the Araihazar region of Bangladesh reported dyspnea among people exposed to As contamination in drinking water and this was found free of their smoking habit (Pesola et al., 2012).

The element manganese (Mn), which is extensively dispersed in terrestrial and coastal environments, is present in trace quantities in the organisms. Mn is a mineral that must be present in all living things at minute levels to maintain various biological processes and life (Li and Yang, 2018). Due to Mn's diverse physiological functions, which frequently hide the sense of its potential toxicity, studies on the severe toxic effects this element has on various environments like water, soil, and air are rare (Queiroz et al., 2021). Increased Mn levels in the drinking water in the Bangladesh region, according to studies among school children, are inversely correlated with students' math achievement scores (Khan et al., 2011). It has been discovered that children of school age in Canada who drink water with high levels of Mn are found to have much greater levels of Mn in their hair samples. There is a substantial correlation between elevated levels of Mn in the hair and elevated levels of hyperactive behaviors (Bouchard et al., 2007). A unique disorder associated with Mn toxicity is manganism. Manganism, also known as Mn poisoning, is a condition that develops as a consequence of prolonged exposure to Mn. James Couper made the initial discovery of it in the year 1837 (Rizvi et al., 2017; Blanc, 2018). Manganism is characterized by an excessive accumulation of Mn in the brain. Parkinson's disease and manganism share several symptoms. Patients with manganism display psychotic symptoms in the early stages of the illness. These symptoms are followed by persistent symptoms linked with changes in extrapyramidal circuits, such as akinetic stiffness, dystonia, and bradyskinesia. Manganism is a neurodegenerative disorder that occurs due to exposure to Mn (Aschner et al., 2009).

Plant-Mediated Removal of Heavy Metals

Heavy metals are substances that are nonbiodegradable i.e., not degraded by any biotic substances or even by any physical progression, and as a result are insistent in the soil for an extended period (Suman et al., 2018). But these HMs are also playing an important role in the biological system. Certain HMs are vital for the physiological and biochemical processes of biological organisms including plants but up to a proper amount (Cempel and Nikel, 2006). If they are present in excess amounts, they may be converted into noxious. On the contrary, non-essential HMs are exceedingly lethal (Fasani et al., 2018). Thus, the removal of such elements is essential.

Phytoremediation is a process of remediation that encompasses the usage of flora to abstract and eradicate fundamental pollutants or reduce their accessibility in soil (Berti and Cunningham, 2000). A more affordable, non-intrusive, and widely accepted method of removing environmental toxins is to use floras to bioremediate polluted soil, water, and air (Singh et al., 2003). The process of phytoremediation can be classified into the following categories (Ralinda and Miller, 1996).

Rhizofiltration

It is the preoccupation, absorption, and condensation of HMs by the root systems of plants. Rhizofiltration is used chiefly for the clearance of contaminated superficial aquatic, sewage as well as excess water encompassing fewer quantities of HMs. The process comprises the adsorption as well as precipitation of the metal pollutants onto or by the roots. Before using the plants for the rhizofiltration process, plants are primarily elevated hydroponically and then relocated to the contaminated water source afterward. Generally, in this process, the plants that are used belong to terrestrial or aquatic habitats, though terrestrial plants are favored due to their fibrous and long roots (Rezania et al., 2016).

Phytoextraction

It is the withdrawal and accretion of impurities in the plant tissue systems consisting of roots as well as surface shoots. To be appropriate for phytoextraction resolves, plant species should follow the following conditions (Vangronsveld et al., 2009):

- It should be metallotoleranant for the elements present in toxic levels,
- It should produce biomass at a rapid rate. and
- It should have the current gathering of HMs in easy-to-harvest parts.

Phytotransformation

It is the dilapidation of complex organic molecules into small molecules as well as the integration of these iotas into plant tissues.

Phytoremediation is growing as an economical way of handling wastes, particularly surplus petroleum hydrocarbons, organic matter, etc. Applications are verified for cleansing up dirtied soil, water, and air.

Phytostimulation

It is plant-assisted bioremediation that stimulates the dilapidation of micro-mycobial dilapidation by the emancipation of exudates or enzymes into the rhizosphere.

Phytostabilization

It entails pollutant absorption and precipitation by plants, as well as lowering their mobility and inhibiting migration to groundwater, the atmosphere, or the food chain. To immobilize HMs beneath a field that restricts their accessibility, which prevents their migration within the network and lowers the likelihood that metallic elements will enter the food chain, phytostabilization is used (Marques et al., 2009).

In the event of excessive HM precipitation or decreased metal accessibility in the rhizosphere, phytostabilization may result in the capture and sequestration of metals within root tissues or adsorption on root cell walls (Gerhardt et al., 2017). The different types of phytoremediation processes are illustrated in Figure 3.

The assortment of apt plant species is decisively aimed at phytostabilization. On the way of achieving the necessity of exceedingly operative phytostabilization, plants should be lenient in HM conditions. To quickly create a vegetative cover in a particular place, plants should have compact roots organization, be able to produce a high quantity of biomass and grow quickly. Plant species that meet the aforementioned criteria have been identified and employed for phytostabilization (Burges et al., 2018).

All the advantageous features overshadow the encounters confronted in utilizing phytoremediation as a key treatment technology. Though bearing in mind, the use of this technology at a particular polluted field or site, certain criteria should be taken under consideration to make the clean-up process more efficient and the least hazardous for the plants used.

Several plant species have been recorded, to date, which has great potential to remediate various HMs in water or soil. Different studies have proposed and supported those plants, like *Brassica juncea* (Siddiqui et al., 2020), *Setaria italica* (Chiang et al., 2011), *Pistia stratiotes* (Das et al., 2014), *Salvinia molesta* (Nithya et al., 2021), *Salvinia minima* (Iha and Bianchini, 2015), *Typha latifolia* (Yang and Shen, 2019) and *Azolla filiculoides* (Naghipour et al., 2018) can efficiently lessen the amount of Cd in water and soil. The plant species reported for the effective remediation of Pb are *Brassica juncea* (Kaur et al., 2015), *Azolla filiculoides* (Naghipour et al., 2018), *Carex pendula* (Yadav et al., 2011), *Pistia stratiotes* (Zahari et al., 2021), *Salvinia minima* (Iha and Bianchini, 2015) and *Typha domingensis* (Mojiri et al., 2013). Similarly, other HMs like Aluminum (Al), Fe, Mn, Ni, and As, various plants have been mentioned in the literature. Table 3 enlists the important plants that have the potential for HM bioremediation.

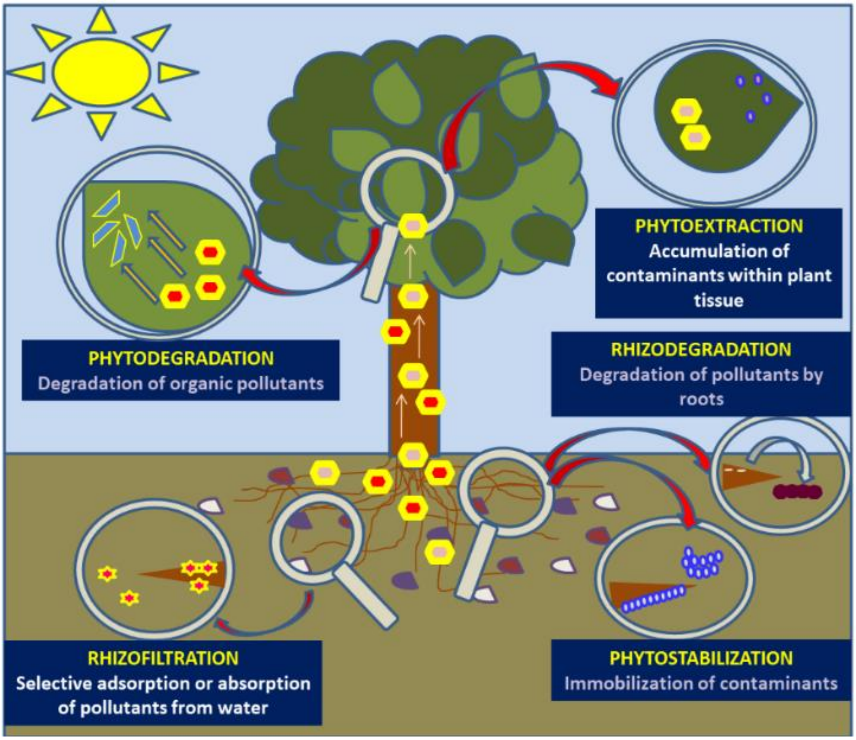


Figure 3. Types of phytoremediation.

Table 3. Plants used to remediate heavy metals

S. No.	Metals remediated/absorbed	Name of the plant	Family	References
1.	Cadmium	*Brassica juncea*	Brassicaceae	Siddiqui et al., 2020
		Setaria italica	Poaceae	Chiang et al., 2011
		Pistia stratiotes	Araceae	Das et al., 2014
		Salvinia molesta	Salviniaceae	Nithya et al., 2021
		Salvinia minima	Salviniaceae	Iha and Bianchini, 2015
		Typha latifolia	Typhaceae	Yang and Shen, 2019
		Azolla filiculoides	Salviniaceae	Naghipour et al., 2018
		Cardaminopsis halleri	Brassicaceae	Chandra et al., 2022
		Cannabis sativa	Cannabaceae	Ahmad et al. 2015
		Brassica oleracea	Brassicaceae	Yadav et al., 2017
		Raphanus sativus	Brassicaceae	Yadav et al., 2017
		Azolla pinnata	Salviniaceae	Rai, 2008
		Cicer aeritinum	Fabaceae	Sumiahadi & Acar, 2018
		Helianthus annuus	Asteraceae	Alaboudi et al., 2018
		Lepidium sativum	Brassicaceae	Vakili & Aboutorab, 2013
		Lactuca sativa	Asteraceae	Sumiahadi & Acar, 2018
		Oryza sativa	Poaceae	Wang et al., 2013; Zhong and Chen, 2020
2.	Lead	*Brassica juncea*	Brassicaceae	Kaur et al., 2015
		Oxycaryum cubense	Cyperaceae	Alves et al., 2014
		Azolla filiculoides	Salviniaceae	Naghipour et al., 2018
		Carex pendula	Cyperaceae	Yadav et al., 2011
		Pistia stratiotes	Araceae	Zahari et al., 2021
		Salvinia minima	Saliviniaceae	Iha and Bianchini, 2015

S. No.	Metals remediated/absorbed	Name of the plant	Family	References
2. (Cont'd	Lead	*Typha domingensis*	Typhaceae	Mojiri et al., 2013
		Azolla filiculoides	Saliviniaceae	Hassanzadeh et al., 2021
		Cucumis sativus	Cucurbitaceae	Kubota et al., 2006; Shehata et al., 2020
		Cicer aeritinum	Fabaceae	Sumiahadi & Acar, 2018
		Brassica napus	Brassicaceae	Park et al., 2012; Kamran et al. 2019
		Brassica nigra	Brassicaceae	Koptsik 2014; Sahay et al., 2020
		Betula occidentalis	Betulaceae	Koptsik 2014; Kanwar et al., 2020
		Cardaminopsis halleri	Brassicaceae	Chandra et al., 2022
		Euphorbia cheiradenia	Euphorbiaceae	Chehregani et al., 2007; Mohsenzadeh & Mohammadzadeh, 2018
		Helianthus annuus	Asteraceae	Alaboudi et al., 2018
		Lantana camara	Verbenaceae	Alaribe & Agamuthu, 2015; Saini et al. 2017
3.	Aluminum	*Pistia stratiotes*	Araceae	Veselý, et al.2012
		Typha sp.	Typhaceae	Bonanno and Cirelli, 2017
4.	Iron	*Pistia stratiotes*	Araceae	Kumar et al., 2019
		Typha domingensis	Typhaceae	Hegazy, et al., 2011
5.	Manganese	*Pistia stratiotes*	Araceae	Lu et al., 2011
		Cnidoscolus multilobus	Euphorbiaceae	Juárez-Santillán, et al., 2010
		Platanus mexicana	Platanaceae	Juárez-Santillán, et al., 2010
		Solanum diversifolium	Solanaceae	Juárez-Santillán, et al., 2010
		Asclepius curassavica	Apocynaceae	Juárez-Santillán, et al., 2010
		Pluchea sympitifolia	Asteraceae	Juárez-Santillán, et al., 2010
		Lactuca sativa	Asteraceae	Sumiahadi & Acar, 2018
7.	Copper	*Eichhornia crassipes*	Pontederiacea	Hammad 2011
		Brassica juncea	Brassicaceae	Sharma et al., 2018
		Brassica napus	Brassicaceae	Park et al., 2012; Kamran et al. 2019

Table 3. (Continued)

S. No.	Metals remediated/absorbed	Name of the plant	Family	References
7. (Cont'd)	Copper	*Brassica oleracea*	Brassicaceae	Yadav et al., 2017
		Raphanus sativus	Brassicaceae	Yadav et al., 2017
		Cardaminopsis halleri	Brassicaceae	Chandra et al., 2022
		Cicer aeritinum L.	Fabaceae	Sumiahadi & Acar, 2018
		Euphorbia cheiradenia	Euphorbiaceae	Chehregani et al., 2007; Mohsenzadeh & Mohammadzadeh, 2018
		Haumaniastrum katangense	Lamiaceae	Sheoran et al., 2009; Mohsenzadeh & Mohammadzadeh, 2018
		Lactuca sativa	Asteraceae	Sumiahadi & Acar, 2018
		Oryza sativa	Poaceae	Wang et al., 2013; Zhong and Chen, 2020
8.	Nickel	*Eichhornia crassipes* (Mart.) Solms	Pontederiacea	Hammad 2011
		Brassica oleracea	Brassicaceae	Yadav et al., 2017
		Raphanus sativus	Brassicaceae	Yadav et al., 2017
		Alyssum murale	Brassicaceae	Bani et al., 2010; Tognacchini et al. 2020
		Euphorbia cheiradenia	Euphorbiaceae	Chehregani et al., 2007; Mohsenzadeh & Mohammadzadeh, 2018
		Lactuca sativa	Asteraceae	Sumiahadi & Acar, 2018
9.	Zinc	*Eichhornia crassipes*	Pontederiacea	Hegazy et al., 2011;
		Typha domingensis	Typhaceae	Hammad 2011
		Arabidopsis halleri	Brassicaceae	Zhao et al., 2001; Spielmann et al., 2020
		Thalaspi caerulescene	Brassicaceae	Ibañéz et al., 2018
		Brassica juncea	Brassicaceae	Sharma et al., 2018
		Brassica napus L.	Brassicaceae	Park et al., 2012; Kamran et al. 2019
		Brassica oleracea	Brassicaceae	Yadav et al., 2017

S. No.	Metals remediated/absorbed	Name of the plant	Family	References
9. (cont'd)	Zinc	*Raphanus sativus*	Brassicaceae	Yadav et al., 2017
		Cardaminopsis halleri	Brassicaceae	Chandra et al., 2022
		Euphorbia cheiradenia	Euphorbiaceae	Chehregani et al., 2007; Mohsenzadeh & Mohammadzadeh, 2018
		Lactuca sativa L.	Asteraceae	Sumiahadi & Acar, 2018
10.	Arsenic	*Cynara cardunculus*	Asteraceae	Llugany et al., 2012
		Eleocharis acicularis	Cyperaceae	Sakakibara et al., 2011; Awa & Hadibarata, 2020
11.	Mercury	*Achillea millefolium*	Asteraceae	Wang et al., 2012; Verma et al., 2021
12.	Synthetic dye	*Arundo donax*	Poaceae	El-Aassar et al., 2018
13.	Chromium	*Cicer aeritinum*	Fabaceae	Sumiahadi & Acar, 2018
		Eichhornia crassipes	Pontederiaceae	Mishra et al., 2009; Ibezim-Ezeani et al., 2020

Algae and Microbe Remediated Removal of Heavy Metals

Bacteria are widespread in the environment. Bacteria come in a variety of morphologies, such as spiral, cocci, rods, and filamentous (Singhal et al., 2021). A simple and effective method for removing contaminants from wastewater, including non-biodegradable substances like HMs, is biosorption by bacteria. The recalcitrant nature of the toxic HMs imposes a significant threat to global health. The existing physiochemical techniques that are deployed in cleaning up the polluted environment are costly and often lead to the production of other hazardous byproducts (Etesami, 2018). For this purpose, some alternative cost-effective eco-friendly methods and sustainable technologies are necessitated to reduce the toxicity of these HMs. Microbe-mediated removal of these HMs is among these cost-effective techniques (Gupta, & Diwan, 2017). Several microbes are quite predominant in the soil rhizosphere that can be exploited for the removal of these toxic metals from the soil (Zeng et al., 2020). This is known as bioremediation, which has been termed a successful eco-friendly technology so far.

Bacteria comprise specific plasmid-mediated systems that encode a range of genes, responsible for the detoxification of HMs (Ojuederie & Babalola, 2017). Bacteria play an important part in the biogeochemical cycle of hazardous HMs and can thus be used in the bioremediation of these heavy metals (Tiwari & Lata, 2018). The bacteria are responsible for the biotransformation of these toxic HMs and are capable for regulation of their homeostasis in the environment. The genes that are responsible for the transformation or mobilization of HMs are usually located on the chromosomes or extrachromosomal genetic determinants more popularly known as plasmids (Igiri et al., 2018).

However, despite the similitude, there is a difference in the efflux properties and resistance properties. The chromosomal genes encode for the resistance properties invoicing essential HMs and such systems are considered more complex than the plasmid-encoded counterparts (Sarma et al., 2019). The plasmid-encoded genes on the contrary are responsible for toxin metal ion efflux or mediate the transfer of the resistance cassettes to other microbes (Jacob et al., 2018). Comparative genomics research has revealed that horizontal gene transfer involving plasmids has been responsible for the spread of HM resistance in the eubacteria groups.

Numerous investigations have also demonstrated the existence of a mechanism that actively contributes to the outflow of such HM ions into the environment. These include exclusion by permeability barrier and enzymatic oxidation. Reduction processes, adsorption, and intracellular precipitation or complex formation (Devi et al., 2022).

Metal decontamination has been viewed by ecologists and agriculture scientists as a significant technical difficulty (Torimiro et al., 2021). There has been a massive upsurge in the contamination of the sediments and crop fields hence developing cost-effective bioremediation techniques is an absolute prerequisite for the decontamination of HMs (Sun et al., 2021). As suggested by research studies, microorganisms are instrumental in changing the chemical properties of HMs.

Bacteria have developed a variety of strategies to develop resistance to HM ions. Research has been performed on the bioremediation of HM ions by microorganisms (Coetzee et al., 2020). Metals including Cu, Zn, Pb, Cd, and Cr can be quickly removed using bacterial biomass (Yesilada et al., 2018). Heavy metal ions are quickly absorbed by the bacterial species due to their unique peptidoglycan cell wall (Znad et al., 2022). The microbial detoxification of HMs involves the following microbiological mechanisms. These include adsorption to the microbial cell surface, the intracellular uptake of heavy from the environment such as soil as well as chemical transformations (Verma et al., 2021). Metal ions are absorbed and sequestered through the process of adsorption when they adhere to the negatively charged surface of a microbial cell (Thakare et al., 2021). The interaction is electrostatic. With the assistance of certain membrane transporters, the metal ions are transported within the bacterial cell and bioaccumulated there (Mishra et al., 2022). The metal ions are then immobilized (Mishra et al., 2022). The main physical interface between metal ions and bacterial biomass is the cell wall of the bacterium. Anionic functional groupings' total negative charge (Zak et al., 2021). Bacteria may remove HMs from wastewater and lessen the quantity of chemical sludge created by exploiting functional groups such as the ketones, aldehydes, and carboxyl groups contained in their cell walls (Zak et al., 2021). For the uptake of metals, both gram-positive and gram-negative microorganisms are utilized.

There are two distinct types of absorption mechanisms that microbes have developed. The transport of metal ions across the bacterial cell membrane is carried out by two different systems, one of which needs cellular energy in the form of ATP and the other of which is a substrate-nonspecific fast system. Such processes instead involve a chemosmotic gradient (George et al., 2021).

Additionally employed as biosorbents are green, red, and brown algae (Jasmin et al., 2020). Bacteria include some functional components that can do ion exchange, including uronic acid, which contains carboxyl and sulfate groups, xylans, galactans, and alginic acid (Jasmin et al., 2020). Algae are advantageous as biosorbents because, unlike other microbes like bacteria or fungi, they often do not create poisonous chemicals. By complexation, the anion carboxyl groups can bind Cd on the surface.

The amino groups have demonstrated effective chelation and electrostatic interaction elimination of Cr. Bioremediation has been carried out using organisms including *Pseudomonas*, *Desulfovibrio*, *Bacillus*, and *Geobacter* (Pratush et al., 2018). According to reports, Aspergillus sp. can remove Cr from tannery wastewater; it did so to the tune of 65 percent of the wastewater's Cr as opposed to 85 percent of the synthetic medium's Cr (Pratush et al., 2018).

In microbial cells, the toxic metal ions are reduced through dissimilatory reduction processes whereas in the case of anaerobic respiration, microbes are known to use metals as a terminal electron transport chain (Xu et al., 2022). An effective efflux system ought to be available to export the metal ions' reduced form to successfully reduce the harmful HM ions. (Xu et al., 2022). As mobilized forms are frequently more poisonous, metal solubilization can have unfavorable effects. Microbes can detoxify and move potentially harmful HMs via a variety of innate microbial defense mechanisms.

The metal-sensitive elements of the bacterium are protected by permeability barriers that exclude metal. For instance, in the case of *Escherischia coli*, the elimination of Cu is attained by the alternation of the porosity of the membrane-channeled porin protein (Ghosh et al., 2022). The resultant mutant has altered permeability to the HMs. Periplasmic sequestration also contributes to Cu resistance by employing periplasmic binding of some forms of Cu (Pal et al., 2022). These have been studied in *Pseudomonas sp.* which comprises a repository of genes cop A, B, C, and D that are located in inner and outer membranes contributing to Cu resistance (Deng et al., 2022). In *Staphylococcus aureus*, another penicillinase containing plasmids that have been associated with membrane permeability and Cu resistance are also observed.

There are several efflux systems or transporters present in microbes that have been identified to cause the exclusion of several HMs. The P type ATPase in an efflux protein is responsible for efflux of Cd in *S. aureus* + (Sreedevi et al., 2022). ABC transporter proteins are found to cause the efflux of Mn in *Streptococcus gordonii* and Ni in *E coli* + (Sreedevi et al., 2022). Resistance, nodulation, and cell division (RND) transporters have been found in several gram-negative bacteria + (Sreedevi et al., 2022). Such transporters along with membrane fusion proteins and outer membrane factors are responsible for the formation of a Trans-envelope pore. This cumulatively forms the CzcCBA efflux pump and has been known to take part in the detoxification of metals like Zn^{2+}, Co^{2+}, and Cd^{2+} (Sreedevi et al., 2022). The HoxN protein is associated with the uptake of Ni^{2+} with high affinity.

Table 4. Microbes used to remediate heavy metals

S. No.	Heavy Metal	Species	Type of Microbe	References
1.	Cadmium	*Ascophyllum nodosum*	Algae	Romera et al, 2007
		Fucus vesiculosus	Algae	Mata et al., 2008
		Burkholderia species	Bacteria	Jiang et al., 2008
		Pseudomonas veronii	Bacteria	Vullo et al., 2008
		Agaricus bisporus	Fungi	Nagy et al., 2014
2.	Lead	*Cladophora fascicularis*	Algae	Deng et al., 2007
		Burkholderia species	Bacteria	Jiang et al., 2008
		Aspergillus fumigatus	Fungi	Kumar Ramasamy et al., 2011
3.	Copper	*Kocuria flava*	Bacteria	Achal et al., 2011
		Aspergillus versicolor	Fungi	Tastan et al., 2010
4.	Zinc	*Ascophyllum nodosum*	Algae	Romera et al, 2007
		Spirogyra spp.	Algae	Mane & Bhosle, 2012
		Pseudomonas veronii	Bacteria	Vullo et al., 2008
5.	Nickel	*Ascophyllum nodosum*	Algae	Holan & Volesky, 1994

The CHR family of proteins is also involved in the detoxification of sulfate and chromate + (Sreedevi et al., 2022). Apart from this, the other well-known transporters are CDF and ars transporters that are involved in the transport of As or the reduction of toxic arsenate to its nontoxic counterpart arsenite (Arora & Chauhan, 2021). The environment, as well as agriculture, has faced major issues over the last decade owing to human activities. Overexposure to HMs leads to the formation of metal conjugates that leads to random exploitation of valuable environmental sources. In conclusion, as supported by the aforementioned arguments, the concept of bioremediation including bacteria is crucial to address such a situation. Modern genetic technology and optimization methods point to a bright future for these technologies. Microorganisms that have undergone genetic modification may be more capable of bio-remediating a variety of pollutants. Agricultural and industrial waste, are currently being evaluated for their potential as bioremediations on a lab and commercial scale (Ummalyma et al., 2018). It is now quite simple to create genetically modified or engineered microorganisms (GEMs) by rearranging the genes, promoters, etc. and this can improve their performance *in situ* thanks to recent advancements in genetic engineering. Several GEMs have been successfully developed and experimentally tested for efficient bioremediation under controlled laboratory conditions (Ummalyma et al., 2018). Through the identification of genes linked to degradation and the creation of suitable bioremediation agents, recombinant DNA techniques can be utilized to improve an organism's capacity to metabolize a xenobiotic (Ummalyma et al., 2018). Site-directed mutagenesis, antisense RNA technology, and polymerase chain reaction (PCR) are some of the various methods investigated by recombinant DNA technology. Table 4 enlists selected algae and microbes used to remediate HMs.

Mechanism of Bioremediation

In this world of environmental pollution-related disasters, water pollution is creating a disastrous effect on human health, agriculture, and the biological and physiological processes of different flora and fauna. The water gets mainly contaminated by industrial wastes and petroleum spills in the oceans. This contains recalcitrant and persistent compounds that put the ecological system and human health at high risk (Hazaimeh and Ahmed, 2021). Bioremediation is the use of microbial processes for remediation, and it has proven to be a successful implementation because of its environmental friendliness, low cost, and highly efficient method with few negative effects. Bioremediation can be *in-situ* as well as *ex-situ* types which depend on various factors like unlimited cost, characteristics of the sites, pollutant type, and concentration. *Ex-situ* type is more costly as compared to *in-situ* type. The installation of technology on polluted sites and the inability to properly view and regulate the subsurface of contaminated areas are the main on-site challenges (Kapahi and Sachdeva, 2019). The two main bioremediation strategies are biostimulation and bioaugmentation, both of which are supported by favorable environmental elements. With numerous variety and complexity in the pollutants, the bioremediation process is not restricted to one for alleviating the pollutants from the sites. Indigenous microorganisms take charge to solve this problem which initiates the process of biodegradation (Azubuike et al., 2016). Heavy metals are ubiquitous in the environment due to the heavy load of industrial pollution. They not only pollute the water but also the agricultural soil (Tegene and Tenkegna, 2020). The productivity of the soil gradually decreases with an increase in the contamination rate. Few of the HMs like Cd, copper (Cu), argon (Ar), silver (Ag), Cr, Zn, Pb, uranium (Ur), radium (Ra), Ni, etc. are considered to be toxic to the plants by inhibiting their natural processes thereby affecting the yield of the crops (Wang et al., 2015). These HM's persistence in the soil over time tends to exhibit mutagenic and carcinogenic qualities that reach the food chain and have a risky impact on humans (Ali et al., 2013; Ahemad and Kibret, 2013). The sewage sludge is treated with anaerobic bacteria. The main aim of the bacteria is to produce methane gas from the treated sludge. The presence of microorganisms in this environment acts as a boon to solve this problem. Microbes like *Proteobacteria* sp., *Bacteroidetes* sp., *Acidobacteria* sp., and *Chloroflexi* sp. are the dominant species used for wastewater management (Nascimento et al., 2018). *Vibrio harveyi* exhibits the capacity for bioaccumulation of HMs like Cd up to 23.3 mg Cd^{2+}/g of dehydrated cells, whereas, a consortium of marine bacteria removes Hg in a bioreactor. Bacteria of Enterobactercloaceae class inherit the potential of HM chelation, by exopolysaccharide secretion and remove them from the polluted environment (Von Canstein et al., 2002; Jalil et al., 2013).

Species like *Rhodobium marinum* and *Rhodobacter sphaeroides*, can also effectively remove HMs like Cu, Zn, Cd, and Pb from polluted locations through biosorption or biotransformation. *Bacillus* spp. and *Pseudomonas aeruginosa* have been utilized to lessen Zn and Cu HMs (Kumar, 2011). Some symbiotic associations of bacteria with plants help them to withstand the toxicity of the HMs of the contaminated environment (Throne-Holst et al., 2007). This mechanism includes biotransformation, extrusion, use of enzymes, generation of exo-polysaccharide (EPS), production of metallothioneins, electrostatic communication, ion exchange, precipitation, redox process, and surface complexion (Javed et al., 2007; Tegene and Tenkegna, 2020). The chief mechanism deals with the oxidation of metals, methylation, decrease in certain enzymes, formation of metal-organic complexion, degradation of metal ligands, metal flux pumps, demethylation, sequestration of intra and extracellular metals permeability barrier exclusion, metal chelator production (Soloman et al., 2009; Kumar et al., 2016). The mechanism of detoxification in fungi is different, which involves, chelating, precipitating, and binding cell walls. In several intercellular activities, substances are transported into intracellular compartments and bound to sulfur compounds, organic acids, peptides, and polyphosphates (Bellion et al., 2006). The absorption of metal cations by the negatively charged bacterial cell wall is called biosorption. It can be metabolism dependent and independent. Sequestration, redox reaction, and species transformation are components of metabolism-dependent bioaccumulation (World health organization c, 2006). This biosorption can be executed by dead or living biomass (Fomina and Gadd, 2014). The microbes uptake the HMs and change their oxidation state to another thereby making the end product harmless (Kamaludeen et al., 2003). To generate energy, they utilize metals and metalloids as electron donors or acceptors. The oxidized metals act as a terminal acceptor of an electron during anaerobic respiration (Barkay et al., 2003; Van et al., 2006). In direct enzymatic reduction, metals are reduced while organic molecules are oxidized. Indirect enzymatic reduction involves the reduction of metal ions during the oxidation of Fe and sulfur. In active transport, the resistance system of microorganisms for HMs is the mechanism that is followed. They export metal ions from the cell. Genetic determinants are localized on chromosomes (Levin et al., 2004; Green-Ruiz, 2006; Yan et al., 2007) and plasmids (Gupta and Mohapatra, 2003; Ortega et al., 2011). Some metal ions like chromate get transported by the sulfate transport system inside the cell (Tegene and Tenkegna, 2020). The cell uptakes Cd, Zn, cobalt (Co), Ni, and Mn through a magnesium transport system e.g., *Ralstonia metallidurans* (*Alcaligenes eutrophus*). The electrochemical gradient allows the exportation of metals from cell to cell. The efflux system consists of proteins of three families' viz. RND (resistance, nodulation, cell division, CDF (cation diffusion facilitator), and P-type ATPases (Niu et al., 2009).

Conclusion

The introduction of pollutants into the aquatic ecosystem is a long-old habit of humans which did not change till today despite compensating for their health. Water pollution stems from several inceptions. Though the river and streams have a self-healing capacity from this effect the ponds, lakes, oceans, and sluggish rivers have almost no capacity to withstand this atrocity of anthropogenic activities. Continuous industrial effluents and sewage release are creating serious threats not only to humans but also to flora and fauna by eutrophication. This eutrophication is a severe disaster to the ecosystem and needs to be immediately addressed. To retard the aggressiveness of water pollution following measures should be followed:

- Strict government laws should be enforced which will create a sense of fear among the public creating awareness. Several amendments and policies related to maintaining water quality came into enforcement in 1886. The River and Harbor Act of 1886 was recodified in the Rivers and Harbors Act of 1899. Federal Water Pollution Control Act (1948), for maintaining the integrity of the nation's water. The Water Quality Act of 1965 provided maintaining of water quality standards within as well as interstate. In 1966, the Clean water restoration act came into confidence which levied a fine of 100$ per day on the polluters who were unable to submit the requisite report. In 1970, Water Quality Improvement Act was brought to expand the certification of water quality. Federal Water Pollution Control Act Amendments of 1972 came into confidence due to the growing concern of water pollution among the people which subsequently became the Clean Water Act (CWA), 1977. Water Pollution Control in India (1993), provided a demonstration to small-scale industries to reduce waste projects where audits were conducted on pulp and paper industries, textiles and dyeing industries, and pesticide industries.
- The main contribution of water pollution can be checked by prohibiting some anthropogenic activities like properly disposing of toxic chemicals (household solvents, bleaching powders, cleaners, paint, etc.), not using fat and grease down the drain, using phosphate-free detergents, eating more organic food, cut down meat eating, avoid plastic containers, and avoid vehicles from leaking and by hugging the strategy of recycling the products. Communities should have hazardous waste collectors who can collect the waste from all the houses of the community and properly dispose of it in government/municipality-allotted areas.
- Installation of the drip-irrigation water system for valuable plants. Plantation of drought-tolerant grasses and plants for landscaping and watering them only in the evening to avoid evaporation shall be practiced.
- Installation of a new generation of biodegradable, efficient, metal-free, non-ion-relating coating and filler for medical devices, i.e.,

antimicrobial inorganic bioglass to provide biocompatible with no cytotoxicity drinking water.

- Installation of smart water purifiers can alleviate the deteriorating water quality and its rising cost.
- The sewage from all over the cities should be treated by microorganisms before their disposal in the water bodies. If the secondary treatment is done, then this wastewater can be reused in sanitary and agricultural systems.
- Some chemical methods of precipitation, ion exchange, reverse osmosis, and coagulation can be practiced.
- Water hyacinth-like water plants can be installed in different places which have the potential of absorbing Cd and Hg and thereby can be potent enough to absorb the pollutants-prone regions which can subsequently reduce the adverse effect to a larger extent.
- Several traditional rituals like cremating dead bodies of humans along with other religious practices, which cause the dumping of waste products into the river should be strictly prohibited.
- Organic fertilizers and pesticides should be used in agricultural practices.
- Lastly, water consumption should be made like an astute citizen and the practice of recycling should be followed whenever possible.

Acknowledgment

The authors are thankful to the library cum information centers of their respective Institutions for providing the support to conduct literature searches using the internet platform.

References

Abarikwu, Sunny O., Rex-Clovis Njoku, Chiamaka J. Lawrence, Iniobong A. Charles, and Jude C. Ikewuchi. (2017). *Pharmaceutical biology*, 55, no. 1, 2161-2169. https://doi.org/10.1080/13880209.2017.1387575.

Achal, Varenyam, Xiangliang Pan, and Daoyong Zhang. (2011). “Remediation of copper-contaminated soil by *Kocuria flava* CR1, based on microbially induced calcite precipitation.” *Ecological Engineering*, 37, no. 10, 1601-1605. https://doi.org/10.1016/j.ecoleng.2011.06.008.

Acosta, José A., S. Martínez Martínez, A. Faz, Rocío Millán, M. A. Muñoz, Tania Terán, and Ricardo Vera. (2011), "Characterization of the potential mercury contamination in the Apolobamba gold mining area, Bolivia." *Spanish Journal of Soil Science: SJSS,* 1, no. 1, 86-99.

Ahemad, Munees, and Mulugeta Kibret. (2013). "Recent trends in microbial biosorption of heavy metals: a review." *Biochemistry and Molecular Biology*, 1, no. 1, 19-26. https://10.12966/bmb.06.02.2013.

Ahmad, Rafiq, Zara Tehsin, Samina Tanvir Malik, Saeed Ahmad Asad, Muhammad Shahzad, Muhammad Bilal, Mohammad Maroof Shah, and Sabaz Ali Khan. (2016). "Phytoremediation potential of hemp (*Cannabis sativa* L.): identification and characterization of heavy metals responsive genes." *CLEAN–Soil, Air, Water.*, 44, no. 2. 195-201.

Ahmad, Sk Akhtar, Manzurul Haque Khan, and Mushfiqul Haque. (2018). "Arsenic contamination in groundwater in Bangladesh: implications and challenges for healthcare policy." *Risk management and healthcare policy*, 251-261. https://doi.org/10.2147/RMHP.S153188.

Ahmed, Jebin, Abhijeet Thakur, and Arun Goyal. (2021). "Industrial wastewater and its toxic effects." 1-14. https://doi.org/10.1039/9781839165399-00001.

Aja, Patrick M., Friday I. Izekwe, Ademola C. Famurewa, Ezebuilo U. Ekpono, Felix E. Nwite, Ikechuku O. Igwenyi, Joshua N. Awoke et al. (2020). "Hesperidin protects against cadmium-induced pancreatitis by modulating insulin secretion, redox imbalance and iNOS/NF-κB signaling in rats." *Life Sciences*, 259, 118268. https://doi.org/10.1016/j.lfs.2020.118268.

Alaboudi, Khalid A., Berhan Ahmed, and Graham Brodie. (2018). "Phytoremediation of Pb and Cd contaminated soils by using sunflower (*Helianthus annuus*) plant." *Annals of agricultural sciences*, 63, no. 1, 123-127. https://doi.org/10.1016/j.aoas.2018.05.007.

Alaribe, F. O., and Agamuthu, P. (2015). Assessment of phytoremediation potentials of *Lantana camara* in Pb impacted soil with organic waste additives. *Ecological Engineering*, 83, 513-520. https://doi.org/10.1016/j.ecoleng.2015.07.001.

Al-Baqami, Najah M., and Reham Z. Hamza. (2021). "Protective effect of resveratrol against hepatotoxicity of cadmium in male rats: antioxidant and histopathological approaches." *Coatings*, 11, no. 5, 594. https://doi.org/10.3390/coatings11050594.

Alengebawy, Ahmed, Sara Taha Abdelkhalek, Sundas Rana Qureshi, and Man-Qun Wang. (2021). "Heavy metals and pesticides toxicity in agricultural soil and plants: Ecological risks and human health implications." *Toxics*, 9, no. 3, 42. https://doi.org/10.3390/toxics9030042.

Al-Forkan, Mohammad, Fahmida Binta Wali, Laila Khaleda, Md Alam, Rahee Hasan Chowdhury, Amit Datta, Md Rahman et al. (2021). "Association of arsenic-induced cardiovascular disease susceptibility with genetic polymorphisms." *Scientific reports*, 11, no. 1, 1-16. https://doi.org/10 .1038/s41598-021-85780-8.

Ali, Hazrat, Ezzat Khan, and Muhammad Anwar Sajad. (2013). "Phytoremediation of heavy metals—concepts and applications." *Chemosphere*, 91, no. 7, 869-881. https://doi.org/10.1016/j.chemosphere.2013.01.075.

Alves, Laize Queiroz, Raildo Mota de Jesus, Alex-Alan Furtado de Almeida, Vânia Lima Souza, and Pedro Antônio Oliveira Mangabeira. (2014). "Effects of lead on anatomy, ultrastructure and concentration of nutrients in plants *Oxycaryum cubense* (Poep. & Kunth) Palla: a species with phytoremediator potential in contaminated watersheds." *Environmental Science and Pollution Research*, 21, 6558-6570. https://doi.org/10.1007/s11356-014-2549-9.

Apanpa-Qasim, Ajoke FI, Adebola A. Adeyi, Sandeep N. Mudliar, Karthik Raghunathan, and Prasant Thawale. (2016). "Examination of lead and cadmium in water-based paints marketed in Nigeria." *Journal of Health and Pollution*, 6, no. 12, 43-49. https://doi.org/10.5696/2156-9614-6.12.43.

Ara, Anjum, and Jawed Ahmad Usmani. (2015). "Lead toxicity: a review." *Interdisciplinary toxicology*, 8, no. 2, 55-64. https://doi.org/10.1515/intox-2015-0009.

Arora, Naveen Kumar, and Reshu Chauhan. (2021). "Heavy metal toxicity and sustainable interventions for their decontamination." *Environmental Sustainability*, 4, 1-3. http://dx.doi.org/10.1007/s42398-021-00164-y.

Arora, Naveen Kumar. (2018). "Bioremediation: a green approach for restoration of polluted ecosystems." *Environmental Sustainability*, 1, no. 4, 305-307. https://doi.org/10.1007/s42398-018-00036-y.

Arregui, Leticia, Marcela Ayala, Ximena Gómez-Gil, Guadalupe Gutiérrez-Soto, Carlos Eduardo Hernández-Luna, Mayra Herrera de Los Santos, Laura Levin et al. (2019). "Laccases: structure, function, and potential application in water bioremediation." *Microbial Cell Factories*, 18, no. 1, 1-33. https://doi.org/10.1186/s12934-019-1248-0.

Asaduzzaman, Mohammad, Imtiaj Hasan, Sultana Rajia, Nazneen Khan, and Kazi Ahmed Kabir. (2016). "Impact of tannery effluents on the aquatic environment of the Buriganga River in Dhaka, Bangladesh." *Toxicology and Industrial Health*, 32, no. 6, 1106-1113. https://doi.org/10.1016/j.ecoleng.2015.07.001.

Aschner, Michael, Keith M. Erikson, Elena Herrero Hernández, and Ronald Tjalkens. (2009). "Manganese and its role in Parkinson's disease: from transport to neuropathology." *Neuromolecular medicine*, 11, 252-266. https://doi.org/10.1007/s12017-009-8083-0.

Astatkie, Higemengist, Argaw Ambelu, and Embialle Mengistie. "Contamination of stream sediment with heavy metals in the Awetu Watershed of Southwestern Ethiopia." *Frontiers in Earth Science*, 9, (2021). 658737. https://doi.org/10.3389/feart.2021.658737.

Awa, Soo Hui, and Tony Hadibarata. (2020). "Removal of heavy metals in contaminated soil by phytoremediation mechanism: a review." *Water, Air, & Soil Pollution*, 231, no. 2 47. https://doi.org/10.1007/s11270-020-4426-0.

Awasthi, Yashika, Arun Ratn, Rajesh Prasad, Manoj Kumar, and Sunil P. Trivedi. (2018). "An *in vivo* analysis of Cr6+ induced biochemical, genotoxicological and transcriptional profiling of genes related to oxidative stress, DNA damage and apoptosis in liver of fish, *Channa punctatus* (Bloch, 1793)." *Aquatic toxicology*, 200, 158-167. https://doi.org/10.1016/j.aquatox.2018.05.001.

Ayoub, Nour, Hiba Mantash, Hassan R. Dhaini, Abbas Mourad, Mohammad Hneino, and Zeina Daher. (2021). "Serum cadmium levels and risk of metabolic syndrome: a cross-sectional study." *Biological trace element research*, 1-9. https://doi.org/10.1007/s12011-020-02502-3.

Azubuike, Christopher Chibueze, Chioma Blaise Chikere, and Gideon Chijioke Okpokwasili. (2016). "Bioremediation techniques–classification based on site of application: principles, advantages, limitations and prospects." *World Journal of Microbiology and Biotechnology*, 32, 1-18.

Bandara, J. M. R. S. H. V. P., Bandara, M. A. Y., Jayasooriya, R. G. P. T., and Rajapaksha, H. (2011). "Pollution of River Mahaweli and farmlands under irrigation by cadmium from agricultural inputs leading to a chronic renal failure epidemic among farmers in NCP, Sri Lanka." *Environmental geochemistry and health*, 33, 439-453. https://doi.org/10.1007/s10653-010-9344-4.

Bani, Aida, Dolja Pavlova, Guillaume Echevarria, Alfred Mullaj, Roger D. Reeves, Jean-Louis J-L. Morel, and Sulejman Sulçe. (2010). "Nickel hyperaccumulation by the species of *Alyssum* and *Thlaspi* (Brassicaceae) from the ultramafic soils of the Balkans." *Botanica Serbica*, 34, no. 1, 3-14.

Barbieri, Flavia Laura, Amandine Cournil, and Jacques Gardon. (2009). "Mercury exposure in a high fish eating Bolivian Amazonian population with intense small-scale gold-mining activities." *International Journal of Environmental Health Research*, 19, no. 4, 267-277. https://doi.org/10.1080/09603120802559342.

Barbone, Fabio, Francesca Valent, Federica Pisa, Fulvio Daris, Vesna Fajon, Darija Gibicar, Martina Logar, and Milena Horvat. (2020). "Prenatal low-level methyl mercury exposure and child development in an Italian coastal area." *NeuroToxicology*, 81, 376-381. https://doi.org/10.1016/j.neuro.2020.09.033.

Barkay, Tamar, Susan M. Miller, and Anne O. Summers. (2003). "Bacterial mercury resistance from atoms to ecosystems." *FEMS microbiology reviews* 27, no. 2-3, 355-384. https://doi.org/10.1016/S0168-6445(03)00046-9.

Barregard, Lars, Gerd Sallsten, Florencia Harari, Eva M. Andersson, Niklas Forsgard, Ola Hjelmgren, Oskar Angerås et al. (2021). "Cadmium exposure and coronary artery atherosclerosis: a cross-sectional population-based study of Swedish middle-aged adults." *Environmental Health Perspectives*, 129, no. 6, 067007. https://doi.org/10.1289/EHP8523.

Baszuk, Piotr, Beata Janasik, Sandra Pietrzak, Wojciech Marciniak, Edyta Reszka, Katarzyna Białkowska, Ewa Jabłońska et al. (2021). "Lung Cancer Occurrence—Correlation with Serum Chromium Levels and Genotypes." *Biological Trace Element Research*, 199, 1228-1236. https://doi.org/10.1007/s12011-020-02240-6.

Bazzi, Wael, Antoine G. Abou Fayad, Aya Nasser, Louis-Patrick Haraoui, Omar Dewachi, Ghassan Abou-Sitta, Vinh-Kim Nguyen et al. (2020). "Heavy metal toxicity in armed conflicts potentiates AMR in *A. baumannii* by selecting for antibiotic and heavy metal co-resistance mechanisms." *Frontiers in microbiology*, 11, 68. https://doi.org/10.3389/fmicb.2020.00068.

Bekturganov, Zakir, Kamshat Tussupova, Ronny Berndtsson, Nagima Sharapatova, Kapar Aryngazin, and Maral Zhanasova. (2016). "Water related health problems in Central Asia—A review." *Water*, 8, no. 6, 219. https://doi.org/10.3390/w8060219.

Bellion, Marc, Mikaël Courbot, Christophe Jacob, Damien Blaudez, and Michel Chalot. (2006). "Extracellular and cellular mechanisms sustaining metal tolerance in ectomycorrhizal fungi." *FEMS microbiology letters*, 254, no. 2, 173-181. https://doi.org/10.1111/j.1574-6968.2005.00044.x.

Berti, William R., and Scott D. Cunningham. (2000). "Phytostabilization of metals." *Phytoremediation of toxic metals: using plants to clean up the environment. Wiley, New York*, 71-88.

Bhatia, Ravi Kant, Deepak Sakhuja, Shyam Mundhe, and Abhishek Walia. (2020). "Renewable energy products through bioremediation of wastewater." *Sustainability*, 12, no. 18 7501. http://dx.doi.org/10.3390/su12187501.

Bhatia, Siddharth, Guru Balamurugan, and Annu Baranwal. (2014). "High arsenic contamination in drinking water hand-pumps in Khap Tola, West Champaran, Bihar, India." *Frontiers in Environmental Science*, 2, 49. https://doi.org/10.3389/fenvs.2014.00049.

Bi, Xiangyang, Mohai Zhang, Yunjie Wu, Zhongbiao Fu, Guangyi Sun, Lihai Shang, Zhonggen Li, and Pengcong Wang. (2020). "Distribution patterns and sources of heavy metals in soils from an industry undeveloped city in Southern China." *Ecotoxicology and Environmental Safety*, 205, 111115. https://doi.org/10.1016/j.ecoenv.2020.111115.

Blanc, Paul D. (2018). "The early history of manganese and the recognition of its neurotoxicity, 1837–1936." *Neurotoxicology*, 64, 5-11. https://doi.org/10.1016/j.neuro.2017.04.006.

Bodeau-Livinec, Florence, Philippe Glorennec, Michel Cot, Pierre Dumas, Séverine Durand, Achille Massougbodji, Pierre Ayotte, and Barbara Le Bot. (2016). "Elevated blood lead levels in infants and mothers in Benin and potential sources of exposure." *International journal of environmental research and public health* 13, no. 3, 316. https://doi.org/10.3390/ijerph13030316.

Bonanno, Giuseppe, and Giuseppe Luigi Cirelli. (2017). "Comparative analysis of element concentrations and translocation in three wetland congener plants: *Typha domingensis*, *Typha latifolia* and *Typha angustifolia*." *Ecotoxicology and Environmental Safety*, 143, 92-101. https://doi.org/10.1016/j.ecoenv.2017.05.021.

Borné, Yan, Lars Barregard, Margaretha Persson, Bo Hedblad, Björn Fagerberg, and Gunnar Engström. (2015). "Cadmium exposure and incidence of heart failure and atrial fibrillation: a population-based prospective cohort study." *BMJ open*, 5, no. 6, e007366. https://doi.org/10.1136/bmjopen-2014-007366.

Bouchard, Maryse, François Laforest, Louise Vandelac, David Bellinger, and Donna Mergler. (2007). "Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water." *Environmental health perspectives*, 115, no. 1 122-127. https://doi.org/10.1289/ehp.9504.

Burges, Aritz, Itziar Alkorta, Lur Epelde, and Carlos Garbisu. (2018). "From phytoremediation of soil contaminants to phytomanagement of ecosystem services in metal contaminated sites." *International journal of phytoremediation* 20, no. 4, 384-397. https://doi.org/10.1080/15226514.2017.1365340.

Camacho, Lucy Mar, Mélida Gutiérrez, Maria Teresa Alarcón-Herrera, Maria de Lourdes Villalba, and Shuguang Deng. (2011). "Occurrence and treatment of arsenic in groundwater and soil in northern Mexico and southwestern USA." *Chemosphere*, 83, no. 3, 211-225. https://doi.org/10.1016/j.chemosphere.2010.12.067.

Cempel, M., and Nikel, G. J. P. J. S. (2006). "Nickel: A review of its sources and environmental toxicology." *Polish journal of environmental studies*, 15, no. 3.

Chakraborti, Dipankar, Mohammad Mahmudur Rahman, Sad Ahamed, Rathindra Nath Dutta, Shyamapada Pati, and Subhash Chandra Mukherjee. (2016). "Arsenic contamination of groundwater and its induced health effects in Shahpur block, Bhojpur district, Bihar state, India: risk evaluation." *Environmental Science and Pollution Research*, 23, 9492-9504. https://doi.org/10.1007/s11356-016-6149-8.

Chandra, Satish, Yogendra Singh Gusain, and Arun Bhatt. (2022). "Metal hyperaccumulator plants and environmental pollution." In *Research Anthology on Emerging Techniques in Environmental Remediation*, pp. 681-693. IGI Global.

Chehregani, Abdolkarim, and Behrouz E. Malayeri. (2007). "Removal of heavy metals by native accumulator plants." *International Journal of Agriculture and Biology (Pakistan)*.

Chen, Zhuo, Zhicai Zuo, Kejie Chen, Zhuangzhi Yang, Fengyuan Wang, Jing Fang, Hengmin Cui et al. (2022). "Activated Nrf-2 pathway by vitamin E to attenuate testicular injuries of rats with sub-chronic cadmium exposure." *Biological Trace Element Research*, 200, no. 4, 1722-1735. https://doi.org/10.1007/s12011-021-02784-1.

Chheang, Lita, Nisakorn Thongkon, Tongchai Sriwiriyarat, and Sudtida Pliankarom Thanasupsin. (2021). "Heavy metal contamination and human health implications in the chan thnal reservoir, Cambodia." *Sustainability*, 13, no. 24, 13538. https://doi.org/10.3390/su132413538.

Chiang, Po Neng, Chih-Yu Chiu, Ming Kuang Wang, and Bi-Tzu Chen. (2011). "Low-molecular-weight organic acids exuded by Millet (*Setaria italica* (L.) Beauv.) roots and their effect on the remediation of cadmium-contaminated soil." *Soil science*, 176, no. 1, 33-38. https://doi.org/10.1097/SS.0b013e318202fdc9.

Choubey, Mayank, Radha Chaube, and Keerikkattil P. Joy. (2015). "*Toxic Effects of Lead Nitrate Pb (NO), on Testis in the Catfish Heteropneustes fossilis*." https://dx.doi.org/10.17311/pharmacologia.2015.63.72.

Chowdhary, Pankaj, Ram Naresh Bharagava, Sandhya Mishra, and Nawaz Khan. (2020). "Role of industries in water scarcity and its adverse effects on environment and human health." *Environmental Concerns and Sustainable Development: Volume 1: Air, Water and Energy Resources*, 235-256. https://doi.org/10.1007/978-981-13-5889-0_12.

d'Errico, Angelo, Jana Zajacova, Anna Cacciatore, Santo Alfonzo, Fabio Beatrice, Fulvio Ricceri, and Guido Valente. (2021). "Exposure to occupational hazards and risk of sinonasal epithelial cancer: results from an extended Italian case–control study." *Occupational and Environmental Medicine*, 78, no. 5, 323-329. https://doi.org/10.1136/oemed-2020-106738.

Das, Gautam, Nabajyoti Das, and Parag Deka. (2020). "*Toxicological effect of mercuric chloride on Heteropneustes fossilis (Bloch) with reference to behavioural and haematological alteration*."

Das, Krishna, Ursula Siebert, Audrey Gillet, Aurélie Dupont, Carole Di-Poï, Sonja Fonfara, Gabriel Mazzucchelli, Edwin De Pauw, and De Pauw-Gillet. (2008). "Mercury immune toxicity in harbour seals: links to in vitro toxicity." *Environmental Health*, 7, no. 1, 1-17. https://doi.org/10.1186/1476-069X-7-52.

Das, Suchismita, Sunayana Goswami, and Anupam Das Talukdar. (2014). "A study on cadmium phytoremediation potential of water lettuce, *Pistia stratiotes* L." *Bulletin of environmental contamination and toxicology*, 92, 169-174. https://doi.org/10.1007/s00128-013-1152-y.

de Matos Mansur, Bruno, Caio Neno Silva Cavalcante, Bruno Rodrigues dos Santos, and Amauri Gouveia. (2012). "Effects of mercury chloride (HgCl2) on Betta splendens aggressive display." *The Spanish journal of psychology*, 15, no. 1, 442-450. https://doi.org/10.5209/rev_sjop.2012.v15.n1.37349.

Deng, Fei, Dongwei Zhang, Liting Yang, Lijuan Li, Yu Lu, Jing Wang, Yujiao Fan, Yanrong Zhu, Xiaowen Li, and Yao Zhang. (2022). "Effects of antibiotics and heavy metals on denitrification in shallow eutrophic lakes." *Chemosphere*, 291, 132948. https://doi.org/10.1016/j.chemosphere.2021.132948.

Deng, Liping, Yingying Su, Hua Su, Xinting Wang, and Xiaobin Zhu. (2007). "Sorption and desorption of lead (II) from waste water by green algae *Cladophora fascicularis*." *Journal of Hazardous Materials*, 143, no. 1-2, 220-225. https://doi.org/10.1016/j.jhazmat.2006.09.009.

Deng, Yujiao, Meng Wang, Tian Tian, Shuai Lin, Peng Xu, Linghui Zhou, Cong Dai et al. (2019). "The effect of hexavalent chromium on the incidence and mortality of human cancers: a meta-analysis based on published epidemiological cohort studies." *Frontiers in oncology*, 9, 24. https://doi.org/10.3389/fonc.2019.00024.

Devi, Rajni, Biswaranjan Behera, Md Basit Raza, Vikas Mangal, Muhammad Ahsan Altaf, Ravinder Kumar, Awadhesh Kumar, Rahul Kumar Tiwari, Milan Kumar Lal, and Brajesh Singh. (2021). "An insight into microbes mediated heavy metal detoxification in plants: a review." *Journal of Soil Science and Plant Nutrition*, 1-23. https://doi.org/10.1007/s42729-021-00702-x.

Du, Peng, Lingrong Zhang, Yuntao Ma, Xinyue Li, Zhenglu Wang, Kang Mao, Na Wang et al. (2020). "Occurrence and fate of heavy metals in municipal wastewater in Heilongjiang Province, China: a monthly reconnaissance from 2015 to 2017." *Water*, 12, no. 3 728. https://doi.org/10.3390/w12030728.

Edelstein, Menahem, and Meni Ben-Hur. (2018). "Heavy metals and metalloids: Sources, risks and strategies to reduce their accumulation in horticultural crops." *Scientia Horticulturae*, 234, 431-444. https://doi.org/10.1016/j.scienta.2017.12.039.

El-Aassar, M. R., Hala Fakhry, Ahmed A. Elzain, Hoda Farouk, and Elsayed E. Hafez. (2018). "Rhizofiltration system consists of chitosan and natural *Arundo donax* L. for removal of basic red dye." *International journal of biological macromolecules*, 120, 1508-1514. https://doi.org/10.1016/j.ijbiomac.2018.09.159.

Elarabany, Naglaa, and Mohammed Bahnasawy. (2019). "Comparative and interactive biochemical effects of sub-lethal concentrations of cadmium and lead on some tissues of the African catfish (*Clarias gariepinus*)." *Toxicological Research*, 35, 249-255. https://doi.org/10.5487/TR.2019.35.3.249.

Fang, Jing, Shenglan Xie, Zhuo Chen, Fengyuan Wang, Kejie Chen, Zhicai Zuo, Hengmin Cui et al. (2021). "Protective effect of vitamin e on cadmium-induced renal oxidative damage and apoptosis in rats." *Biological Trace Element Research*, 1-13. https://doi.org/10.1007/s12011-021-02606-4.

Fasani, Elisa, Anna Manara, Flavio Martini, Antonella Furini, and Giovanni DalCorso. (2018). "The potential of genetic engineering of plants for the remediation of soils contaminated with heavy metals." *Plant, cell & environment*, 41, no. 5, 1201-1232. https://doi.org/10.1111/pce.12963.

Fenga, Concettina, Silvia Gangemi, Valentina Di Salvatore, Luca Falzone, and Massimo Libra. (2017). "Immunological effects of occupational exposure to lead." *Molecular medicine reports*, 15, no. 5, 3355-3360. https://doi.org/10.3892/mmr.2017.6381.

Filippini, Tommaso, Lauren A. Wise, and Marco Vinceti. (2022). "Cadmium exposure and risk of diabetes and prediabetes: a systematic review and dose-response meta-analysis." *Environment International*, 158, 106920. https://doi.org/10.1016/ j.envint. 2021.106920.

Fomina, Marina, and Geoffrey Michael Gadd. (2014). "Biosorption: current perspectives on concept, definition and application." *Bioresource technology*, 160, 3-14. https://doi.org/10.1016/j.biortech.2013.12.102.

Gaur, Vivek Kumar, Poonam Sharma, Prachi Gaur, Sunita Varjani, Huu Hao Ngo, Wenshan Guo, Preeti Chaturvedi, and Reeta Rani Singhania. (2021). "Sustainable mitigation of heavy metals from effluents: toxicity and fate with recent technological advancements." *Bioengineered*, 12, no. 1, 7297-7313. https://doi.org/10.1080/21655979.2021.1978616.

George, Fanny, Séverine Mahieux, Catherine Daniel, Marie Titécat, Nicolas Beauval, Isabelle Houcke, Christel Neut et al. (2021). "Assessment of Pb (II), Cd (II), and Al (III) removal capacity of bacteria from food and gut ecological niches: Insights into biodiversity to limit intestinal biodisponibility of toxic metals." *Microorganisms*, 9, no. 2, 456. https://doi.org/10.3390/microorganisms9020456.

Gerhardt, Karen E., Perry D. Gerwing, and Bruce M. Greenberg. (2017). "Opinion: Taking phytoremediation from proven technology to accepted practice." *Plant Science* 256 170-185. https://doi.org/10.1016/j.plantsci.2016.11.016.

Ghosh, Sougata, Joorie Bhattacharya, Rahul Nitnavare, and Thomas J. Webster. (2022). "Heavy metal removal by Bacillus for sustainable agriculture." In *Bacilli in Agrobiotechnology: Plant Stress Tolerance, Bioremediation, and Bioprospecting*, pp. 1-30. Cham: Springer International Publishing, https://doi.org/10.1007/978-3-030-85465-2_1.

Giger, Walter. (2009). "The Rhine red, the fish dead—the 1986 Schweizerhalle disaster, a retrospect and long-term impact assessment." *Environmental Science and Pollution Research*, 16, 98-111. https://doi.org/10.1007/s11356-009-0156-y.

Golabek, Tomasz, Barbara Darewicz, Maria Borawska, Renata Markiewicz, Katarzyna Socha, and Jacek Kudelski. (2009). "Lead concentration in the bladder tissue and blood of patients with bladder cancer." *Scandinavian journal of urology and nephrology*, 43, no. 6, 467-470. https://doi.org/10.3109/00365590903198991.

Green-Ruiz, Carlos. (2006). "Mercury (II) removal from aqueous solutions by nonviable *Bacillus* sp. from a tropical estuary." *Bioresource technology*, 97, no. 15, 1907-1911. https://doi.org/10.1016/j.biortech.2005.08.014.

Guédron, Stéphane, David Point, D. Acha, Sylvain Bouchet, Pascale Anabelle Baya, Emmanuel Tessier, Mathilde Monperrus et al. (2017). "Mercury contamination level and speciation inventory in Lakes Titicaca & Uru-Uru (Bolivia): Current status and future trends." *Environmental pollution*, 231, 262-270. https://doi.org/10.1016/ j.envpol.2017.08.009 .

Gupta, Pratima, and Batul Diwan. (2017). "Bacterial exopolysaccharide mediated heavy metal removal: a review on biosynthesis, mechanism and remediation strategies." *Biotechnology Reports*, 13, 58-71. https://doi.org/10.1016/ j.btre.2016.12.006.

Gupta, Rani, and Harapriya Mohapatra. (2003). "Microbial biomass: an economical alternative for removal of heavy metals from waste water." *Indian journal of experimental biology* 41, no 9, 945–966.

Hammad, Doaa M. (2011). "Cu, Ni and Zn phytoremediation and translocation by water hyacinth plant at different aquatic environments." *Australian journal of basic and applied sciences* 5, no. 11, 11-22.

Handa, Kriti, and Rajinder Jindal. (2021). "Estimating the hepatotoxic impact of hexavalent chromium on *Ctenopharyngodon idellus* through a multi-biomarker study." *Environmental Advances*, 5, 100108. https://doi.org/10.1016/ j.envadv.2021.100108.

Hassanzadeh, Mahsa, Rahmat Zarkami, and Roghayeh Sadeghi. (2021). "Uptake and accumulation of heavy metals by water body and *Azolla filiculoides* in the Anzali wetland." *Applied Water Science*, 11, no. 6, 91. https://doi.org/10.1007/s13201-021-01428-y.

Hazaimeh, Mohammad Daher, and Enas S. Ahmed. (2021). "Bioremediation perspectives and progress in petroleum pollution in the marine environment: a review." *Environmental Science and Pollution Research*, 28, no. 39, 54238-54259. https://doi.org/10.1007/s11356-021-15598-4.

Hedayati, Aliakbar. (2012). "Effect of marine mercury toxicity on immunological responses of seabream." *Asian Journal of Animal Sciences*, 6, no. 1, 1-12. https://dx.doi.org/10.3923/ajas.2012.1.12.

Hegazy, A. K., Abdel-Ghani, N. T., and El-Chaghaby, G. A. (2011). "Phytoremediation of industrial wastewater potentiality by Typha domingensis." *International Journal of Environmental Science & Technology*, 8, 639-648. https://doi.org/10.1007/BF0 3326249.

Holan, Z. R., and Volesky, B. (1994). "Biosorption of lead and nickel by biomass of marine algae." *Biotechnology and bioengineering*, 43, no. 11, 1001-1009. https://doi.org/ 10.1002/bit.260431102.

Hou, Shuangxing, Lianfang Yuan, Pengpeng Jin, Bojun Ding, Na Qin, Li Li, Xuedong Liu, Zhongliang Wu, Gang Zhao, and Yanchun Deng. (2013). "A clinical study of the effects of lead poisoning on the intelligence and neurobehavioral abilities of children." *Theoretical Biology and Medical Modelling* 10, no. 1, 1-9. https://doi.org/10.1186/ 1742-4682-10-13.

Houessionon, MG Karel, Edgard-Marius D. Ouendo, Catherine Bouland, Sylvia A. Takyi, Nonvignon Marius Kedote, Benjamin Fayomi, Julius N. Fobil, and Niladri Basu. (2021). "Environmental heavy metal contamination from Electronic Waste (e-waste) recycling activities worldwide: A systematic review from 2005 to 2017." *International* *journal of environmental research and public health*, 18, no. 7, 3517. https://doi.org/10.3390/ijerph18073517.

Huff, James, Ruth M. Lunn, Michael P. Waalkes, Lorenzo Tomatis, and Peter F. Infante. (2007). "Cadmium-induced cancers in animals and in humans." *International journal of occupational and environmental health*, 13, no. 2, 202-212. https://doi.org/10.1179/oeh.2007.13.2.202.

Ibañéz, Sabrina G., Ana L. Wevar Oller, Cintia E. Paisio, Lucas G. Sosa Alderete, Paola S. González, María I. Medina, and Elizabeth Agostini. (2018). "The challenges of remediating metals using phytotechnologies." *Heavy metals in the environment: microorganisms and bioremediation*. CRC Press, Taylor & Francis, 173-191.

Ibezim-Ezeani, M. U., and Ihunwo, O. C. (2020). "Assessment of Pb, Cd, Cr and Ni in water and water hyacinth (*Eichhornia crassipes*) plant from Woji Creek, Rivers State, Nigeria." *Journal of Applied Sciences and Environmental Management*, 24, no. 4, 719-727. https://dx.doi.org/10.4314/jasem.v24i4.26.

Idrees, Nida, B. Tabassum, Elsayed Fathi Abd_Allah, Abeer Hashem, Robeena Sarah, and Mohammad Hashim. (2018). "Groundwater contamination with cadmium concentrations in some West UP Regions, India." *Saudi journal of biological sciences*, 25, no. 7, 1365-1368. https://doi.org/10.1016/j.sjbs.2018.07.005.

Igiri, Bernard E., Stanley IR Okoduwa, Grace O. Idoko, Ebere P. Akabuogu, Abraham O. Adeyi, and Ibe K. Ejiogu. (2018). "Toxicity and bioremediation of heavy metals contaminated ecosystem from tannery wastewater: a review." *Journal of toxicology*, 2018, https://doi.org/10.1155/2018/2568038.

Iha, Danilo Sinhei, and Irineu Bianchini Jr. (2015). "Phytoremediation of Cd, Ni, Pb and Zn by *Salvinia minima*." *International journal of phytoremediation*, 17, no. 10, 929-935. https://doi.org/10.1080/15226514.2014.1003793.

Ilyas, Muhammad, Waqas Ahmad, Hizbullah Khan, Saeeda Yousaf, Muhammad Yasir, and Anwarzeb Khan. (2019). *Reviews on environmental health*, 34, no. 2, 171-186. https://doi.org/10.1515/reveh-2018-0078.

Jacob, Jaya Mary, Chinnannan Karthik, Rijuta Ganesh Saratale, Smita S. Kumar, Desika Prabakar, K. Kadirvelu, and Arivalagan Pugazhendhi. (2018). "Biological approaches to tackle heavy metal pollution: a survey of literature." *Journal of environmental management*, 217, 56-70. https://doi.org/10.1016/j.jenvman.2018.03.077.

Jaishankar, Monisha, Tenzin Tseten, Naresh Anbalagan, Blessy B. Mathew, and Krishnamurthy N. Beeregowda. (2014). "Toxicity, mechanism and health effects of some heavy metals." *Interdisciplinary toxicology*, 7, no. 2, 60. https://doi.org/10.2478/intox-2014-0009.

Jalil, Md Abdul, Md Nannu Mian, and Muhammad Khalilur Rahman. (2013). "Using plastic bags and its damaging impact on environment and agriculture: An alternative proposal." *International Journal of Learning & Development*, 3, no. 4, 1-14. https://doi.org/10.5296/ijld.v3i4.4137.

Jarvis, Peter, Katie Quy, Jitka Macadam, Marc Edwards, and Marjorie Smith. (2018). "Intake of lead (Pb) from tap water of homes with leaded and low lead plumbing systems." *Science of the Total Environment*, 644, 1346-1356. https://doi.org/10.1016/j.scitotenv.2018.07.064.

Jasmin, M. Y., Fadhil Syukri, M. S. Kamarudin, and Murni Karim. (2020). "Potential of bioremediation in treating aquaculture sludge." *Aquaculture*, 519, 734905. https://doi.org/10.1016/j.aquaculture.2019.734905.

Javed, Muhammad Mohsin, Ikram-ul-Haq, and Farrukh Shahbaz. (2007). "Biosorption of mercury from industrial effluent by fungal consortia." *Bioremediation journal*, 11, no. 3, 149-153. https://doi.org/10.1080/10889860701548705.

Jeong, Jihyun, Sang-moon Yun, Minkyeong Kim, and Young Ho Koh. (2020). "Association of blood cadmium with cardiovascular disease in Korea: from the Korea National Health and Nutrition Examination Survey 2008–2013 and 2016." *International Journal of Environmental Research and Public Health*, 17, no. 17, 6288. https://doi.org/10.3390/ijerph17176288

Jiang, Chun-yu, Xia-fang Sheng, Meng Qian, and Qing-ya Wang. (2008). "Isolation and characterization of a heavy metal-resistant *Burkholderia* sp. from heavy metal-contaminated paddy field soil and its potential in promoting plant growth and heavy metal accumulation in metal-polluted soil." *Chemosphere*, 72, no. 2, 157-164. https://doi.org/10.1016/j.chemosphere.2008.02.006.

Jin, Yuanliang, David O'Connor, Yong Sik Ok, Daniel CW Tsang, An Liu, and Deyi Hou. (2019). "Assessment of sources of heavy metals in soil and dust at children's playgrounds in Beijing using GIS and multivariate statistical analysis." *Environment international*, 124, 320-328. https://doi.org/10.1016/j.envint.2019.01.024.

Juárez-Santillán, Luis Felipe, Carlos Alexander Lucho-Constantino, Gabriela Alejandra Vázquez-Rodríguez, Nayeli Mariel Cerón-Ubilla, and Rosa Icela Beltrán-Hernández. (2010). "Manganese accumulation in plants of the mining zone of Hidalgo, Mexico." *Bioresource technology*, 101, no. 15, 5836-5841. https://doi.org/10.1016/j.biortech.2010.03.020.

Junaid, Muhammad, Muhammad Zaffar Hashmi, Yu-Mei Tang, Riffat Naseem Malik, and De-Sheng Pei. (2017). "Potential health risk of heavy metals in the leather manufacturing industries in Sialkot, Pakistan." *Scientific reports*, 7, no. 1, 8848. https://doi.org/10.1038/s41598-017-09075-7.

Kamaludeen, Sara PB, Mallavarapu Megharaj, Albert L. Juhasz, Nabrattil Sethunathan, and Ravi Naidu. (2003). "Chromium-microorganism interactions in soils: remediation implications." *Reviews of Environmental Contamination and Toxicology*, 93-164. https://doi.org/10.1007/0-387-21728-2_4.

Kamran, Muhammad, Zaffar Malik, Aasma Parveen, Li Huang, Muhammad Riaz, Saqib Bashir, Adnan Mustafa, Ghulam Hassan Abbasi, Bin Xue, and Umeed Ali. (2020). "Ameliorative effects of biochar on rapeseed (*Brassica napus* L.) growth and heavy metal immobilization in soil irrigated with untreated wastewater." *Journal of Plant Growth Regulation*, 39, 266-281. https://doi.org/10.1007/s00344-019-09980-3.

Kanwar, Varinder Singh, Ajay Sharma, Arun Lal Srivastav, and Rani Lata. (2020). "Correction to: Phytoremediation of toxic metals present in soil and water environment: A critical review." *Environmental Science and Pollution Research International*, 27, no. 36, 44861-44862. https://doi.org/10.1007/s11356-020-11461-0.

Kapahi, Meena, and Sarita Sachdeva. (2019). "Bioremediation options for heavy metal pollution." *Journal of health and pollution*, 9, no. 24, https://doi.org/10.5696/2156-9614-9.24.191203.

Karrari, Parissa, Omid Mehrpour, and Mohammad Abdollahi. (2012). "A systematic review on status of lead pollution and toxicity in Iran; Guidance for preventive measures." *DARU Journal of Pharmaceutical Sciences*, 20, 1-17. https://doi.org/10.1186/1560-8115-20-2.

Karthikeyan1, Sivakumar, Shanmugasundaram Arumugam, Jayaprakash Muthumanickam, Prabakaran Kulandaisamy, Muthusamy Subramanian, Ramachandran Annadurai, Venkatramanan Senapathi, and Selvam Sekar. (2021). "Causes of heavy metal contamination in groundwater of Tuticorin industrial block, Tamil Nadu, India." *Environmental Science and Pollution Research*, 28, 18651-18666. https://doi.org/10.1007/s11356-020-11704-0.

Kaur, Leela, Kasturi Gadgil, and Satyawati Sharma. (2015). "Phytoextraction based on Indian mustard (*Brassica juncea* arawali) planted on spiked soil by aliquot amount of Lead and Nickel." *EQA-International Journal of Environmental Quality*, 17, 13-23. https://doi.org/10.6092/issn.2281-4485/5817.

Kaur, Tejinder, and Jyoti Budhwar. (2021). "Arsenical keratoses: Case report from nonendemic area of Amritsar." *Clinical Dermatology Review*, 5, no. 1, 117.

Khan, Khalid, Pam Factor-Litvak, Gail A. Wasserman, Xinhua Liu, Ershad Ahmed, Faruque Parvez, Vesna Slavkovich et al. (2011). "Manganese exposure from drinking water and children's classroom behavior in Bangladesh." *Environmental health perspectives*, 119, no. 10, 1501-1506. https://doi.org/10.1289/ehp.1003397.

Kobya, M., Demirbas, E., Parlak, N. U., and Yigit, S. (2010). "Treatment of cadmium and nickel electroplating rinse water by electrocoagulation." *Environmental technology*, 31, no. 13, 1471-1481. https://doi.org/10.1080/09593331003713693.

Kocman, David, Simon J. Wilson, Helen M. Amos, Kevin H. Telmer, Frits Steenhuisen, Elsie M. Sunderland, Robert P. Mason, Peter Outridge, and Milena Horvat. (2017). "Toward an assessment of the global inventory of present-day mercury releases to freshwater environments." *International journal of environmental research and public health*, 14, no. 2, 138. https://doi.org/10.3390/ijerph14020138.

Koptsik, G. N. (2014). "Problems and prospects concerning the phytoremediation of heavy metal polluted soils: a review." *Eurasian Soil Science*, 47, 923-939. https://doi.org/10.1134/S1064229314090075.

Kubier, Andreas, Richard T. Wilkin, and Thomas Pichler. (2019). "Cadmium in soils and groundwater: a review." *Applied Geochemistry*, 108, 104388. https://doi.org/10.1016/j.apgeochem.2019.104388.

Kubota, Masaharu, and Kazufumi Nishi. (2006). "Salicylic acid accumulates in the roots and hypocotyl after inoculation of cucumber leaves with *Colletotrichum lagenarium*." *Journal of plant physiology*, 163, no. 11, 1111-1117. https://doi.org/10.1016/j.jplph.2005.09.005.

Kumar Ramasamy, Rajesh, Shankar Congeevaram, and Kaliannan Thamaraiselvi. (2011). "Evaluation of isolated fungal strain from e-waste recycling facility for effective sorption of toxic heavy metal Pb (II) ions and fungal protein molecular characterization—a mycoremediation approach." *Asian J. Exp. Biol. Sci*, 2, 342-347.

Kumar, Arun, Md Samiur Rahman, Mohammad Ali, Pascal Salaun, Arthur Gourain, Suresh Kumar, Ranjit Kumar et al. (2022). "Assessment of disease burden in the arsenic exposed population of Chapar village of Samastipur district, Bihar, India, and related mitigation initiative." *Environmental Science and Pollution Research*, 1-17. https://doi.org/10.1007/s11356-021-18207-6.

Kumar, Arun, Mohammad Ali, Ranjit Kumar, Mukesh Kumar, Prity Sagar, Ritu Kumari Pandey, Vivek Akhouri et al. (2021a). "Arsenic exposure in Indo Gangetic plains of Bihar causing increased cancer risk." *Scientific Reports*, 11, no. 1, 2376. https://doi.org/10.1038/s41598-021-81579-9.

Kumar, Arun, Rishav Kumar, Md Samiur Rahman, Mohammad Ali, Ranjit Kumar, Neha Nupur, Aman Gaurav et al. (2021b). "Assessment of arsenic exposure in the population of Sabalpur village of Saran District of Bihar with mitigation approach." *Environmental Science and Pollution Research*, 28, 43923-43934. https://doi.org/10.1007/s11356-021-13521-5.

Kumar, Dinesh, Zarna Patel, Priti Pandit, Ramesh Pandit, Amrutlal Patel, Madhvi Joshi, and Chaitanya Joshi. (2021). "Textile industry wastewaters from Jetpur, Gujarat, India, are dominated by Shewanellaceae, Bacteroidaceae, and Pseudomonadaceae harboring genes encoding catalytic enzymes for textile dye degradation." *Frontiers in Environmental Science*, 9. 720707. https://doi.org/10.3389/fenvs.2021.720707.

Kumar, Naveen, Arvind Kumar, Binny Marry Marwein, Daneshver Kumar Verma, Ilakiya Jayabalan, Agam Kumar, Duraisamy Ramamoorthy, and Naveen Kumar. (2021). "Agricultural activities causing water pollution and its mitigation–A review." *International Journal of Modern Agriculture*, 10, no. 1, 1-21.

Kumar, S., Chaurasia, P., and Kumar, A. (2016). "Isolation and characterization of microbial strains from textile industry effluents of Bhilwara, India: analysis with bioremediation." *J Chem Pharm Res*, 8, no. 4, 143-150.

Kumar, Sunil. (2011). "Composting of municipal solid waste." *Critical reviews in biotechnology*, 31, no. 2, 112-136. https://doi.org/10.3109/07388551.2010.492207.

Kumar, Vinod, Jogendra Singh, Ashu Saini, and Pankaj Kumar. (2019). "Phytoremediation of copper, iron and mercury from aqueous solution by water lettuce (*Pistia stratiotes* L.)." *Environmental Sustainability*, 2, 55-65.https://doi.org/10.1007/s42398-019-00050-8.

Lee, Byung-Kook, Jaeouk Ahn, Nam-Soo Kim, Chan Boo Lee, Jungsun Park, and Yangho Kim. (2016). "Association of blood pressure with exposure to lead and cadmium: analysis of data from the 2008–2013 Korean National Health and Nutrition Examination Survey." *Biological trace element research*, 174, 40-51. https://doi.org/10.1007/s12011-016-0699-y.

Lellis, Bruno, Cíntia Zani Fávaro-Polonio, João Alencar Pamphile, and Julio Cesar Polonio. (2019). "Effects of textile dyes on health and the environment and bioremediation potential of living organisms." *Biotechnology Research and Innovation*, 3, no. 2, 275-290. https://doi.org/10.1016/j.biori.2019.09.001.

Levallois, Patrick, Prabjit Barn, Mathieu Valcke, Denis Gauvin, and Tom Kosatsky. (2018). "Public health consequences of lead in drinking water." *Current environmental health reports*, 5, 255-262. https://doi.org/10.1007/s40572-018-0193-0.

Levin, L., L. Papinutti, and F. Forchiassin. (2004). "Evaluation of Argentinean white rot fungi for their ability to produce lignin-modifying enzymes and decolorize industrial dyes." *Bioresource Technology*, 94, no. 2, 169-176. https://doi.org/10.1016/j.biortech.2003.12.002.

Li, Aoyun, Jinxue Ding, Ting Shen, Zhaoqing Han, Jiabin Zhang, Zain Ul Abadeen, Muhammad Fakhar-e-Alam Kulyar, Xin Wang, and Kun Li. (2021). "Environmental hexavalent chromium exposure induces gut microbial dysbiosis in chickens." *Ecotoxicology and Environmental Safety*, 227, 112871. https://doi.org/10.1016/j.ecoenv.2021.112871.

Li, Changfeng, Kehai Zhou, Wenqiang Qin, Changjiu Tian, Miao Qi, Xiaoming Yan, and Wenbing Han. (2019). "A review on heavy metals contamination in soil: effects, sources, and remediation techniques." *Soil and Sediment Contamination: An International Journal*, 28, no. 4, 380-394. https://doi.org/10.1080/ 15320383.2019.1592108.

Li, Dong, HaoJie Lin, Min Zhang, Jing Meng, LiYou Hu, and Bo Yu. (2021). "Urine cadmium as a risk factor for osteoporosis and osteopenia: a meta-analysis." *Frontiers in Medicine*, 510. https://doi.org/10.3389/fmed.2021.648902.

Li, Longman, and Xiaobo Yang. (2018). "The essential element manganese, oxidative stress, and metabolic diseases: links and interactions." *Oxidative medicine and cellular longevity*, 2018, https://doi.org/10.1155/2018/7580707.

Liang, Yaya, Xiaoyun Yi, Zhi Dang, Qin Wang, Houmei Luo, and Jie Tang. (2017). "Heavy metal contamination and health risk assessment in the vicinity of a tailing pond in Guangdong, China." *International journal of environmental research and public health*, 14, no. 12, 1557. https://doi.org/10.3390/ijerph14121557.

Lin, Hung-Chen, Wei-Ming Hao, and Pao-Hsien Chu. (2021). "Cadmium and cardiovascular disease: An overview of pathophysiology, epidemiology, therapy, and predictive value." *Revista Portuguesa de Cardiologia (English Edition)*, 40, no. 8, 611-617. https://doi.org/10.1016/j.repc.2021.01.009.

Lin, Li, Haoran Yang, and Xiaocang Xu. (2022). "Effects of water pollution on human health and disease heterogeneity: a review." *Frontiers in Environmental Science*, 975. https://doi.org/10.3389/fenvs.2022.880246.

Lin, Ming-Hsien, Chung-Yi Li, Ya-Yun Cheng, and How-Ran Guo. (2022). "Arsenic in drinking water and incidences of leukemia and Lymphoma: implication for its dural effects in carcinogenicity." *Frontiers in Public Health*, 10, https://doi.org/10.3389/fpubh.2022.863882.

Liu, Jing, Yong Jun Liu, Yu Liu, Zhe Liu, and Ai Ning Zhang. (2018). "Quantitative contributions of the major sources of heavy metals in soils to ecosystem and human health risks: A case study of Yulin, China." *Ecotoxicology and environmental safety*, 164, 261-269. https://doi.org/10.1016/j.ecoenv.2018.08.030.

Liu, Qiling, Rongqiang Zhang, Xiang Wang, Xiangli Shen, Peili Wang, Na Sun, Xiangwen Li, Xinhui Li, and Chunxu Hai. (2019). "Effects of sub-chronic, low-dose cadmium exposure on kidney damage and potential mechanisms." *Annals of translational medicine*, 7, no. 8, https://doi.org/10.21037/atm.2019.03.66.

Llugany, Mercè, Roger Miralles, Isabel Corrales, Juan Barceló, and Charlotte Poschenrieder. (2012). "*Cynara cardunculus* a potentially useful plant for remediation of soils polluted with cadmium or arsenic." *Journal of Geochemical Exploration*, 123, 122-127. https://doi.org/10.1016/j.gexplo.2012.06.016.

Lu, Qin, Zhenli L. He, Donald A. Graetz, Peter J. Stoffella, and Xiaoe Yang. (2011). "Uptake and distribution of metals by water lettuce (*Pistia stratiotes* L.)."

Environmental Science and Pollution Research, 18, 978-986. https://doi.org/10.1007/s11356-011-0453-0.

Madrigal, Jessica M., Ana C. Ricardo, Victoria Persky, and Mary Turyk. (2019). "Associations between blood cadmium concentration and kidney function in the US population: Impact of sex, diabetes and hypertension." *Environmental research*, 169, 180-188. https://doi.org/10.1016/j.envres.2018.11.009.

Mahey, Sonia, Rakesh Kumar, Manik Sharma, Vinod Kumar, and Renu Bhardwaj. (2020). "A critical review on toxicity of cobalt and its bioremediation strategies." *SN Applied Sciences*, 2, 1-12. https://doi.org/10.1007/s42452-020-3020-9.

Mane, P. C., and Bhosle, A. B. (2012). "*Bioremoval of some metals by living algae Spirogyra sp. and Spirullina sp. from aqueous solution*." 571-576.

Marques, Ana P. G. C., António O. S. S. Rangel, and Paula M. L. Castro. (2009). "Remediation of heavy metal contaminated soils: phytoremediation as a potentially promising clean-up technology." *Critical Reviews in Environmental Science and Technology*, 39, no. 8, 622-654. https://doi.org/10.1080/10643380701798272.

Martinez, Victor D., Emily A. Vucic, Daiana D. Becker-Santos, Lionel Gil, and Wan L. Lam. (2011). "Arsenic exposure and the induction of human cancers." *Journal of toxicology*, 2011, https://doi.org/10.1155/2011/431287.

Maruyama, Kimio, Takashi Yorifuji, Toshihide Tsuda, Tomoko Sekikawa, Hiroto Nakadaira, and Hisashi Saito. (2012). "Methyl mercury exposure at Niigata, Japan: results of neurological examinations of 103 adults." *Journal of Biomedicine and Biotechnology*, 2012, https://doi.org/10.1155/2012/635075.

Mata, Y. N., Blazquez, M. L., Ballester, A., Gonzalez, F., and Munoz, J. A. (2008). "Characterization of the biosorption of cadmium, lead and copper with the brown alga *Fucus vesiculosus*." *Journal of hazardous materials*, 158, no. 2-3, 316-323. https://doi.org/10.1016/j.jhazmat.2008.01.084.

Mayer, Jonathan E., and Rose H. Goldman. (2016). "Arsenic and skin cancer in the USA: the current evidence regarding arsenic-contaminated drinking water." *International journal of dermatology*, 55, no. 11, e585-e591. https://doi.org/10.1111/ijd.13318.

Men, Cong, Ruimin Liu, Qingrui Wang, Lijia Guo, and Zhenyao Shen. (2018). "The impact of seasonal varied human activity on characteristics and sources of heavy metals in metropolitan road dusts." *Science of the Total Environment*, 637, 844-854. https://doi.org/10.1016/j.scitotenv.2018.05.059.

Miao, Xiao-Xiang, Yan-Qin Ji, Xian-Zhang Shao, Huan Wang, Quan-Fu Sun, and Xu Su. (2013). "Radioactivity of drinking-water in the vicinity of nuclear power plants in China based on a large-scale monitoring study." *International journal of environmental research and public health*, 10, no. 12, 6863-6872. https://doi.org/10.3390/ijerph10126863.

Mikucka, Wioleta, and Magdalena Zielińska. (2020). "Distillery stillage: characteristics, treatment, and valorization." *Applied Biochemistry and Biotechnology*, 192, 770-793. https://doi.org/10.1007/s12010-020-03343-5.

Miller, Ralinda R. (1996). "Phytoremediation, technology overview report." *Ground-Water Remediation Technologies Analysis Center*, *Series O*, 3, 26.

Mishra, Virendra Kumar, and Tripathi, B. D. (2009). "Accumulation of chromium and zinc from aqueous solutions using water hyacinth (*Eichhornia crassipes*)." *Journal of*

Hazardous Materials, 164, no. 2-3, 1059-1063. https://doi.org/10.1016/j.jhazmat.2008.09.020.

Mohsenzadeh, Fariba, and Roghayeh Mohammadzadeh. (2018). "Phytoremediation ability of the new heavy metal accumulator plants." *Environmental & Engineering Geoscience*, 24, no. 4, 441-450. https://doi.org/10.2113/EEG-2123.

Mojiri, Amin, Hamidi Abdul Aziz, Mohammad Ali Zahed, Shuokr Qarani Aziz, and M. Razip B. Selamat. (2013). "Phytoremediation of heavy metals from urban waste leachate by southern cattail (*Typha domingensis*)." *International Journal of Scientific Research in Environmental Sciences*, 1, no. 4, 63-70.

Naghipour, Dariush, Seyed Davoud Ashrafi, Mozhgan Gholamzadeh, Kamran Taghavi, and Mohammad Naimi-Joubani. (2018). "Phytoremediation of heavy metals (Ni, Cd, Pb) by Azolla filiculoides from aqueous solution: A dataset." *Data in brief*, 21, 1409-1414. https://doi.org/10.1016/j.dib.2018.10.111.

Nagy, Boldizsar, Carmen Mânzatu, Andrada Măicăneanu, Cerasella Indolean, Lucian Barbu-Tudoran, and Cornelia Majdik. (2017). and nonlinear regression analysis for heavy metals removal using *Agaricus bisporus* macrofungus." *Arabian Journal of Chemistry*, 10, S3569-S3579. https://doi.org/10.1016/j.arabjc.2014.03.004.

Nascimento, Altina Lacerda, Adijailton Jose Souza, Pedro Avelino Maia Andrade, Fernando Dini Andreote, Aline Renée Coscione, Fernando Carvalho Oliveira, and Jussara Borges Regitano. (2018). "Sewage sludge microbial structures and relations to their sources, treatments, and chemical attributes." *Frontiers in Microbiology*, 9, 1462. https://doi.org/10.3389/fmicb.2018.01462.

Nasiadek, Marzenna, Marian Danilewicz, Krystyna Sitarek, Ewa Świątkowska, Adam Daragó, Joanna Stragierowicz, and Anna Kilanowicz. (2018). "The effect of repeated cadmium oral exposure on the level of sex hormones, estrous cyclicity, and endometrium morphometry in female rats." *Environmental Science and Pollution Research*, 25, 28025-28038. https://doi.org/10.1007/s11356-018-2821-5.

Nessa, Fazilatun, Khan, S. A., and Abu Shawish, K. Y. I. (2016). "Lead, cadmium and nickel contents of some medicinal agents." *Indian journal of pharmaceutical sciences*, 78, no. 1, 111. https://doi.org/10.4103/0250-474X.180260.

Ngoc, Nguyen Thi Minh, Nguyen Van Chuyen, Nguyen Thi Thu Thao, Nguyen Quang Duc, Nguyen Thi Thu Trang, Nguyen Thi Thanh Binh, Hoang Cao Sa., et al. (2020). "Chromium, cadmium, lead, and arsenic concentrations in water, vegetables, and seafood consumed in a coastal area in Northern Vietnam." *Environmental health insights*, 14, 1178630220921410. https://doi.org/10.1177/1178630220921410.

Nithya, T. G., Snega Priya, P., and Kamaraj, M. (2021). "Bioremediation of Heavy Metals Using Salvina Molesta–A Freshwater Aquatic Weed." *Strategies and Tools for Pollutant Mitigation: Avenues to a Cleaner Environment*, 337-353. https://doi.org/10.1007/978-3-030-63575-6_16.

Niu, Gui-Lan, Jun-Jie Zhang, Shuo Zhao, Hong Liu, Nico Boon, and Ning-Yi Zhou. (2009). "Bioaugmentation of a 4-chloronitrobenzene contaminated soil with *Pseudomonas putida* ZWL73." *Environmental Pollution*, 157, no. 3, 763-771. https://doi.org/10.1016/j.envpol.2008.11.024.

Ojuederie, Omena Bernard, and Olubukola Oluranti Babalola. (2017). "Microbial and plant-assisted bioremediation of heavy metal polluted environments: a review."

International journal of environmental research and public health, 14, no. 12, 1504. https://doi.org/10.3390/ijerph14121504.

Ortega, Scarlet Nere, Marcia Nitschke, Ana Maria Mouad, Maria Diva Landgraf, Maria Olímpia Oliveira Rezende, Mirna Helena Regali Seleghim, Lara Durães Sette, and André Luiz Meleiro Porto. (2011). "Isolation of Brazilian marine fungi capable of growing on DDD pesticide." *Biodegradation*, 22, 43-50. https://doi.org/10.1007/s10532-010-9374-8.

Oyewopo, Adeoye O., Kehinde S. Olaniyi, Samuel O. Olojede, Sodiq K. Lawal, Oluwatobi A. Amusa, and Isaac O. Ajadi. (2020). "*Hibiscus sabdariffa* extract protects against cadmium-induced ovarian toxicity in adult Wistar rats." *International Journal of Physiology, Pathophysiology and Pharmacology*, 12, no. 4, 107.

Oyewopo, Adeoye O., Kehinde S. Olaniyi, Samuel O. Olojede, Sodiq K. Lawal, Oluwatobi A. Amusa, and Isaac O. Ajadi. (2020). "*Hibiscus sabdariffa* extract protects against cadmium-induced ovarian toxicity in adult Wistar rats." *International Journal of Physiology, Pathophysiology and Pharmacology*, 12, no. 4, 107. https://doi.org/10.1080/1040841X.2021.1970512.

Park, Jiyeon, Ju-Yong Kim, and Kyoung-Woong Kim. (2012). "Phytoremediation of soil contaminated with heavy metals using *Brassica napus*." *Geosystem Engineering*, 15, no. 1, 10-18. https://doi.org/10.1080/12269328.2012.674428.

Park, Jong-Hwan, Jim J. Wang, Ran Xiao, Scott M. Pensky, Manoch Kongchum, Ronald D. DeLaune, and Dong-Cheol Seo. (2018). "Mercury adsorption in the Mississippi River deltaic plain freshwater marsh soil of Louisiana Gulf coastal wetlands." *Chemosphere*, 195, 455-462. https://doi.org/10.1016/ j.chemosphere.2017.12.104.

Pesola, Gene R., Faruque Parvez, Yu Chen, Alauddin Ahmed, Rabiul Hasan, and Habibul Ahsan. (2012). "Arsenic exposure from drinking water and dyspnoea risk in Araihazar, Bangladesh: a population-based study." *European Respiratory Journal*, 39, no. 5, 1076-1083. https://doi.org/10.1183/09031936.00042611.

Piñeiro, Xulia Fandiño, Mauro T. Ave, Narmeen Mallah, Francisco Caamaño-Isorna, A. Nuria Guisández Jiménez, Duarte Nuno Vieira, Flaviano Bianchini, and José Ignacio Muñoz-Barús. (2021). "Heavy metal contamination in Peru: Implications on children's health." *Scientific reports*, 11, no. 1, 22729. https://doi.org/10.1038/s41598-021-02163-9.

PP, S., and Johanna Rajkumar. (2020). "Hepatotoxic effect of lead and hepatoprotective effect of *Hydrilla verticillata* on hepatic transcriptional and physiological response in edible fish *Labeo rohita*." *Drug and Chemical Toxicology*, 45, no. 3, 1276-1283. https://doi.org/10.1080/01480545.2020.1815762.

Pratush, Amit, Ajay Kumar, and Zhong Hu. (2018). "Adverse effect of heavy metals (As, Pb, Hg, and Cr) on health and their bioremediation strategies: a review." *International Microbiology*, 21, 97-106. https://doi.org/10.1111/j.1462-2920.2004.00639.x.

Queiroz, Hermano M., Samantha C. Ying, Macon Abernathy, Diego Barcellos, Fabricio A. Gabriel, Xose L. Otero, Gabriel N. Nobrega, Angelo F. Bernardino, and Tiago O. Ferreira. (2021). "Manganese: The overlooked contaminant in the world largest mine tailings dam collapse." *Environment international*, 146, 106284. https://doi.org/10.1016/j.envint.2020.106284.

Rafati-Rahimzadeh, Mehrdad, Mehravar Rafati-Rahimzadeh, Sohrab Kazemi, and Ali Akbar Moghadamnia. (2014). "Current approaches of the management of mercury poisoning: need of the hour." *DARU Journal of Pharmaceutical Sciences*, 22, 1-10. https://doi.org/10.1186/2008-2231-22-46.

Rahman, Md Samiur, Arun Kumar, Ranjit Kumar, Mohammad Ali, Ashok Kumar Ghosh, and Sushil Kumar Singh. (2019). "Comparative quantification study of arsenic in the groundwater and biological samples of Simri village of Buxar District, Bihar, India." *Indian journal of occupational and environmental medicine*, 23, no. 3, 126. https://doi.org/10.4103/ijoem.IJOEM_240_18.

Rai, Prabhat Kumar. (2008). "Phytoremediation of Hg and Cd from industrial effluents using an aquatic free floating macrophyte *Azolla pinnata*." *International journal of phytoremediation*, 10, no. 5, 430-439. https://doi.org/10.1080/15226510802100606.

Rajput, Ritu Singh, Sonali Pandey, and Seema Bhadauria. (2017). "Status of water pollution in relation to industrialization in Rajasthan." *Reviews on environmental health* 32, no. 3 245-252. https://doi.org/10.1515/reveh-2016-0069.

Rehman, Kanwal, Fiza Fatima, Iqra Waheed, and Muhammad Sajid Hamid Akash. (2018). "Prevalence of exposure of heavy metals and their impact on health consequences." *Journal of cellular biochemistry*, 119, no. 1, 157-184. https://doi.org/10.1002/jcb.26234.

Rezania, Shahabaldin, Shazwin Mat Taib, Mohd Fadhil Md Din, Farrah Aini Dahalan, and Hesam Kamyab. (2016). "Comprehensive review on phytotechnology: heavy metals removal by diverse aquatic plants species from wastewater." *Journal of hazardous materials*, 318, 587-599. https://doi.org/10.1016/j.jhazmat.2016.07.053.

Rizvi, Imran, Ravindra Kumar Garg, Hardeep Singh Malhotra, Neeraj Kumar, and Ravi Uniyal. (2017). "Manganese, manganism and other neurodegenerative diseases: Is it a cause of concern?" *Neurology India*, 65, no. 6, 1248. https://doi.org/10.4103/0028-3886.217970.

Roberts, Sarah, Jennifer K. Adams, Anson W. Mackay, George EA Swann, Suzanne McGowan, Neil L. Rose, Virginia Panizzo et al. (2020). "Mercury loading within the selenga river basin and Lake Baikal, Siberia." *Environmental Pollution*, 259, 113814. https://doi.org/10.1016/j.envpol.2019.113814.

Romera, E., González, F., Ballester, A., Blázquez, M. L., and Munoz, J. A. (2007). "Comparative study of biosorption of heavy metals using different types of algae." *Bioresource technology*, 98, no. 17, 3344-3353. https://doi.org/10.1016/j.biortech.2006.09.026.

Rousseau, Marie-Claude, Kurt Straif, and Jack Siemiatycki. (2005). "IARC carcinogen update." *Environmental Health Perspectives*, 113, no. 9, A580-A581. https://doi.org/10.1289/ehp.113-1280416.

Sahay, S., Inam, A., and Iqbal, S. (2020). "Risk analysis by bioaccumulation of Cr, Cu, Ni, Pb and Cd from wastewater-irrigated soil to *Brassica* species." *International Journal of Environmental Science and Technology*, 17, 2889-2906. https://doi.org/10.1007/s13762-019-02580-4,

Saini, Vipin Kumar, Surindra Suthar, Chaudhari Karmveer, and Kapil Kumar. (2017). "Valorization of toxic weed *Lantana camara* L. biomass for adsorptive removal of lead." *Journal of Chemistry*, 2017, https://doi.org/10.1155/2017/5612594.

Sakakibara, Masayuki, Yuko Ohmori, Nguyen Thi Hoang Ha, Sakae Sano, and Koichiro Sera. (2011). "Phytoremediation of heavy metal-contaminated water and sediment by *Eleocharis acicularis*." *CLEAN–Soil, Air, Water*, 39, no. 8, 735-741. https://doi.org/10.1002/clen.201000488.

Sandhya, Mishra, Yaohua Huang, Jiayi Li, Xiaozhen Wu, Zhe Zhou, Qiqi Lei, Pankaj Bhatt, and Shaohua Chen. (2022). "Biofilm-mediated bioremediation is a powerful tool for the removal of environmental pollutants." *Chemosphere*, 133609. https://doi.org/10.1016/j.chemosphere.2022.133609.

Sanyal, Tamalika, Pritha Bhattacharjee, Somnath Paul, and Pritha Bhattacharjee. (2020). "Recent advances in arsenic research: significance of differential susceptibility and sustainable strategies for mitigation." *Frontiers in public health*, 8, 464. https://doi.org/10.3389/fpubh.2020.00464.

Sarma, Hemen, S. Sonowal, and M. N. V. Prasad. (2019). "Plant-microbiome assisted and biochar-amended remediation of heavy metals and polyaromatic compounds─ a microcosmic study." *Ecotoxicology and Environmental Safety*, 176, 288-299. https://doi.org/10.1016/j.ecoenv.2019.03.081.

Shaji, E., Santosh, M., Sarath, K. V., Pranav Prakash, Deepchand, V., and Divya, B. V. (2021). "Arsenic contamination of groundwater: A global synopsis with focus on the Indian Peninsula." *Geoscience frontiers*, 12, no. 3, 101079. https://doi.org/10.1016/j.gsf.2020.08.015.

Sharma, Rahul, Pinki Rani Agrawal, Ravi Kumar, and Gaurav Gupta. (2021). "Current scenario of heavy metal contamination in water." *Contamination of Water*, 49-64. http://dx.doi.org/10.1016/B978-0-12-824058-8.00010-4.

Sharma, Resham, Renu Bhardwaj, Vandana Gautam, Shagun Bali, Ravdeep Kaur, Parminder Kaur, Manik Sharma et al. (2018). "Phytoremediation in waste management: Hyperaccumulation diversity and techniques." *Plants Under Metal and Metalloid Stress: Responses, Tolerance and Remediation*, 277-302. https://doi.org/10.1007/978-981-13-2242-6_11.

Shaw, Pallab, Paritosh Mondal, Arpan Dey Bhowmik, Arindam Bandyopadhyay, Muthammal Sudarshan, Anindita Chakraborty, and Ansuman Chattopadhyay. (2022). "Environmentally relevant hexavalent chromium disrupts elemental homeostasis and induces apoptosis in zebrafish liver." *Bulletin of Environmental Contamination and Toxicology*, 108, no. 4, 716-724. https://doi.org/10.1007/s00128-021-03427-w.

Shehata, Hanaa S., and Tarek M. Galal. (2020). "Trace metal concentration in planted cucumber (*Cucumis sativus* L.) from contaminated soils and its associated health risks." *Journal of Consumer Protection and Food Safety*, 15, 205-217. https://doi.org/10.1007/s00003-020-01284-z.

Sheoran, V., Sheoran, A. S., and Poonia, P. (2009). *Minerals Engineering*, 22, no. 12, 1007-1019. https://doi.org/10.1016/j.mineng.2009.04.001.

Shimod, K. P., Vineethkumar, V., Prasad, T. K., and Jayapal, G. (2022). "Effect of urbanization on heavy metal contamination: a study on major townships of Kannur District in Kerala, India." *Bulletin of the National Research Centre*, 46, no. 1, 1-14. https://doi.org/10.1186/s42269-021-00691-y.

Shirani, Mahboube, Keramat Nezhad Afzali, Sayka Jahan, Vladimir Strezov, and Mojtaba Soleimani-Sardo. (2020). "Pollution and contamination assessment of heavy metals in the sediments of Jazmurian playa in southeast Iran." *Scientific reports*, 10, no. 1, 1-11. https://doi.org/10.1038/s41598-020-61838-x.

Siddiqui, Husna, Khan Bilal Mukhtar Ahmed, Fareen Sami, and Shamsul Hayat. (2020). "Phytoremediation of cadmium contaminated soil using *Brassica juncea*: influence on PSII activity, leaf gaseous exchange, carbohydrate metabolism, redox and elemental status." *Bulletin of Environmental Contamination and Toxicology*, 105, 411-421. https://doi.org/10.1007/s00128-020-02929-3.

Signes-Pastor, Antonio J., Pablo Martinez-Camblor, Emily Baker, Juliette Madan, Margaret F. Guill, and Margaret R. Karagas. (2021). "Prenatal exposure to arsenic and lung function in children from the New Hampshire Birth Cohort Study." *Environment international*, 155, 106673. https://doi.org/10.1016/j.envint.2021.106673.

Singh, Ajay Kumar, and Ram Chandra. (2019). "Pollutants released from the pulp paper industry: Aquatic toxicity and their health hazards." *Aquatic toxicology*, 211, 202-216. https://doi.org/10.1016/j.aquatox.2019.04.007.

Singh, Nitika, Abhishek Kumar, Vivek Kumar Gupta, and Bechan Sharma. (2018). "Biochemical and molecular bases of lead-induced toxicity in mammalian systems and possible mitigations." *Chemical Research in Toxicology*, 31, no. 10, 1009-1021. https://doi.org/10.1021/acs.chemrestox.8b00193.

Singh, O. V., and Jain, R. K. (2003). "Phytoremediation of toxic aromatic pollutants from soil." *Applied microbiology and biotechnology*, 63, 128-135. https://doi.org/10.1007/s00253-003-1425-1.

Singhal, Muskan, Swapnali Jadhav, Swaroop S. Sonone, Mahipal Singh Sankhla, and Rajeev Kumar. (2021). "Microalgae based sustainable bioremediation of water contaminated by pesticides." *Biointerface Res. Appl. Chem*, 12, 149-169. https://doi.org/10.33263/BRIAC121.149169.

Skerfving, Staffan B., and Copplestone, J. F. (1976). "Poisoning caused by the consumption of organomercury-dressed seed in Iraq." *Bulletin of the World Health Organization*, 54, no. 1, 101.

Sohrabi, Masoudreza, Zahedin Kheiri, Ali Gholami, Mehran Haghighi, Fahimeh Safarnejad Temeshkel, Mahmood Khoonsari, Majid Reza Adelani et al. (2019). "The Comparison of the Plasma Levels of the Lead Element in Patients with Gastrointestinal Cancers and Healthy Individuals." *Asian Pacific Journal of Cancer Prevention: APJCP*, 20, no. 9, 2639. https://doi.org/10.31557/APJCP.2019.20.9.2639.

Soloman, Poppana Antony, Chiya Ahmed Basha, Manickam Velan, Veerappan Ramamurthi, Kandasamy Koteeswaran, and Natesan Balasubramanian. (2009). (2009). "Electrochemical degradation of Remazol Black B dye effluent." *CLEAN–soil, air, water, 37*, no. 11, 889-900. https://doi.org/10.1002/clen.200900055.

Spielmann, Julien, Hassan Ahmadi, Maxime Scheepers, Michael Weber, Sarah Nitsche, Monique Carnol, Bernard Bosman et al. (2020). "The two copies of the zinc and cadmium ZIP6 transporter of *Arabidopsis halleri* have distinct effects on cadmium tolerance." *Plant, cell & environment*, 43, no. 9, 2143-2157. https://doi.org/10.1111/pce.13806.

Sreedevi, P. R., Suresh, K., and Guangming Jiang. (2022). "Bacterial bioremediation of heavy metals in wastewater: A review of processes and applications." *Journal of Water Process Engineering*, 48, 102884. https://doi.org/10.1016/ j.jwpe.2022.102884.

Srivastav, Ajai K., Rubi Rai, Nobuo Suzuki, Diwakar Mishra, and Sunil K. Srivastav. (2013). "Effects of lead on the plasma electrolytes of a freshwater fish, *Heteropneustes fossilis*." *International Aquatic Research*, 5, 1-7. https://doi.org/10.1186/2008-6970-5-4.

Srivastava, Vaibhav, Abhijit Sarkar, Sonu Singh, Pooja Singh, Ademir SF De Araujo, and Rajeev P. Singh. (2017). "Agroecological responses of heavy metal pollution with special emphasis on soil health and plant performances." *Frontiers in Environmental Science*, 5, 64. https://doi.org/10.3389/fenvs.2017.00064.

Srivastava, Vaibhav, Abhijit Sarkar, Sonu Singh, Pooja Singh, Ademir SF De Araujo, and Rajeev P. Singh. (2017). "Agroecological responses of heavy metal pollution with special emphasis on soil health and plant performances." *Frontiers in Environmental Science*, 5, 64. https://doi.org/10.3389/fpls.2018.01476.

Sumiahadi, A., and Acar, R. (2018). "A review of phytoremediation technology: heavy metals uptake by plants." In *IOP conference series: earth and environmental science*, vol. 142, no. 1, p. 012023. IOP Publishing, https://doi.org/10.1088/1755-1315/142/1/012023.

Sun, Hong, Jason Brocato, and Max Costa. (2015). "Oral chromium exposure and toxicity." *Current environmental health reports*, 2, 295-303. https://doi.org/10.1007/s40572-015-0054-z.

Sun, Wenjie, Kai Cheng, Kevin Y. Sun, and Xingmao Ma. (2021). "Microbially mediated remediation of contaminated sediments by heavy metals: A critical review." *Current Pollution Reports*, 7, 201-212. https://doi.org/10.1007/s40726-021-00175-7.

Taştan, Burcu Ertit, Sevgi Ertuğrul, and Gönül Dönmez. (2010). *Bioresource technology*, 101, no. 3, 870-876. https://doi.org/10.1016/j.biortech.2009.08.099.

Tegene, Birhanu Gizaw, and Tesfaye Alemu Tenkegna. (2020). "Mode of action, mechanism and role of microbes in bioremediation service for environmental pollution management." *J. Biotechnol. Bioinform. Res*, 116, 39-50. https://doi. org/10.47363/JBBR/2020.

Thakare, Mayur, Hemen Sarma, Shraddha Datar, Arpita Roy, Prajakta Pawar, Kanupriya Gupta, Soumya Pandit, and Ram Prasad. (2021). "Understanding the holistic approach to plant-microbe remediation technologies for removing heavy metals and radionuclides from soil." *Current Research in Biotechnology*, 3, 84-98. http://dx.doi.org/10.1016/j.crbiot.2021.02.004.

Throne-Holst, Mimmi, Alexander Wentzel, Trond E. Ellingsen, Hans-Kristian Kotlar, and Sergey B. Zotchev. (2007). "Identification of novel genes involved in long-chain n-alkane degradation by *Acinetobacter* sp. strain DSM 17874." *Applied and environmental microbiology*, 73, no. 10, 3327-3332. https://doi.org/10.1128/AEM.00064-07.

Tiwari, Shalini, and Charu Lata. (2018). "Heavy metal stress, signaling, and tolerance due to plant-associated microbes: an overview." *Frontiers in plant science*, 9, 452. https://doi.org/10.3389/fpls.2018.00452.

Tognacchini, Alice, Theresa Rosenkranz, Antony van der Ent, Gaylord Erwan Machinet, Guillaume Echevarria, and Markus Puschenreiter. (2020). "Nickel phytomining from industrial wastes: Growing nickel hyperaccumulator plants on galvanic sludges."

Journal of environmental management, 254, 109798. https://doi.org/10.1016/j.jenvman.2019.109798.

Tong, Yongjuan, Qi Zhang, Jiuju Cai, Chengkang Gao, Lianyong Wang, and Peng Li. (2018). "Water consumption and wastewater discharge in China's steel industry." *Ironmaking & Steelmaking* 45, no. 10 868-877. https://doi.org/10.1080/03019233.2018.1538180.

Torimiro, Nkem, Oluwafemi B. Daramola, Olusegun D. Oshibanjo, Frank O. Otuyelu, Bolanle A. Akinsanola, Omolola O. Yusuf, Odunayo T. Ore, and Richard K. Omole. (2021). "Ecorestoration of heavy metals and toxic chemicals in polluted environment using microbe-mediated nanomaterials." *International Journal of Environmental Bioremediation & Biodegradation*, 9, 8-21.

Tumolo, Marina, Valeria Ancona, Domenico De Paola, Daniela Losacco, Claudia Campanale, Carmine Massarelli, and Vito Felice Uricchio. (2020). "Chromium pollution in European water, sources, health risk, and remediation strategies: An overview." *International journal of environmental research and public health*, 17, no. 15, 5438. https://doi.org/10.3390/ijerph17155438.

Ummalyma, Sabeela Beevi, Ashok Pandey, Rajeev K. Sukumaran, and Dinabandhu Sahoo. (2018). "Bioremediation by microalgae: current and emerging trends for effluents treatments for value addition of waste streams." *Biosynthetic technology and environmental challenges*, 355-375. https://doi.org/10.1007/978-981-10-7434-9_19.

Vakili, A. H., and Aboutorab, M. (2013). "The potential of Lepidium sativum for phytoremediation of contaminated soil with cadmium." *IJSRK Journal*, 1, 20-24.

van Beilen, Jan B., Enrico G. Funhoff, Alexander van Loon, Andrea Just, Leo Kaysser, Manuel Bouza, René Holtackers, Martina Röthlisberger, Zhi Li, and Bernard Witholt. (2006). "Cytochrome P450 alkane hydroxylases of the CYP153 family are common in alkane-degrading eubacteria lacking integral membrane alkane hydroxylases." *Applied and environmental microbiology*, 72, no. 1, 59-65. https://doi.org/10.1128/AEM.72.1.59-65.2006.

Van der Kuijp, Tsering Jan, Lei Huang, and Christopher R. Cherry. (2013). *Environmental Health*, 12, 1-10. https://doi.org/10.1186/1476-069X-12-61.

Vangronsveld, Jaco, Rolf Herzig, Nele Weyens, Jana Boulet, Kristin Adriaensen, Ann Ruttens, Theo Thewys et al. (2009). "Phytoremediation of contaminated soils and groundwater: lessons from the field." *Environmental Science and Pollution Research*, 16, 765-794. https://doi.org/10.1007/s11356-009-0213-6.

Vanham, Davy, Lorenzo Alfieri, Martina Flörke, Stefania Grimaldi, Valerio Lorini, Ad de Roo, and Luc Feyen. (2021). "The number of people exposed to water stress in relation to how much water is reserved for the environment: a global modelling study." *The Lancet Planetary Health*, 5, no. 11, e766-e774. https://doi.org/10.1016/S2542-5196(21)00234-5.

Verma, Ayushi, Arpita Roy, and Navneeta Bharadvaja. (2021). "Remediation of heavy metals using nanophytoremediation." In *Advanced oxidation processes for effluent treatment plants*, pp. 273-296. Elsevier.

Verma, Chanchal, Sangeeta Madan, and Athar Hussain. (2016). "Heavy metal contamination of groundwater due to fly ash disposal of coal-fired thermal power plant, Parichha, Jhansi, India." *Cogent Engineering*, 3, no. 1, 1179243. https://doi.org/10.1080/23311916.2016.1179243.

Verma, Shulbhi, Pankaj Bhatt, Amit Verma, Harish Mudila, Parteek Prasher, and Eldon R. Rene. (2021)."Microbial technologies for heavy metal remediation: effect of process conditions and current practices." *Clean Technologies and Environmental Policy*, 1-23. https://doi.org/10.1007/s10098-021-02029-8.

Veselý, Tomáš, Lukáš Trakal, Marek Neuberg, Jiřina Száková, Ondřej Drábek, Václav Tejnecký, Miluše Balíková, and Pavel Tlustoš. (2012). "Removal of Al, Fe and Mn by Pistia stratiotes L. and its stress response." *Open Life Sciences*, 7, no. 6, 1037-1045. https://doi.org/10.2478/s11535-012-0099-z.

Vijaya, P., Harsimran Kaur, Nancy Garg, and Suman Sharma. (2020). *The Journal of Basic and Applied Zoology*, 81, 1-11. https://doi.org/10.1186/s41936-020-00160-4 .

Von Canstein, Harald, Sven Kelly, Ying Li, and Irene Wagner-Döbler. (2002). "Species diversity improves the efficiency of mercury-reducing biofilms under changing environmental conditions." *Applied and environmental microbiology*, 68, no. 6, 2829-2837. https://doi.org/10.1128/AEM.68.6.2829-2837.2002 .

Von Canstein, Harald, Sven Kelly, Ying Li, and Irene Wagner-Döbler. (2002). "Species diversity improves the efficiency of mercury-reducing biofilms under changing environmental conditions." *Applied and environmental microbiology*, 68, no. 6, 2829-2837. https://doi.org/10.1016/j.biortech.2007.10.060.

Wang, Guoqiang, A. Yinglan, Hong Jiang, Qing Fu, and Binghui Zheng. (2015). "Modeling the source contribution of heavy metals in surficial sediment and analysis of their historical changes in the vertical sediments of a drinking water reservoir." *Journal of Hydrology*, 520, 37-51. https://doi.org/10.1016/j.jhydrol.2014.11.034 .

Wang, Jianxu, Xinbin Feng, Christopher WN Anderson, Ying Xing, and Lihai Shang. (2012). "Remediation of mercury contaminated sites–a review." *Journal of hazardous materials*, 221, 1-18. https://doi.org/10.1016/j.jhazmat.2012.04.035.

Wang, Jicang, Huali Zhu, Shu Lin, Ke Wang, Hongwei Wang, and Zongping Liu. (2021). "Protective effect of naringenin against cadmium-induced testicular toxicity in male SD rats." *Journal of Inorganic Biochemistry*, 214, 111310. https://doi.org/10.1016/j.jinorgbio. 2020.111310.

Wang, Xun, Haixin Yao, Ming Hung Wong, and Zhihong Ye. (2013). "Dynamic changes in radial oxygen loss and iron plaque formation and their effects on Cd and As accumulation in rice (*Oryza sativa* L.)." *Environmental geochemistry and health*, 35, 779-788. https://doi.org/10.1007/s10653-013-9534-y.

Word Health Organization. (2022). *Arsenic Key Facts*. Retrieved from: https://www.who.int/news-room/fact-sheets/detail/arsenic.

World Bank. *Wastewater A Resource that Can Pay Dividends for People, the Environment, and Economies, Says World Bank*. 2020. Retrieved from: https://www.worldbank.org/en/news/press-release/2020/03/19/wastewater-a-resource-that-can-pay-dividends-for-people-the-environment-and-economies-says-world-bank.

World Health Organization. (2022). "*Lead poisoning*." https://www.who.int/news-room/fact-sheets/detail/lead-poisoning-and-health.

Wu, Haitao, Zhiqiang Gai, Yunxia Guo, Yunwei Li, Yu Hao, and Zhi-Nan Lu. (2020). "Does environmental pollution inhibit urbanization in China? A new perspective through residents' medical and health costs." *Environmental Research*, 182, 109128. https://doi.org/10.1016/j.envres.2020.109128 .

Wu, Jun, Jian Lu, Leiming Li, Xiuyun Min, and Yongming Luo. (2018). *Chemosphere*, 201, 234-242. https://doi.org/10.1016/j.chemosphere.2018.02.122.

Wu, Yen-Hung, Jhong-Ching Lin, Tzu-Yi Wang, Tzeng-Jih Lin, Meng-Chi Yen, Yao-Hua Liu, Pei-Lin Wu, Fen-Wei Chen, Yueh-Lun Shih, and I. Yeh. (2020). "Hexavalent chromium intoxication induces intrinsic and extrinsic apoptosis in human renal cells." *Molecular Medicine Reports*, 21, no. 2, 851-857. https://doi.org/10.3892/mmr.2019.10885.

Wu, Yen-Hung, Jhong-Ching Lin, Tzu-Yi Wang, Tzeng-Jih Lin, Meng-Chi Yen, Yao-Hua Liu, Pei-Lin Wu, Fen-Wei Chen, Yueh-Lun Shih, and I. Yeh. (2020). "Hexavalent chromium intoxication induces intrinsic and extrinsic apoptosis in human renal cells." *Molecular Medicine Reports*, 21, no. 2, 851-857. https://doi.org/10.1136/oemed-2012-100931.

Xu, Rui, Qian Li, Yongbin Yang, Shengming Jin, Lang Liao, Zhenguo Wu, Zhe Yin et al. (2022). "Removal of heavy metal (loid) s from aqueous solution by biogenic FeS–kaolin composite: Behaviors and mechanisms." *Chemosphere*, 299, 134382. https://doi.org/10.1016/j.chemosphere.2022.134382.

Yadav, Brijesh K., Maarten A. Siebel, and Johan JA van Bruggen. (2011). "Rhizofiltration of a heavy metal (lead) containing wastewater using the wetland plant *Carex pendula*." *CLEAN–Soil, Air, Water*, 39, no. 5, 467-474. https://doi.org/10.1002/clen.201000385.

Yadav, Krishna Kumar, Neha Gupta, Vinit Kumar, and Jitendra Kumar Singh. (2017). "Bioremediation of heavy metals from contaminated sites using potential species: a review." *Indian J. Environ. Prot*, 37, no. 1, 65.

Yan, Qiu-Xiang, Qing Hong, Peng Han, Xiao-Jun Dong, Yu-Jia Shen, and Shun-Peng Li. (2007). "Isolation and characterization of a carbofuran-degrading strain *Novosphingobium* sp. FND-3." *FEMS microbiology letters*, 271, no. 2, 207-213. https://doi.org/10.1111/j.1574-6968.2007.00718.x.

Yang, Yan, and Qianyong Shen. (2020). "Phytoremediation of cadmium-contaminated wetland soil with Typha latifolia L. and the underlying mechanisms involved in the heavy-metal uptake and removal." *Environmental Science and Pollution Research*, 27, 4905-4916. https://doi.org/10.1007/s11356-019-07256-7.

Yao, Maolin, Qibing Zeng, Peng Luo, Baofei Sun, Bing Liang, Shaofeng Wei, Yuyan Xu, Qingling Wang, Qizhan Liu, and Aihua Zhang. (2021). "Assessing the risk of coal-burning arsenic-induced liver damage: a population-based study on hair arsenic and cumulative arsenic." *Environmental Science and Pollution Research*, 28, 50489-50499. https://doi.org/10.1007/s11356-021-14273-y.

Yesilada, Ozfer, Emre Birhanli, and Hikmet Geckil. (2018). "Bioremediation and decolorization of textile dyes by white rot fungi and laccase enzymes." *Mycoremediation and Environmental Sustainability*, Volume 2, 121-153. https://doi.org/10.1007/978-3-319-77386-55.

Yorifuji, Takashi. (2020). "Lessons from an early-stage epidemiological study of Minamata disease." *Journal of epidemiology*, 30, no. 1, 12-14. https://doi.org/10.2188/jea.JE 20190089.

Yorifuji, Takashi. (2020). "Lessons from an early-stage epidemiological study of Minamata disease." *Journal of epidemiology*, 30, no. 1, 12-14. https://doi.org/10.3389/fmars.2019.00754.

Yu, Xinjian, Ri-Qing Yu, Duan Gui, Xiyang Zhang, Fenping Zhan, Xian Sun, and Yuping Wu. (2018). "Hexavalent chromium induces oxidative stress and mitochondria-mediated apoptosis in isolated skin fibroblasts of Indo-Pacific humpback dolphin." *Aquatic Toxicology*, 203, 179-186. https://doi.org/10.1016/j.aquatox.2018.08.012.

Yu, Zhe, Shi-Feng Xu, Jun-Liang Zhao, Lei Zhao, Ai-Zhong Zhang, and Mu-Yang Li. (2021). "Toxic effects of hexavalent chromium (Cr6+) on bioaccumulation, apoptosis, oxidative damage and inflammatory response in *Channa asiatica*." *Environmental Toxicology and Pharmacology*, 87, 103725. https://doi.org/10.1016/j.etap.2021.103725.

Zahari, Nur Zaida, Ng Sean Fong, Fera Nony Cleophas, and S. A. Rahim. (2021). "The Potential of *Pistia stratiotes* in the Phytoremediation of Selected Heavy Metals from Simulated Wastewater." *Int. J. Technol*, 12, 613-624. https://doi.org/10.14716/ijtech.v12i3.4236.

Zeng, Jie, Guilin Han, and Kunhua Yang. (2020). "Assessment and sources of heavy metals in suspended particulate matter in a tropical catchment, northeast Thailand." *Journal of Cleaner Production*, 265, 121898. https://doi.org/10.1016/j.jclepro.2020.121898.

Zeng, Weimin, Fang Li, Chenchen Wu, Runlan Yu, Xueling Wu, Li Shen, Yuandong Liu, Guanzhou Qiu, and Jiaokun Li. (2020). "Role of extracellular polymeric substance (EPS) in toxicity response of soil bacteria *Bacillus* sp. S3 to multiple heavy metals." *Bioprocess and biosystems engineering*, 43, 153-167. https://doi.org/10.1007/s00449-019-02213-7.

Zhang, L., Zhou, Y., Cheng, Y., Lu, W., and Liang, Y. (2021). Effect of different types of industrial wastewater on the bacterial community of urban rivers. *Journal of Freshwater Ecology*, 36(1), 31-48. https://doi.org/10.1080/02705060.2021.1871978.

Zhao, F. J., Lombi, E., and Breedon, T. M. S. P. (2000). "Zinc hyperaccumulation and cellular distribution in *Arabidopsis halleri*." *Plant, Cell & Environment*, 23, no. 5, 507-514. https://doi.org/10.1046/j.1365-3040.2000.00569.x.

Zhao, Qilei, Meihua Guo, Thomas H. Hostetter, Hongzhu Chen, Liwang Lin, and Xin Hai. (2021). "Effect of renal impairment on arsenic accumulation, methylation capacity, and safety in acute promyelocytic leukemia (APL) patients treated with arsenic trioxide." *Expert Review of Clinical Pharmacology*, 14, no. 9, 1173-1182. https://doi.org/10.1080/17512433.2021.1938549.

Zhitkovich, Anatoly. (2011). "Chromium in drinking water: sources, metabolism, and cancer risks." *Chemical research in toxicology*, 24, no. 10, 1617-1629. https://doi.org/10.1021/tx200251t.

Zhong, Yuqing, and Jiajia Chen. (2020). "Ameliorative effects of Lanthanum (III) on Copper (II) stressed rice (*Oryza sativa*) and its molecular mechanism revealed by transcriptome profiling." *Plant physiology and biochemistry*, 152, 184-193. https://doi.org/10.1016/j.plaphy.2020.05.004.

Znad, Hussein, Md Rabiul Awual, and Sri Martini. (2022). "The utilization of algae and seaweed biomass for bioremediation of heavy metal-contaminated wastewater." *Molecules*, 27, no. 4, 1275. https://doi.org/10.3390/ molecules27041275.

Zwolak, Aneta, Magdalena Sarzyńska, Ewa Szpyrka, and Kinga Stawarczyk. (2019). "Sources of soil pollution by heavy metals and their accumulation in vegetables: A review." *Water, air, & soil pollution*, 230, 1-9. https://doi.org/10.1007/s11270-019-4221-y.

ADVANCES IN PHARMACOGNOSY AND PHYTOCHEMISTRY OF DIABETES

EDITED BY
UCHENNA ESTELLA ODOH
HABIBU TIJJANI
CHUKWUEBUKA EGBUNA

PUBLISHED BY
IPS INTELLIGENTSIA PUBLISHING SERVICES
THE PUBLISHER PAR EXCELLENCE

Advances in Pharmacognosy and Phytochemistry of Diabetes

Advances in Pharmacognosy and Phytochemistry of Diabetes

Editors

Prof. Uchenna Estella Odoh
Department of Pharmacognosy and Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria.

Dr. Habibu Tijjani
Department of Biochemistry, Natural Product Research Laboratory, Bauchi State University Gadau, Nigeria.

Dr. Chukwuebuka Egbuna
Nutritional Biochemistry and Toxicology Unit, African Centre of Excellence for Public Health and Toxicological Research (ACE-PUTOR), University of Port-Harcourt, Rivers State, Nigeria.

Intelligentsia Publishing Services
The publisher par excellence

Chapter 6

Alkaloids of Natural Origin with Promising Anti-Diabetic Properties

Sanchita Seal[1], Somnath Kar[2], Sushreya Pal[3], Soumi Datta[4], Atithi Debnath[5], Swastika Bannerji[6], Dwaipayan Sinha[7*]

[1]Department of Botany, PolbaMahavidyalaya, Polba, West Bengal- 712148, India
[2]Department of Botany, Holy Cross College, Jubatara, Lembucherra, Agartala, Tripura-799210, India
[3]Industrial Section Indian Museum, Botanical Survey of India, 1 Sudder Street, KolkataWest Bengal-700016, India.
[4]Bioactive Natural Product Laboratory, School of Interdisciplinary Sciences and Technology, JamiaHamdard, Hamdard Nagar, New Delhi- 110062
[5]Department of Botany Tripura University, Suryamaninagar, Tripura-799022, India
[6]Kairali College of +3 Science, Champua, Keonjhar, Odisha-758041, India
[7]Department of Botany, Government General Degree College, Mohanpur, Paschim Medinipur, West Bengal-721436, India.
*Corresponding author Email: dwaipayansinha@hotmail.com; ORCiD: https://orcid.org/0000-0001-7870-8998

How to cite this chapter: Seal, S., Kar, S., Pal, S., Datta, S., Debnath, A., Bannerji, S. and Sinha, D. (2023). Alkaloids of Natural Origin with Promising Anti-Diabetic Properties. In. Odoh, U.E., Tijjani, H. and Egbuna, C. (Eds) Advances in Pharmacognosy and Phytochemistry of Diabetes. Onitsha: IPS Intelligentsia Publishing Services, Pp. 61-83. DOI:

Abstract

"Diabetes" doubled in prevalence worldwide in past two decades. The prevalence of type 2 diabetes in children, adolescents, and young adults is one of the most concerning trends in this rapid increase.Inspite of the desperate efforts of public health care organisations to control if not eradicate the disease, the diabetes cases is keeping on increasing at an alarming rate. Diabetes is defined by a state of hyperglycemia that can be treated with several synthetic medications in addition to insulin therapy but these alternatives are expensive and have a greater risk. Alkaloids are a family of simple nitrogen containg organic compounds that are found in nature.. Alkaloids have been found to have a wide variety of therapeutic benefits in the biological realm, including anti-diabetic characteristics. To that regard, we set out to compile a comprehensive literature review on the beneficial effects of plants, and their extracted alkaloid components for the treatment and control of diabetes along with their mode of action. In this comprehensive analysis, we have shown show how alkaloids are effective in lowering blood sugar levels in biological system. This chapter sheds insight on the function of alkaloids derived from various widely available plant products as anti-diabetes and illustrates the mechanism by which they function in this regard. According to this comprehensive review, alkaloids are a potent candidate to prevent and control diabetes and help identify new anti-hyperglycemic drugs.

Keywords: Alkaloids, Diabetes, Glucose, Hyperglycemia, Insulin, Glucagon

6.1 Introduction

Diabetes is a disease characterized by hyperglycemia due to imperfections in insulin release and activity. These defects can occur in one or both of the pancreas and the liver. Diabetes is linked to persistent hyperglycemia, which can cause long-term damage as well as failure in a variety of organs (1).The development of diabetes is influenced by a number of different pathological processes. These comprise the autoimmune obliteration of the pancreatic β cells (2) resulting in insulin deficit, to anomalies that lead to resistance to the action of insulin (Freeman and Pennings, 2022)(3). The insufficient influence of insulin on tissues is at the root of the abnormalities in glucose, lipid, and protein metabolism that characterize diabetes (American diabetes association) (4)(5)(6). According to projections made by the International Diabetes Federation, the people who have the ailment would more than double from its current prevalence of 425 million in 2017 to 629 million in 2045 (7). This ailment can be categorized into four primary categories: type 1, 2, gestational, and secondary or other specialised types (8).Type 2 diabetes (T2D) impacted 437.9 million people worldwide in 2019,having an age-standardized point occurrence of 5282.9 cases per million people, a 49% rise since past 30 years. In 2019, there were 1472.9 thousand fatalities from T2D, with an age-standardized fatality rate of 18.5 per million people, up 10.8% from 1990. Type 2 variant caused 66.3 million DALYs in the globe in 2019, having an age-standardized rate of 801.5 DALYs per million, a rise of 27.6% since past 30 years(9). Diabetes type 2 and the co-morbidities that come along with it are responsible for 1million fatalities globally and consume a large amount of medical resources.Developed areas, such as Europe, exhibit significantly higher prevalence rates, which continue to climb despite the implementation of various public health measures (10). The diabetes-related complications are the single most important factor in determining a patient's overall quality of life (11). It is common for patients to have both impaired insulin production and impaired insulin action, and it is frequently difficult to determine which anomaly is the main contributor to hyperglycemia (12). A societal definition of diabetes incorporates the economic burden the condition places on society due to both the expensive nature of its treatment and the related early morbidity and mortality (13). This chapter will give a briad overview about diabetes and how can this be managed by alkaloids of plant origin. In the next section, an illustration of the types of diabetes would be given.

6.2 Types of Diabetes

The overwhelming bulk of diabetes are of two etiopathogenetic groups. The T1D, has an utter absence of insulin discharge as its aetiology. The more popular T2D is triggered by resistance to and inadequate compensating insulin discharge. However, a lot of subcategories each having specific patterns have also been demarcated in diabetes. This section will briefly discuss about selected major categories of the ailment.

6.2.1 Type-I diabetes

This variant is synonymous to juvenile-onset diabetes, is brought on as a consequence of an autoimmune procedure that degenerates pancreatic β-cells, impairing pancreas' ability to generate insulin. It is characterized by acute onset, partial insulin dependency, and ketoacidosis (14). It accounts for 5-10% of all known cases in the western world and is brought on by auto-immune, genetic, and/or environmental causes (15). Common symptoms usually include excess urination and sugar discharge with urine (polyuria and glycosuria), increased hunger, weight loss, vision changes also fatigue (16).

6.2.2 Type-II diabetes

Over 90% of so called diabetic cases which are recorded in the western world are Type-II variant, often described non-insulin-reliant diabetes mellitus (DM). In general, persons with type II diabetes either synthesize adequate insulin that is useless. The development of Type II occurs in the middle or later life and is substantially more common than other types (14). Type-II variant, have a comparatively slow onset. Typically, the condition's primary symptom is insulin resistance, which is initially partially offset by increased insulin production by pancreatic beta-cells (also referred to as hyperinsulinemia). A result of exhaustion, combined effects of insulin resistance and reduced discharge reduce the amount of glucose that is taken up and used by skeletal muscle through the act of insulin and the ability of insulin to synchronize the generation of hepatic glucose (17). Because of upsurge in older population, the prevalence of obesity, moreover, the rise in sedentary behavior, type II diabetes is quickly approaching epidemic levels (18). In addition to Type II diabetes, indiviguals with other metabolic disorders like hypertension, obesity, and polycystic ovarian syndrome, might possess insulin resistance (19)

6.2.3 Gestation diabetes

Except for women who likely have overt pre-gestational diabetes, gestation diabetes is also widely known to possess carbohydrate aversion that manifests or is discovered for the first time during pregnant (20). It is a typical medical problem during pregnancy and is linked to a higher rate of unfavorable consequences (neurological and cognitive adversities might be observed) (21)(Langer et al.,2005). Even though the problem usually doesn't linger post delivery, affected women should keep a check against postpartum diabetes if it persists , they generally have a greater danger of suffering from T2D(19).

6.2.4 Other forms of Diabetes

This category includes maturity-onset diabetes of young caused owing to inheritance of a defective gene set which is responsible for insulin production from the pancreas (22), an autosomal dominant family form of diabetes characterized by mutagenic changes bought about in certain b-cell or liver's hepatic genes (such as HNF homeobox A (HNF-1a) and glucokinase). Surplus or superabundance of certain hormones like corticosteroids or certain drug abundance i.e. immune check point inhibitors in the treatment of cancer, protease inhibitors in HIV virus infection etc stimulates other well-characterized forms of diabetes. Hemochromatosis-related diabetes is another kind of diabetes which is associated with pancreatic disease (19).

6.3 Global Scenario of Diabetes

Over last 20 years, the dominance of diabetes has nearly twiced globally. The incidence of T2D in kids and lower age people is one of the concerning trends in this speedy increase.. Even though classic risk factors for T2D still exist, recent research has focused on understanding how epigenetic processes and the intrauterine milieu contribute to the disease. (such as genetic, new lifestyle exposure, and behavioral risks) have received attention (23). Organizations like International Diabetes Federation and World Health Organisation are known to keep a regular update of people affected worldwide (24). Since 1994, there has been a significant rise in the number of diabetic population. (25) . In 2006, Resolution 61/225,14 adopted by the UN General Assembly, called for diabetes to be recognized as a global public wellbeing issue(26). The UN General Assembly declaration in 2011 on deterrence and governing of certain non-communicable ailments (27) was trailed by declaration by The World Health Organization to bring down the death rate of such ailments by about 25% by the year 2025 (28). Since then the government has taken initiatives to control the disease. Reports of the International Diabetes Federation predicts approximately 600 million individuals living with the ailment worldwide by the year 2035, up from the previously predicted estimate of 382 million (which was a previously expected value for 2030) in the year 2013(23). The countries known to have a greater number of diabetes cases were: Egypt, Japan, Turkey, Indonesia, Russia, Brazil, Mexico, USA, China, and India. According to recent reports in terms of the prevalence of DM, India comes in second place after China. This disease is more of a burden and a great challenge for developing nations than developed nations due to a comparatively lower income to support expensive medications(29). In so called developed nations, the abundance of this disease is usually higher among the immigrants from underdeveloped nations. Occurrence of diabetes is also higher among the indigenous people of developing nations like Australia and Canada (30) .

Diabetes is a significant contributor to deadly and fatal COVID-19 results. 3,799 papers and 91 research were evaluated and analyzed to better understand the connection between diabetes and COVID-19. Significant findings were that T1D patients were more likely to experience COVID-19-related excess fatalities and critical illnesses than type-2 variant patients, and that meager glycaemic management was a risk factor for severe COVID-19 outcomes (31).Future challenges are huge. Economic growth and increased availability of care will boost treatment and lead to an untenable rise in diabetes-related health costs. Both wealthy and emerging nations are and also will be affected by this global economiccatastrophe (32)(33) Cost-effective inventions with minimum side effects might be a way out.

6.4 Present-day treatment of Type 2 diabetes or sugar diabetes

Diabetes treatment depends on what type of diabetes a patient is having. Certain tests prescribed to patients who are likely to have Type I or Type II diabetes or are pre-diabetes are: Glycated hemoglobin investigation, Fasting and random blood sugar examination and oral glucose tolerance examination (34). A more or less normal body weight, regular exercise, good food habit, and a proper diet are the most essential for the management of diabetes(35). HaemoglobinA1C testing provides a more comprehensive picture of the effectiveness of your diabetes treatment regimen than repeated daily blood sugar checks. A higher A1C level could indicate that you need to adjust your oral medication, insulin regimen, or diet.

Type 1 diabetes treatment includes insulin injections or pumps, carbohydrate tracking, and blood sugar monitoring. Type 1 diabetics may consider islet cell or pancreas transplants (36). Diet adjustments, sugar levels testing, consumable diabetic medicines, insulin, or a mixture of these are used to treat T2D(37).

Insulinshotsis very essential to patients surviving with type-1 diabetes. Often insulin injections are also prescribed to indiviguals surviving with type-2 diabetes or gestation diabetes. Since stomach enzymes interfere with insulin's ability to work, it is impossible to take insulin doses orally to lower blood sugar (38). A huge ink pen-like instrument well known as an insulin pen or a very fine needle and syringes are mostly used to inject insulin (39). Specific insulin dosages can be programmed into an insulin pump. In accordance with meals, level of exercise, or blood sugar level, it can be modified to release more or less insulin (40).

Drugs that are administered orally or intravenously.Diabetes medicines increase insulin production. Some reduce insulin needs by preventing the liver from producing and releasing glucose(41). Sulfonylurea insulin secretagogues includes: Glyburide, Glipizide, Chlorpropamide, and Glimepiride. Repaglinide and nateglinide are two examples of short-acting nonsulfonylurea insulin secretagogues(42). Biguanides (Metformin) one of the well-known drugs against type II diabetes acts by preventing hepatic gluconeogenesis and lowering hepatic glucose synthesis, it largely improves insulin sensitivity in liver (43).Both acarbose, voglibose, and miglitol act as inhibitors of alpha-glucosidase. By delaying carbohydrate absorption, these medications can lower postprandial hyperglycemia by up to 50 mg/dL(44). Orlistat is an intestinal lipase inhibitor, while saxagliptin and sitagliptin are dipeptidyl peptidase-IV inhibitors. Insulin sensitizers such as rosiglitazone and pioglitazone are among some of the anti-hyperglycemic agents known to be consumed orally (45). Combination therapy or using multiple oral medications with various modes of action increases the effectiveness of lowering hemoglobin A1c levels (46). Some of the approved combination therapy includes sulfonylureas and metformin, metformin and thiazolidinediones, sulfonylureas and thiazolidinediones, etc (47). Figure 6.1 displays the various treatment strategies to control type-2 diabetes. SGLT2 inhibitors are another option. They hinder kidneys from reabsorbing blood-filtered sugar (48). Pancreatic transplant is another available option for T1D patients (49).

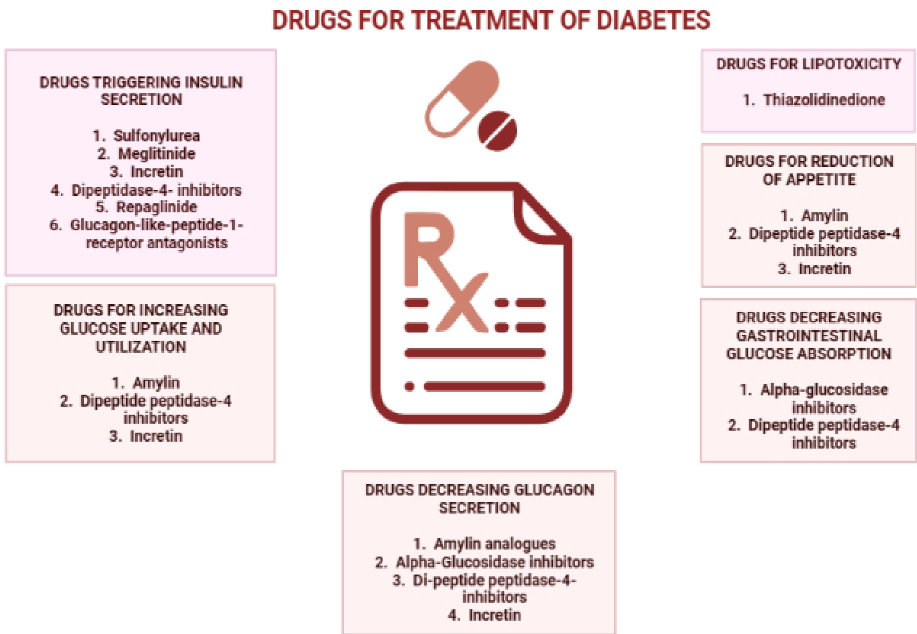


Figure 6.1: Present-day management, possible and relevant treatments of sugar diabetes.

Figure 6.1 shows the different forms of complications due to type-2 diabetes and their respective prescribed drugs as prescribed by health physicians.

6.5 Why focus on herbal medications?

Herbal alternatives to chemical alternatives offer various advantages. The first is the complete absence of any negative side effects that could endanger your health or even your life, or the least severe side effects ever(50). According to reports, around 1.5 million people in the US are admitted to various hospitals each year as result of adverse drug reactions (51). Synthetic drugs have several drawbacks, including the development of the body's resistance to various medications after prolonged or improper use (52). As a result, doctors recommend new and more potent drugs to cure and relieve the sickness, which decreases the drugs' efficacy and harms the body.

For the first time, Ayurveda under the category of Prameha and Madumeha discussed the importance of diet in the deterrence, causation, and management of diabetes. The Ayurvedic classics CarakaSamhita, SusrutaSamhita, and others provide accurate descriptions of the impact that diet, customs, and lifestyle have in Prameha and Madhumeha, that are parallel to diabetes (53). Nearly 67% of the population, who are diagnosed with DM, are treated using about 700 different recipes., more than 400 plants have been included(54). Numerous in vivo tests on animals to verify the claimed activity have shown the hypoglycemic property of several plants, which has already been described in numerous kinds of literature (55).

It has been reported that even certain mostly prescribed diabetic drugs are known to be responsible for undesirable effects. For example- Stomach ache and diarrhea is a common side-effects of alpha-glucosidase inhibitors (56). Therapies with biguanides and thiazolidinediones might cause kidney damage, weight gain or heart failure, and anemia respectively (57). Regardless of the numerous benefits of incretin-based medications in the remediation of type-2 variant, significant gastrointestinal issues like vomiting, indigestion, a sour stomach,, nausea, and diarrhea continue to be present (58). The clinical trial of the SGLT 2 inhibitors was unsuccessful because of safety issues (59). Moreover, certain drugs for the remediation of diabetic neuropathy are known to have detrimental effects i.e. tricyclic anti-depressants like desipramine, and amitriptyline known to induce relief from pain in diabetic neuropathy, overdosage might lead to death (60) ; Carbamazepine an anti- convulsant known to regulate neuropathic pain also leads to bone marrow suppression and osteoporosis (61).

Although there are many treatments and medications on the market to treat diabetics, their drawbacks, including high cost, poor pharmacokinetics, and drug resistance, makes it imperative to switch from these so called chemical medications to natural, traditional medicines in the form of a herbal remedy.Clinical research has shown that several herbs, including *Ficusracemosa* bark, *Portulacaoleracea* L. seeds, *Cinnamomum cassia*, *Scopariadulcis,* and *Curcumin longa*, have anti-diabetic properties (62). Hence, to ensure a safe future there should be a gradual shift to herbal therapy. The next section will discuss about alkaloids and its antidiabetic potentials.

6.6 Introduction to alkaloids

Carl F. W. Meissner, a German chemist, first used the term "alkaloid" in 1819. It was based on the Arabic term al-qali, which is related to soda's original phyto-source (63). Alkaloids are low-molecular-weight substances that account for one-fifth of plants' secondary metabolites (64).Alkaloids are substances found in nature that typically consist of oxygen, carbon, hydrogen, and nitrogen. They are largely present in plants, particularly in some blooming plants (65).A plant's secondary metabolism produces alkaloids from terpenes, purines, amino acids, or pyrimidines.(66). Their heterocyclic ring might contain one or more nitrogen atoms. Additionally, this group contains some related neutral and even slightly acidic chemicals (67). There are three major types of alkaloids, and they are called real alkaloids, proto-alkaloids, and pseudo-alkaloids, respectively. While pseudo-alkaloids cannot be synthesised from amino acids, genuine alkaloids and protoalkaloids may (63). True alkaloids possess a N-containing a heterocyclic ring and originate fromamino acids, having efficient bioactivity (68). They produce water miscible salts with amino acids (63) . Although they likewise originate from amino acids, proto-alkaloids lack a nitrogen moiety in a heterocyclic structure (68). The carbon backbone of pseudo-alkaloids is simple and not generated from an amino acid (69).An important significant ecological role of alkaloids is their usage by plants as a means of self-defense against the aggression of other creatures. Alkaloids are known to be produced throughout the plant world and are primarily found in higher plants, including those in the Ranunculaceae, Papaveraceae, Menispermaceae, Leguminosae, and Loganiaceae, etc families (70). They are just one of the many phytochemicals found in plants that are observed to be protective in function by lowering the risk of many illnesses and disorders. They are also among the earliest natural products still being used by people today for pharmaceuticals that are essential as medicinal agents (71). Figure 6.2 is a pictorial representation showing the anti-diabetic potentials of plant derived bio-active compounds (mainly alkaloids) and their channeization into development of novel anti-diabetic drugs based on their mode of action.

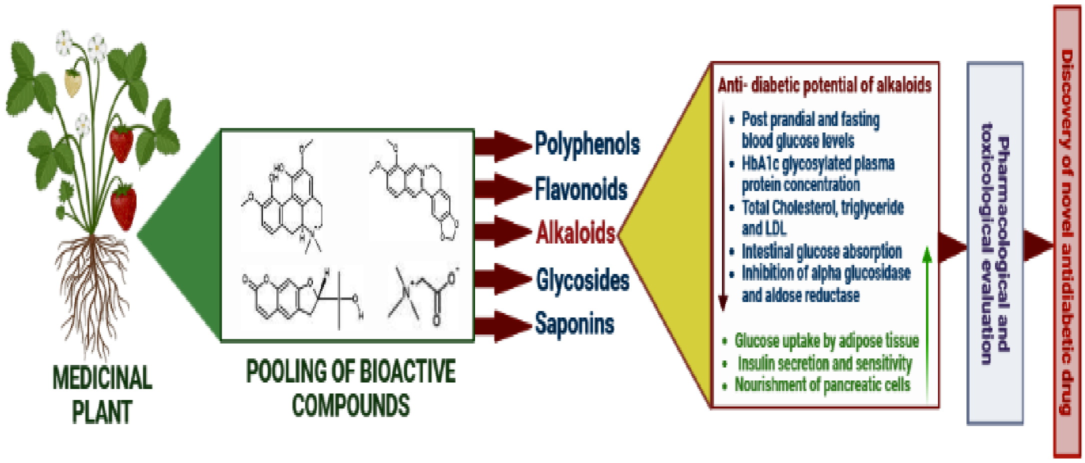


Figure 6.2: Development of antidiabetic drugs based on plants

Current diabetes treatment is reliant on synthetic medications, many of which have negative effects of which it including immediate sugar lowering, lowering of lipid concentration and increase in obesity the most important (17). Because of this, there is a constant requirement to create brand-new, improved medications as alternatives for the control and remediation of the disease. There is consequently a pressing need to create novel therapeutic compounds with different targets and alternative mechanisms of action as the same prolonged, multidrug treatment regimen has been employed in the therapy of diabetes for half a century (17). Alkaloids like Berberine, palmatine, vindoline, nigelladines, vindolidine, nigelladines, vindolicine, vindolinine, coptisine, Vindogentianine, epiberberine, and jatrorrhizine are some among the reported alkaloids which are useful in diabetes cure or remediation(Singh et al.,2022).Numerous commercially available medications are alkaloidal in nature (70). In parallel, significant attempts are being made by researchers worldwide to transition additional alkaloids from the lab bench to the market (72).

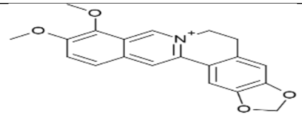
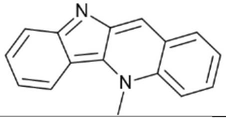
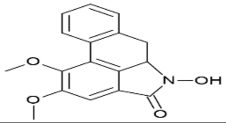
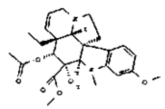
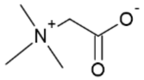
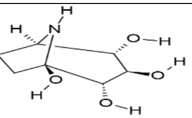
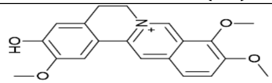
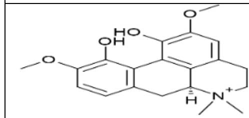
6.6.1 Phyto-alkaloids in the remediation of diabetes

A total of 12,000 alkaloids from plants with varying medicinal relevance have been evaluated (73). Alkaloids can exist as homo-oligomers or hetero-oligomers and are usually found as units of one to four. Heterocyclic/non-heterocyclic chemical structure and biological or natural origins are used to categorize them. Alkaloids are one of the many phytochemicals in plants that is protective by lowering the risk of many illnesses and disorders. To prevent formation of enzyme-substrate complex, which in turn lowers enzyme activity, alkaloids are known to attach to the active sites of enzymes which are associated in digestion (45). Regulatory frameworks which govern the research and utilization of botanical drugs have recently attracted the attention of the Food and Drug Administration (FDA) and Europe Middle East and Africa, who have also evaluated them. This intense interest has given the natural products sector a considerable boost and significantly cut the entry barriers for botanicals and associated goods (74). Some of the widely available plant species with anti-diabetic forms which are or have the potentials of being suitable diabetic drugs are discussed in this section. Table 6.1 presents the anti- diabetic potencial of a few well known alkaloids derived from some common plant sources along with its structure.

6.6.1.3 Adhatoda vasica

This plant is also coloquially called as Basak. The leaf extracts derived from this plant is an important inclusion in several known ayurvedic medicinal formulations (79). Quinazoline alkaloids, including vasicinone, vasicine, vasicol, adhavasicinone, deoxyvasicinone, vasicinol, and some minor chemicals in the same series, are known to be produced by the plant species (80). Vasicine and vasicinol, two intestinal sucrase inhibitors, were isolated from the leaves of *A. vasica*. Hence, can be traced as potent alpha- glucosidase inhibitors (81)and can be used formulated in diabetes treatment.

Table 6.1: Selected Alkaloids having antidiabetic potential

Name	Plant	Plant Part	Chemical structure	Antidiabetic potential	Reference
Berberine	*Berberisaristata*	Roots, stem, rhizomes, bark, fruits		Inhibition of alpha glucosidase	(167)
				Reduction of glucose transportation in intestinal epithelium and GLUT 2 translocation	(168)
				Activation of AMPK	(169)
Cryptolepine	*Cryptolepissanguinolenta*	Root bark		Regeneration of beta cells of pancreas. Reversal of diabetes induced increase in levels of cholesterol, triglyceride, low density lipo-proteins and reduced high density lipoprotein	(131)
Piperumbellactum	*Piper umbellatum*	Branches		Inhibition of alpha glucosidase	(170)
Vindoline I	*Catharanthusroseus*	Leaf	 (Vindoline)	Inhibition of protein tyrosine phosphatase activity	(76)
Vindolidine II					
Vindolicine III					
Vindolinine IV					
Vindogentianine	*Catharanthusroseus*			Increased uptake of glucose by cells and inhibition of protein tyrosine phosphatase	(77)
Betaine	*Beta vulgaris*	Rhizome		Reduction of fasting blood sugar	(171)
				Reduction in levels of HbA1c, serum glucose and fats	(172)
calystegines	*Daturastramonium, Solanumtuberosum*	Whole plant	 (B2)	Inhibition of alpha galactosidase and beta xylosidase and beta glucosidase	(173)
Jatrorrhizine	*Tinosporacordifolia*	Stem		Decrease in levels of glucse in serum. Induction of insulin secretion.	(161)
Magnoflorine					

6.6.1.4 Piper umbellatum
This plant belongs to a shruby habit that is found in the Brazilian Atlantic Forest, Savannah, and Amazon. It is very frequently used to treat gastrointestinal issues in folk medicine throughout many nations. *Piper umbellatum*'s alkaloid piperumbellactam A, B, and C exhibit a significant alpha-glucosidase inhibitory action (82). Another research examines the impact of methanolic leaf extracts of *P.umbellatum* and *Perseaamericana* on the inhibitory action of the enzymes associated in digestion of starch. The findings demonstrate that the examined extracts significantly reduced the activities of alpha-glucosidase, aldosereductase, maltase-glucoamylase, and aldehyde reductase. It is to be noted that no such reports on inhibition of the activity of beta-glucosidase were examined. Hence, have potentials to be used as anti-diabetics (83).

6.6.1.5 Tinospora cordifolia
This plant is widely known as Guduchi, giloy, gurjo or heart-leaved moon seed is an indigenous variety belonging to tropical regions of the Indian sub-continent. This plant has had a widespread contribution to ancient ayurvedic drugs and folk medicines since, prehistoric times. Due to the occurrence of several pharmaceutically significant chemicals from a variety of categories, including alkaloids, glycosides, steroids, diterpenoid lactones, sesquiterpenoids, etc all portions of the plant are quite helpful (84). Both *in-vitro* and *in-vivo* reports of the effects of extracts obtained from plant stems, particularly palmatine (a protoberberine alkaloid), is known as an insulin-mimicking hormone and also known to stimulate insulin release (85). It is evident that Tinosporacordifolia stem extract significantly reduces blood sugar levels in diabetic animals and outperforms insulin by 50% to 58% (86).

6.6.1.6 Tribulus terrestris
The plant is an annual herbaceous plant (known for forming mats) belonging to the Zygophyllaceae. It is known to have a long history of being valued as a valuable medicinal plant (87). Tribulusterrestris produces the imidazoline alkaloids harmane and nor-harmane, which increase insulin synthesis in the pancreatic membrane by triggering the imidazoline-I attaching sites. In isolated humans Langerhans islets, nor-harmane, pinoline (carbolines) and harmane, increase insulin discharge by more than twice. Harmane boosts insulin synthesis in a glucose-dependant way (88).

6.6.1.7 Berberis aristata
The plant is a spinous herb, also known as "Daruhaldhi and Chitra," and is a native of the northern Himalayas. From the Himalayas to Sri Lanka, Bhutan, and mountainous portions of Nepal, the plant is extensively dispersed. It was discovered that the amount of berberine in *B. aristata*'s root and stem varied with altitude. It was discovered that plants growing at lower elevations have more berberine. Potassium and soil moisture levels have an impact on a plant's berberine content as well (89). Protoberberine and an alkaloid of the bisisoquinoline class are found in*Berberisaristata*(90).The ability of berberine to block alpha-glucoside and lessen intestinal epithelial glucose transportation is assumed to be the cause of its antihyperglycemic effects. On gluconeogenesis and glucose usage in the Caco-2 cells, there was no discernible effect. Berberine is an AMP protein kinase activator (AMPK). Negative stimulation of mitochondrial function and triggerring of AMPK is related to the inhibition of alpha-glucosidase(91).

6.6.1.8 Lobia chinensis
The plant is used in conventional Chinese medicine. *Lobia* is a small perennial herb. This plant is widely found in East Asia which includes Korea, China, and Japan (92). Two pyridinium alkaloids, radicamines A and B, have been identified and discovered in this family which is known to have anti- diabetic potentials. Radicamines A and B, the herb's two primary active ingredients, were examined for their ability to suppress the enzyme alpha-glucosidase. The biological activity of these two new, aromatic-ringed poly-hydroxy alkaloids is comparable to that of the alpha-glucosidase inhibitor one-deoxynojirimycin [93].

6.6.1.9 Lepidium sativum
The plant commonly known as garden cress is a rapidly growing herb that is edible as well as annual (94). Lepidine or semi-lepidine which is a variety of imidazole alkaloid can be extracted from this plant. These substances were found to have significant hypoglycemic effects. This effect might be produced by reducing oxidative stress and controlling enzymatic activity. Its ability to lower blood sugar levels may be mediated by escalation of the amount of pancreatic insulin synthesised by the remaining islet cells (83).

6.6.1.10 Tecoma stans

It is a small shrub or a tree is known for its distribution in the western hemisphere tropics and sub-tropics and was known to produce three important alkaloids namely - boschniakine, 5-hydroxyskitanthine, and tecomine well known in Bignoniaceae. In normoglycemic rat adipocytes, it was discovered that tecomin significantly increased basal glucose absorption. It was traditionally used in Mexico to control diabetes (95).

Several other plant species are also reported as well such as *Stewartiachirayita (*swerchirin)*, Talinumpaniculatum (*Javaberine A, B)*, Penaresschulzai (*schulzaines A,B,C), *Dysideaavara (*avarol), *Syzygiummalaccense*(Casuarine-6-o-a- glucoside), etc which are sources of alkalloids which are potent anti-diabetic agents and hence, can be widely used in drug formulations (83).

6.7 Selected phyto-alkaloids with anti-diabetic potentials

6.7.1. Berberine

The Berberidaceae family includes approximately 500 species from the genus *Berberis*(96) and known to secrete an isoquinoline alkaloid, a type of alkaloinds called protoberberine(97) called 'berberine'. Apart from the family Berberidaceae, berberine is also present among the members of the family Ranunculaceae and Papaveraceae. According to Ahrendt, 1961, genus *Berberis* are evergreen shrubs having spine angled/sulcated yellow-colored bark. Leaves are elliptic, obovate, or oblong-shaped with red oblong fruits and yellow flowers (98).

The phytomoleculeberberine is reported to be found in species native to Asia and America like barberry and goldenseal respectively It is found in roots, stem, rhizomes, bark, fruits and rarely in leaves (99), mostly in barberry plant species but also found in celandine (*Chelidoniummajus*), amur cork (*Phellodendronamurense*), goldenseal (*Hydrastiscanadensis*, (100) and meadow rue (*Thalictrumrochebrunianum*). Berberine is mostly extracted from stem and *Berberis* roots (101). Roots of *B. aristata*yields around 5% and stem bark 4.2% of berberine.; while other species like *B. asiatica*, *B. aquifolium, B. petiolaris,B.thunbergii*, and *B.vulgaris* yield 0.43%(102). Yina et al., (2012)(103) confirmed 5.2-7.7% in *Rhizomacoptidis* (Huang Lian), 4-8% in *B. sargentiana*, *Phellodendronamurense*, *Coptischinensis* roots; 2-4% in barks of *P. amurense*(99), and roots/stems of *Tinosporacordifolia*(104).

Berberine is a naturally occurring chemical compound with basic nitrogen atoms and neutral or weakly acidic properties with molecular formula as $C_{20}H_{19}NO_5$(105). Phenylalanine or tyrosine is the known precursor for berberine biosynthesis (Singh and Sharma, 2018). Several pharmacological properties are associated with berberine - antibacterial, anti-asthma, anti-cancer (106), anti-inflammatory (107), antidiabetic, an anti-oxidant(108), and anti-toxicity (109). Berberine inhibits disaccharide activity in Caco-2 cells by impeding alpha-glucosidase and reducing the intestinal epithelium carries glucose, acting as an anti-hyperglycemic., therefore result as an anti-hyperglycemic agent (91) .

6.7.2. Cryptolepine

Cryptolepis sanguinolenta, is a flowering shrub with slender twining stems, a belongs to family apocynaceae, and a originated in West Africa and possess wide array of pharmacological potential including anti-hyperglycaemic, antithrombotic, antihypertensive, antibacterial, anticancer, anti-inflammatory, antipyretic, antifungal, antiprotozoal, antipyretic, renovascularvasodilatory effects, antiplasmodial(110)(111)(112)(113) and antimalarial (114)(115). Cryptolepine is the key pharmaco-active alkaloid present in *C. sanguinolenta* attributed to these pharmacological effects (116)(117)(118)(119)(120). The aqueous *C. sanguinolenta* extract roots, with no toxicity reported, is used as a daily tonic in Ghana (Africa) for controlling malaria (121).

In 1931, another alkaloid called indoloquinoline, the roots of *C. sanguinolenta* were used to isolate the drug cryptolepine.(122)(115), and to date, these are extensively been used in Ghana and Nigeria (123)(124)(125). Cryptolepine is a linearly bonded alkaloid that has the chemical structure of an indolo (3, 2-b) quinoline ring.(126), whereas isocryptolepine is an angularly bonded alkaloid having an indolo (3, 2-c) quinoline moiety. Two independent study groups(127)(128) testified the occurrence of related alkaloids-namely isocryptolepine(129) and cryptosanguinolentine respectively(127)(130). Cryptolepine is known to induce generation of beta cells of pancreas. Moreover, reversal of diabetes induce increase in levels of cholesterol, triglyceride, low density lipo-proteins and reduced high density lipoprotein(131).

Thus, *C. sanguinolenta* serves as a potential medicinal plant with medicinal properties in the healing of an array of diseases from antimalarial to cancer therapies (115).

6.7.3. Piper umbellactam

Piper umbellactum, is obtained from the plant *Piper umbellactum* Linn. The Indian, Indonesian, and Malaysian tropical rainforests, as well as other Asian and American tropic regions, are home to this plant (115). This adventitious shrub has broad, round branches with a height range of 1.5 to 4 meters. The branches of *P. umbellatum* yielded three alkaloids: piperumbellactam A, piperumbellactam B, and piperumbellactam C. All three of these derivatives demonstrated a moderate inhibition of alpha-glucosidase enzyme, with IC50 values of 98.07 0.44, 43.80 0.56, and 29.64 0.46, respectively (116). Dietary polysaccharides were hydrolyzed by digestive enzymes, which raised blood glucose levels. Postprandial hyperglycemia is caused by the hydrolytic breakdown of oligosaccharides into bioavailable monosaccharides. The α-Glucosidase enzyme, a member of the hydrolase family, is produced by intestinal brush border cells and is responsible for this phenomenon. Inhibiting the digestive enzymes with phytomolecules is extensively practiced methods for decreasing postprandial blood glucose levels (117). To prevent the creation of the enzyme-substrate complex and thus decrease enzyme activity, alkaloids like piperumbellactum may bind to the active locations of these digestive enzymes. Recent research demonstrated that seven secondary metabolites were produced as a result of multiple chromatographic steps performed *on P. umbellatum* branches using a concentration of n-BuOH fraction (118)

6.7.4. Catharanthine, Vindoline and Vindolinine

Apocynaceous plants, such as *Rauvolfiaserpentina* and others, have long piqued the curiosity of the scientific community since they may provide a wealth of potentially life-saving medications (132) catechin, a terpeneindole alkaloid, is derived from the medicinal herbs *Catharanthus roseus* and *Tabernaemontana divaricata*. There is a lack of understanding about the biochemical pathway that converts strictosidine to catharanthine. Vinblastine is synthesized from two separate compounds, one of which being catharanthine (133).

Vindoline is obtained from *C.roseus*, amongst the most investigated therapeutic plants. Clinically relevant anti-cancer drugs vinblastine and vincristine have vindoline as biosynthetic and synthetic precursors (134) (135). *Catharanthus roseus*, the most common and well-studied plant in Madagascar, is home to vindolinine, one of the most significant monomeric alkaloids (136). *Catharanthus roseus*, *R. serpentina*, *R. sellowii*, *Leuconotiseugenifolius*, *Tabernaemontanadivaricata,* and others in the Apocynaceae family are some of the most prevalent sources of the alkaloids. These medicinal alkaloids are indole alkaloids, with a tryptamine moiety obtained from tryptophan and a terpenoid constituent obtained from the secologanin. Deglucosylatedstrictosidine may be used to produce indole alkaloids like catharanthine and vindoline. Misra et al. (1996) (137) compiled the results of many studies showing this to be the case. The formation of indole alkaloids by plants is a multi-enzyme process(137). The enzymes responsible for producing the indole alkaloids in *C.roseus* have been intensively analyzed(137). Vinblastine, a dimericindole alkaloid, is produced when vindoline is reacted with catharanthine through horseradish peroxidase.

Because of its extensive record of usage in the cure of diabetes, *C. roseus* was included in Canadian research exploring insulin substitutes. While there has been no evidence of sensitivity from any plant extract, random blood observations have shown that extracts from specific leaves accumulate alkaloids, which might cause a decline in the quantity of wbcs (granulocytes in particular). Researchers in the 1960s discovered vinblastine as well as vincristine from the plant's indolic alkaloid chemical combination of more than 70 after this finding prompted in vitro tests with leukemia cells. Svodoba in Lilly discovered that these extracts were effective against P-1534 leukemia in animals. *C.roseus* is used conventionally to cure diabetes in Asia and Africa. However, only trials using crude extracts have proven the plant's antidiabetic activity(138)(139).

Tiong et al. (2013) observed that the dichloromethane leaf extract of *C. roseus* inhibited the development of diabetes by enhancing glucose uptake by pancreatic (-TC6) as well as myoblastic cells (C2C12) (76). Four alkaloids were ontained from a dichloromethane leaf extract of this plant that stimulated glucose assimilation in pancreatic -TC6 cells and myoblast C2C12 (140).

Catharanthusroseus alkaloids, such as catharanthine, vindoline, and vindolinine, were reported reduce blood sugar in both normal and streptozotocin stimulated diabetic rats. Normal and diabetic rabbits have decreased blood glucose levels when given leeurosine, vindoline, vindolinine, or catharanthine (83). *Catharanthusroseus* contains the dimeric alkaloids vincristine and vinblastine, which have been successfully utilized to cure diabetes in many nations across the planet. According to studies (141) of Chattopadhyay, 1999, an alcholic extract (ethanol) of *C. roseus* leaves have significant lipid lowering and antidiabetic effects in a separate study. Because adipose tissue reacts to insulin to fulfill the body's sugar demands, free fatty acid levels increase when nutritional consumption exceeds the capability of fat cells to hold additional calories. This further reduces the already low oxygen levels in adipose tissue. The enhanced membrane localization of transporters like GLUT4 and the IRS-1/phosphatidylinositol kinase/AKT pathway all work together to facilitate glucose absorption. However, this process is inhibited by the presence of free fatty acids. In this way, high triglyceride levels influence glucose metabolism by fostering the growth of subclinical insulin resistance and cell dysfunction (142) While the addition of *C. roseus* ethanolic extract to atorvastatin did not alter the effectiveness of either drug against hyperlipidemia, adding it to sitagliptin significantly increased its effectiveness against diabetes (143) .

6.7.5. Betaine, achyranthine

The Amaranthaceae family is one of several plant families that might legitimately claim the title of "world's most numerous and diverse plant family." Many plant species in the family Amaranthaceae have anti-diabetic effects. In the following paragraphs, we'll have a more in-depth look at some of these species. *Achyranthes aspera* (144), *Amaranthus caudates* (145), *Alternanthera halimifolia*, *Chenopodium ambrosioides* (144), and *Gossypium halimifolium* (145) etc. All three of these compounds—betaine and achyranthine may be found in plants belonging to the genus Amaranthaceae. These groups of alkaloids are all significant in their way. Three different compounds have been isolated from the *A. aspera* plant. The compounds in concern are achyranthine, and betaine. Each of these molecules has a role in the digestion and use of carbohydrates (146).

The effectiveness of an ethanolic extract of *A. aspera* seeds as an anti-diabetic medication was determined by administering the extract to rats with diabetes induced by streptozocin (STZ) (300-600 mg/kg). The seeds of *A. aspera* were extracted in ethanol and administered to the rats. To determine whether the extract worked as planned, we conducted this experiment. The patient's blood glucose level drops more than it would have with the standard drug glibenclamide after 28 days of treatment with the extract by oral administration (147). Administering the plant extract, which also reduces the overall amount of glucose in the blood, may treat diabetes in mice induced by exposure to alloxan. This, in turn, protects the animals from the potentially negative outcomes that may have resulted from the oxidative stress they endured. Triterpenoidoleanolic acid stimulates insulin secretion in rat islets as well as INS-1 832/13 cells. In contrast, it does not cause an increase in cAMP or intracellular Ca2+ ion concentrations. As a matter of fact, it has the opposite effect. Glucose levels may be lowered by boosting the receptor's sensitivity to the hormone through the usage of oleanolic acid due to its capacity to block beta-glucosidase while concurrently activating TGR5 G-protein receptors. This is because oleanolic acid has these features (148).

Animals were given STZ, a medication that causes diabetes in animals, and an alcoholic extract of A. *aspera* was for the antidiabetic effects effect. Diabetes was triggered by the application of streptozotocin (STZ) to the rats. *A. aspera* aqueous extract drastically reduced the animal's blood glucose levels after administration, prompting researchers to conclude that the drug was responsible for the observed effect (144). Researchers conducted an electrophoretic examination on *A. aspera* plant seeds to prove without a shadow of a doubt that the proteinaceous amylase inhibitor was obtained from inside those seeds. It was discovered that the created beta-amylase inhibitor could withstand both heat and proteolysis (149). To test *A. aspera*'s anti-diabetic potential, alloxan-induced diabetic rats were given an ethanolic extract. At a dosage of 400 mg per kg, the ethanolic extract considerably decreased pancreatic BSL in the study individuals, demonstrating 95% anti-diabetic effectiveness. In this case, the drug did the trick.This objective was greatly helped by the fact that the extract could be consumed orally (150). To gauge the efficacy of the treatment for diabetes, the inhibitory action of amylase measured in vitro glucose absorption experiments. It was done so that the findings could be compared to those of the clinical studies. The goal was to evaluate the efficacy of the treatment. The methanolic extract showed -amylase inhibitory potential of 29.75% to 71.97% when tested at doses stretching from 5 to 25 mg per ml (151). After a week of treatment, the anti-diabetic effects of *A. aspera* tea are most noticeable at a fasting blood glucose reading of around 229.4 mg per dl.Testing the patients' blood sugar levels before and after they drank the tea allowed us to reach this conclusion (152).

6.7.6. Aegeline, marmesin and marmelosin

Aegle marmelos leaves contain several bioactive compounds, including aegelin, lupeol, rutin, marmesinin, b-sitosterol, marmelin etc. The active ingredients aegelin, beta- and delta-sitosterol, marmalosin, and marmesin are responsible for the drug's diabetic-lowering effects(153). Diabetic rats showed substantial improvements in blood sugar levels after being orally fed an ethanolic extract of *A. marmelos* leaves. Reducing amylase and intestinal disaccharidase enzyme activity reflected a reduction in carbohydrate breakdown and absorption as a consequence of increased insulin action to absorb glucose in peripheral tissue (154). Upadhya et al. (2004) treated diabetic rats with an extract of *A. marmelos* leaf at a dosage of 500 milligrammes per kilogramme(155) to evaluate the hypoglycemic and antioxidant effects of this extract. Male albino rats were arbitrarily split into three groups in order to investigate the impact of *A. marmelos* extract on the onset and progression of diabetes (Group I, II and III). After four weeks, the mice in Group III exhibited lower blood sugar levels than the mice in Group II (155). Maqbool et al., 2019, suggest that the effects of *A. marmelos* on blood glucose and weight are comparable to those of insulin (156). The leaf juice of *A. marmelos* is useful in treating diabetic mellitus, as shown by recent studies, thanks to the bioactive components aegelin 2, scopoletin, and sitosterol(156).

6.7.7. Calystegine-B

A class of alkaloids known as calystegines is obtained mostly from Solanaceae plants. The nortropane skeleton of this class of alkaloid has a number of hydroxy groups in various locations. The calystegine B-group is composed of the tetrahydroxycalystegines derivatives (157) Foods from the Solanaceae family, including potatoes, peppers and paprika were discovered to contain high concentrations of calystegines(158). A powerful regulator of glucosidases and R-galactosidases among them is calystegine B2. The inhibition of rice R-glucosidase is essential for this glucoside's efficacy. Calystegine B2's glycosidase inhibitory action was considerably decreased by the addition of two glucosyl or galactosyl substituent residues. R-glucosidase inhibitors, which suppress intestinal R-glucosidases, can be employed to manage DM by reducing the activity of the internal insulin-producing pancreas and the hyperglycemic effects of food (159). The α-Glucosidase inhibitors, such cyalystegine B2, postpone but do not stop the process of ingested carbs absorption. Consequently, there is a decrease in peaks of insulin and glucose levels of postprandial.

6.7.8 Jatrorrhizine, Magnoflorine, Palmatine

Jatrorrhizine, magnoflorine, and palmatine exhibit anti-diabetic effects through processes that release insulin or imitate insulin, hence reducing postprandial hyperglycemia (160). They are mostly present in *Tinospora sp*. By boosting insulin secretion, jatrorrhizine, and magnoflorine have an in vitro hypoglycemic impact on RINm5F cells at concentrations of 20 μg per ml in each, and they can prevent hepatic gluconeogenesis in rat hepatocytes at a dose-dependent manner with the concentrations 5-80 μg/ml (161). These three alkaloids were found to increase insulin discharge and decrease hepatic gluconeogenesis *in vivo* glucose-laden rats at a concentration of 40 mg per kg (161). Inhibition of α-glucosidase and aldose reductase demonstrated the potential of jatrorrhizine, palmatine, and magnoflorine as hypoglycemic agents.

Jatrorrhizine, palmatine, and magnoflorine with an IC_{50} of 3.23 μg per ml, 3.45 μg/ml, and 1.25 μg/ml have an inhibitory effect against Lens Aldose reductase, which was pooled from Wistar rats (162). In another experiment, jatrorrhizine, palmatine, and magnoflorine inhibit α-glucosidase with an in vitro IC_{50} of 36.25 μg per ml, 23.46 μg per ml, and 9.8 μg per ml respectively (153). In HepG2 cells, jatrorrhizine and palmatine demonstrated in vitro anti-diabetic action through a dose-dependent glucose-lowering impact, with the effect beginning to manifest at a very low concentration (0.6 μM). Jatrorrhizine at a dose of 100 mg per kg led to a reduction in body weight, better glucose tolerance, and increased insulin sensitivity in a hyperlipidemia mouse model (163). By activating the Akt/AMPK/eNOS signaling pathway, lowering IL-1β and tumor necrosis factor α (TNF-α), jatrorrhizine (at 50, 100 mg/kg dose) protected diabetic rats and recovered vascular endothelial dysfunction in the blood vessels (164). By enhancing the expression of insulin receptor substrate 2, phosphoinositide-3-kinase regulatory subunit 1, phosphorylated protein kinase B, phospho-AMP-activated protein kinase, and glucose transporter 4/1/2, jatrorrhizine controlled glucose absorption and utilization and decreased insulin resistance (Zhu et al., 2018)(165). Magnoflorine substantially reduced ONOO (-)-mediated tyrosine nitration in a dose-dependent way and showed remarkable inhibitory action against protein tyrosine phosphatase 1B, according to Lineweaver-Burk and Dixon's plots (166). Figure 6.3 illustrates selected antidiabetic activity of *Tinospora* alkaloids.

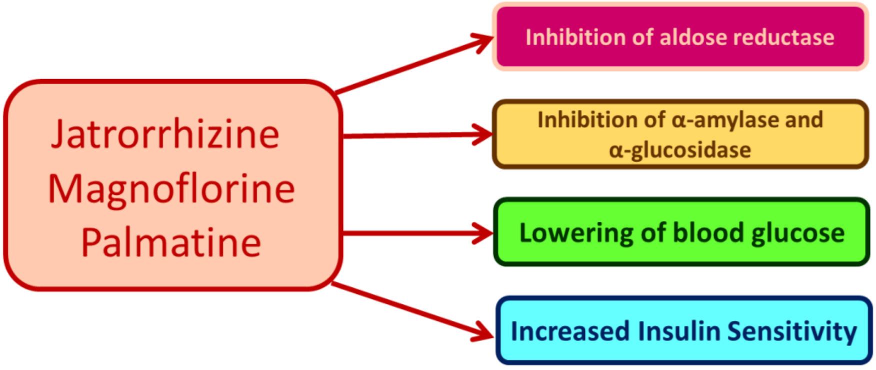


Figure 6.3: Selected *Tinospora* alkaloids and their mode of antidiabetic action

6.8 Mode of action of alkaloidalphytoconstituents

6.8.1 Inhibition of Advanced Glycation End Products

Advanced Glycation End Products (AGEs) are a hazardous class of chemicals that are produced by nonenzymatic interactions between the amino moiety in biomolecules, and nucleic acids and the carbonyl moiety in reducing sugars. (174). These compounds can be formed endogenously within the tissues or exogenously by dietary sources under normal or pathological conditions through direct breakdown of the Schiff base, modification by dicarbonyl compounds, and interactions between AGE precursor molecules and Amadori products (175). There is direct nexus found between AGEs and different human diseases related to hyperglycemia, cardiovascular diseases, liver and gastrointestinal disorders, neurodegenerative diseases, development of aging-related conditions, and even cancer. This is actually owing to the capacity of AGEs to produce reactive oxygen and nitrogen species, which leads to altered protein functions, cellular dysfunction, apoptosis, and consequently multi-tissue or organ failure (176).

Several phytochemicals have shown prospective results in the inhibition of the formation of AGEs. These have beenshown to be relatively safe for human intake, unlike their synthetic counterparts. Alkaloids from *Ocoteaparanapiacabensis* leaves inhibits AGEs formation. These are benzylisoquinoline alkaloids, viz 7-hydroxy-1-(4′-hydroxy benzyl)-6-methoxy-2,2-N, 6,7-dihydroxy-1-(4′-hydroxy benzyl)-2, 2-N, N-dimethyl-1,2,3,4-tetrahydroisoquinoline, N-methylhigenamine, and magnocurarine, which have shown the potential to inhibit the AGEs formation (177). Ethanolic fractions of *Melissa officinalis*, have shown strongly inhibits AGE generation in the later stages of the process of glycation(178). Consumption of green tea and coffee significantly reduces the accumulation of AGEs, formation of dicarbonyl compounds and inhibits protein glycation. (179). Other plant-based alkaloids include Leonurin from *Herbaleonuri*(180), and Berberine from *Rhizomacoptidis*(181) also possess properties to inhibit AGEs formation. So, various mechanisms are associated in the process of inhibition of AGEs by these phytochemicals such as shielding amino moieties, reduction or removal of active carbonyl moieties, scavenging free radicals, etc.

6.8.2. Inhibition of digestive enzymes like amylase and glucosidase

Inhibition of digestive enzymes by different phytoconstituents is a very effective way for the treatment of T2D. The primary enzymes like α-amylase and α-glucosidasecatalyze the hydrolysis of various dietary polysaccharides, thereby increasing blood glucose level. (45). There are several plant alkaloids extracted which showed efficiency in binding with the competitive or non-competitive sites of these digestive enzymes which subsequently reduces the hydrolysis of polysaccharides into glucose.

The extracts of *Combretum dolichopetalum* root have proved promising results for treatment of diabetes. The constituents include two alkaloids, phenolic acidsand terpenoids showed significant antidiabetic potential compared to glibenclamide (standard drug) when tested in diabetic mice models (182).

Quinazoline alkaloids, vasicinol, and vasicine from leaf extracts of *Adhatodavasica* competitively inhibit α-glucosidase, Ki (183 and 82 μM) with IC_{50} (250 and 125 μM), respectively (81). Palmatine, an isoquinoline alkaloid hinders α-amylase and α-glucosidase actions (183). Oriciacridone C, Oriciacridone F, and 1,3,5-trihydroxy-4- (c,c-dimethylallyl)-acridone extracted from the bark of

Veprisglaberrima exhibited an inhibitory effect of α-glucosidase (56, 34.05, and 17 mM respectively) (184).

Also, Carbazole alkaloids extracted from *Murrayakoenigii* viz., O-methyl mahanine, O-methyl mukonal, mahanine, bisgerayafoline D, bismahanimbinol, and bispyrayafoline, show inhibition of α-glucosidase activity (IC_{50} = 46.1, 77.5, 21.4, 38.7, 51.3, and 29.1 μM resp.) (185). Another alkaloid from the same plant, mahanimbine exhibited α-amylase and α-glucosidase attenuating activities (186).

Piperumbellactam extracted from the branches of *P.umbellatum* viz. show the α-glucosidase inhibitory properties (170).The steroidal alkaloids from *Sarcococcasaligna*, viz. holaphylline and sarcovagine D exhibited a noticeable lessening of blood glucose levels in diabetic rats induced by streptozotocin(187). Koenidine and O-methylmurrayamine A minimized the level of blood glucose by roughly 22.5% and 24.6%, respectively, during 0–5 hours in the streptozotocin-triggered diabetic rat compared to metformin (25.9%) (188). Another indole alkaloid, Vindogentianine from *C.roseus* also displays the attenuation of α-amylase and α-glucosidase enzymes inferring its healing capacity against DM(77)

6.8.3. Improvement of glucose uptake

Enhancement of glucose uptake is another reliable and promising strategy for the reatment of DM by the translocation of glucose transporter 4 (189). Several phyto-alkaloids have enhanced glucose absorption. Carbazole-based alkaloids like 8,8″-biskoenigine, koenimbine, O-methylmurrayamine A, koenidine, mahanimbine, and murrayazoline, extracted from *Murrayakoenigii* , when administered to L6-GLUT4myc rat myoblast cell line and reported the ability of glucose uptake by 1.41, 1.34, 1.42, and 1.26 fold, respectively(188).

Tecomine extracted from *Tecomastans* was reported to induce the rate of glucose absorption in rat adipocytes with an EC_{50} of 6.79 $\times 10^{-9}$ M(95). Vindolicine III isolated from *C.roseus* showed the ability to increase both glucose and carotenoid absorption in β-TC6 and C2C12 cells, thus proving advantageous in the management of high blood sugar (76). Vindogentianine also induces a noteworthy rise in glucose absorption in the TC6 pancreas and C2C12 muscle cells (77).

Alkaloids trigger the translocation of the GLUT4 transporter by triggering AMP-activated protein kinase through allosteric modulation. Since it controls the glucose transporter and serves as the cell's fuel sensor, AMP-activated protein kinase is a vital enzyme. It induces glucose absorption and regulates insulin secretion. The detailed investigation suggested that alkaloids trigger the GLUT4 translocation through the the AKT (Ser473)-dependent signaling path (190). Isoquinoline alkaloids like protoberberines also showed increased glucose absorption by articulating more insulin receptors and inhibiting AMPK, PTP1B, and DPP-IV. Trigonelline is also reported to increase the GK, G6Pase quotient in the liver. Aegeline, enhance GLUT-4 translocation and boost intracellular Ca^{2+} signaling (83). Piperidine alkaloids also showed significant potential in the management of diabetes by increasing basal glucose absorption, decreasing blood glucose levels, enhancing insulin synthesis, and triggering AMPK and PPAR-γ, thus regulating T2D(142).

6.8.4. Increase in insulin secretion

Glucagon and insulin are secreted by the pancreatic cells and deploy antagonistic impacts on peripheral organs to regulate blood sugar. By increasing muscle glucose uptake, reducing hepatic glucose synthesis, and decreasing lipolysis, insulin reduces blood sugar levels. Glucagon raises blood sugar levels by increasing the rate of gluconeogenesis and lipolysis (191). In a normal scenario, glucose-dependent insulin tropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) stimulate the secretion of insulin in response to consumed meals (192). GLP-1 is synthesized by the proglucagon gene in the L-cells of the upper gastrointestinal tract. GLP-1 stimulates the synthesis and secretion of insulin, decreases glucagon levels, diminishes appetite, and improves islet-cell differentiation in pancreas in response to ingested meals. GIP is another glycoprotein, synthesized by the gip gene in the K cells, found in the upper gastrointestinal tract that aids glucose metabolism by enhancing the rate of insulin release. GIP is also associated in the metabolism of fat cells , regulation of fatty acid production, boosts lipid–protein activity, and promotes β-cell proliferation thus increasing cellular growth (193). Due to DPP-4 activity, GIP and GLP-1 have very short half-lives ranging from 4 mins and 1-2 mins respectively. Thus, suppression of DPP-4 can restore the equilibrium between insulin and glucagon (194).

Numerous studies have already shown that inhibiting DPP-4 increases β-cell mass, capacity, and shape through the generation of incretin, which influences the ongoing absorption of insulin after meals to lessen blood sugar levels. (195). The quinolizidine alkaloids, viz.lupanine, 13-hydoxy-lupanine, and 17-oxo-lupanine, isolated from *Lupinus* sp., can stimulate the release of insulin in a glucose-dependent way (196). Lupanine boosts the activation of insulin-releasing genes and inhibits ATP-sensitive potassium channels to promote insulin production (197). Palmatine and berberine also reported antidiabetic efficiency by inhibiting DPP-4 with IC_{50} of 8.7, and 13.3 μM, respectively (183).

6.8.5. Inhibition of aldose reductase and protein tyrosine phosphatase -1B

Aldose reductase (AR), is an enzyme in the sorbitol-aldose reductase pathway (polyol pathway), catalyzes the reduction of glucose to sorbitol, resulting in towering accretion of intracellular reactive oxygen species in variety of tissues affected by DM including eyes, heart, kidneys, and neurons.. Sorbitol poorly penetrates through the cell membrane and also metabolized slowly, thus increasing intracellular accumulation of sorbitol and fructose (its metabolite), leading to osmotic swelling and finally hyperglycemia. In normal glycemia, it helps in the detoxification of lethal aldehyde molecules in extrahepatic tissue, osmoregulation in the kidney, reduction of catecholamines and steroids, and production of fructose for the maturation of sperm. But during hyperglycemia, cataractogenesis occurs due to exorbitant sorbitol levels and osmotic stress. In addition, it can also trigger glycative stress and increase the production of ROS by binding with the receptors. AR inhibitors are used to delay the onset of such complications (198)(83).

In the last few years, many anti-diabetic molecules with antioxidant and AR inhibitory functions have been reported. Alkaloids like berberine sulfate , berberine chloride, berberine iodide, palmatine iodide, and palmatine sulfate, which are extracted from the roots of *Coptis japonica* demonstrated anti-AR activity with an IC_{50} ranging from 13.45 to 51.78 nM (199). Isoquinoline alkaloids like magnoflorine, palmatine,andjatrorrhizine, isolated from the stem of *Tinosporacordifolia* also inhibited the male Wistar rats lens AR with an IC_{50} of 1.25, 3.45,and 3.23 µg per mL, respectively (162). Epiberberine, coptisine, and groenlandicine, extracted from *Coptischinensis* rhizome, also reported anti-AR activity with an IC_{50} of 168.10, 187.27, and 154.19 µM respectively. Detailed investigations reported that the dioxymethylene group and its oxidized form in the A and D rings of protoberberine alkaloids are accountable for the anti-AR activity (198).

Protein tyrosine phosphatase 1B (PTP-1B) is another enzyme that is ubiquitously expressed in several tissues like the liver, adipose tissue, skeletal muscle, brain, etc., and localized at the ER. PTP-1B is associated with several signal transduction pathways for its tyrosine phosphatase activity (200). PTP-1B is a negative regulator of the insulin and leptin signaling pathways, as it dephosphorylates the tyrosine residue of the insulin receptor and suppresses the insulin signaling pathway. PTP1B may thus represent a potential therapeutic target for Type II diabetes. In vivo, PTP-1B interacts with the insulin receptor PTK as well as the insulin receptor and insulin receptor substrate 1 (IRS1).Thus, inhibition of PTP-1B lead towards the escalation of insulin receptor and insulin receptor substrates 1 and 2 phosphorylation, thus triggering an enhancement in glucose uptake (201). Many phyto-alkaloids already showed their ability to inhibit PTP-1B. Protoberberine alkaloids extracted from *Coptischinensis*Franch also showed a significant anti-PTP-1B activity Magnoflorine and coptisine showed a non-competitive type of inhibition while berberine and epiberberine showed a mixed type of inhibition against PTP-1B (166). Using p-nitrophenyl phosphate as the substrate, canthinone alkaloids such as 3,4-dimethyl- canthin-5,6-dione, 4-ethyl-3-methyl-canthin-5,6- dione, eurycomine E, 5-methoxy-canthin-6-one, picrasidine L, and 5- acethoxy-canthin-6-one also showed inhibitory action against PTP-1B with an IC_{50} of 24.72, 27.83, 19.18, 20.30, 19.80 and 28.89 µM, respectively (202). Picrasidine L repressed PTP-1B in a competitive mode, but the others did not(202). Vindogentianine isolated from *C.roseus* also showed anti-PTP-1B activity having an IC_{50} of 15.28 µg per mL (77).

6.9 Conclusion

Diabetes, mainly T2D is one of the largest global health emergencies of this century and leading causes of mortality, followed by cardiovascular diseases, respiratory diseases, and cancer. A chronic, systemic metabolic disorder like T2D or DM can never be cured, it can only be managed or controlled by applying proper medications. To manage the ever-increasing epidemicity of this disease, researches are being conducted throughout the world to explore new anti-diabetic agents.

The present therapies for the management of DM are commonly confined to the use of man-made or allopathic anti-diabetic medicines. Though these medications serve the purpose well, but they exhibit numerous long-term side effects including, hepatitis, obesity, cardiovascular risk, gastrointestinal disorders, severe hypoglycemia, etc. Due to these adverse effects of synthetic drugs, scientists have inclined more toward evaluating new plant-based products that have anti-diabetic properties. Although phyto-constituents are easily obtainable and inexpensive, yet they need to be properly isolated, purified, evaluated and finally put to clinical trials before marketing them as drugs.

Different plant-based metabolites, especially alkaloids that work effectively against infections and support healthcare solutions with minimal side effects. The phytoconstituents having active agents in controlling DM should be further studied, investigated, and put through adequate clinical trials to maximize their potential as an antidiabetic drug so that these can be transformed from theoretical to practical use replacing synthetic medications.

References

1. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med [Internet]. 2020 Oct 4;10(04):174–88. Available from: http://www.thieme-connect.de/DOI/DOI?10.4103/ajm.ajm_53_20
2. Yoon J-W, Jun H-S. Autoimmune Destruction of Pancreatic β Cells. Am J Ther [Internet]. 2005 Nov;12(6):580–91. Available from: https://journals.lww.com/00045391-200511000-00015
3. Freeman AM, Pennings N. Insulin Resistance [Internet]. StatPearls. 2022. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30835074
4. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care [Internet]. 2009 Jan 1;32(Supplement_1):S62–7. Available from: https://diabetesjournals.org/care/article/32/Supplement_1/S62/25047/Diagnosis-and-Classification-of-Diabetes-Mellitus
5. Gougeon R. Insulin Resistance of Protein Metabolism in Type 2 Diabetes and Impact on Dietary Needs: A Review. Can J Diabetes [Internet]. 2013 Apr;37(2):115–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1499267113000087
6. Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. Diabetes Res Clin Pract [Internet]. 2011 Aug;93:S52–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822711700146
7. Rahelić D. [7TH EDITION OF IDF DIABETES ATLAS--CALL FOR IMMEDIATE ACTION]. Lijec Vjesn [Internet]. 2016;138(1–2):57–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27290816
8. Sapra A, Bhandari P. Diabetes Mellitus [Internet]. StatPearls. 2022. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30644346
9. Safiri S, Karamzad N, Kaufman JS, Bell AW, Nejadghaderi SA, Sullman MJM, et al. Prevalence, Deaths and Disability-Adjusted-Life-Years (DALYs) Due to Type 2 Diabetes and Its Attributable Risk Factors in 204 Countries and Territories, 1990-2019: Results From the Global Burden of Disease Study 2019. Front Endocrinol (Lausanne) [Internet]. 2022 Feb 25;13. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2022.838027/full
10. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health [Internet]. 2019;10(1):107. Available from: https://www.atlantis-press.com/article/125921499
11. Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev [Internet]. 1999 May;15(3):205–18. Available from: https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1520-7560(199905/06)15:3%3C205::AID-DMRR29%3E3.0.CO;2-O
12. Begum S, Afroz R, Khanam Q, Khanom A, Choudhury T. Diabetes Mellitus and Gestational Diabetes Mellitus. J Paediatr Surg Bangladesh [Internet]. 2015 Jun 30;5(1):30–5. Available from: https://www.banglajol.info/index.php/JPSB/article/view/23887
13. Arredondo A, Reyes G. Health Disparities from Economic Burden of Diabetes in Middle-income Countries: Evidence from México. Folli F, editor. PLoS One [Internet]. 2013 Jul 12;8(7):e68443. Available from: https://dx.plos.org/10.1371/journal.pone.0068443
14. Gorus FK, Weets I, Pipeleers DG. - to: T. J. Wilkin (2001) The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. Diabetologia 44: 914–921. Diabetologia [Internet]. 2002 Feb;45(2):288–9. Available from: http://link.springer.com/10.1007/s00125-001-0724-2
15. Hansen MP. Type 1 diabetes and polyglandular autoimmune syndrome: A review. World J Diabetes [Internet]. 2015;6(1):67. Available from: http://www.wjgnet.com/1948-9358/full/v6/i1/67.htm
16. Haftu H, Gebrearegay H, Berhane A. Malnutrition-Modulated Diabetes Mellitus in Children, Rare Disease with Atypical Presentation: Case Report. Diabetes, Metab Syndr Obes Targets Ther [Internet]. 2020 Aug;Volume 13:3069–74. Available from: https://www.dovepress.com/malnutrition-modulated-diabetes-mellitus-in-children-rare-disease-with-peer-reviewed-article-DMSO
17. Shukla, P., Singh, S., Saxena, N., & Tripathi GK. Anti-Diabetics: A Critical Overview. Res Explor. 2018;VI(17):113–20.
18. Hills AP, Arena R, Khunti K, Yajnik CS, Jayawardena R, Henry CJ, et al. Epidemiology and determinants of type 2 diabetes in south Asia. Lancet Diabetes Endocrinol [Internet]. 2018 Dec;6(12):966–78. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213858718302043
19. Egan AM, Dinneen SF. What is diabetes? Medicine (Baltimore) [Internet]. 2022 Oct;50(10):615–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1357303922001797
20. Bianchi C, de Gennaro G, Romano M, Battini L, Aragona M, Corfini M, et al. Early vs. standard screening and treatment of gestational diabetes in high-risk women – An attempt to determine relative advantages and disadvantages. Nutr Metab Cardiovasc Dis [Internet]. 2019 Jun;29(6):598–603. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0939475319300602
21. Langer O, Yogev Y, Most O, Xenakis EMJ. Gestational diabetes: The consequences of not treating. Am J Obstet Gynecol [Internet]. 2005 Apr;192(4):989–97. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002937804019970
22. Giuffrida FMA, Reis AF. Genetic and clinical characteristics of maturity-onset diabetes of the young. Diabetes, Obes Metab [Internet]. 2005 Jul;7(4):318–26. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1463-1326.2004.00399.x
23. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol [Internet]. 2014 Jan;2(1):56–64. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213858713701128
24. King H, Aubert RE, Herman WH. Global Burden of Diabetes, 1995–2025: Prevalence, numerical estimates, and projections. Diabetes Care [Internet]. 1998 Sep 1;21(9):1414–31. Available from: https://diabetesjournals.org/care/article/21/9/1414/22253/Global-Burden-of-Diabetes-1995-2025-Prevalence
25. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia [Internet]. 2019 Jan 31;62(1):3–16. Available from: http://link.springer.com/10.1007/s00125-018-4711-2
26. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nat Rev Endocrinol [Internet]. 2016 Oct 8;12(10):616–22. Available from:

http://www.nature.com/articles/nrendo.2016.105
27. Mensah GA, Mayosi BM. The 2011 United Nations High-Level Meeting on Non-Communicable Diseases: The Africa agenda calls for a 5-by-5 approach. South African Med J [Internet]. 2012 Nov 8;103(2):77. Available from: http://www.samj.org.za/index.php/samj/article/view/6347
28. Second Joint Mission of the United Nations Interagency Task Force on the Prevention and Control of Noncommunicable Diseases [Internet]. World Health Organization. 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/273712/WHO-NMH-NMA-18.91-eng.pdf
29. Grant P. Management of diabetes in resource-poor settings. Clin Med (Northfield Il) [Internet]. 2013 Feb 18;13(1):27–31. Available from: https://www.rcpjournals.org/lookup/doi/10.7861/clinmedicine.13-1-27
30. Tillin T, Hughes AD, Godsland IF, Whincup P, Forouhi NG, Welsh P, et al. Insulin Resistance and Truncal Obesity as Important Determinants of the Greater Incidence of Diabetes in Indian Asians and African Caribbeans Compared With Europeans. Diabetes Care [Internet]. 2013 Feb 1;36(2):383–93. Available from: https://diabetesjournals.org/care/article/36/2/383/38145/Insulin-Resistance-and-Truncal-Obesity-as
31. Abu-Farha M, Al-Mulla F, Thanaraj TA, Kavalakatt S, Ali H, Abdul Ghani M, et al. Impact of Diabetes in Patients Diagnosed With COVID-19. Front Immunol [Internet]. 2020 Dec 1;11. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2020.576818/full
32. Herman WH. The Economic Costs of Diabetes: Is It Time for a New Treatment Paradigm? Diabetes Care [Internet]. 2013 Apr 1;36(4):775–6. Available from: https://diabetesjournals.org/care/article/36/4/775/37878/The-Economic-Costs-of-Diabetes-Is-It-Time-for-a
33. Standl E, Khunti K, Hansen TB, Schnell O. The global epidemics of diabetes in the 21st century: Current situation and perspectives. Eur J Prev Cardiol [Internet]. 2019 Dec 26;26(2_suppl):7–14. Available from: https://academic.oup.com/eurjpc/article/26/2_suppl/7-14/5925429
34. Kazeminezhad B, Taghinejad H, Borji M, Tarjoman A. The Effect of Self-Care on Glycated Hemoglobin and Fasting Blood Sugar Levels on Adolescents with Diabetes. J Compr Pediatr [Internet]. 2018 May 19;9(2). Available from: https://brieflands.com/articles/jcp-62661.html
35. Asif M. The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. J Educ Health Promot [Internet]. 2014;3(1):1. Available from: http://www.jehp.net/text.asp?2014/3/1/1/127541
36. 7. Approaches to Glycemic Treatment. Diabetes Care [Internet]. 2016 Jan 1;39(Supplement_1):S52–9. Available from: https://diabetesjournals.org/care/article/39/Supplement_1/S52/28757/7-Approaches-to-Glycemic-Treatment
37. Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front Endocrinol (Lausanne) [Internet]. 2017 Jan 24;8. Available from: http://journal.frontiersin.org/article/10.3389/fendo.2017.00006/full
38. Carino GP, Mathiowitz E. Oral insulin delivery1Abbreviations: GI, gastrointestinal; IDDM, insulin-dependent diabetes mellitus; IU, international units; NIDDM, non-insulin-dependent diabetes mellitus; PIN, phase inversion nanoencapsulation; ZOT, zona occludens toxin.1. Adv Drug Deliv Rev [Internet]. 1999 Feb;35(2–3):249–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0169409X98000751
39. Sachdeva V, K. Banga A. Microneedles and their Applications. Recent Pat Drug Deliv Formul [Internet]. 2011 May 1;5(2):95–132. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1872-2113&volume=5&issue=2&spage=95
40. Aleppo G, Webb KM. Integrated Insulin Pump and Continuous Glucose Monitoring Technology in Diabetes Care Today: A Perspective of Real-Life Experience With the Minimed™ 670G Hybrid Closed-Loop System. Endocr Pract [Internet]. 2018 Jul;24(7):684–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1530891X20353866
41. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nat Rev Dis Prim [Internet]. 2015 Jul 23;1(1):15019. Available from: https://www.nature.com/articles/nrdp201519
42. Melander A. Kinetics-Effect Relations of Insulin-Releasing Drugs in Patients With Type 2 Diabetes. Diabetes [Internet]. 2004 Dec 1;53(suppl_3):S151–5. Available from: https://diabetesjournals.org/diabetes/article/53/suppl_3/S151/13844/Kinetics-Effect-Relations-of-Insulin-Releasing
43. Foretz M, Guigas B, Viollet B. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. Nat Rev Endocrinol [Internet]. 2019 Oct 22;15(10):569–89. Available from: http://www.nature.com/articles/s41574-019-0242-2
44. McMahon MM. Management of Parenteral Nutrition in Acutely Ill Patients With Hyperglycemia. Nutr Clin Pract [Internet]. 2004 Apr 24;19(2):120–8. Available from: http://doi.wiley.com/10.1177/0115426504019002120
45. Adhikari B. Roles of Alkaloids from Medicinal Plants in the Management of Diabetes Mellitus. Mastinu A, editor. J Chem [Internet]. 2021 Oct 31;2021:1–10. Available from: https://www.hindawi.com/journals/jchem/2021/2691525/
46. Inzucchi SE. Oral Antihyperglycemic Therapy for Type 2 Diabetes. JAMA [Internet]. 2002 Jan 16;287(3):360. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.287.3.360
47. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations. Ann Intern Med [Internet]. 2011 May 3;154(9):602. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-154-9-201105030-00336
48. Chawla G, Chaudhary KK. A complete review of empagliflozin: Most specific and potent SGLT2 inhibitor used for the treatment of type 2 diabetes mellitus. Diabetes Metab Syndr Clin Res Rev [Internet]. 2019 May;13(3):2001–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1871402119301158
49. Dholakia S, Mittal S, Quiroga I, Gilbert J, Sharples EJ, Ploeg RJ, et al. Pancreas Transplantation: Past, Present, Future. Am J Med [Internet]. 2016 Jul;129(7):667–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002934316301991
50. van Lenteren JC. The state of commercial augmentative biological control: plenty of natural enemies, but a frustrating lack of uptake. BioControl [Internet]. 2012 Feb 28;57(1):1–20. Available from: http://link.springer.com/10.1007/s10526-011-9395-1
51. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol [Internet]. 1998 Mar 4;45(3):301–8. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-

2125.1998.00667.x
52. Nutt D, King LA, Saulsbury W, Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. Lancet [Internet]. 2007 Mar;369(9566):1047–53. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673607604644
53. Prasad GP, Babu G, Swamy GK. A contemporary scientific support on role of ancient ayurvedic diet and concepts in diabetes mellitus (madhumeha). Anc Sci Life [Internet]. 2006 Jan;25(3–4):84–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22557212
54. Chang CLT, Lin Y, Bartolome AP, Chen Y-C, Chiu S-C, Yang W-C. Herbal Therapies for Type 2 Diabetes Mellitus: Chemistry, Biology, and Potential Application of Selected Plants and Compounds. Evidence-Based Complement Altern Med [Internet]. 2013;2013:1–33. Available from: http://www.hindawi.com/journals/ecam/2013/378657/
55. Li W., Zheng H., Bukuru J, De Kimpe N. Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J Ethnopharmacol [Internet]. 2004 May;92(1):1–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874104000315
56. Voglibose: An Alpha Glucosidase Inhibitor. J Clin DIAGNOSTIC Res [Internet]. 2013; Available from: http://www.jcdr.net/article_fulltext.asp?issn=0973-709x&year=2013&volume=7&issue=12&page=3023&issn=0973-709x&id=3838
57. Thulé PM. Mechanisms of current therapies for diabetes mellitus type 2. Adv Physiol Educ [Internet]. 2012 Dec;36(4):275–83. Available from: https://www.physiology.org/doi/10.1152/advan.00094.2012
58. Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-Based Therapies for the Treatment of Type 2 Diabetes: Evaluation of the Risks and Benefits. Diabetes Care [Internet]. 2010 Feb 1;33(2):428–33. Available from: https://diabetesjournals.org/care/article/33/2/428/27303/Incretin-Based-Therapies-for-the-Treatment-of-Type
59. Jones D. Diabetes field cautiously upbeat despite possible setback for leading SGLT2 inhibitor. Nat Rev Drug Discov [Internet]. 2011 Sep;10(9):645–6. Available from: http://www.nature.com/articles/nrd3546
60. Tahrani AA, Askwith T, Stevens MJ. Emerging drugs for diabetic neuropathy. Expert Opin Emerg Drugs [Internet]. 2010 Dec 27;15(4):661–83. Available from: http://www.tandfonline.com/doi/full/10.1517/14728214.2010.512610
61. Chong MS, Hester J. Diabetic Painful Neuropathy. Drugs [Internet]. 2007;67(4):569–85. Available from: http://link.springer.com/10.2165/00003495-200767040-00006
62. Arora K, Tomar PC, Mohan V. Diabetic neuropathy: an insight on the transition from synthetic drugs to herbal therapies. J Diabetes Metab Disord [Internet]. 2021 Dec 25;20(2):1773–84. Available from: https://link.springer.com/10.1007/s40200-021-00830-2
63. Dey P, Kundu A, Kumar A, Gupta M, Lee BM, Bhakta T, et al. Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). In: Recent Advances in Natural Products Analysis [Internet]. Elsevier; 2020. p. 505–67. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128164556000159
64. Heinrich M, Mah J, Amirkia V. Alkaloids Used as Medicines: Structural Phytochemistry Meets Biodiversity—An Update and Forward Look. Molecules [Internet]. 2021 Mar 25;26(7):1836. Available from: https://www.mdpi.com/1420-3049/26/7/1836
65. Hussain G, Rasul A, Anwar H, Aziz N, Razzaq A, Wei W, et al. Role of Plant Derived Alkaloids and Their Mechanism in Neurodegenerative Disorders. Int J Biol Sci [Internet]. 2018;14(3):341–57. Available from: http://www.ijbs.com/v14p0341.htm
66. Jerzykiewicz J. [Alkaloids of Solanaceae (nightshade plants)]. Postepy Biochem [Internet]. 2007;53(3):280–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18399356
67. Gangasani JK, Pemmaraju DB, Murthy USN, Rengan AK, Naidu VGM. Chemistry of herbal biomolecules. In: Herbal Biomolecules in Healthcare Applications [Internet]. Elsevier; 2022. p. 63–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323858526000184
68. Fielding BC, da Silva Maia Bezerra Filho C, Ismail NSM, Sousa DP de. Alkaloids: Therapeutic Potential against Human Coronaviruses. Molecules [Internet]. 2020 Nov 24;25(23):5496. Available from: https://www.mdpi.com/1420-3049/25/23/5496
69. Casciaro B, Mangiardi L, Cappiello F, Romeo I, Loffredo MR, Iazzetti A, et al. Naturally-Occurring Alkaloids of Plant Origin as Potential Antimicrobials against Antibiotic-Resistant Infections. Molecules [Internet]. 2020 Aug 9;25(16):3619. Available from: https://www.mdpi.com/1420-3049/25/16/3619
70. Debnath B, Singh WS, Das M, Goswami S, Singh MK, Maiti D, et al. Role of plant alkaloids on human health: A review of biological activities. Mater Today Chem [Internet]. 2018 Sep;9:56–72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2468519418300685
71. Kumar Gp, Khanum F. Neuroprotective potential of phytochemicals. Pharmacogn Rev [Internet]. 2012;6(12):81. Available from: http://www.phcogrev.com/article/2012/6/12/1041030973-784799898
72. Pan S-Y, Zhou S-F, Gao S-H, Yu Z-L, Zhang S-F, Tang M-K, et al. New Perspectives on How to Discover Drugs from Herbal Medicines: CAM's Outstanding Contribution to Modern Therapeutics. Evidence-Based Complement Altern Med [Internet]. 2013;2013:1–25. Available from: http://www.hindawi.com/journals/ecam/2013/627375/
73. Ziegler J, Facchini PJ. Alkaloid Biosynthesis: Metabolism and Trafficking. Annu Rev Plant Biol [Internet]. 2008 Jun 1;59(1):735–69. Available from: https://www.annualreviews.org/doi/10.1146/annurev.arplant.59.032607.092730
74. Chauhan, A., Sharma, P. K., Srivastava, P., Kumar, N., & Dudhe R. Plants Having Potential Antidiabetic Activity: A Review. Der Pharm Lett. 2010;2(3):369–87.
75. Fernando T, Senaviratne P, Siriwardane D, Madushani H. White root disease of Murraya koenigii from Sri Lanka caused by Rigidoporus microporus. J Natl Sci Found Sri Lanka [Internet]. 2016 Sep 28;44(3):347. Available from: https://jnsfsl.sljol.info/article/10.4038/jnsfsr.v44i3.8015/
76. Tiong S, Looi C, Hazni H, Arya A, Paydar M, Wong W, et al. Antidiabetic and Antioxidant Properties of Alkaloids from Catharanthus roseus (L.) G. Don. Molecules [Internet]. 2013 Aug 15;18(8):9770–84. Available from: http://www.mdpi.com/1420-3049/18/8/9770
77. Tiong SH, Looi CY, Arya A, Wong WF, Hazni H, Mustafa MR, et al. Vindogentianine, a hypoglycemic alkaloid from Catharanthus roseus (L.) G. Don (Apocynaceae). Fitoterapia [Internet]. 2015 Apr;102:182–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0367326X15000301
78. Zhang L, Wei G, Liu Y, Zu Y, Gai Q, Yang L. Antihyperglycemic and antioxidant activities of total alkaloids from Catharanthus roseus in streptozotocin-induced diabetic rats. J For Res [Internet]. 2016 Feb;27(1):167–74. Available from: http://link.springer.com/10.1007/s11676-015-0112-2
79. DeFilipps RA, Krupnick GA. The medicinal plants of Myanmar. PhytoKeys [Internet]. 2018 Jun 28;102:1–341. Available from: https://phytokeys.pensoft.net/articles.php?id=24380
80. Claeson UP, Malmfors T, Wikman G, Bruhn JG. Adhatoda vasica: a critical review of ethnopharmacological and toxicological data. J Ethnopharmacol [Internet]. 2000

Sep;72(1–2):1–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874100002257
81. Gao H, Huang Y-N, Gao B, Li P, Inagaki C, Kawabata J. Inhibitory effect on α-glucosidase by Adhatoda vasica Nees. Food Chem [Internet]. 2008 Jun;108(3):965–72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0308814607012587
82. Ge Q, Chen L, Yuan Y, Liu L, Feng F, Lv P, et al. Network Pharmacology-Based Dissection of the Anti-diabetic Mechanism of Lobelia chinensis. Front Pharmacol [Internet]. 2020 Mar 20;11. Available from: https://www.frontiersin.org/article/10.3389/fphar.2020.00347/full
83. Behl T, Gupta A, Albratty M, Najmi A, Meraya AM, Alhazmi HA, et al. Alkaloidal Phytoconstituents for Diabetes Management: Exploring the Unrevealed Potential. Molecules [Internet]. 2022 Sep 9;27(18):5851. Available from: https://www.mdpi.com/1420-3049/27/18/5851
84. Kumar P, Kamle M, Mahato DK, Bora H, Sharma B, Rasane P, et al. Tinospora cordifolia (Giloy): Phytochemistry, Ethnopharmacology, Clinical Application and Conservation Strategies. Curr Pharm Biotechnol [Internet]. 2020 Oct 22;21(12):1165–75. Available from: https://www.eurekaselect.com/181533/article
85. Rasouli H, Yarani R, Pociot F, Popović-Djordjević J. Anti-diabetic potential of plant alkaloids: Revisiting current findings and future perspectives. Pharmacol Res [Internet]. 2020 May;155:104723. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043661819315786
86. Agrawal SS, Naqvi S, Gupta SK, Srivastava S. Prevention and management of diabetic retinopathy in STZ diabetic rats by Tinospora cordifolia and its molecular mechanisms. Food Chem Toxicol [Internet]. 2012 Sep;50(9):3126–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0278691512004103
87. Nikolova A, Vassilev A. A Study on Tribulus Terrestris L. Anatomy and Ecological Adaptation. Biotechnol Biotechnol Equip [Internet]. 2011 Jan 16;25(2):2369–72. Available from: http://www.tandfonline.com/doi/abs/10.5504/BBEQ.2011.0032
88. Cooper EJ, Hudson AL, Parker CA, Morgan NG. Effects of the β-carbolines, harmane and pinoline, on insulin secretion from isolated human islets of Langerhans. Eur J Pharmacol [Internet]. 2003 Dec;482(1–3):189–96. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299903024361
89. Andola HC, Gaira KS, Rawal RS, Rawat MSM, Bhatt ID. Habitat-Dependent Variations in Berberine Content of Berberis asiatica Roxb. ex. DC. in Kumaon, Western Himalaya. Chem Biodivers [Internet]. 2010 Feb;7(2):415–20. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cbdv.200900041
90. Potdar D, Hirwani RR, Dhulap S. Phyto-chemical and pharmacological applications of Berberis aristata. Fitoterapia [Internet]. 2012 Jul;83(5):817–30. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0367326X12001190
91. The Antihyperglycaemic Activity of Berberine Arises from a Decrease of Glucose Absorption. Planta Med [Internet]. 2003 Jul;69(7):632–6. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2003-41121
92. CHEN M-W, CHEN W-R, ZHANG J-M, LONG X-Y, WANG Y-T. Lobelia chinensis: chemical constituents and anticancer activity perspective. Chin J Nat Med [Internet]. 2014 Feb;12(2):103–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1875536414600169
93. SHIBANO M, TSUKAMOTO D, MASUDA A, TANAKA Y, KUSANO G. Two New Pyrrolidine Alkaloids, Radicamines A and B, as Inhibitors of .ALPHA.-Glucosidase from Lobelia chinensis LOUR. Chem Pharm Bull [Internet]. 2001;49(10):1362–5. Available from: http://www.jstage.jst.go.jp/article/cpb/49/10/49_10_1362/_article
94. Painuli S, Quispe C, Herrera-Bravo J, Semwal P, Martorell M, Almarhoon ZM, et al. Nutraceutical Profiling, Bioactive Composition, and Biological Applications of Lepidium sativum L. de Oliveira FL, editor. Oxid Med Cell Longev [Internet]. 2022 Jan 19;2022:1–20. Available from: https://www.hindawi.com/journals/omcl/2022/2910411/
95. Costantino L, Raimondi L, Pirisino R, Brunetti T, Pessotto P, Giannessi F, et al. Isolation and pharmacological activities of the Tecoma stans alkaloids. Farm [Internet]. 2003 Sep;58(9):781–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014827X03001332
96. Rounsaville TJ RT. Ploidy levels and genome sizes of Berberis L. and Mahonia Nutt. species, hybrids, and cultivars. Hort Sci. 2010;45:1029–33.
97. Ikuta A, Itokawa H. Berberine: Production Through Plant (Thalictrum spp.) Cell Cultures. In 1988. p. 282–93. Available from: http://link.springer.com/10.1007/978-3-642-73026-9_15
98. AHRENDT LWA. Berberis and Mahonia. Bot J Linn Soc [Internet]. 1961 May;57(369):1–410. Available from: https://academic.oup.com/botlinnean/article-lookup/doi/10.1111/j.1095-8339.1961.tb00889.x
99. Singh N, Sharma B. Toxicological Effects of Berberine and Sanguinarine. Front Mol Biosci [Internet]. 2018 Mar 19;5. Available from: http://journal.frontiersin.org/article/10.3389/fmolb.2018.00021/full
100. Gruenwald J, Brendler T JC. PDR for herbal medicines. Medical Economics Company: New Jersey; 2000.
101. B. Gaikwad S, Krishna Mohan G, Rani MS. Phytochemicals for Diabetes Management. Pharm Crop [Internet]. 2014 Nov 14;5(1):11–28. Available from: http://benthamopen.com/ABSTRACT/TOPHARMCJ-5-11
102. Chopra RN, Nayar SL CI. Glossary of Indian Medicinal Plants. Council of Scientific and Industrial Research: New Delhi; 1996.
103. Yin J, Ye J, Jia W. Effects and mechanisms of berberine in diabetes treatment. Acta Pharm Sin B [Internet]. 2012 Aug;2(4):327–34. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2211383512000871
104. Singh SS, Pandey SC, Srivastava S, Gupta VS, Patro B GA. Chemistry and medicinal properties of Tinospora cordifolia (Guduchi). Indian J Pharmacol. 2003;35(2):83–91.
105. Chao J, Liao J-W, Peng W-H, Lee M-S, Pao L-H, Cheng H-Y. Antioxidant, Analgesic, Anti-Inflammatory, and Hepatoprotective Effects of the Ethanol Extract of Mahonia oiwakensis Stem. Int J Mol Sci [Internet]. 2013 Jan 30;14(2):2928–45. Available from: http://www.mdpi.com/1422-0067/14/2/2928
106. Yu F-S, Yang J-S, Lin H-J, Yu C-S, Tan T-W, Lin Y-T, et al. Berberine inhibits WEHI-3 leukemia cells in vivo. In Vivo [Internet]. 2007;21(2):407–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17436595
107. Lin K, Liu S, Shen Y, Li Q. Berberine Attenuates Cigarette Smoke-Induced Acute Lung Inflammation.

Inflammation [Internet]. 2013 Oct 21;36(5):1079–86. Available from: http://link.springer.com/10.1007/s10753-013-9640-0
108. Abd El-Wahab AE, Ghareeb DA, Sarhan EE, Abu-Serie MM, El Demellawy MA. In vitro biological assessment of berberis vulgaris and its active constituent, berberine: antioxidants, anti-acetylcholinesterase, anti-diabetic and anticancer effects. BMC Complement Altern Med [Internet]. 2013 Dec 5;13(1):218. Available from: https://bmccomplementalternmed.biomedcentral.com/articles/10.1186/1472-6882-13-218
109. Čerňáková M, Košťálová D, Kettmann V, Plodová M, Tóth J, Dřímal J. Potential antimutagenic activity of berberine, a constituent of Mahonia aquifolium. BMC Complement Altern Med [Internet]. 2002 Dec 19;2(1):2. Available from: http://bmccomplementalternmed.biomedcentral.com/articles/10.1186/1472-6882-2-2
110. Dwuma-Badu D, Ayim JSK, Fiagbe NIY, Knapp JE, Schiff PL, Slatkin DJ. Constituents of West African Medicinal Plants XX: Quindoline from Cryptolepis sanguinolenta. J Pharm Sci [Internet]. 1978 Mar;67(3):433–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022354915398828
111. Ablordeppey SY, Fan P, Li S, Clark AM, Hufford CD. Substituted Indoloquinolines as New Antifungal Agents. Bioorg Med Chem [Internet]. 2002 May;10(5):1337–46. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0968089601004011
112. Noamesi B, Bamgbose S. The Alpha-Adrenoceptor Blocking Properties of Cryptolepine on the Rat Isolated Vas Deferens. Planta Med [Internet]. 1980 May 29;39(05):51–6. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2008-1074902
113. Tackie AN, Boye GL, Sharaf MHM, Schiff PL, Crouch RC, Spitzer TD, et al. Cryptospirolepine, a Unique Spiro-nonacyclic Alkaloid Isolated from Cryptolepis sanguinolenta. J Nat Prod [Internet]. 1993 May 1;56(5):653–70. Available from: https://pubs.acs.org/doi/abs/10.1021/np50095a001
114. Ansah C, Mensah KB. A review of the anticancer potential of the antimalarial herbal cryptolepis sanguinolenta and its major alkaloid cryptolepine. Ghana Med J [Internet]. 2013 Sep;47(3):137–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24391229
115. Osafo N, Mensah KB, Yeboah OK. Phytochemical and Pharmacological Review of Cryptolepis sanguinolenta (Lindl.) Schlechter. Adv Pharmacol Sci [Internet]. 2017;2017:1–13. Available from: https://www.hindawi.com/journals/aps/2017/3026370/
116. Olajide OA, Bhatia HS, de Oliveira ACP, Wright CW, Fiebich BL. Anti-neuroinflammatory properties of synthetic cryptolepine in human neuroblastoma cells: Possible involvement of NF-κB and p38 MAPK inhibition. Eur J Med Chem [Internet]. 2013 May;63:333–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0223523413000901
117. Domfeh SA, Narkwa PW, Quaye O, Kusi KA, Awandare GA, Ansah C, et al. Cryptolepine inhibits hepatocellular carcinoma growth through inhibiting interleukin-6/STAT3 signalling. BMC Complement Med Ther [Internet]. 2021 Dec 2;21(1):161. Available from: https://bmccomplementalternmed.biomedcentral.com/articles/10.1186/s12906-021-03326-x
118. Pal H, Katiyar S. Cryptolepine, a Plant Alkaloid, Inhibits the Growth of Non-Melanoma Skin Cancer Cells through Inhibition of Topoisomerase and Induction of DNA Damage. Molecules [Internet]. 2016 Dec 21;21(12):1758. Available from: http://www.mdpi.com/1420-3049/21/12/1758
119. Olajide O, Pinheiro de Oliveira A, Unekwe J, Wright C, Fiebich B. Cryptolepis sanguinolenta (Lindl.) Schltr. root extract inhibits prostaglandin production in IL-1b stimulated SK-N-SH neuronal cells. Planta Med [Internet]. 2010 Aug 24;76(12). Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0030-1264899
120. Cimanga K, De Bruyne T, Pieters L, Vlietinck AJ, Turger CA. In Vitro and in Vivo Antiplasmodial Activity of Cryptolepine and Related Alkaloids from Cryptolepis sanguinolenta. J Nat Prod [Internet]. 1997 Jul 1;60(7):688–91. Available from: https://pubs.acs.org/doi/10.1021/np9605246
121. Bugyei K, Boye G, Addy M. Clinical efficacy of a tea-bag formulation of Cryptolepis sanguinolenta root in the treatment of acute uncomplicated falciparum malaria. Ghana Med J [Internet]. 2011 Aug 17;44(1). Available from: http://www.ajol.info/index.php/gmj/article/view/68849
122. Boye G. L. AO. Proceedings of the First International Symposium on Cryptolepine. University of Science and Technology; 1983.
123. Delvaux E. Sur la Cryptolepine. (On Cryptolepine.). J Pharm Belg. 1931;13(955).
124. Gellért E, Raymond-Hamet, Schlittler E. Die Konstitution des Alkaloids Cryptolepin. Helv Chim Acta [Internet]. 1951;34(2):642–51. Available from: https://onlinelibrary.wiley.com/doi/10.1002/hlca.19510340228
125. Boye GL AO. Medicinal Plants in Ghana. In: Wagner and N.R. Farnsworth, editor. Economic and Medicinal Plants Research. Academic Press, London, UK; 1990. p. 32–3.
126. T. Parvatkar P, S. Parameswaran P, G. Tilve S. Isolation, Biological Activities and Synthesis of Indoloquinoline Alkaloids: Cryptolepine, Isocryptolepine and Neocryptolepine. Curr Org Chem [Internet]. 2011 Apr 1;15(7):1036–57. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1385-2728&volume=15&issue=7&spage=1036
127. Pousset J-L, Martin M-T, Jossang A, Bodo B. Isocryptolepine from Cryptolepis sanguinolenta. Phytochemistry [Internet]. 1995 Jun;39(3):735–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/003194229400925J
128. Sharaf MHM, Schiff PL, Tackie AN, Phoebe CH, Johnson RL, Minick D, et al. The isolation and structure determination of cryptomisrine, a novel indolo[3,2- b]quinoline dimeric alkaloid from cryptolepis sanguinolenta. J Heterocycl Chem [Internet]. 1996 May;33(3):789–97. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jhet.5570330343
129. Irvine FR. Woody Plants of Ghana with Special Reference to Their Uses. Oxford University Press, London; 1961. 143–144 p.
130. Sharaf MHM, Schiff PL, Tackie AN, Phoebe CH, Martin GE. Two new indoloquinoline alkaloids from cryptolepis sanguinolenta: Cryptosanguinolentine and cryptotackieine. J Heterocycl Chem [Internet]. 1996 Mar;33(2):239–43. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jhet.5570330204
131. Ameyaw E, Koffuor G, Asare K, Konja D, Dubois A, Kyei S, et al. Cryptolepine, an indoloquinoline alkaloid, in the management of diabetes mellitus and its associated complications. J Intercult Ethnopharmacol [Internet]. 2016;5(3):263. Available from: http://www.scopemed.org/fulltextpdf.php?mno=223703
132. Raffauf RF, Flagler MB. Alkaloids of the Apocynaceae. Econ Bot [Internet]. 1960 Jan;14(1):37–55. Available from: http://link.springer.com/10.1007/BF02859365
133. Verma A, Laakso I, Seppänen-Laakso T, Huhtikangas A, Riekkola M-L. A Simplified Procedure for Indole Alkaloid Extraction from Catharanthus roseus Combined with a Semi-synthetic Production Process for Vinblastine. Molecules [Internet]. 2007 Jul 5;12(7):1307–15. Available from: http://www.mdpi.com/1420-3049/12/7/1307

134. Liu J, Zhu J, Tang L, Wen W, Lv S, Yu R. Enhancement of vindoline and vinblastine production in suspension-cultured cells of Catharanthus roseus by artemisinic acid elicitation. World J Microbiol Biotechnol [Internet]. 2014 Jan 18;30(1):175–80. Available from: http://link.springer.com/10.1007/s11274-013-1432-z
135. Sasaki Y, Kato D, Boger DL. Asymmetric Total Synthesis of Vindorosine, Vindoline, and Key Vinblastine Analogues. J Am Chem Soc [Internet]. 2010 Sep 29;132(38):13533–44. Available from: https://pubs.acs.org/doi/10.1021/ja106284s
136. Almagro L, Fernández-Pérez F, Pedreño M. Indole Alkaloids from Catharanthus roseus: Bioproduction and Their Effect on Human Health. Molecules [Internet]. 2015 Feb 12;20(2):2973–3000. Available from: http://www.mdpi.com/1420-3049/20/2/2973
137. Misra N, Luthra R, Kumar S. Enzymology of indole alkaloid biosynthesis in Catharanthus roseus. Indian J Biochem Biophys [Internet]. 1996 Aug;33(4):261–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8936815
138. Sulkes A, Collins JM. Reappraisal of some dosage adjustment guidelines. Cancer Treat Rep [Internet]. 1987 Mar;71(3):229–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3815390
139. Raju MG, Satyanarayana S KK. Safety of Gliclazide with the aqueous extract of Vinca rosea on pharmacodynamic activity in normal and alloxan induced diabetic rats. J Pharm Res. 2012;5(3):1555–8.
140. Özçelik B, Kartal M, Orhan I. Cytotoxicity, antiviral and antimicrobial activities of alkaloids, flavonoids, and phenolic acids. Pharm Biol [Internet]. 2011 Apr 11;49(4):396–402. Available from: http://www.tandfonline.com/doi/full/10.3109/13880209.2010.519390
141. Chattopadhyay R. A comparative evaluation of some blood sugar lowering agents of plant origin. J Ethnopharmacol [Internet]. 1999 Nov;67(3):367–72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874199000951
142. Shehadeh MB, Suaifan GARY, Abu-Odeh AM. Plants Secondary Metabolites as Blood Glucose-Lowering Molecules. Molecules [Internet]. 2021 Jul 17;26(14):4333. Available from: https://www.mdpi.com/1420-3049/26/14/4333
143. Azam K, Rasheed MA, Omer MO, Altaf I, Akhlaq A. Anti-hyperlipidemic and anti-diabetic evaluation of ethanolic leaf extract of Catharanthus roseus alone and in combination therapy. Brazilian J Pharm Sci [Internet]. 2022;58. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1984-82502022000100506&tlng=en
144. Kumar A, Gnananath K, Gande S, Goud E, Rajesh P NS. Anti diabetic Activity of Ethanolic Extract of Achyranthes asperaLeaves in Streptozotocin induced diabetic rats. J Pharm Res. 2011;4(7):3124–5.
145. Girija K, Lakshman K, Udaya C, Sabhya Sachi G, Divya T. Anti–diabetic and anti–cholesterolemic activity of methanol extracts of three species of Amaranthus. Asian Pac J Trop Biomed [Internet]. 2011 Apr;1(2):133–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2221169111600117
146. Akhtar MS, Iqbal J. Evaluation of the hypoglycaemic effect of Achyranthes aspera in normal and alloxan-diabetic rabbits. J Ethnopharmacol [Internet]. 1991 Jan;31(1):49–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/0378874191901432
147. Vijayaraj R, Kumar KN, Mani P, Senthil J, Jayaseelan T KG. Hypoglycemic and antioxidant activity of Achyranthes aspera seed extract and its effect on streptozotocin induced diabetic rats. Int J Biol Pharm Res. 2016;7:23-28.
148. Talukder. In vitro free radical scavenging and anti-hyperglycemic activities of Achyranthes aspera extract in alloxan-induced diabetic mice. Drug Discov Ther [Internet]. 2012; Available from: http://www.ddtjournal.com/getabstract.php?id=616
149. Hivrale VK, Chougule NP, Giri AP, Chhabda PJ, Kachole MS. Biochemical characterisation of α-amylase inhibitors from Achyranthes aspera and their interactions with digestive amylases of coleopteran and lepidopteran insects. J Sci Food Agric [Internet]. 2011 Aug 15;91(10):1773–80. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jsfa.4380
150. Zambare MR, Bhosale UA, Somani RS, Yegnanarayan R TK. Achyranthes aspera (Agadha): Herb That Improves Pancreatic function in Alloxan Induced Diabetic Rats. Asian J Pharm Biol Res. 2011;1(2).
151. N Srinivasulu, P Mallaiah, G Sudhakar BSBR and DSK. Alpha amylase inhibitory activity and in vitro glucose uptake in psoas muscle and adipose tissue of male wistar rats of leaf methanolic extract of Achyranthes aspera. J Pharmacogn Phytochem. 2016;5(3):176–80.
152. Njideka BE, Theophilus AEN, Ugochukwu NT. Use of Achyranthes aspera Linn Tea as Antidiabetic and Hypolipidemic Herbal Tea. Int J Heal Sci Res. 2019;9(2):32–8.
153. Patel MB, Mishra S. Isoquinoline Alkaloids from Tinospora cordifolia Inhibit Rat Lens Aldose Reductase. Phyther Res [Internet]. 2012 Sep;26(9):1342–7. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ptr.3721
154. Ansari P, Afroz N, Jalil S, Azad S Bin, Mustakim MG, Anwar S, et al. Anti-hyperglycemic activity of Aegle marmelos (L.) corr. is partly mediated by increased insulin secretion, α-amylase inhibition, and retardation of glucose absorption. J Pediatr Endocrinol Metab [Internet]. 2017 Jan 1;30(1). Available from: https://www.degruyter.com/document/doi/10.1515/jpem-2016-0160/html
155. Upadhya S, Shanbhag KK, Suneetha G, Balachandra Naidu M, Upadhya S. A study of hypoglycemic and antioxidant activity of Aegle marmelos in alloxan induced diabetic rats. Indian J Physiol Pharmacol [Internet]. 2004 Oct;48(4):476–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15907058
156. Nigam V, Nambiar VS. Aegle marmelos leaf juice as a complementary therapy to control type 2 diabetes – Randomised controlled trial in Gujarat, India. Adv Integr Med [Internet]. 2019 Mar;6(1):11–22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2212958817300174
157. Dr�ger B, Funck C, H�hler A, Mrachatz G, Nahrstedt A, Portsteffen A, et al. Calystegines as a new group of tropane alkaloids in Solanaceae. Plant Cell Tissue Organ Cult [Internet]. 1994 Sep;38(2–3):235–40. Available from: http://link.springer.com/10.1007/BF00033882
158. Binaglia M, Baert K, Schutte M, Serafimova R. Overview of available toxicity data for calystegines. EFSA J [Internet]. 2019 Jan;17(1). Available from: http://doi.wiley.com/10.2903/j.efsa.2019.5574
159. Khacheba I, Boussoussa H, Djeridane A, Bekhaoua A, Bensayah N, Yousfi M. α-Glucosidase Inhibitory Effect and Antioxidant Activity of the Extracts of Eighteen Plant Traditionally Used in Algeria for Diabetes. Curr Enzym Inhib [Internet]. 2017 Feb 2;13(1):67–78. Available from: https://www.eurekaselect.com/144320/article
160. Hung TM, Lee JP, Min BS, Choi JS, Na M, Zhang X, et al. Magnoflorine from Coptidis Rhizoma Protects High

Density Lipoprotein during Oxidant Stress. Biol Pharm Bull [Internet]. 2007;30(6):1157–60. Available from: http://www.jstage.jst.go.jp/article/bpb/30/6/30_6_1157/_article

161. Patel MB, Mishra S. Hypoglycemic activity of alkaloidal fraction of Tinospora cordifolia. Phytomedicine [Internet]. 2011 Sep;18(12):1045–52. Available from: https://linkinghub.elsevier.com/retrieve/pii/S094471131100153X

162. Patel MB, Mishra SM. Magnoflorine from Tinospora cordifolia stem inhibits α-glucosidase and is antiglycemic in rats. J Funct Foods [Internet]. 2012 Jan;4(1):79–86. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1756464611000739

163. Yang W, She L, Yu K, Yan S, Zhang X, Tian X, et al. Jatrorrhizine hydrochloride attenuates hyperlipidemia in a high-fat diet-induced obesity mouse model. Mol Med Rep [Internet]. 2016 Oct;14(4):3277–84. Available from: https://www.spandidos-publications.com/10.3892/mmr.2016.5634

164. Wang, Y., Zhang, H., and Zhang X. Effects of Jatrorrhizine on Akt/AMPK/eNOS Signaling Pathways in Blood Vessel of Diabetes Rats. Her Med. 2017;12:1107–11.

165. Zhu S-L, Lei T, Gao X, Tu J. [Jatrorrhizine regulates GLUTs with multiple manners for hypoglycemic effect in insulin-resistance 3T3-L1 adipocytes]. Zhongguo Zhong Yao Za Zhi [Internet]. 2018 Mar;43(6):1215–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29676131

166. Choi JS, Ali MY, Jung HA, Oh SH, Choi RJ, Kim EJ. Protein tyrosine phosphatase 1B inhibitory activity of alkaloids from Rhizoma Coptidis and their molecular docking studies. J Ethnopharmacol [Internet]. 2015 Aug;171:28–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874115003451

167. Li Z-Q, Zuo D-Y, Qie X-D, Qi H, Zhao M-Q, Wu Y-L. Berberine acutely inhibits the digestion of maltose in the intestine. J Ethnopharmacol [Internet]. 2012 Jul;142(2):474–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874112003327

168. Zhang M, Yang H, Yang E, Li J, Dong L. Berberine Decreases Intestinal GLUT2 Translocation and Reduces Intestinal Glucose Absorption in Mice. Int J Mol Sci [Internet]. 2021 Dec 28;23(1):327. Available from: https://www.mdpi.com/1422-0067/23/1/327

169. Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, et al. Berberine, a Natural Plant Product, Activates AMP-Activated Protein Kinase With Beneficial Metabolic Effects in Diabetic and Insulin-Resistant States. Diabetes [Internet]. 2006 Aug 1;55(8):2256–64. Available from: https://diabetesjournals.org/diabetes/article/55/8/2256/12348/Berberine-a-Natural-Plant-Product-Activates-AMP

170. Tabopda TK, Ngoupayo J, Liu J, Mitaine-Offer A-C, Tanoli SAK, Khan SN, et al. Bioactive aristolactams from Piper umbellatum. Phytochemistry [Internet]. 2008 May;69(8):1726–31. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0031942208001118

171. Grizales AM, Patti M-E, Lin AP, Beckman JA, Sahni VA, Cloutier E, et al. Metabolic Effects of Betaine: A Randomized Clinical Trial of Betaine Supplementation in Prediabetes. J Clin Endocrinol Metab [Internet]. 2018 Aug 1;103(8):3038–49. Available from: https://academic.oup.com/jcem/article/103/8/3038/5025795

172. Evran B, Aydın AF, Uğuralp B, Sar M, Doğru-Abbasoğlu S, Uysal M. Betaine treatment decreased serum glucose and lipid levels, hepatic and renal oxidative stress in streptozotocin-induced diabetic rats. Turkish J Biochem [Internet]. 2018 Jul 26;43(4):343–51. Available from: https://www.degruyter.com/document/doi/10.1515/tjb-2016-0183/html

173. Asano N, Kato A, Matsui K, Watson AA, Nash RJ, Molyneux RJ, et al. The effects of calystegines isolated from edible fruits and vegetables on mammalian liver glycosidases. Glycobiology [Internet]. 1997;7(8):1085–8. Available from: https://academic.oup.com/glycob/article-lookup/doi/10.1093/glycob/7.8.1085

174. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced Glycation End Products. Circulation [Internet]. 2006 Aug 8;114(6):597–605. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.621854

175. Song Q, Liu J, Dong L, Wang X, Zhang X. Novel advances in inhibiting advanced glycation end product formation using natural compounds. Biomed Pharmacother [Internet]. 2021 Aug;140:111750. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0753332221005321

176. Rungratanawanich W, Qu Y, Wang X, Essa MM, Song B-J. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. Exp Mol Med [Internet]. 2021 Feb 10;53(2):168–88. Available from: https://www.nature.com/articles/s12276-021-00561-7

177. Freitas L de, Valli M, Dametto AC, Pennacchi PC, Andricopulo AD, Maria-Engler SS, et al. Advanced Glycation End Product Inhibition by Alkaloids from Ocotea paranapiacabensis for the Prevention of Skin Aging. J Nat Prod [Internet]. 2020 Mar 27;83(3):649–56. Available from: https://pubs.acs.org/doi/10.1021/acs.jnatprod.9b01083

178. Miroliaei M, Khazaei S, Moshkelgosha S, Shirvani M. Inhibitory effects of Lemon balm (Melissa officinalis, L.) extract on the formation of advanced glycation end products. Food Chem [Internet]. 2011 Nov;129(2):267–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0308814611005887

179. Zawada A, Machowiak A, Rychter AM, Ratajczak AE, Szymczak-Tomczak A, Dobrowolska A, et al. Accumulation of Advanced Glycation End-Products in the Body and Dietary Habits. Nutrients [Internet]. 2022 Sep 25;14(19):3982. Available from: https://www.mdpi.com/2072-6643/14/19/3982

180. Huang L, Yang X, Peng A, Wang H, Lei X, Zheng L, et al. Inhibitory effect of leonurine on the formation of advanced glycation end products. Food Funct [Internet]. 2015;6(2):584–9. Available from: http://xlink.rsc.org/?DOI=C4FO00960F

181. Wu D, Wen W, Qi C-L, Zhao R-X, Lü J-H, Zhong C-Y, et al. Ameliorative effect of berberine on renal damage in rats with diabetes induced by high-fat diet and streptozotocin. Phytomedicine [Internet]. 2012 Jun;19(8–9):712–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0944711312000876

182. Uzor PF, Osadebe PO. Antidiabetic activity of the chemical constituents of Combretum dolichopetalum root in mice. EXCLI J [Internet]. 2016;15:290–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27298614

183. Okechukwu P, Sharma M, Tan WH, Chan HK, Chirara K, Gaurav A, et al. In-vitro anti-diabetic activity and in-silico studies of binding energies of palmatine with alpha-amylase, alpha-glucosidase and DPP-IV enzymes. Pharmacia [Internet]. 2020 Nov 27;67(4):363–71. Available from: https://pharmacia.pensoft.net/article/58392/

184. Wansi JD, Wandji J, Mbaze Meva'a L, Kamdem Waffo AF, Ranjit R, Khan SN, et al. .ALPHA.-Glucosidase Inhibitory and Antioxidant Acridone Alkaloids from the Stem Bark of Oriciopsis glaberrima ENGL. (Rutaceae). Chem Pharm Bull [Internet]. 2006;54(3):292–6. Available from: http://www.jstage.jst.go.jp/article/cpb/54/3/54_3_292/_article

185. Uvarani C, Jaivel N, Sankaran M, Chandraprakash K, Ata A, Mohan PS. Axially chiral biscarbazoles and biological evaluation of the constituents from Murraya koenigii. Fitoterapia [Internet]. 2014 Apr;94:10–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0367326X14000100

186. Dineshkumar B, Mitra A MM. Antidiabetic and hypolipidemic effects of mahanimbine (carbazole alkaloid) from murraya koenigii (rutaceae) leaves. Int J Phytomedicine. 2010;2(1):22–30.
187. Ullah Jan N, Ali A, Ahmad B, Iqbal N, Adhikari A, Inayat-ur-Rehman, et al. Evaluation of antidiabetic potential of steroidal alkaloid of Sarcococca saligna. Biomed Pharmacother [Internet]. 2018 Apr;100:461–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0753332217312702
188. Patel OPS, Mishra A, Maurya R, Saini D, Pandey J, Taneja I, et al. Naturally Occurring Carbazole Alkaloids from Murraya koenigii as Potential Antidiabetic Agents. J Nat Prod [Internet]. 2016 May 27;79(5):1276–84. Available from: https://pubs.acs.org/doi/10.1021/acs.jnatprod.5b00883
189. Stanford KI, Goodyear LJ. Exercise and type 2 diabetes: molecular mechanisms regulating glucose uptake in skeletal muscle. Adv Physiol Educ [Internet]. 2014 Dec;38(4):308–14. Available from: https://www.physiology.org/doi/10.1152/advan.00080.2014
190. Tsuchiya A, Kanno T, Nishizaki T. PI3 kinase directly phosphorylates Akt1/2 at Ser473/474 in the insulin signal transduction pathway. J Endocrinol [Internet]. 2014 Jan;220(1):49–59. Available from: https://joe.bioscientifica.com/view/journals/joe/220/1/49.xml
191. Ruud J, Steculorum SM, Brüning JC. Neuronal control of peripheral insulin sensitivity and glucose metabolism. Nat Commun [Internet]. 2017 May 4;8(1):15259. Available from: https://www.nature.com/articles/ncomms15259
192. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: Similarities and differences. J Diabetes Investig [Internet]. 2010 Feb;1(1–2):8–23. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.2040-1124.2010.00022.x
193. Yamane S, Harada N, Inagaki N. Mechanisms of fat-induced gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide secretion from K cells. J Diabetes Investig [Internet]. 2016 Apr 14;7(S1):20–6. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jdi.12467
194. Guasch L, Ojeda MJ, González-Abuín N, Sala E, Cereto-Massagué A, Mulero M, et al. Identification of Novel Human Dipeptidyl Peptidase-IV Inhibitors of Natural Origin (Part I): Virtual Screening and Activity Assays. Uversky VN, editor. PLoS One [Internet]. 2012 Sep 12;7(9):e44971. Available from: https://dx.plos.org/10.1371/journal.pone.0044971
195. Deacon CF. Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. Front Endocrinol (Lausanne) [Internet]. 2019 Feb 15;10. Available from: https://www.frontiersin.org/article/10.3389/fendo.2019.00080/full
196. García López PM, de la Mora PG, Wysocka W, Maiztegui B, Alzugaray ME, Del Zotto H, et al. Quinolizidine alkaloids isolated from Lupinus species enhance insulin secretion. Eur J Pharmacol [Internet]. 2004 Nov;504(1–2):139–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299904010143
197. Wiedemann M, Gurrola-Díaz C, Vargas-Guerrero B, Wink M, García-López P, Düfer M. Lupanine Improves Glucose Homeostasis by Influencing KATP Channels and Insulin Gene Expression. Molecules [Internet]. 2015 Oct 20;20(10):19085–100. Available from: http://www.mdpi.com/1420-3049/20/10/19085
198. Jung HA, Yoon NY, Bae HJ, Min B-S, Choi JS. Inhibitory activities of the alkaloids from Coptidis Rhizoma against aldose reductase. Arch Pharm Res [Internet]. 2008 Nov 21;31(11):1405–12. Available from: http://link.springer.com/10.1007/s12272-001-2124-z
199. Lee H-S. Rat Lens Aldose Reductase Inhibitory Activities of Coptis japonica Root-Derived Isoquinoline Alkaloids. J Agric Food Chem [Internet]. 2002 Nov 1;50(24):7013–6. Available from: https://pubs.acs.org/doi/10.1021/jf0206740
200. Cho H. Protein Tyrosine Phosphatase 1B (PTP1B) and Obesity. In 2013. p. 405–24. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780124077669000171
201. Lankatillake C, Huynh T, Dias DA. Understanding glycaemic control and current approaches for screening antidiabetic natural products from evidence-based medicinal plants. Plant Methods [Internet]. 2019 Dec 7;15(1):105. Available from: https://plantmethods.biomedcentral.com/articles/10.1186/s13007-019-0487-8
202. Sasaki T, Li W, Higai K, Koike K. Canthinone alkaloids are novel protein tyrosine phosphatase 1B inhibitors. Bioorg Med Chem Lett [Internet]. 2015 May;25(9):1979–81. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0960894X15002103.

Advances in Pharmacognosy and Phytochemistry of Diabetes

This book entitled 'Advances in Pharmacognosy and Phytochemistry of Diabetes' uncovers the longstanding tradition of using medicinal plants to treat diabetes, showcasing their growing popularity due to effective results and fewer side effects compared to conventional therapies. As the global prevalence of diabetes continues to rise, the book addresses the increasing inclination towards natural remedies for managing this condition. The content covers the use of plants in diabetes treatment, the therapeutic potential of phytochemicals, and how these natural compounds target various human metabolic pathways. With a focus on simplicity, the book provides insights into the diverse classes of phytochemicals, such as terpenoids, flavonoids, alkaloids, and glycosides, shedding light on their roles in controlling blood sugar levels and managing associated complications. Written for a broad audience, including industries, educational institutions, and health experts, this book serves as a practical guide for those seeking natural alternatives in diabetes care. It demystifies the science behind phytochemicals, offering valuable knowledge for navigating the world of diabetes treatment with a focus on plant-based solutions.

Edited by Prof. Uchenna Estella Odoh, Dr. Habibu Tijjani & Dr. Chukwuebuka Egbuna

ADVANCES IN PHARMACOGNOSY AND PHYTOCHEMISTRY OF DIABETES

EDITED BY
UCHENNA ESTELLA ODOH
HABIBU TIJJANI
CHUKWUEBUKA EGBUNA

PUBLISHED BY
IPS INTELLIGENTSIA PUBLISHING SERVICES
THE PUBLISHER PAR EXCELLENCE

Advances in Pharmacognosy and Phytochemistry of Diabetes

Advances in Pharmacognosy and Phytochemistry of Diabetes

Editors

Prof. Uchenna Estella Odoh
Department of Pharmacognosy and Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria.

Dr. Habibu Tijjani
Department of Biochemistry, Natural Product Research Laboratory, Bauchi State University Gadau, Nigeria.

Dr. Chukwuebuka Egbuna
Nutritional Biochemistry and Toxicology Unit, African Centre of Excellence for Public Health and Toxicological Research (ACE-PUTOR), University of Port-Harcourt, Rivers State, Nigeria.

Intelligentsia Publishing Services
The publisher par excellence

Chapter 7

Glycosides from Natural Sources in Treatment of Diabetes Mellitus

Soumi Datta[1], Pomila[2], Manika Bhatia[3], Dwaipayan Sinha[4*], Poornima Sharma[5], Sanchita Seal[6], Murad Muhammad[7], Swastika Banerjee[8], Somnath Kar[9], Tapas Das[10], Laxmi Kumari Gupta[11], Asha Kadam[12]

[1]Bioactive Natural Product Laboratory, School of Interdisciplinary Sciences and Technology, Jamia Hamdard, Hamdard Nagar, New Delhi- 110062.
[2]Department-chemistry, College of Basic science and humanities. Punjab Agricultural University, Ludhiana, Punjab-141004, India.
[3]TERI School of Advanced Studies, Vasant Kunj Institutional Area, New Delhi, Delhi-110070, India
[4]Department of Botany, Government General Degree College, Mohanpur, Paschim Medinipur, West Bengal-721436, India.
[5]Regional Institute of Education, Shyamla Hills, Bhopal, Madhya Pradesh-462013, India.
[6]Department of Botany, Polba Mahavidyalaya, Polba, West Bengal- 712148, India.
[7]Phyto-ecology Lab. Department of Botany, University of Peshawar, Peshawar Pakistan.
[8]Kairali College of +3 Science, Champua, Keonjhar, Odisha-758041, India.
[9]Department of Botany, Holy Cross College, Jubatara, Lembucherra, Agartala, Tripura-799210, India
[10]Department of Botany, University of Kalyani, Kalyani, Nadia, West Bengal- 741235, India.
[11]Bioprocess Development Laboratory, Department of Biotechnology, National Institute of Technology Warangal, Warangal, Telangana- 506004, India.
[12]P.G.Department of Botany, Dada Patil Mahavidylaya, Karjat, Ahmednagar, Maharashtra-414402, India.
*Corresponding author: Email: dwaipayansinha@hotmail.com; ORCiD: https://orcid.org/0000-0001-7870-8998

How to cite this chapter: Datta, S., Pomila, Bhatia, M., Sinha, D., Sharma, P., Seal, S. et al. (2023). Glycosides from Natural Sources in Treatment of Diabetes Mellitus. In. Odoh, U.E., Tijjani, H. and Egbuna, C. (Eds) Advances in Pharmacognosy and Phytochemistry of Diabetes. Onitsha: IPS Intelligentsia Publishing Services, Pp. 84-114. DOI:

Abstract
One of the most common causes of mortality indeveloping nations is diabetes. The treatment of diabetes involves the use of numerous synthetic substances. But these medications shows many adverse health issues. Therefore, there is a critical requirement need for novel therapeutics that can aid in the improved management of diabetes. Herbal medicines have been used for their therapeutic benefits in a variety of illness situations since ancient times. One of the finest solutions for treating a variety of disorders, including diabetes, is a natural medicine made from medicinal plants. Numeroussecondary metabolites such as phenolics, terpenoids, sterols, glycosides, andalkaloids, etc. are produced by plants.Non-sugar moiety (which is called aglycone) is connected to a sugar portion (glycone) by a glycosidic bond to form glycosides. Numerous plants contain glycosides, which an enzyme can then hydrolyze to create glycone and aglycone. Numerous biological functions have been attributed to various glycosides and aglycones. Significantly effective anti-diabetic activity has been documented for various types of glycosides such as coumarin, cardiac, anthraquinone, rutin, puerarin, cyanogenic, gymnemic acid I, thiogylosides, and stevioside. Aglycones with antidiabetic properties include strictinin, christinin-A, and securigenin. Their antidiabetic effect is influenced through the insulin secretion is induced and is inhibitedof enzymes. The glycemic control of enzymes α-amylase, α-glucosidase, and tyrosine phosphatase 1B. This book chapter review aims to outline current advances in the synthesis of prospective antidiabetic O, N and C glycosides and their mode of action.

Keywords: O-glycosides, N-glycosides, C-glycosyl, Glycogen, phosphorylase inhibitor, diabetes

7.1 Introduction
Diabetes mellitus (DM) is a protractedclass of ailment caused due to metabolic issues that is spread worldwide and have almost doubled in the last two decades (1) characterized by hyperglycemia. It is caused by the erratic metabolism of proteins and fats, resulting in increasing levels of blood glucose (2). Poor synthesis of insulin by the pancreas or inappropriate useutilization of insulin by cells results in rise of glucose in the blood as a cell cannot metabolize. Diabetes is mainly of three types:
a) Type 1 (T1DM): Insulin not produced by the pancreas.

b) Type 2 (T2DM): Insulin produced is not utilized by resistant body cells.
c) Type 3(T3DM): Pregnancy and childbirth-induced complications resulting in diabetes due to gestational reasons and increases the risk of diabetes (Type 2) in both mother and to the next generation.

Apart from these three types, two more categories of glucose intolerance are listed; which are an intermediary between normal and diabetic glucose levels in the blood - IFG (impaired fasting glucose) and IGT (impaired fasting glycemia) although the conversion is not mandatory, such people have a higher risk of cardiovascular disorders (CVD) than compared to normal people. Uncontrolled diabetes leads to several health issues, like- as loss of vision, kidney malfunction, cardiovascular diseases (CVD), lower limb amputations, strokes, reduced life, erectile dysfunction, and disability. Symptoms of DM include weight loss, enhanced appetite, excessive thirst, and polyuria (3).

In developed and developing countries, diabetes has become a major challenge in the 21st century as it is the major reason for death. The treatment of diabetes is done with synthetic drugs, however, due to the adverse effects of these therapeutic drugs, so it is an immediate call to develop alternate new therapies, especially with herbal formulations for its management and treatment. Ayurveda and herbal drugs are well accepted over the ages for their medicinal properties and ability to heal and cure various diseases; therefore natural products can be one of the best alternatives to manage and treat DM. Secondary metabolites or bioactive molecules with therapeutic properties like saponins, alkaloids, glycosides, anthraquinones, sterols,terpenoids, flavonoids, and tannins, are synthesized by the plants. Glycosides are glycone (sugar unit) connected to aglycone (non-sugar) through glycosidic linkage. These are synthesized by plants under biotic or abiotic stress conditions and via the enzyme, hydrolysis produces glycone and aglycone, which are known to have many pharmacological activities. Glycosides depending upon the linkage caused by the glycosidic bond are categorized into four, namely- O-Glycosides (plants have abundantly), C- Glycosides (hydrolysis resilient), S- Glycosides (thioglycosides), and N- Glycosides (found in nucleosides).

A few examples of glycosides reported to have important hyperglycemic activities are puerarin, stevioside, rutin, gymnemic acid I, christinin-A, securigenin, and strictinin (4). These glycosides actively participate in the pro-activation of insulin secretion, and enzyme inhibited (α-amylase, PTP1B, and α-glucosidase) responsible for glycemic control (3); and they may be linked to declining in the absorption of glucose and enhanced secretion of insulin and glucose uptake. Therefore, a holistic and systematic approach including preclinical and clinical data is required to develop new drugs from glycosides.

7.2 Present-day management of diabetes

Prediabetes and diabetes can be cured with the support of comprehensive diabetic care, which involves modifying one's lifestyle, taking medications, and monitoring blood glucose levels. With the appropriate lifestyle adjustments, the risk of diabetes can be decreased by 58% over three years. (5). *Dietary control is crucial for those with diabetes; a 7% weight loss is thought to improve cholesterol, glucose levels, andblood pressure. The American Diabetic Association (ADA) advises patients with weakened glucose forbearance , fasting plasma glucose, and hemoglobin A1C (HbA1C) values between 5.7 and 6.4% to follow a striict diet along with proper exercise regimen (5).* Although a low-calorie diet helps people lose weight, low-carbohydrate diets can cause hypoglycemia, headaches, and constipation. Complex fiber and whole grains may regulate glucose, (6), while exercise can reduce HbA1C by 0.66 without reducing weight (7). A total of eight pathophysiological pathways induce hyperglycemia in DMnamelyincreased lipolysis, inhanced reabsorption of renal glucose, decreased incretin effect in the small intestine, brain, declined insulin secretion, elevated secretion of glucagon, increased glucose production in the liver, impaired glucose tolerance, and neurotransmitter dysfunction along with resistance of insulin (8).

Glycemic control is crucial for those with DM since it eventually aids in the prevention of the disease. The effectiveness, cost, side effects, weight gain, comorbidities, and hypoglycemia of drug use must be carefully considered. If after 2-3 months of lifestyle adjustments, there is still no favorable glycemic shift or an HbA1C level of 6.5%, pharmaceutical treatment must be administered right away.

By promoting medication and delaying therapy, microvascular damage can be minimized(9). It was shown that lifestyle monotherapy produced better outcomes than lifestyle therapy when compared with the method of administering the only drug to cure diabetes, and lifestyle monotherapy is a therapy incorporating a similar sort of lifestyle alterations (10).

Thiazolidinedione, Biguanides, meglitinide, sulfonylureas, DPP-4 inhibitors, □□glucosidase inhibitors, and SGLT2 inhibitors are examples of oral diabetes medications. Combine two oral drugs or insulin if HbA1C increases to 7.5% while taking medication or 9% at first (11). **Table 7.1** provides a succinct summary of drug classes, their regulatory pathway, and associated side effects.

Table 7.1: Mechanisms of various classes of anti-diabetic drugs and their related side effects.

Class of antidiabetic drug	**Regulation pathway**	**Adverse effects**	**Citation**
Biguanide	AMP kinase activation (12)	Vitamin B12 deficiency,	(13)
		anemia and neuropathy	(14)
Dipeptidyl peptidase 4	Incretin associated pathways (15)	cardiovascular disease risk	(16)
		Pancreatitis	(17)
		Upper RTI infection	(18)
Sodium-glucose cotransporter (SGLT2) inhibitor	Rapamycin, sirtuin 1, and hypoxia-inducible factor paths. (19)	Genital mycosis	(20)
		Bone fractures	(21)
		Ketoacidosis	(22)
Human recombinant Insulin	Receptor tyrosine kinase (RTK)pathway (23)	Allergy to injection components	(24)
GLP-1 agonists	Indorses β-cell glucose metabolism via mTOR-dependent HIF-1α activation (25)	Nausea	(26)
		Thyroid cancer	(27)
Sulfonylurea	Inhibit the ATP-sensitive potassium channels (28)	Cardiovascular disease risk	(29)
Thiazolidinedione	Targets Peroxisome proliferator-activated receptor gamma (30)	Cardiovascular risks	(31)
		Bladder cancer	(32)
		Fractures	(33)

7.3 Advantages of Herbal medicines

As stated earlier, conventional medicines for the management of diabetes have side effects which once again opens a new arena of treatment for the associated ailments. This not only increases the agony of the patients but also increases the overall expenditure. This has led scientists to search for alternative approaches for the treatment of not only diabetes but also a several other diseases. Over the past years, there is significant growth in the usage of herbal medicines and supplements, with at least 80% of individuals using them for some aspect of primary healthcare (34).Traditional medicine is used by 80% of the world's inhabitants. 170 of the 194 WHO Member States have conveyed using traditional medicine based on herbs or herbal formulations, and respective authorities have askedfor WHO's support in assembling solid proof and data for the same(35).People with diabetes were more likely than other patient groups to use complementary and alternative medicine (CAM). Fear of adverse effects, discontent with medical professionals, and the higher expense of contemporary medicine were the main justifications for utilizing CAM for the treatment of diabetes.Higher levels of medication adherence and improved comprehension of the necessity of lifestyle adjustments for diabetes management throughout CAM treatment and simple access to CAM without a prescription from a physician were other factors that provided an edge in this regard (36). Keeping all the scenarios in mind, in this chapter, an effort has been made to comprehensively highlight the importance of glycosides as an antidiabetic agent. Detailed information about the source of antidiabetic glycosides along with their sources and mechanism of action has also been illustrated.

7.4 Classification of Glycosides

A typical glycoside comprises two structural moieties one is the monosaccharide (sugar part) known as term"glycone" and the other one is called "aglycone". Both moieties are bonded with each other via means of a glycosidic bond (37). Figure 7.1 depicts the typical structure of glycosides. Based on the basic structural framework, glycosides can be categorized based onthe following groups:

A. **Glycone**

The carbohydrate group refers to a glycone inside the structure of a glycoside. The most frequent glycone is glucose and hence the name glucosides (37). Apart from glucose, fructose, glucuronic acid, and arabinose can be found as glycone. The presence of these sugary groups makes glycosides hydrophilic (38).

B. Aglycone

The non-carbohydrate entity of glucosides which is accountable for most of the pharmacological properties of the glycosides is known as aglycone also termed genin (39).

C. Glycoside Linkage

A glycoside bond is a bridge between the glycone and the aglycone parts of a typical glycoside (Figure 1). The nature of the glycosidic bond varies depending on the functional groups present on the aglycone part(37). Generally, glycoside linkage is resistant to water hydrolysis and only breaks either by the action of an acid or alkali.

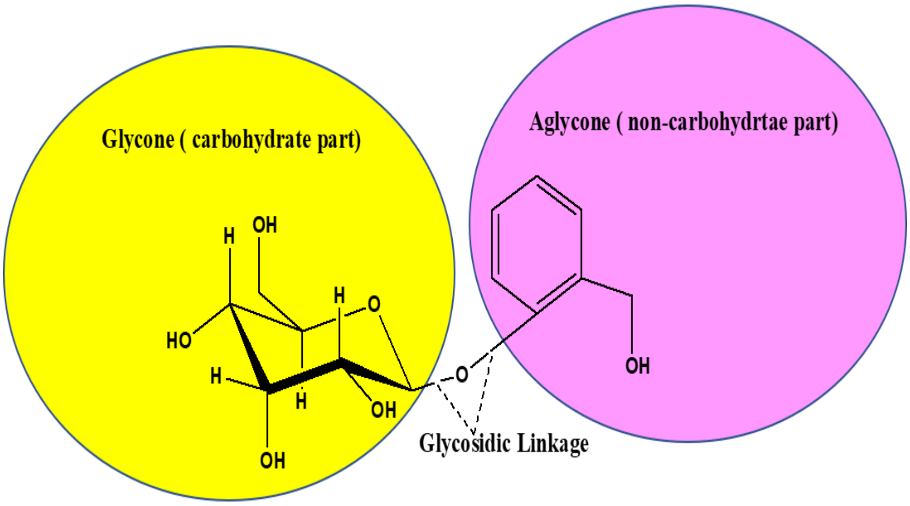


Figure 7.1: Molecular structure of a glycoside

7.4.1 Classification based on glycone

Depending upon the structure of the sugar moiety present in the glucoside, the glycone can be categorized as given in table 7.2.

7.4.1.1 Classification on basis of glycosidic linkage

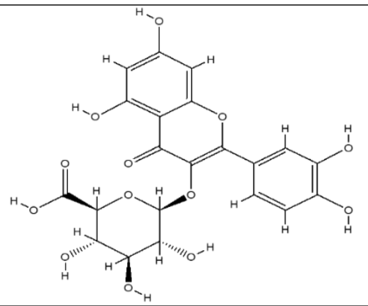
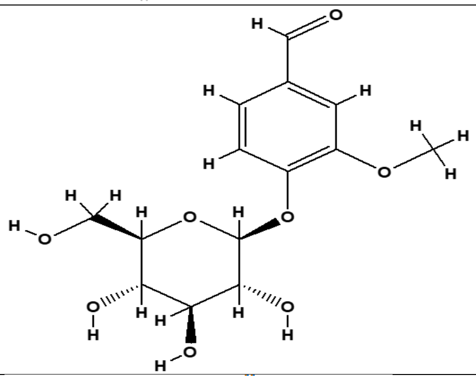
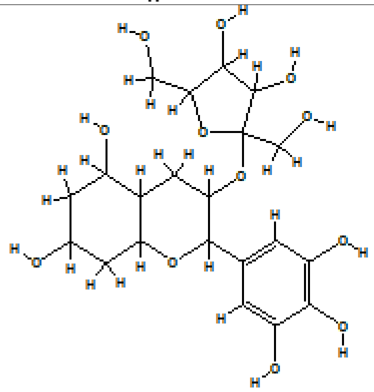
O-glycosides: When the glycone part of the glucoside is made to bond with aglycone via condensation through an oxygen atom, such glycosides are called o-**glycosides** (42). Examples of O-glycosides involve amygdalin, arbutin, cardiac glycosides, salicin and anthraxquinone glycosides like sennosides etc.

N-glycoside: N-glycosides are generated when the N of the amino group (-NH) of the aglycon is attached to the glycone and established a C-N-S linkage (43).Examples of N-glycosides are nucleosides,RNA, cofactors,DNA and a diversity of antiviral and anti-neoplastic medications, etc(43).

S-glycosides: Those glycosides which involved C-S-C linkage between the glycon and genin moiety come under the S- glycosides. For example, Sinigrin, and Glucosinolates.

C-**glycosides:** Among all, C-glycosides attracted much more attention comparatively due to their enormous therapeutic properties (43). When both the carbohydrate and non- carbohydrates part of the glycosides are attached via C-C bond such types of glycosides are known as C-glycosides. For example Aloin, barbaloin, cascaroside, and flavan glycosides, among others, are anthraquinone glycosides that directly connect a sugar molecule to the C atom of the aglycon (38).

Table 7.2: Categorization of glucosides on the basis of glycone

Glycoside name	Glycone part	Structure	Plant source	Reference
Glucuronide	Glucuronic acid		*Theobroma grandiflorum*, *Eucalyptus cypellocarpa*,	(40)
Glucoside	Glucose		Vanilla plant	(41)
Fructoside	Fructose		*Viola* and *Delphinium*	(38)

7.4.2 Classification on basis of aglycone

7.4.2.1 Anthracene glycoside

As the name indicates anthracene glycoside, contains anthracene as an aglycone group (37) and is found in the majority of vegetable cathartics such as Rhubarb ,Ser, Aloe, and Cascara(44). These chemical compounds are recognized for their medicinal therapeutics characteristics for centuries likeantimicrobial potential(45), anti-inflammatory, and laxative agents (46). Recently, they used in the treatment of cancer, multiple sclerosis, arthritis and constipation (47). A few examples of anthracene glycosides along with their respective sources are mentioned in table 7.3 while Figure 7.2 depicts their chemical structure.

7.4.2.2 Cardiac or Sterol glycosides

Cardiac (sterol) glycosides are those classes of glycosides that contain a sterol nucleus framework and a lactone ring which are further connected to the glycone moiety via condensation reaction (48). Examples of sterol or cardiac glycosides along with their respective sources are mentioned below in table 7.3 while figure 7.3 depicts their chemical forms. These sterol glycosides increase the contractions rate to enhancethe heart's output by working on a sodium-potassium pump (49) and hence employedin the handling of heart problemsand cardiac rhythm. Nowadays, this category of glycosides is also used for the treatment of cancer cells as studies indicate, cardiac glycosides do not interfere with the proliferation of normal cells and kill only cancerous cells (50).

Table 7.3: Various types of glycosides and their plant sources

Sl No.	Type of Glycoside	Examples	Plant Sources	Family	Reference
1.	Anthraquinone Glycoside	Aloe-emodin-8-glycoside	*Aloe barbadensis*	Liliaceae	(65)
		Rhein-8-glycoside	*Rheum palmatum*	Polygonaceae	(65)
		Barbaloin	*Aloe barbadensis*	Liliaceae	(65)
		Sennoside A & B	*Cassia angustifolia*	Leguminosae	(65)
		Chrysophanol	*Kniphofia sp.*	Asphodelaceae	(66)
2.	Sterol or Cardiac glycosides	Digitoxigenin	*Digitalis purpurea*	Scrophulariaceae	(67)
		Digioxigenin	*Digitalis lanata*	Scrophulariaceae	(67)
		Ouabagenin	*Strophanthus gratus*	Apocyanaceae	(68)
		Strophanthidin	*Strophanthus kombe*	Apocyanaceae	(65)
3.	Saponin glycosides	Steroidal glycosides Eg. Diosgenin	*Dioscorea deltoidea*	Dioscoreaceae	(69)
		Triterpene glycosides Eg. Ginsenoside Rb1 & panaxosides	*Panax ginseng*	Araliaceae	(70) (71)
4.	Cyanogenetic	Amygdalin	*Prunus dulcis*	Rosaceae	(72)
		Prunasin	*Prunus serotina*	Rosaceae	(73)
5.	Isothicyanate glycosides (glucosinolates)	Sinigrin(glucosinolate)	*Brassica nigra*	Cruciferae	(65)
6.	Flavone glycosides	Gingkolide A, B, C	*Gingko biloba*	Gingkoaceae	(74)
		Rutene	*Fagopyrum esculentum*	Polygonaceae	(75)
		Silybin, Silychrystin	*Silybus marianum*	Asteraceae	(76)
		Hesperedin	*Citrus aurantium*	Rutaceae	(77)
7.	Aldehyde glycosides	Iso- vanillin	*Hemidesmis indicus*	Asclepiadaceae	(78)
		Gluco- vanillin	*Vanilla planifolia*	Orchidaceae	(79)
8.	Phenol glycosides	Arbutin	*Arctostaphylos uva-ursi*	Ericaceae	(80)
		Salicin		*Salix achmophylla*	(81)
		Chalcone		*Maclura(Chlorophora) tinctoria*	(82)
		Flavanone		*Maclura(Chlorophora) tinctoria*	(82)

7.4.2.3 Saponin Glycosides

The term saponin refers to soap-like compounds which capable of producing foams and they are quite abundant as natural plant products (51)**.**In the case of saponin glycosides, triterpene, as well as steroid backbones are aglycone moieties (51).Examples of saponin glycosides and respective sources are discussed below in table 7.3 while figure 7.4 depicts their structure**.**Anti-inflammatory (52), anti-herbivore activity,antimicrobial, (53), anti-parasitic, anti-cancer (54),and antiviral potential (55)are also reported for saponin glycosides.

 ISBN: 978-978-780-772-9.

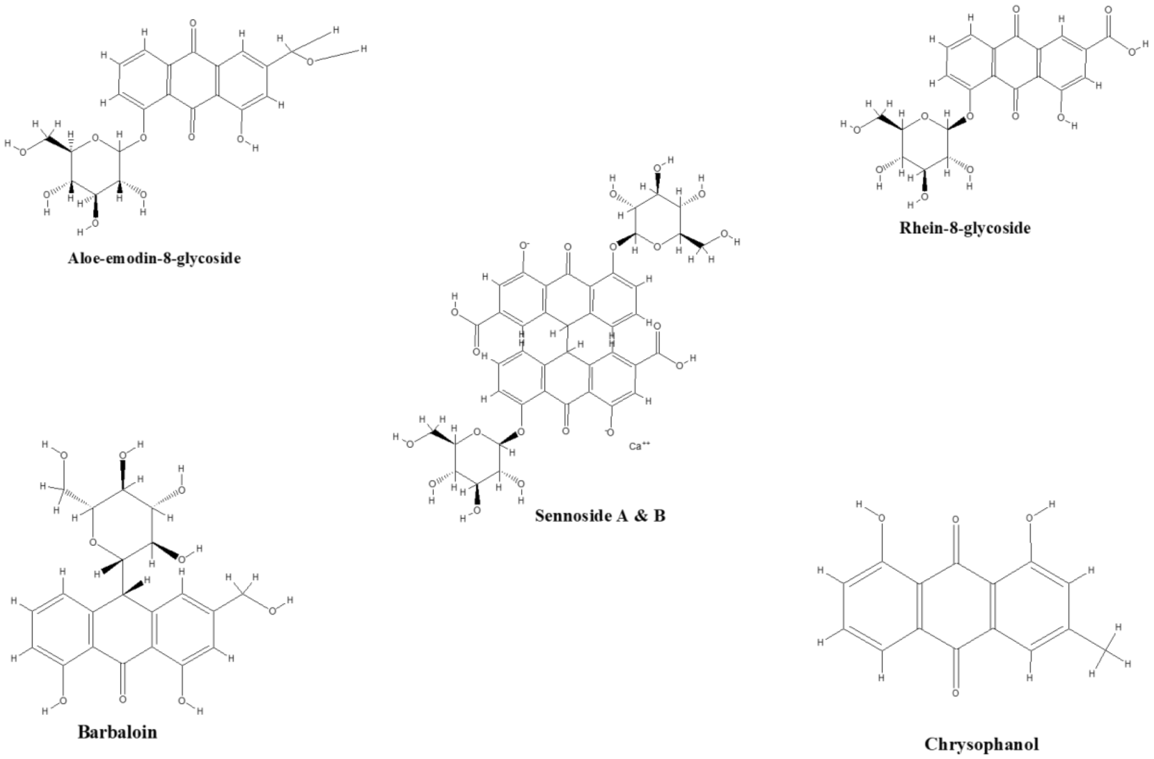


Figure 7.2: Chemical structures of selected anthracence glycosides

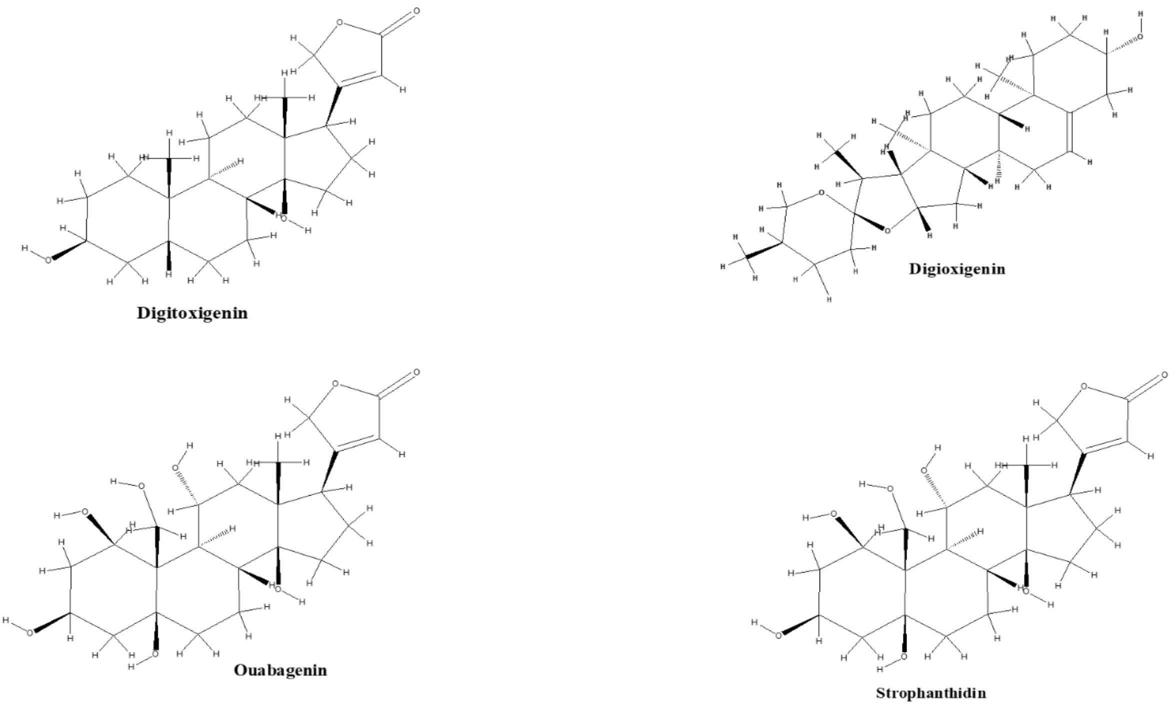
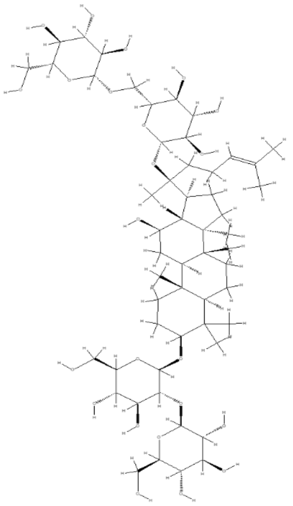
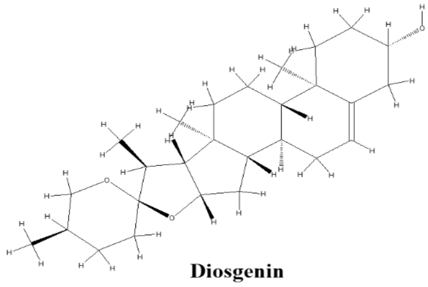


Figure 7.3: Molecular structures of few sterol glycosides



Ginsenoside Rb1s

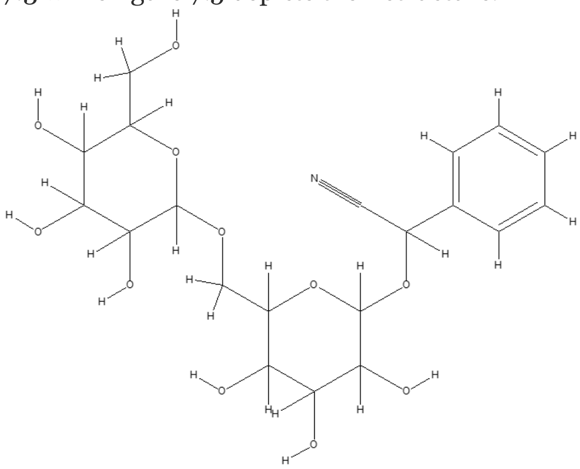


Diosgenin

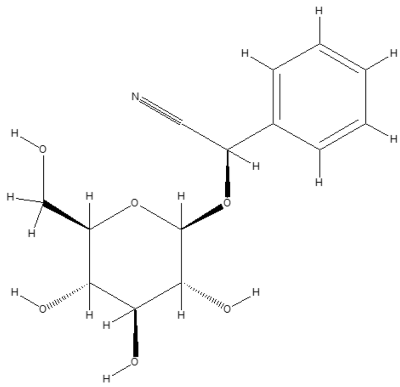
Figure 7.4: Molecular structures of two Saponin Glycosides

7.4.2.4 Cyanogenetic glycosides

The cyanogenetic glycosides are those aglycone which contains CN group in their corresponding structures along with heteroatom nitrogen (56)**.** As glycosides, they belong to typical *O*-β-glycoside and are found in plant tissues (57)**.** The presence of these glycosides, made the plants protect themselves against the distinct animals as they release the cyanide which can act as poison for the attackers (57)**.**A few examples of cyanogenic glycosides along with their respective sources are mentioned below in table 7.3 while figure 7.5 depicts their structure.



Amygdalin

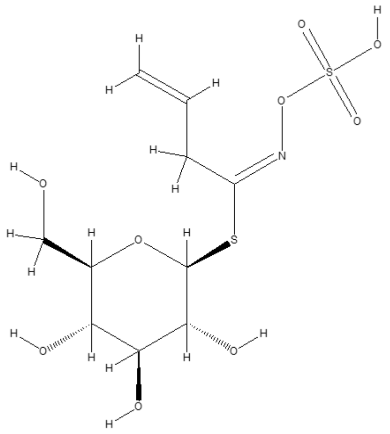


Prunasin

Figure 7.5: Molecular structures of cyanogenetic glycosides.

7.4.2.5 Isothicyanate glycosides

Sulfur is present in the structure of the aglycone part of the isothiocyanate glycosides and established a (-NCS) bonding with the carbohydrate moiety of the glycoside. The studies show that isothiocyanate glycosides are recognized for their anti-inflammatory and antioxidant potential(58)**.**Examples of isothiocyanate glycosides along with their respective sources are mentioned below in table 7.3 while figure 7.6 elucidates the molecularstructure of one of the representatives.



Sinigrin

Figure 7.6: Molecularstructure of Sinigrin

- **Flavone Glycosides**

Flavone glycosides contain flavonoid structures as an aglycone portion which is responsible for the physiochemical properties (59). On exposure to extreme heat and solar rays, flavone glycosides are released by the plants to protect them (60). Furthermore, flavonoid glycosides also exhibited properties like anti-cancer, ant-atherosclerosis, and anti-inflammatory in humans (61). Examples of flavone glycosides along with their respective sources are mentioned below in table 7.3 while figure 7.7 elucidates its structure.

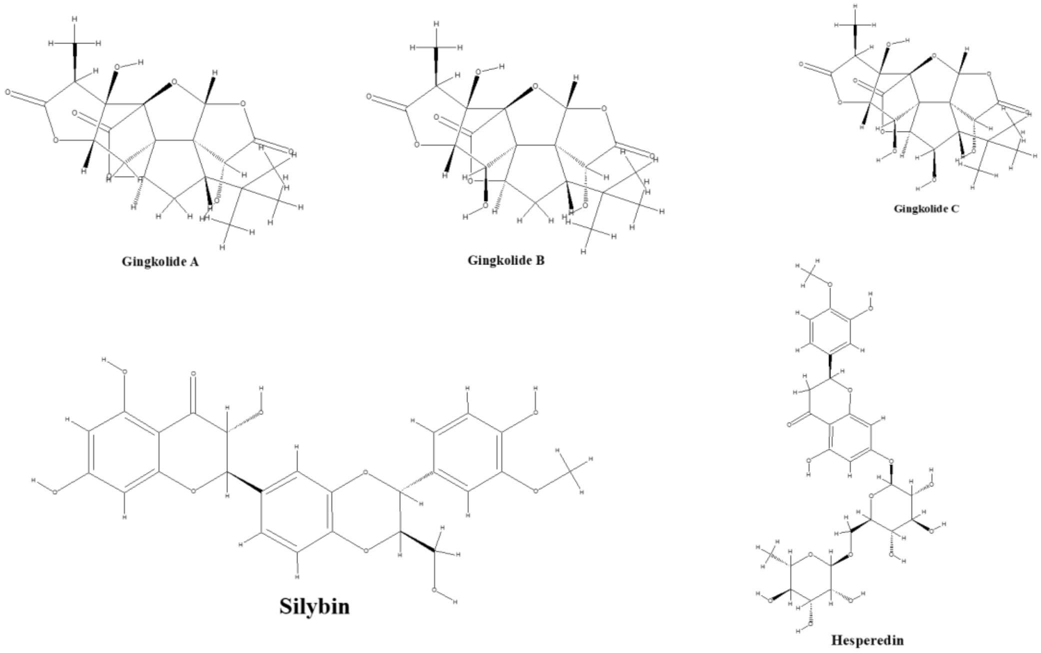
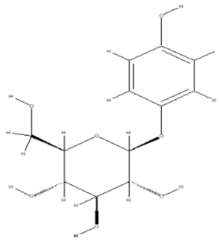


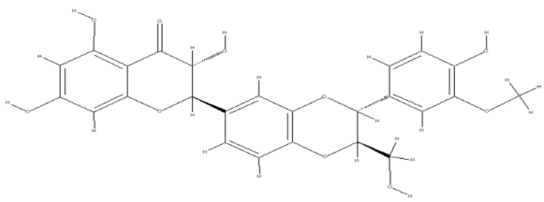
Figure 7.7: Molecular of different flavone glycosides

- **Phenyl glycosides**

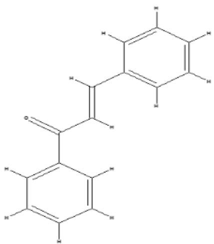
In phenyl glycosides, phenol and its derivatives are acting as aglycone groups. A few examples of phenyl glycosides along with their respective sources are mentioned below in table 7.3 while figure 7.8 elucidates its structure. Like cyanogenetic glycosides, phenol glycosides are also responsible for herbivore defenses in plants (62). Phenolic glycosides are generally optically active and established C-O-C linkage to the glycone group which can be hydrolyzed in the presence of acid and alkali (63). Few derivatives of phenyl glycosides are examined for antivirus evaluation (64).



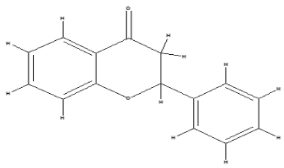
Arbutin



Salicin



Chalcone

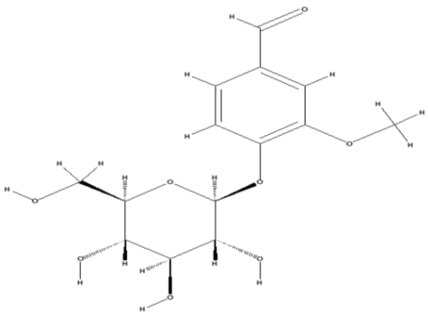


Flavanone

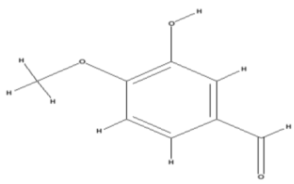
Figure 7.8: Shows the structure of different phenyl glycosides

- **Aldehyde glycosides**

Structurally, aldehyde glycosides are similar to phenolic glycosides only with the difference in aldehydic group (CHO group) (38). Aldehyde glycosides are famous in the food industries as they are used as a sweetener and flavoring agent (38). A few examples of aldehyde glycosides along with their respective sources are mentioned below in table 7.3 while figure 7.9 elucidates its structure.



Gluco- vanillin



Iso- vanillin

Figure 7.9: Molecular structures of aldehyde glycosides

7.5 Role of Glycosides in the regulation of Diabetes

The secondary metabolites, which after glycosylation result in a variety of glycosides. Numerous benefits of glycosylation include better dispersion, solubility, amphiphilicity, metabolism, etc. Different types of glycosides, such as glycosylated flavanoids (flavonols, isoflavonoids, flavanones, flavanols, anthocyanidins, cardiac glucosides, etc.), glycosylated lipids (diacylglycerols, sphingolipids, etc.), and glycosylated phytosterols, can be extracted from plants and have shown significant health benefits (83). Glycosides are utilized for the control of diabetes and some of the main targets are tumor necrosis factor (TNF), transforming growth factor (TGF), nuclear factor-kB (NF-kB), poly (ADP-ribose) polymerase (PARP), cytokines, etc. Pathways like hexosamine pathway, and polyol pathway are used by glycosides as their mode of action (84).

Researchers have been studying the role of glycosides in diabetes for millennia, and their research is still ongoing, they covered O-glycosides, N-glycosides, and even C-glycosides, from which most of the approved anti-diabetic drugs like dapagliflozin, canagliflozin, ipragliflozin, etc., were prepared. C-glycosides are comparatively more stable and have an increased oral bioavailability as compared to the others and hence were adapted for use. Phlorizin, an O-glycoside natural product, improves insulin resistance and decreases plasma glucose levels by enhancing glucose excretion (85). The metabolic pathways and certain molecules like AMP-activated protein kinase (AMPK), glycogen synthase kinase 3 (GSK3), acetyl-Co-A carboxylase (ACC), etc., involved in insulin generation, glycogen synthesis, glycolysis, pancreatic cell secretions, etc. are altered to generate hypoglycemic effects and raise insulin sensitivity. These phytochemicals target numerous metabolic pathways to produce the necessary anti-diabetic effects. Additionally, they have a role in the translocation of glucose transporter 4 (GLUT4) and the activation of phosphoinositide 3-kinase (PI3K) (86)(87).

The majority of plant-based glycosides have anti-inflammatory and anti-oxidant capabilities, which gives them a distinct advantage in the management of metabolic inflammation associated with diabetes. The usage of these natural glycosides and other phytochemicals also addresses other issues and difficulties, such as the lowering of insulin levels and glycemic index (88). Table 7.4 illustrates selected anti-diabetic phyto-glycosides and briefly states their respective effects in the remediation of diabetes.

7.6 Mode of action of glycosides

7.6.1 O-Glycosides as anti-diabetic sources and their mode of action

The most prevalent type of glycosides in plants are o-glycosides and are formed when a glycoside bond is formed when a sugar moiety called glycone (monosaccharide) is abridged with either aromatic or aliphatic alcohol (aglycone or genin) or another sugar molecule through an oxygen molecule (37). In plants, enzyme glycosyltransferases modulate the secondary metabolites and result in the biosynthesis of glycosides, which further require surplus reactions like acylation, degradation, and oxidation (37)(38)(158). C-glycosyl and O-glycosides, molecules are known to exhibit antidiabetic activities (85). According to Brito-Arias, 2007, there are several chemical reactions methodologies responsible for the coupling and formation of O-glycosides, namely the Armed-disarmed approach, Fischer reaction, Fusion method, various types of reactions-like Glycal, Helferich, Michael, Imidate, Koenigs-Knorr, groups exiting in various ways, using the solid-phase method, and Sulfur reaction(43). The prime pathway for O-glycosylation comprises a dehydration reaction between the moiety potassium phenoxideand [(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetyloxy-6-bromooxan-2-yl]methyl to producean acetylated derivative followed by the hydrolysis in the presence of base to synthesized the final product i.e., phenyl-β-D-glucopyranoside. However, the inception of the novel method, some modulations have been incorporated particularly for aromatic glycosides. In living organisms, the polymer glycogen is the main energy source which consists of α-1, 4- and α-1, 6- glucose units (159)(160). The two enzymes linked and responsible for polysaccharide formation.

A natural plant metabolite called phlorizin (Figure 7.10) is a type of O-glycoside (161)extracted from the apple (*Malus pumila*) and bark part of the pearin which position 2' of a -D-glucopyranosyl residue is linked to an aryl -D-glucoside (phloretin) by a glycosidic bond. It is known to lower blood glucose levels by enhanced excretion of renal glucose due to developed insulin resistance (149); but this compound is not much used as an antidiabetic drug it has certain side effects onenzyme glucosidases resulting in hydrolysis sensitivity, random.

Ethanolic extracts of guava leaves have reported antidiabetic activities, especially for T2DM (144). The flavonol-glycoside components (162) found in guava are guaijaverin, isoquercitrin (figure 7.11), hyperoside, and Peltatoside responsible for the hyperglycaemic activities.

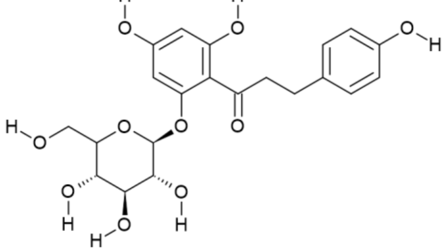


Figure 7.10: Molecular structure of Phlorezin.

Table 7.4: Glycosides and effects

Family	**Plant Species**	**Glycoside Name**	**Effects**	**References**
Acanthaceae	*Clinacanthus nutans*	4,6,8-Megastigmatrien-3-One, 1′,2′-Bis(Acetyloxy)-3′,4′-Didehydro-2′-Hydro-Β,Ψ-Carotene, N-Isobutyl-2-Nonen-6,8-Diynamide	α-Glucosidase inhibitor, hypoglycemic	(89)
Amaranthaceae	*Amaranthus caudatus*	Squalene, Quercetin, Betacarotene, Catechins	α-Amylase inhibitor, controls hyperglycemia, α-Glucosidase inhibitor	(90)
Apiaceae	*Eryngium foetidum*	Quercetin	α-Glucosidase inhibitor, antihyperglycemic	(91)
Apiaceae	*Ligusticum porteri*	3-(Z)-Butylidenephthalide, Myristicin and Ferulic Acid	α-Glucosidase inhibitor, antihyperglycemic	(92)
Lamiaceae	*Melissa officinalis*	Ferulic Acid, Rosmarinic Acid, Luteolin, Chlorogenic Acid, Luteolin-Glucoside, Apigenin-, Isochlorogenic Acid, Esculin	α-Amylase inhibitor, antidiabetic, improves insulin resistance	(93)
Araliaceae	*Panax ginseng*	Ginsenoside Rb1	lower insulin resistance and blood glucose	(94)(95)
Araliaceae	*Panax quinquefolium*	Vin α-ginsenoside R3	Improves insulin secretion	(96)
Asclepiadaceae	*Gymnemasylvestre*	Gymnemic Acids, Gurmarin, gymnemosides	Improved blood sugar homeostasis, hypoglycemic action, anti-hyperglycemic, regeneration of pancreatic β cells	(97)
Asteraceae	*Artemisia vulgaris*	Caffeoylquinic Acid	α-Amylase inhibitor, α-Glucosidase inhibitor, antidiabetic	(98)
Asteraceae	*Brickellia cavanillesii*	Sesquiterpenes, Curcumene, Spathulenol, Caryophyllene Oxide	α-Glucosidase inhibitor	(99)
Asteraceae	*Taraxacum officinale*	Taraxacin	Alters glycogen synthesis pathway, hypoglycemic	(100)
Amaranthaceae	*Beta vulgaris*	Vitexin, Acacetin	Antidiabetic effects	(101)
Bignoniaceae	*Oroxylum indicum*	Baicalein, Catechin, Luteolin, Quercetin	α-Glucosidase inhibitor	(102)
Brassicaceae	*Nasturtium officinale*	Glucosinolates	α-Glucosidase inhibitor	(103)
Celastraceae	*Salacia oblonga*	Quercetin, Kaempferol	α-Glucosidase inhibitor increases insulin sensitivity	(104)
Celastraceae	*Salacia reticulata*	Salacinol, Kotalanol, And De-O-Sulfonated Kotalanol.	Antidiabetic, hypoglycemic	(105)

Celastraceae	*Salacia reticulate*	Kotalanol, salacinol	Alters glycogen synthesis and insulin secretion pathway, hypoglycemic	(106)
Cleomaceae	*Cleome droserifolia*	Quercetin, Isorhamnetin, Kaempferol	Inhibit α-amylase and α-glucosidase	(107)
Clusiaceae	*Garcinia mangostana*	Geraniin	α-Glucosidase inhibitor, antihyperglycemic, α-Amylase inhibitor	(108)
Convolvulaceae	*Ipomoeabatatas*	Glycoprotein, Anthocyanins, Alkaloids, And Flavonoids	Inhibits intestinal α-glucosidase	(109)
Convolvulaceae	*Ipomoea aquatica*	Caffeoylquinic Acid, Quercetin, Caffeolyquinic Acid	α-Glucosidase inhibitor	(110)
Cucurbitaceae	*Citrullus colocynthis*	Citrullol, colocynthin, elaterin, elatericin B, colosynthetin	Alters glycogen synthesis pathway, antihyperglycemic, anti-inflammatory	(111)
Cucurbitaceae	*Luffa cylindnica*	Momordin-a, luffin-a	Alters glycogen synthesis and insulin secretion pathway, hypoglycemic	(112)
Cucurbitaceae	*Momordica charantia*	Momordin, momordicine, charantin, Momorcharaside A and B, momorcharin A and B	Increases insulin sensitivity, hypoglycemic	(113)
Cyperaceae	*Kyllinga monocephala*	Quercetin	α-Glucosidase inhibitor lowers blood glucose levels	(114)
Davalliaceae	*Davallia formosana*	Epicatechin-3-O-B-D-Allopyranoside	Antidiabetic, hypoglycemic	(115)(116)
Dryopteridaceae	*Dryopteris cycadina*	B-Sitosterol, Quercetin	α-Glucosidase inhibitor, antihyperglycemic	(117)
Ericaceae	*Arbutus andrachne*	Benzothiazole	α-Glucosidase inhibitor	(118)
Ericaceae	*Vaccinium oxycoccos*	Benzothiazole	α-Glucosidase inhibitor	(119)
Ericaceae	*Vaccinum arctostaphylus*	Benzothiazole	α-Glucosidase inhibitor	(120)
Euphorbiaceae	*Euphorbia thymifolia*	Quercetin, Quercitrin, Cosmosiin, Kaempferol, Amyrine, B-Sitosterol, Campesterol, Caryophyllene, Limonene, Phytol, Piperitenone, Safranal, Stigmasterol, Taraxerol, Euphorbol, 24 Methylene	α-Glucosidase inhibitor, antihyperglycemic	(121)
Fabaceae	*Astragalus mongolicus*	Astragalosides, Isoastragalosides,, Cycloartanes, Agroastragalosides I And II, Oleananes	Antidiabetic, hypoglycemic	(38)
Fabaceae	*Galega officinalis*	Galegine	Antidiabetic, controls high blood sugar levels	(122)
Fabaceae	*Peltophorum pterocarpum*	Myricetin	α-Glucosidase inhibitor, increased insulin sensitivity	(123)
Fabaceae	*Sophora japonica*	Quinoline, Catechin	α-Glucosidase inhibitor	(124)

Fabaceae	*Trigonella foenum graecum*	C-glycosides	Helps in glucose transportation, metabolizes carbohydrates, improves insulin sensitivity	(125)
Geraniaceae	*Geranium collinum*	Kaempferol	α-Glucosidase inhibitor, antidiabetic	(126)
Hypericaceae	*Hypericum triquetrifolium*	Catechin	α-Glucosidase inhibitor, antidiabetic	(127)
Juglandaceae	*Juglans regia*	Chlorogenic Acid, Kaempferol, Quercetin	Decreases blood glucose levels and improves insulin sensitivity.	(128)
Lamiaceae	*Perilla frutescens*	Luteolin, Rosmarinic Acid, Caffeic Acid, Apigenin	α-Glucosidase inhibitor, antihyperglycemic	(129)
Lamiaceae	*Rosmarinus officinalis*	Luteolin	α-Glucosidase inhibitor	(130)
Lamiaceae	*Salvia miltiorrhiza*	Steviol Glycosides, Stevioside, Rebaudioside A	GLUT4 translocation, and phosphoinositide 3-kinase (PI3K) activation	(131)
Lamiaceae	*Scutellaria baicalensis*	Aglycones, Baicalein, Wogonin, Oroxylin A	α-Glucosidase inhibitor	(132)
Lamiaceae	*Zataria multiflora*	Carvacrol	α-Glucosidase inhibitor, antihyperglycemic, improves insulin sensitivity	(133)
Lecythidaceae	*Careya arborea*	Kaempferol 3-Oglucopyranoside, Quercetin 3-O-(6-O-Glucopyranosyl)-Gluco Pyranoside, Quercetin 3-O-Glucopyranoside	α-Glucosidase inhibitor, antidiabetic	(134)
Meliaceae	*Azadirachta indica*	Xanthones	α-Glucosidase inhibitor	(135)
Menispermaceae	*Tinospora cordifollia*	Tinosporine, cordifolide, tinosporide, cordifole, columbin	Alters glycolysis pathways, hypoglycemic	(136)
Moraceae	*Artocarpus champeden*	Myricetin, Europetin	α-Glucosidase inhibitor, antihyperglycemic	(137)
Moraceae	*Ficus bengalensis*	Leucocyanidin, pelarogonidin	Alters glycogen synthesis and insulin secretion pathway, hypoglycemic	(138)
Moraceae	*Ficus racemosa*	Kuwanon L,Mulberrofuran G, Sanggenon C, Moracenin D, Mortatarin C, Sanggenon G, Sanggenon O, Sanggenol A, Sanggenon W, Nigrasin F, Sanggenol G, Mortatarin B	α-Glucosidase inhibitor	(139)
Moraceae	*Morus alba*	Kuwanon L, Mulberrofuran G, Sanggenon C, Moracenin D, Mortatarin C, Sanggenon G, Sanggenon O, Sanggenol A, Sanggenon W, Nigrasin F, Sanggenol G, Mortatarin B, Astragalin, scopolin, skimmin, roscoside II	α-Glucosidase inhibitor, improves insulin sensitivity, Pancreatic β cells regeneration	(140)

 ISBN: 978-978-780-772-9.

Myristicaceae	*Horsfieldia amygdalina*	Quinoline, Catechin	α-Glucosidase inhibitor, hypoglycemic	(124)
Myrtaceae	*Cleistocalyx operculatus*	Catechin	α-Glucosidase inhibitor	(141)
Myrtaceae	*Eucalyptus urophylla*	Kuwanon L,Mulberrofuran G, Sanggenon C, Moracenin D, Mortatarin C, Sanggenon G, Sanggenon O, Sanggenol A, Sanggenon W, Nigrasin F	α-Glucosidase inhibitor	(142)
Myrtaceae	*Psidium guajava*	Quercetin	Antihyperglycemic and antioxidative potential	(143) (144)
Myrtaceae	*Syzygium cumini*	Myricetin, Europetin	α-Glucosidase inhibitor, antihyperglycemic	(137)
Orobanchaceae	*Cistanche tubulosa*	Acteoside, Echinacoside, isoacteoside	Hypoglycemic	(145)
Oxalidaceae	*Averrhoa bilimbi*	Triacontanol, Dotriacontanyl Docosanoate, Oleanolic Acid, Ursolic Acid	α-Glucosidase inhibitor, hypoglycemic, antidiabetic	(146)
Piperaceae	*Piper lolot*	Quinoline, Catechin	α-Glucosidase inhibitor	(124)
Polygonaceae	*Polygonum multiflorum*	*Cis*-THSG (*Cis*-2,3,5,4′-Tetrahydroxystilbene 2-*O*-B-Glucopyranoside)	Anti-diabetic and Antioxidant potential	(147)
Portulaca Oleracea	*Portulaca oleracea*	Oleuropein	Modulate insulin secretion, antioxidative effect	(148)
Ericaceae	*Calluna vulgaris*	Arbutin	Anti-inflammatory, Anti-diabetic, Diuretic	(38)
Rosaceae	*Pyrus communis*	Arbutin	Anti-inflammatory, Anti-diabetic, diuretic	(38)
Rosaceae	*Pyrus communis*	Phlorizin	Decreases plasma glucose, improved insulin sensitivity, increased glucose excretion	(149)
Rosaceae	*Rosa damascene*	Myrcene, Kaempferol And Quercetin	α-Glucosidase inhibitor, hypoglycemic	(150)
Rubiaceae	*Cinchona succirubra*	Quinoline	α-Glucosidase inhibitor	(117)
Rubiaceae	*Hintonia latiflora*	Quinoline, Coutareagenin, Phenylcoumarin	α-Glucosidase inhibitor	(151)
Rubiaceae	*Mitragyna innermis*	Quinoline	α-Amylase inhibitor	(152)
Rubiaceae	*Paederia lanuginosa*	Quinoline, Catechin	α-Glucosidase inhibitor, decreases blood glucose levels	(124)
Salvadoracae	*Salvadora persica*	Salvadorine, Quercetin	α-Glucosidase inhibitor, hypoglycemic	(153)
Santalaceae	*Osyris alba*	Quercitrin, Phloroglucinol	α-Glucosidase inhibitor	(154)
Saxifragaceae	*Bergenia crassifolia*	Arbutin, Hydroquinone, Glycoside, Pyrogallol, Acetylsalicylic Acid, Caffeoyl Quinic, Fumaric, Furan carboxylic, Gallic acid, Malic acid, Protocatechuic Quinic Acid, Ellagic Acid	Anti-inflammatory, Anti-diabetic, Diuretic	(38)
Solanaceae	*Lycium barbarum*	Kaempferol, quercetin, Caffeic acid, chlorogenic acid, Rutin, Neochlorogenic acid, Luteolin	Hypoglycemic	(155)

Malvaceae	*Helicteres isora*	Cucurbitacin B, isocucurbitacin B	Alters glycogen synthesis pathway, hypoglycemic	(112)
Theaceae	*Camellia sinensis*	Ferulic Acid, Rosmarinic Acid, Luteolin, Luteolin-7-Glucoside, Apigenin-7-Glucoside, Isochlorogenic Acid, Esculin, Chlorogenic Acid	α-Amylase inhibitor, hypoglycemic	(93)
Theaceae	*Camellia sinensis*	Catechins	α-Amylase inhibitor, controls hyperglycemia, α-Glucosidase inhibitor	(90)
Tiliaceae	*Tilia cordata*	Rutoside, Hyperoside, Quercitrin, Isoquercitrin, Astragalin, Tyliroside	Anti-diabetic, hypoglycemic	(38)
Tiliaceae	*Tilia vulgaris*	Hyperoside, Rutoside, Tyliroside, Quercitrin, Isoquercitrin, Astragalin	Diuretic, Anti-diabetic, increases insulin release	(38)
Tiliaceae	*Tilia.platyphyllos*	Astragalin, Tyliroside, Rutoside, Hyperoside, Quercitrin, Isoquercitrin	Anti-diabetic, anti-inflammatory	(38)
Ericaceae	*Arctostaphylos uvaursi*	Arbutin, eriolin	Alters glycogen synthesis pathway, antihyperglycemic, anti-inflammatory	(156)
Vitaceae	*Leea indica*	Quercetin, Gallic Acid, Lupeol, B-Sitosterol, Ursolic Acid, Mollic Acid Arabinoside, And Mollic Acid Xyloside	Anti-diabetic increases insulin sensitivity	(157)

 ISBN: 978-978-780-772-9.

Polygonum multiflorum root reported the presence of a significant bioactive O-glycoside called trans-2,3,5,4′-tetrahydroxystilbene 2-O-β- glucopyranoside known to exhibit antioxidant and antidiabetic activity; however since the roots have a low concentration of the bioactive molecule, Tang et al., (2017) synthesized cis- 2,3,5,4′-tetrahydroxystilbene 2-O-β-glucopyranoside by mimicking the original process of *P. multiflorum*(147). Both the forms- trans- and cis-THSG are assessed for the treatment of T2DM; where the latter was found to be more effective than the former one. Functional foods can also be used for the treatment of diabetics either alone or coupled with the existing therapies.

The biosynthesis and evaluation of O-glycoside are achieved by discriminatory inhibitor consisting of azobenzene moiety coupled to anomeric carbon of glucose molecule by glycosidic bond (163). They showed that selective photo control may regulate the catalytic activities of prime enzymes associated with the metabolism of glycogen, thus opening an avenue toward the treatment and management of glycogen metabolism-related disorders.

Many scientists have worked on various plant species to isolate natural sources of O-glycoside like glycosides extracted from *Stevia rebaundiana*, called steviol glycosides are used widely as calorie-free sweeteners and are useful for patients with various metabolic syndrome, T2DM, and obesity (164). Stevioside and steviol most likely stimulate the glucocorticoid receptor (GR)and hence, have negative effects on metabolism, while the glycosides (steviol and steviol glycosides) employ glucocorticoid receptor-arbitrated effect the cancer Jurkat cells (164).

Ipomoea purpurea, commonly known as morning glory ofconvolvulaceae family is the main reservoir of bioactive therapeutic compounds (resin glycosides), with anti-diabetic activities for non-insulin-dependent T2DM prevention and treatment (165). Due to α-glucosidases' inhibitory action, resin-type glucosides administer postprandial levels of glucose and thus are important as anti-hyperglycaemic.

In Vietnam, a traditional herb named *Gynostemma longipes* is used to treat T2DM by tribal communities as this compound shows special effective stimulatory effects (166). Several bioactive molecules, especially O-Glycosides isolated from various species of Ficus is known to exhibit anti-diabetic pharmacological activities as it causes increased secretion of insulin and reduced glucose level in the blood (167). Mollic acid arabinoside, a natural O-glycoside isolated from hydroalcoholic and alcoholic extracts from leaves of *Leea indica* demonstrated hypoglycemic activity by reducing the glucose levels in the blood significantly (168). It is reported that the daily consumption of green tea, moderates homeostasis of blood glucose, regulates postprandial hyperglycemia, and thus prevents causing of T2DM (169). The O-glycoside kaempferol isolated from *C. sinensis* reported inhibitory action Kaempferol diglycoside revealed α-glucosidase inhibition with an IC_{50} of 40.02 4.61 M, whilst -amylase inhibition was observed with an IC_{50} of 0.09 0.02 M (170).

Natural O-glycosides flavonols- quercetin and quercetin glycosides isolated from solid waste onion (*Allium cepa*) demonstrated substantial anti-hyperglycaemic properties and were tested for antioxidant activities, enzyme inhibitory, and cytotoxicity (171). Similarly, isoquercetin (Figure 7.11) demonstrated the effects of anti-diabetes as it reduces the blood glucose level, insulin, and modulated enzyme genes responsible for mRNA expression of insulin and carbohydrate-metabolizing (172). These results are in synchronization with glibenclamide, the standard drug for DM. Therefore, such findings indicate the possibility of isoquercetin as a therapeutic drug in the future for treating DM. However, the hydrolytic instability of O-glycosides often results in the formation of various analogs of carbohydrates like N- or C-glycosides used as medicinal agents, which are discussed in the next section.

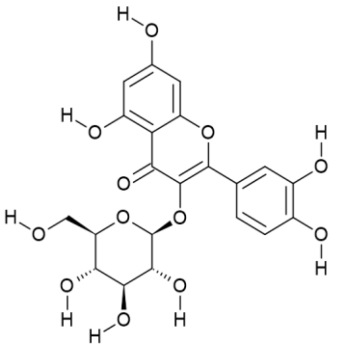


Figure 7. 11: Molecular structure of isoquercetin.

7.6.2 N-Glycosides as anti-diabetic sources and their mode of action

In N-glycosides, a glycoside bond is formed when a sugar moiety (monosaccharide) is abridged with either aromatic or aliphatic alcohol or another sugar molecule through the nitrogen of NH. As discussed in section 6.1, GP inhibition is one of the most researched approaches to deal with T1DM (85), therefore

N-glycosides like N-(β-dglucopyranosyl) amides (173), and derivatives of N-(d-glucopyranosyl)-N'-acyl urea (174), are known to exhibit anti-diabetic activities as they function as the most effective GP inhibitor of glucose analogs.

Earlier the amide-based inhibitor, [N-(β-d-glucopyranosyl) acetamide was known to be aefficient inhibitor of GP, urea derivatives namely [N-(β-d-glucopyranosyl)-N'-acyl] with correctly positioned and rightly sized.While N-(d-glucopyranosyl)-N'-acyl is the most potent analog of glucose inhibitor, the linked hydrophobic group to the amide part produced a more effective GP inhibitor(174)(175). The urea derivative is known to be a better inhibitor of GP than N-(β-d-glucopyranosyl) 3-(2-naphthyl)-propenoic amide (175).

Staudinger protocol was applied to study the conversion of 2, 3, 4, 6-tetra-O-acetyl—dglucopyranosyl and 2-acetamido-3, 4, 6-tri-O-acetyl-2-deoxy—dglucopyranosyl azides into the corresponding per-O-acetylated N-(-dglycopyranosyl) amides is described (175); followed by Zemplén deacetylation method to remove the protecting groups. Czifrák et al., 2006 reported that 3-(N-β-d-glucopyranosyl-carbamoyl) propanoic acid was the best inhibitor(176).

Similarly, with the use of glucopyranosylammonium carbamate, the efficacy of GP inhibitor N-(β-d-glucopyranosyl)-N′-substituted ureas can be magnificently enhanced (177). For the synthesis and assessment, several O-peracetylated N-(d-glucopyranosyl)-carboxamides with isoxazole or 1,2,3-triazole rings were considered., and a new derivative of GP inhibitor was reported (178). In 2014, screening of silicon in N-acyl-β-d-glucopyranosylamines Zinc database was reported as probable Glycogen Phosphorylase (GP) inhibitors (179).

Triazoles are another class of N-Glycosides, therapeutically important for their mechanism of bioisomerism with the peptide bonds due to dynamic involvement in H_2 bonding, and strong dipole moments making the triazoles oxidative/ reductive and hydrolysis stable (85). By using copper as a catalyst in the azide-alkyne cycloaddition (CuAAC), 1, 2, and 3-1 H-triazolyl glycohybrids, a triazole containing twin sugar moieties, were successfully synthesized (180).

The inhibitors were formed as a result of 1,3-dipolar cycloaddition reactions of glycosyl azides to give 2, 3-unsaturated alkynyl glycosides along with few glycol-hybrids which showed significant activities against target enzyme like glucose-6-phosphatase, GPand α-glucosidase and (180). Chu et al. (2016) studied the consequence of the C6-substitution on the inhibition of SGLT2 by N-indolylglucosides and reported that the sugar moiety position at C6 is very crucial for the suppression of SGLT2 (181). However,in rats, the compound (R=acetyl) induced excretion of glucose (182).

Understanding the characterization of interfaces resulting in their binding to the enzymes is crucial for designing efficient drugs. A derivative of acridone which made from glucose (GLAC) and inhibitor of GLAC compound is considered as a superior inhibitors of glucose-6-phosphatase; where all compounds are glucose derivatives, and cyclopropane rings crucial for GP and enables for the investigation of minor interactions in the catalytic region. It is included in the structure of two of the active inhibitors (183).

Among the N-glycosides series, the most efficient inhibitors of SGLT and GPb are N-uracil glycoside; 1, 2, 3-triazolyl N-glycosides and N-indolylglycosides (85). Canagliflozin, empagliflozin, luseogliflozinand tofogliflozin are a few of the approved marketed medications based on glycoside (85).

7.6.3 C-Glycosides as anti-diabetic sources and their mode of action

In C-glycosides, a glycoside bond is formed when a sugar moiety (monosaccharide) is abridged with either aromatic or aliphatic alcohol or another sugar molecule through a carbon molecule. Aglycone is coupled with C1 carbon (an anomeric carbon) of the compound glycone, which present in two diastereo isomers i.e α and β forms, while the enzymes like β-glucosidases are responsible for the degradation of the glycosidic linkages as these are unstable and vulnerable to hydrolysis. The plants' active glycosides are usually β-linked (37)(38)(158). C-glycoside molecules are hydrolysis resistant in nature.

C-Glycosides without being converted to the prodrug, are metabolically more stable than O-glycosides with enhanced plasma exposure and bioavailability (184). Under the category of C-glycosyl derivatives, mainly there are two types-aromatic and heteroaromatic. C-glycosylarenes are an aromatic type of C-glycosides that have gained much importance in recent times. Researchers have observed that the inhibitors can provide the active catalytic site and lessen the transition state conformation of 280s at the same position as d-glucose loop by enabling various attachments to Asn284 and Asp283 of this loop (185). Yet another new drug, recently, known asprotein tyrosine phosphatase 1B(PTB1B) has been discoveredto treat T2DM (186), and subsequently β-C-glycosyl and β-C glycosiduronic acid quinones molecules were invented as sugar-based PTP1B inhibitors (187).

Dapagliflozin was discovered in 2008 as the T2DM treatment using a selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor(188); where it is assumed that the selective SGLT2 does not undergo O-glucosidase degradation and helps in the decline of glucose level in blood. In rats, Dapagliflozin is a better stimulator than SGLT2 inhibitors for glucosuria.

Puerarin and several derivatives, an isoflavone C-glucoside are used to treat diabetics (189). It was observed that i the isoflavone moiety was responsible for the uptake of glucose and C-glucose and may be accountable for increasesthe water solubility in puerarin.

The C-glucosides with a heterocyclic ring are metabolically better and stable SGLT2 inhibitors as compared to O-glucoside (190). Canagliflozin, a thiophene derivative is considered to be an SGLT2 inhibitor that is significantly potent and selective, and known to exhibit anti-diabetic properties; first SGLT2 inhibitor to receive US approval and undergoing regulatory review in the European Union is Canagliflozin(191)(192).

An array was produced and tested for hSGLT1 and hSGLT2 C-aryl glucosides with different substituents at the distal aryl ring's 4′ locationhuman inhibitors(193). Zhang et al., (2011) reported the hyperglycaemic activity of bexagliflozin has IC50 values are 5.6 μM for SGLT1 and 2 nM for SGLT2 against humans(194). Among the novel derivatives of benzothiophene discovered, the efficacy of ipragliflozin was very high and functioned as a selective SGLT2 inhibitor (195).

D-gluco- and d-xylopyranosylidene-spirohydantoins and thiohydantoins are synthesized from extremely regio-, chemo- and stereospecific methods using six steps from the equivalent free sugar (196). The function of particular H2 bridges in binding to enzyme inhibitors was reported in the studies on d-gluco and d-xylo spiro-hydantoins, as well as N- (d-glucopyranosyl) amides (196). C-(β-d-glucopyranosyl) heterocycles were prepared with acidic, neutral, and basic characteristics in the heterocyclic moieties (197); where benzimidazole was regarded as the most effective inhibitor (197).

Three β-d-glucopyranose analogs of were studied to check the increased affinity of GP, which in turn will help in the treatment of DM (198). These molecules were 2-(β-d-glucopyranosyl)-benzothiazole, 2-(β-d-glucopyranosyl)-5-methyl-1,3,4-oxadiazole, and 2-(β-d-glucopyranosyl)-Benzim idazole; and they showed that the inhibitors may be fitted in the active catalytic site of Transition-state GP (198). The researchers were able to compare the inhibitory efficacy of various C-glucopyranosyl indoles, pyrroles, and modified C-glucopyranosyl imidazolesagainst glycogen phosphatase(199). Sim et al., (2010), suggested a methodology to check the glucose levels in the blood, particularly for T2DM-i.e. to target the intestinal glucosidases and α-amylases that use α-glucosidase inhibitors miglitol and acarbose(105). One such target is maltase-glucoamylase (ntMGAM)'s N-terminal catalytic domain, which is oneof the fourintestinal enzyme activity of glycoside hydrolase 31 causing hydrolysis of end starch products into glucose.

Extensive research was carried out by Kyriakis et al., (2018) on recent hyperglycaemic molecules, their molecular targets, and their mode of action(200). Kerru and his co-workers revealed the usage of heterocyclic scaffolds for their biological evaluation as inhibitors against the corresponding molecular targets(201). The study listed a varied target range that includes- G protein-coupled receptors (GPCR), α-glucosidase, aldose reductase glucagon receptor (GCGr), peroxisome proliferator-activated receptor-γ (PPAR-γ), PTP1B, fructose-1,6-bisphosphatase (FBPase), sodium-glucose co-transporter-2 (SGLT2phosphoenolpyruvate carboxykinase (PEPCK) and GP.

7.7 Stevioside: The natural sweetener

The leaves of the Paraguayan and Brazilian natural plant *Stevia rebaudiana*, a genus of the sunflower family, contain the steviol glycoside known as stevioside. In 1931, two French chemists, M. Bridel and R. Lavielle, discovered stevioside and named it after the plant genus from which it originated (202). In 1980, Tomoya Ogawa and his colleagues at what is now known as the Institute of Physical and Chemical Research in Wak, Japan (also known as Riken) reported that they had successfully completed the entire synthesis of stevioside(203).

For hundreds of years, South Americans have relied on a sweetener prepared from the dried leaves of the *S. rebaudiana* plant (204). Figure 7.12 reflects on Stevioside extraction from *S. rebaudiana* (leaf source) and its drug formulation. Recently, stevioside and its glycoside relative rebaudioside have been "discovered" in various regions of the world as a non-nutritive substitute for table sugar (205). The two active ingredients in *Stevia*are called stevioside and rebaudioside (sucrose). One gram of stevioside is said to be able to replace 300 grams of sucrose (206). People's interest in adding sweets to their cuisine has skyrocketed during the past few decades. The universal market for high-intensity sweeteners is anticipated to be worth $1.146 billion in 2010, according to market research (207).

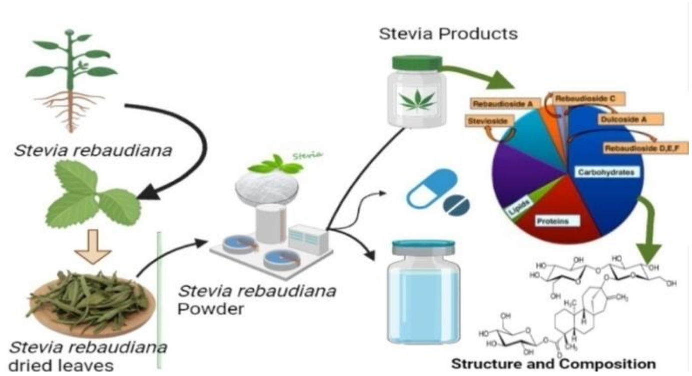


Figure 7.12: Schematic representation of Stevioside extraction from *Stevia rebaudiana*leaves and its drug formulation.

7.7.1 Sources of Stevioside

Flowers, leaves, and stems the plant contain sweet-tasting glycosides, but the roots do not while the leaves contain 5–20% stevioside and rebaudioside A (208). According to Srivastava & Chaturvedi, 2022, the blooms contain 0.9–1% by weight of them(209). Steviol glycosides are vital to the world economy, hence synthetic methods have been developed to synthesize them. Steviol glycosides also convert intorebaudioside Aand stevioside (210). The percentages of rebaudioside A and stevioside in leaves range from 5% to 20% (211). Flowers typically have less than 1% (weight/weight) of these compounds (212). Synthetic methods have been developed to synthesize steviol glycosides because of their importance to the global economy (213). Steviol glycosides serve as a precursor for the production of rebaudioside A and stevioside (214). Glycoside extraction in Brazil produces 60 %stevioside and zero steviol or isosteviol, making it suitable for usage in food, beverages, pharmaceuticals, and soft drinks. Brazil produces for domestic distribution (215). Canada, the Czech Republic, India, and Russia process stevioside in large quantities (216)(217).

7.7.2 Antihyperglycemic activity of stevioside

Herbal supplements and acupuncture are just two examples of the complementary and alternative medicine treatments that today's patients are using to keep their diabetes under control. In South American countries, *S. rebaudiana* extract has been used to treat diabetes for decades (218). Its primary component, stevioside, is extremely sweet but has zero calories, and just a trace quantity is required for sweetening purposes (219). Stevioside has been extensively investigated for its ant diabetic potential. Table 7.5 illustrates a few studies related to antihyperglycemic activity of Stevioside.

Table 7.5: Selected reports depicting antidiabatic potential of stevioside

Experimental system	Dose of stevioside given	Outcome	Reference
Type 2 diabetic humans	1g	Reduction in glucagon and glucose level	(220)
Goto Kakizaki rat	0.025g per kg	Antihyperglycemic potential (incremental area of glucose response curve). Improved insulin response and suppression of glucagon concentration.	(221)
Wistar rats	500-2500mg per kg of body weight as suuplement with high fat diet	Normalization of hyperlipidemia. Reduction of damage of tissue in diabetic animals	(222)
Wistar rats	2500mg per kg of body weight	Improvement of levels of blood glucose, insulin resistance indices and very low density lipoprotein.	(223)
3T3-L1 cells		Increase in glucose uptake by the cells	(224)

 ISBN: 978-978-780-772-9.

7.8 Patents of successfully marketed drugs obtained from phyto-glycoside sources (1994 onwards)

The invention is a process which offers novel ways of representation or finding technical solution to the existing problems. A patent is a unique right granted to an invention. In order to get a patent, the technical details of the inventions must be provided in public domain.Patents are useful, practical concepts that have real-world applications. They are not just abstract ideas. Patents support the development of breakthroughs and new technology in every field by rewarding ideas.The international legal foundation for patents is made up of the treaties that WIPO overseas as well as local, national, and international legislation.

Many plants store their chemicals primarily as inactive glycosides (225). Enzyme hydrolysis, which separates the chemical from the sugar component and renders it useful, can activate them (226). These plant glycosides are frequently used in medical practice.

Some of these phytochemicals obtained from different plants are listed in the table 7.6, as patent filed during the last few years.

7.9 Conclusion

The condition known as DM can develop when insulin does not function properly, leading to an increased level of glucose in the blood. Diabetes that is persistent and cannot be managed effectively can eventually lead to complications that include multiple factors. The care of diabetes in modern times involves the use of many medicines, each of which can expedite several adverse consequences that are potentially fatal, such as - cardiovascular diseases and cholesterol.

Within the scope of this review, the anti-diabetic benefits of a variety of glycosides derived from natural resources have been addressed. O-glycosides are the most prevalent form of glycoside that exhibits antidiabetic activity; they do this by lowering blood sugar levels (by decreased glucose absorption and increased insulin production) and by blocking α-glucosidase (via increased insulin resistance). N-glycosides are useful in controlling the type 1 diabetes. Majority of the most powerful N-glycosides accomplish this by inhibiting SGLT as well as GP. The molecules known as C-glycosides are unaffected to metabolic breakdown and hydrolysis. In order to cureDM, C-glycosides are extremely effective against proteininhibitors such as PTP1B a as well as SGLT2. Moreover, stevioside, a strong O-glycoside, is anti-hyperglycemic and hyperlipidemic.Recently, stevioside and its glycoside relative rebaudioside have been "discovered" in various regions of the world as a non-nutritive substitute for table sugar. Stevia effectively decreased glucose levels in the patients of type 2 diabetic disorder.

Many phyo- glycosides have been discovered and patentized so far and seen to have an anti-diabetic effectas well but, their formulations into drugs and clinical research is much to be focused on. Complex chemical drug regime has successfully affected the incidence of drug adherence and efficacy. So, a gradual shift from regular chemical anti-diabetics to drugs with herbal formulations ensures fewer side effects and safety for future generations. Because of this, glycosides require an approach that is methodical and concentrated on experimental and clinical trials, which will assist in the creation of novel medications for diabetes with the combined efforts of researchers worldwide.

References

1. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol [Internet]. 2014 Jan;2(1):56–64. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213858713701128
2. Gojka Roglic. WHO Global report on diabetes: A summary. Int J Noncommunicable Dis. 2016;1(1):3–8.
3. Adki KM, Kulkarni YA. Glycosides from Natural Sources in the Treatment of Diabetes Mellitus. In: Structure and Health Effects of Natural Products on Diabetes Mellitus [Internet]. Singapore: Springer Singapore; 2021. p. 81–102. Available from: http://link.springer.com/10.1007/978-981-15-8791-7_5
4. Guerriero G, Berni R, Muñoz-Sanchez J, Apone F, Abdel-Salam E, Qahtan A, et al. Production of Plant Secondary Metabolites: Examples, Tips and Suggestions for Biotechnologists. Genes (Basel) [Internet]. 2018 Jun 20;9(6):309. Available from: http://www.mdpi.com/2073-4425/9/6/309
5. Tuso P. Prediabetes and Lifestyle Modification: Time to Prevent a Preventable Disease. Perm J [Internet]. 2014 Sep;18(3):88–93. Available from: http://www.thepermanentejournal.org/doi/10.7812/TPP/14-002
6. Riccardi G, Rivellese AA. Effects of Dietary Fiber and Carbohydrate on Glucose and Lipoprotein Metabolism in Diabetic Patients. Diabetes Care [Internet]. 1991 Dec 1;14(12):1115–25. Available from: https://diabetesjournals.org/care/article/14/12/1115/16477/Effects-of-Dietary-Fiber-and-Carbohydrate-on
7. Umpierre D. Physical Activity Advice Only or Structured Exercise Training and Association With HbA 1c Levels in Type 2 Diabetes. JAMA [Internet]. 2011 May 4;305(17):1790. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2011.576
8. DeFronzo RA. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes [Internet]. 2009 Apr 1;58(4):773–95. Available from: https://diabetesjournals.org/diabetes/article/58/4/773/117/From-the-Triumvirate-to-the-Ominous-Octet-A-New
9. Bailey C. The Current Drug Treatment Landscape for Diabetes and Perspectives for the Future. Clin Pharmacol Ther [Internet]. 2015 Aug;98(2):170–84. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cpt.144

Table 7.6: Patents of glycosides derived from plantsources and their use in the remediation of diabetes.

Patent Title	Patent ID	Year	Inventor (s)	SPECIFIC FIELD OF INVENTION	References
Plant extract for prophylaxis and treatment of hyperglycemic disease.	EP2226076A1	2009	Henning Vollert	1. The subject of the invention is the extraction of a Brassica plant leaf extract for the treatment and/or prevention of a hyperglycemic illness which is known to be arich source of flavonoids or glycosides. Extracts are reported to contain active substances with higher SGLT-1 inhibitory activity.	(227)
Substituted fused heterocyclic c-glycosides	EP1679965A4	2004	Philip Rybczynski, Maud Urbanski, Xiaoyan Zhang	1. This invention relates to a novel technique for treating a patient suffering from diabetes Syndrome X, or problems related to those conditions. 2. The method of the invention involves combining one or more antidiabetic medications with one or more glucose reabsorption (SGLT) inhibitors to create a medication for treating a condition.	(228)
Anti-diabetic agent and use thereof	JP2010248130A	2009	Satoshi Kumazawa, Tsumoru Watanabe, Nobuyuki Kusano, Yoshiharu Ito, Atsuko Ezawa	1. This invention is related to 6-hydroxy kaempferol-3-o-rutinoside, antidiabeticflavonoid glycoside extracted from plants like Safflower (*Carthamus tinctorius L.)* 2. It shows α-glucosidase supressive activity.	(229)
Bauhinia hupehara C. and its extracts in the treatment of diabetes.	CN1919229B	2005	Zhao Yimin, Shan Junjie, Zhao Qizhi	1. The extract from the Chinese medicinal plant *Bauhinia hupehara*is used to lower blood sugar and reduce fat. 2. The extract contains polyphenol acid, saponin, and flavones (including flavone glycosides). 3. The extract shows weight loosing and blood sugar lowering properties in alloxan diabetic mouse.	(230)
Use of *Cyclocarya paliurus* glycoside compounds for preparing medicament for curing diabetes	CN101254200A	2007	Yu Qiang	1. Cyclocarya paliurus lljinskaja pharmaceutically acceptable salt or glycosidic compounds from leaves is characterized in this invention and is used for the treatment of diabetes. 2. It can dramatically reduce the symptoms of diabetes in alloxan-treated diabetic mice and stop the blood sugar from rising, which has a protective impact.	(231)
Substituted fused heterocyclic C-glycosides	US7482330B2	2004	Philip Rybczynski Maud Urbanski Xiaoyan Zhang	1. The compounds including substituted fused heterocyclic C-glycosides, as well as their applications for them, are thesubject of the invention. 2. A procedure for reducing mammal blood glucose that entails giving the animal being treated an effective dosage of a formula compound (IV).	(228)
C-Glycosides and preparation thereof as antidiabetic agents	GB2359554A	2001	Hiroshi Tomiyama Yoshinori Kobayashi Atsushi Noda Akira Tomiyama Tsuyoshi Tomiyama	1. A method of preparation of C- Glycosides of general formula (I), a salt containing acceptable pharmaceutical ingredients and use in Diabetes control.	(232)
Methods of treating diabetes mellitus and clycogen storage disease	US5817634A	1994	Elias Meezan , Stephen M. Manzella	1. Method of priming the incorporation of glucose into an oligosaccharide having alpha(1-4) glycosidic linkage.	(233)

References (Cont'd)

10. Wittmeier KD, Wicklow BA, Sellers EA, Griffith AT, Dean HJ, McGavock JM. Success with lifestyle monotherapy in youth with new-onset type 2 diabetes. Paediatr Child Health [Internet]. 2012 Mar;17(3):129–32. Available from: https://academic.oup.com/pch/article-lookup/doi/10.1093/pch/17.3.129

11. Chamberlain JJ, Rhinehart AS, Shaefer CF, Neuman A. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med [Internet]. 2016 Apr 19;164(8):542. Available from: http://annals.org/article.aspx?doi=10.7326/M15-3016

12. Ouyang J, Parakhia RA, Ochs RS. Metformin Activates AMP Kinase through Inhibition of AMP Deaminase. J Biol Chem [Internet]. 2011 Jan;286(1):1–11. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925820541902

13. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: an association to bear in mind. World J Diabetes [Internet]. 2021 Jul 15;12(7):916–31. Available from: https://www.wjgnet.com/1948-9358/full/v12/i7/916.htm

14. Donnelly LA, Dennis JM, Coleman RL, Sattar N, Hattersley AT, Holman RR, et al. Risk of Anemia With Metformin Use in Type 2 Diabetes: A MASTERMIND Study. Diabetes Care [Internet]. 2020 Oct 1;43(10):2493–9. Available from: https://diabetesjournals.org/care/article/43/10/2493/35897/Risk-of-Anemia-With-Metformin-Use-in-Type-2

15. Kennedy L, Freeman JS. Role of the incretin pathway in the pathogenesis of type 2 diabetes mellitus. Cleve Clin J Med [Internet]. 2009 Dec;76(12 suppl 5):S12–9. Available from: https://www.ccjm.org//lookup/doi/10.3949/ccjm.76.s5.03

16. Komamine M, Kajiyama K, Ishiguro C, Uyama Y. Cardiovascular risks associated with dipeptidyl peptidase-4 inhibitors monotherapy compared with other antidiabetes drugs in the Japanese population: A nationwide cohort study. Pharmacoepidemiol Drug Saf [Internet]. 2019 Sep 23;28(9):1166–74. Available from: https://onlinelibrary.wiley.com/doi/10.1002/pds.4847

17. Chou H-C, Chen W-W, Hsiao F-Y. Acute Pancreatitis in Patients with Type 2 Diabetes Mellitus Treated with Dipeptidyl Peptidase-4 Inhibitors: A Population-Based Nested Case-Control Study. Drug Saf [Internet]. 2014 Jul 24;37(7):521–8. Available from: http://link.springer.com/10.1007/s40264-014-0171-x

18. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts TC, Leufkens HG. Use of Dipeptidyl Peptidase-4 Inhibitors and the Reporting of Infections: A Disproportionality Analysis in the World Health Organization VigiBase. Diabetes Care [Internet]. 2011 Feb 1;34(2):369–74. Available from: https://diabetesjournals.org/care/article/34/2/369/39139/Use-of-Dipeptidyl-Peptidase-4-Inhibitors-and-the

19. Fukushima K, Kitamura S, Tsuji K, Wada J. Sodium–Glucose Cotransporter 2 Inhibitors Work as a "Regulator" of Autophagic Activity in Overnutrition Diseases. Front Pharmacol [Internet]. 2021 Oct 21;12. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2021.761842/full

20. Lega IC, Bronskill SE, Campitelli MA, Guan J, Stall NM, Lam K, et al. Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: A population-based study of older women and men with diabetes. Diabetes, Obes Metab [Internet]. 2019 Nov 21;21(11):2394–404. Available from: https://onlinelibrary.wiley.com/doi/10.1111/dom.13820

21. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: A meta-analysis. Diabetes Metab Res Rev [Internet]. 2017 Sep;33(6):e2903. Available from: https://onlinelibrary.wiley.com/doi/10.1002/dmrr.2903

22. Hampp C, Swain RS, Horgan C, Dee E, Qiang Y, Dutcher SK, et al. Use of Sodium–Glucose Cotransporter 2 Inhibitors in Patients With Type 1 Diabetes and Rates of Diabetic Ketoacidosis. Diabetes Care [Internet]. 2020 Jan 1;43(1):90–7. Available from: https://diabetesjournals.org/care/article/43/1/90/35940/Use-of-Sodium-Glucose-Cotransporter-2-Inhibitors

23. GREENE MW, MORRICE N, GAROFALO RS, ROTH RA. Modulation of human insulin receptor substrate-1 tyrosine phosphorylation by protein kinase Cdelta. Biochem J [Internet]. 2004 Feb 15;378(1):105–16. Available from: https://portlandpress.com/biochemj/article/378/1/105/41043/Modulation-of-human-insulin-receptor-substrate-1

24. Kim GJ, Kim SB, Jo S Il, Shin JK, Kwon HS, Jeong H, et al. Two Cases of Allergy to Insulin in Gestational Diabetes. Endocrinol Metab [Internet]. 2015;30(3):402. Available from: http://e-enm.org/journal/view.php?doi=10.3803/EnM.2015.30.3.402

25. Carlessi R, Chen Y, Rowlands J, Cruzat VF, Keane KN, Egan L, et al. GLP-1 receptor signalling promotes β-cell glucose metabolism via mTOR-dependent HIF-1α activation. Sci Rep [Internet]. 2017 Jun 1;7(1):2661. Available from: https://www.nature.com/articles/s41598-017-02838-2

26. Filippatos TD, Panagiotopoulou T V., Elisaf MS. Adverse Effects of GLP-1 Receptor Agonists. Rev Diabet Stud [Internet]. 2014;11(3–4):202–30. Available from: http://www.soc-bdr.org/content/e4/e887/volRdsVolumes14222/issRdsIssues14231/chpRdsChapters14232/strRdsArticles14678/?preview=preview

27. Bezin J, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, et al. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Diabetes Care [Internet]. 2023 Feb 1;46(2):384–90. Available from: https://diabetesjournals.org/care/article/46/2/384/147888/GLP-1-Receptor-Agonists-and-the-Risk-of-Thyroid

28. Martin GM, Kandasamy B, DiMaio F, Yoshioka C, Shyng S-L. Anti-diabetic drug binding site in a mammalian KATP channel revealed by Cryo-EM. Elife [Internet]. 2017 Oct 24;6. Available from: https://elifesciences.org/articles/31054

29. Azoulay L, Suissa S. Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies. Diabetes Care [Internet]. 2017 May 1;40(5):706–14. Available from: https://diabetesjournals.org/care/article/40/5/706/36863/Sulfonylureas-and-the-Risks-of-Cardiovascular

30. Wang YL, Frauwirth KA, Rangwala SM, Lazar MA, Thompson CB. Thiazolidinedione Activation of Peroxisome Proliferator-activated Receptor γ Can Enhance Mitochondrial Potential and Promote Cell Survival. J Biol Chem [Internet]. 2002 Aug;277(35):31781–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S002192582070030X

31. Yen F, Wei JC, Chiu L, Hsu C, Hou M, Hwu C. Thiazolidinediones were associated with higher risk of cardiovascular events in patients with type 2 diabetes and cirrhosis. Liver Int [Internet]. 2021 Jan 11;41(1):110–22. Available from: https://onlinelibrary.wiley.com/doi/10.1111/liv.14714

32. Bazelier MT, de Vries F, Vestergaard P, Leufkens HGM, De Bruin ML. Use of thiazolidinediones and risk of bladder cancer: disease or drugs? Curr Drug Saf [Internet]. 2013 Nov;8(5):364–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24215315

33. Habib ZA, Havstad SL, Wells K, Divine G, Pladevall M, Williams LK. Thiazolidinedione Use and the Longitudinal Risk of Fractures in Patients with Type 2 Diabetes Mellitus. J Clin Endocrinol Metab [Internet]. 2010 Feb 1;95(2):592–600. Available from: https://academic.oup.com/jcem/article/95/2/592/2596749

34. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol [Internet]. 2014;4. Available from: http://journal.frontiersin.org/article/10.3389/fphar.2013.00177/abstract

35. WHO establishes the Global Centre for Traditional Medicine in India [Internet]. World Health Organization.

Available from: https://www.who.int/news/item/25-03-2022-who-establishes-the-global-centre-for-traditional-medicine-in-india
36. Vishnu N, Mini GK, Thankappan KR. Complementary and alternative medicine use by diabetes patients in Kerala, India. Glob Heal Epidemiol Genomics [Internet]. 2017 May 15;2:e6. Available from: https://www.cambridge.org/core/product/identifier/S2054420017000069/type/journal_article
37. Soto-Blanco B. Herbal glycosides in healthcare. In: Herbal Biomolecules in Healthcare Applications [Internet]. Elsevier; 2022. p. 239–82. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323858526000214
38. Bartnik M, Facey PC. Glycosides. In: Pharmacognosy [Internet]. Elsevier; 2017. p. 101–61. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128021040000081
39. Khan H, Pervaiz A, Intagliata S, Das N, Nagulapalli Venkata KC, Atanasov AG, et al. The analgesic potential of glycosides derived from medicinal plants. DARU J Pharm Sci [Internet]. 2020 Jun 14;28(1):387–401. Available from: http://link.springer.com/10.1007/s40199-019-00319-7
40. Yang H, Protiva P, Cui B, Ma C, Baggett S, Hequet V, et al. New Bioactive Polyphenols from Theobroma g randiflorum ("Cupuaçu"). J Nat Prod [Internet]. 2003 Dec 1;66(11):1501–4. Available from: https://pubs.acs.org/doi/10.1021/np034002j
41. Voisine R, Carmichael L, Chalier P, Cormier F, Morin A. Determination of Glucovanillin and Vanillin in Cured Vanilla Pods. J Agric Food Chem [Internet]. 1995 Oct 1;43(10):2658–61. Available from: https://pubs.acs.org/doi/abs/10.1021/jf00058a019
42. Gangasani JK, Pemmaraju DB, Murthy USN, Rengan AK, Naidu VGM. Chemistry of herbal biomolecules. In: Herbal Biomolecules in Healthcare Applications [Internet]. Elsevier; 2022. p. 63–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323858526000184
43. Marco Brito-Arias. N-Glycosides. In: Synthesis and Characterization of Glycosides [Internet]. Boston, MA: Springer US; p. 138–78. Available from: http://link.springer.com/10.1007/978-0-387-70792-1_3
44. 5. ANTHERACENE GLYCOSIDES. In: Medicinal Plant Glycosides [Internet]. University of Toronto Press; 1967. p. 63–72. Available from: https://www.degruyter.com/document/doi/10.3138/9781487584771-005/html
45. Pandey DK BR. The influence of dual inoculation with Glomus mossae and Azotobacter on growth and barbaloin content of Aloe vera. Am J Sustain Agric. 2009;3(4):703–14.
46. Simpson D, Amos S. Other Plant Metabolites. In: Pharmacognosy [Internet]. Elsevier; 2017. p. 267–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128021040000123
47. Malik EM, Müller CE. Anthraquinones As Pharmacological Tools and Drugs. Med Res Rev [Internet]. 2016 Jul;36(4):705–48. Available from: https://onlinelibrary.wiley.com/doi/10.1002/med.21391
48. Fu J, Wu Z, Zhang L. Clinical applications of the naturally occurring or synthetic glycosylated low molecular weight drugs. In 2019. p. 487–522. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1877117319300390
49. Patel S. Plant-derived cardiac glycosides: Role in heart ailments and cancer management. Biomed Pharmacother [Internet]. 2016 Dec;84:1036–41. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0753332216314251
50. Kanji S, MacLean RD. Cardiac Glycoside Toxicity. Crit Care Clin [Internet]. 2012 Oct;28(4):527–35. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0749070412000577
51. Mugford ST, Osbourn A. Saponin Synthesis and Function. In: Isoprenoid Synthesis in Plants and Microorganisms [Internet]. New York, NY: Springer New York; 2012. p. 405–24. Available from: http://link.springer.com/10.1007/978-1-4614-4063-5_28
52. Osbourn A. Saponins and plant defence — a soap story. Trends Plant Sci [Internet]. 1996 Jan;1(1):4–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1360138596800161
53. Mugford ST, Qi X, Bakht S, Hill L, Wegel E, Hughes RK, et al. A Serine Carboxypeptidase-Like Acyltransferase Is Required for Synthesis of Antimicrobial Compounds and Disease Resistance in Oats. Plant Cell [Internet]. 2009 Oct 2;21(8):2473–84. Available from: https://academic.oup.com/plcell/article/21/8/2473/6095511
54. Sparg SG, Light ME, van Staden J. Biological activities and distribution of plant saponins. J Ethnopharmacol [Internet]. 2004 Oct;94(2–3):219–43. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874104002557
55. Podolak I, Galanty A, Sobolewska D. Saponins as cytotoxic agents: a review. Phytochem Rev [Internet]. 2010 Sep 25;9(3):425–74. Available from: http://link.springer.com/10.1007/s11101-010-9183-z
56. Lechtenberg M. Cyanogenic Glycosides and Biogenetically Related Compounds in Higher Plants and Animals. In: eLS [Internet]. Wiley; 2021. p. 1–18. Available from: https://onlinelibrary.wiley.com/doi/10.1002/9780470015902.a0029316
57. Vetter J. Plant cyanogenic glycosides. Toxicon [Internet]. 2000 Jan;38(1):11–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0041010199001282
58. Burčul F, Generalić Mekinić I, Radan M, Rollin P, Blažević I. Isothiocyanates: cholinesterase inhibiting, antioxidant, and anti-inflammatory activity. J Enzyme Inhib Med Chem [Internet]. 2018 Jan 1;33(1):577–82. Available from: https://www.tandfonline.com/doi/full/10.1080/14756366.2018.1442832
59. Srinivasan S, Vinothkumar V, Murali R. Antidiabetic Efficacy of Citrus Fruits With Special Allusion to Flavone Glycosides. In: Bioactive Food as Dietary Interventions for Diabetes [Internet]. Elsevier; 2019. p. 335–46. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128138229000229
60. Shao Y, Jiang J, Ran L, Lu C, Wei C, Wang Y. Analysis of Flavonoids and Hydroxycinnamic Acid Derivatives in Rapeseeds (Brassica napus L. var. napus) by HPLC-PDA–ESI(−)-MS n /HRMS. J Agric Food Chem [Internet]. 2014 Apr 2;62(13):2935–45. Available from: https://pubs.acs.org/doi/10.1021/jf404826u
61. Cartea ME, Francisco M, Soengas P, Velasco P. Phenolic Compounds in Brassica Vegetables. Molecules [Internet]. 2010 Dec 30;16(1):251–80. Available from: http://www.mdpi.com/1420-3049/16/1/251
62. Boeckler GA, Gershenzon J, Unsicker SB. Phenolic glycosides of the Salicaceae and their role as anti-herbivore defenses. Phytochemistry [Internet]. 2011 Sep;72(13):1497–509. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0031942211000677
63. Hopkinson SM. The chemistry and biochemistry of phenolic glycosides. Q Rev Chem Soc [Internet]. 1969;23(1):98. Available from: http://xlink.rsc.org/?DOI=qr9692300098

64. Arita H, Sugita K, Nomura A, Sato K, Kawanami J. Studies on antiviral glycosides. Synthesis and biological evaluation of various phenyl glycosides. Carbohydr Res [Internet]. 1978 Apr;62(1):143–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008621500833868
65. Nandi K, Ghosh R, Mondal S, Sen DDJ, Saha DD. Source, isolation & impact of glycone and aglycone in human body. World J Pharm Sci [Internet]. 2021;09(11):103–13. Available from: https://wjpsonline.com/index.php/wjps/article/view/source-isolation-impact-glycone-aglycone-human-body/929
66. Ito H, Nishida Y, Yamazaki M, Nakahara K, Michalska-Hartwich M, Furmanowa M, et al. Chrysophanol Glycosides from Callus Cultures of Monocotyledonous Kniphofia spp. (Asphodelaceae). Chem Pharm Bull [Internet]. 2004;52(10):1262–4. Available from: http://www.jstage.jst.go.jp/article/cpb/52/10/52_10_1262/_article
67. Patil JG, Ahire ML, Nitnaware KM, Panda S, Bhatt VP, Kishor PBK, et al. In vitro propagation and production of cardiotonic glycosides in shoot cultures of Digitalis purpurea L. by elicitation and precursor feeding. Appl Microbiol Biotechnol [Internet]. 2013 Mar 19;97(6):2379–93. Available from: http://link.springer.com/10.1007/s00253-012-4489-y
68. Gupta AS. Strategic Approaches for the Purification of Glycosides from Natural Sources. In: Natural Bio-active Compounds [Internet]. Singapore: Springer Singapore; 2019. p. 129–47. Available from: http://link.springer.com/10.1007/978-981-13-7154-7_5
69. Nazir R, Gupta S, Dey A, Kumar V, Yousuf M, Hussain S, et al. In vitro propagation and assessment of genetic fidelity in Dioscorea deltoidea, a potent diosgenin yielding endangered plant. South African J Bot [Internet]. 2021 Aug;140:349–55. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0254629920309960
70. SHI W, WANG Y, LI J, ZHANG H, DING L. Investigation of ginsenosides in different parts and ages of Panax ginseng. Food Chem [Internet]. 2007;102(3):664–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0308814606004420
71. Lin N, Cai D-L, Jin D, Chen Y, Shi J-J. Ginseng Panaxoside Rb1 Reduces Body Weight in Diet-Induced Obese Mice. Cell Biochem Biophys [Internet]. 2014 Jan 4;68(1):189–94. Available from: http://link.springer.com/10.1007/s12013-013-9688-3
72. Luo KK, Kim DA, Mitchell-Silbaugh KC, Huang G, Mitchell AE. Comparison of amygdalin and benzaldehyde levels in California almond (Prunus dulcis) varietals. Acta Hortic [Internet]. 2018 Oct;(1219):1–8. Available from: https://www.actahort.org/books/1219/1219_1.htm
73. Santos Pimenta LP, Schilthuizen M, Verpoorte R, Choi YH. Quantitative Analysis of Amygdalin and Prunasin in Prunus serotina Ehrh. using 1 H-NMR Spectroscopy. Phytochem Anal [Internet]. 2014 Mar;25(2):122–6. Available from: https://onlinelibrary.wiley.com/doi/10.1002/pca.2476
74. Xie J, Ding C, Ge Q, Zhou Z, Zhi X. Simultaneous determination of ginkgolides A, B, C and bilobalide in plasma by LC–MS/MS and its application to the pharmacokinetic study of Ginkgo biloba extract in rats. J Chromatogr B [Internet]. 2008 Mar 15;864(1–2):87–94. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1570023208000858
75. Çelik SA, Kan A, Ayran İ, Çoksarı G. Investigation of routine contents of buckwheat (Fagopyrum esculentum Moench) cultivated in Turkey. Int J Agric Environ Food Sci [Internet]. 2018 Oct 15;2(Special 1):196–8. Available from: https://dergipark.org.tr/en/doi/10.31015/jaefs.18035
76. Smith WA, Lauren DR, Burgess EJ, Perry NB, Martin RJ. A Silychristin Isomer and Variation of Flavonolignan Levels in Milk Thistle (Silybum marianum) Fruits. Planta Med [Internet]. 2005 Jul;71(9):877–80. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2005-864187
77. Zhou P, Zheng M, Li X, Zhou J, Shang Y, Li Z, et al. A consecutive extraction of pectin and hesperidin from Citrus aurantium L.:Process optimization, extract mechanism, characterization and bio-activity analysis. Ind Crops Prod [Internet]. 2022 Aug;182:114849. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0926669022003326
78. Murti PBR, Seshadri TR. A study of the chemical components of the roots ofDecalepis Hamiltonii. Proc Indian Acad Sci - Sect A [Internet]. 1942 Aug;16(2):135. Available from: http://link.springer.com/10.1007/BF03170463
79. Yang H, Barros-Rios J, Kourteva G, Rao X, Chen F, Shen H, et al. A re-evaluation of the final step of vanillin biosynthesis in the orchid Vanilla planifolia. Phytochemistry [Internet]. 2017 Jul;139:33–46. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0031942217301528
80. Braga VC de C, Pianetti GA, César IC. Comparative stability of arbutin in <scp>*Arctostaphylos uva-ursi*</scp> by a new comprehensive stability-indicating HPLC method. Phytochem Anal [Internet]. 2020 Nov 4;31(6):884–91. Available from: https://onlinelibrary.wiley.com/doi/10.1002/pca.2953
81. Shah ZA, Hameed A, Ahmed A, Simjee SU, Jabeen A, Ullah A, et al. Cytotoxic and anti-inflammatory salicin glycosides from leaves of Salix acmophylla. Phytochem Lett [Internet]. 2016 Sep;17:107–13. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1874390016301100
82. Cioffi G, Escobar LM, Braca A, De Tommasi N. Antioxidant Chalcone Glycosides and Flavanones from Maclura (Chlorophora) t inctoria. J Nat Prod [Internet]. 2003 Aug 1;66(8):1061–4. Available from: https://pubs.acs.org/doi/10.1021/np030127c
83. Kytidou K, Artola M, Overkleeft HS, Aerts JMFG. Plant Glycosides and Glycosidases: A Treasure-Trove for Therapeutics. Front Plant Sci [Internet]. 2020 Apr 7;11. Available from: https://www.frontiersin.org/article/10.3389/fpls.2020.00357/full
84. Yeram PB, Kulkarni YA. Glycosides and Vascular Complications of Diabetes. Chem Biodivers [Internet]. 2022 Oct;19(10). Available from: https://onlinelibrary.wiley.com/doi/10.1002/cbdv.202200067
85. Pałasz A, Cież D, Trzewik B, Miszczak K, Tynor G, Bazan B. In the Search of Glycoside-Based Molecules as Antidiabetic Agents. Top Curr Chem [Internet]. 2019 Aug 5;377(4):19. Available from: http://link.springer.com/10.1007/s41061-019-0243-6
86. Bharti SK, Krishnan S, Kumar A, Kumar A. Antidiabetic phytoconstituents and their mode of action on metabolic pathways. Ther Adv Endocrinol Metab [Internet]. 2018 Mar 12;9(3):81–100. Available from: http://journals.sagepub.com/doi/10.1177/2042018818755019
87. Muhammad I, Rahman N, Gul-E-Nayab, Nishan U, Shah M. Antidiabetic activities of alkaloids isolated from medicinal plants. Brazilian J Pharm Sci [Internet]. 2021;57. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1984-82502021000100543&tlng=en
88. Kong M, Xie K, Lv M, Li J, Yao J, Yan K, et al. Anti-inflammatory phytochemicals for the treatment of diabetes and its complications: Lessons learned and future promise. Biomed Pharmacother [Internet]. 2021 Jan;133:110975. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0753332220311677
89. Liu X, Lai D, Liu Q, Zhou L, Liu Q, Liu Z. Bioactivities of a New Pyrrolidine Alkaloid from the Root Barks of Orixa japonica. Molecules [Internet]. 2016 Dec 2;21(12):1665. Available from: http://www.mdpi.com/1420-3049/21/12/1665
90. Vinholes J, Vizzotto M. Synergisms in alpha-glucosidase inhibition and antioxidant activity of Camellia

sinensis L. Kuntze and Eugenia uniflora L. Ethanolic Extracts. Pharmacognosy Res [Internet]. 2017;9(1):101. Available from: https://www.phcogres.com/article/2017/9/1/1041030974-8490197797
91. Hussain M. Food Contamination: Major Challenges of the Future. Foods [Internet]. 2016 Mar 23;5(4):21. Available from: http://www.mdpi.com/2304-8158/5/2/21
92. Brindis F, Rodríguez R, Bye R, González-Andrade M, Mata R. (Z)-3-Butylidenephthalide from Ligusticum porteri, an α-Glucosidase Inhibitor. J Nat Prod [Internet]. 2011 Mar 25;74(3):314–20. Available from: https://pubs.acs.org/doi/10.1021/np100447a
93. Funke I, Melzig MF. Traditionally used plants in diabetes therapy: phytotherapeutics as inhibitors of alpha-amylase activity. Rev Bras Farmacogn [Internet]. 2006 Mar;16(1):1–5. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-695X2006000100002&lng=en&nrm=iso&tlng=en
94. Tian W, Chen L, Zhang L, Wang B, Li XB, Fan KR, et al. Effects of ginsenoside Rg1 on glucose metabolism and liver injury in streptozotocin-induced type 2 diabetic rats. Genet Mol Res [Internet]. 2017;16(1). Available from: http://www.funpecrp.com.br/gmr/year2017/vol16-1/pdf/gmr-16-01-gmr.16019463.pdf
95. Zhou P, Xie W, He S, Sun Y, Meng X, Sun G, et al. Ginsenoside Rb1 as an Anti-Diabetic Agent and Its Underlying Mechanism Analysis. Cells [Internet]. 2019 Feb 28;8(3):204. Available from: https://www.mdpi.com/2073-4409/8/3/204
96. Vuksan V, Sievenpiper JL, Koo VYY, Francis T, Beljan-Zdravkovic U, Xu Z, et al. American Ginseng (Panax quinquefolius L) Reduces Postprandial Glycemia in Nondiabetic Subjects and Subjects With Type 2 Diabetes Mellitus. Arch Intern Med [Internet]. 2000 Apr 10;160(7):1009. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.160.7.1009
97. Kosaraju J, Dubala A, Chinni S, Khatwal RB, Satish Kumar MN, Basavan D. A molecular connection of Pterocarpus marsupium, Eugenia jambolana and Gymnema sylvestre with dipeptidyl peptidase-4 in the treatment of diabetes. Pharm Biol [Internet]. 2014 Feb;52(2):268–71. Available from: http://www.tandfonline.com/doi/full/10.3109/13880209.2013.823550
98. Olennikov DN, Chirikova NK, Kashchenko NI, Nikolaev VM, Kim S-W, Vennos C. Bioactive Phenolics of the Genus Artemisia (Asteraceae): HPLC-DAD-ESI-TQ-MS/MS Profile of the Siberian Species and Their Inhibitory Potential Against α-Amylase and α-Glucosidase. Front Pharmacol [Internet]. 2018 Jul 12;9. Available from: https://www.frontiersin.org/article/10.3389/fphar.2018.00756/full
99. Escandón-Rivera S, González-Andrade M, Bye R, Linares E, Navarrete A, Mata R. α-Glucosidase Inhibitors from Brickellia cavanillesii. J Nat Prod [Internet]. 2012 May 25;75(5):968–74. Available from: https://pubs.acs.org/doi/10.1021/np300204p
100. Broadhurst CL, Polansky MM, Anderson RA. Insulin-like Biological Activity of Culinary and Medicinal Plant Aqueous Extracts in Vitro. J Agric Food Chem [Internet]. 2000 Mar 1;48(3):849–52. Available from: https://pubs.acs.org/doi/10.1021/jf9904517
101. Mohammed HS, Abdel-Aziz MM, Abu-Baker MS, Saad AM, Mohamed MA, Ghareeb MA. Antibacterial and Potential Antidiabetic Activities of Flavone C-glycosides Isolated from Beta vulgaris Subspecies cicla L. var. Flavescens (Amaranthaceae) Cultivated in Egypt. Curr Pharm Biotechnol [Internet]. 2019 Aug 8;20(7):595–604. Available from: http://www.eurekaselect.com/172546/article
102. Wang R-Y, Su P-J, Li B, Zhan X-Q, Qi F-M, Lv C-W, et al. Two new aromatic derivatives from Codonopsis pilosula and their α-glucosidase inhibitory activities. Nat Prod Res [Internet]. 2022 Oct 2;36(19):4929–35. Available from: https://www.tandfonline.com/doi/full/10.1080/14786419.2021.1912749
103. Klimek-Szczykutowicz M, Szopa A, Ekiert H. Chemical composition, traditional and professional use in medicine, application in environmental protection, position in food and cosmetics industries, and biotechnological studies of Nasturtium officinale (watercress) – a review. Fitoterapia [Internet]. 2018 Sep;129:283–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0367326X18305719
104. Chelladurai GRM, Chinnachamy C. Alpha amylase and Alpha glucosidase inhibitory effects of aqueous stem extract of Salacia oblonga and its GC-MS analysis. Brazilian J Pharm Sci [Internet]. 2018 May 14;54(1). Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1984-82502018000100606&lng=en&tlng=en
105. Sim L, Jayakanthan K, Mohan S, Nasi R, Johnston BD, Pinto BM, et al. New Glucosidase Inhibitors from an Ayurvedic Herbal Treatment for Type 2 Diabetes: Structures and Inhibition of Human Intestinal Maltase-Glucoamylase with Compounds from Salacia reticulata. Biochemistry [Internet]. 2010 Jan 26;49(3):443–51. Available from: https://pubs.acs.org/doi/10.1021/bi9016457
106. Huang TH, He L, Qin Q, Yang Q, Peng G, Harada M, et al. Salacia oblonga root decreases cardiac hypertrophy in Zucker diabetic fatty rats: inhibition of cardiac expression of angiotensin II type 1 receptor. Diabetes, Obes Metab [Internet]. 2008 Jul;10(7):574–85. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1463-1326.2007.00750.x
107. Abdel Motaal A, Salem HH, Almaghaslah D, Alsayari A, Bin Muhsinah A, Alfaifi MY, et al. Flavonol Glycosides: In Vitro Inhibition of DPPIV, Aldose Reductase and Combating Oxidative Stress are Potential Mechanisms for Mediating the Antidiabetic Activity of Cleome droserifolia. Molecules [Internet]. 2020 Dec 11;25(24):5864. Available from: https://www.mdpi.com/1420-3049/25/24/5864
108. Palanisamy UD, Ling LT, Manaharan T, Appleton D. Rapid isolation of geraniin from Nephelium lappaceum rind waste and its anti-hyperglycemic activity. Food Chem [Internet]. 2011 Jul;127(1):21–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0308814610016912
109. Akhtar N, Akram M, Daniyal M, Ahmad S. Evaluation of antidiabetic activity of Ipomoea batatas L. extract in alloxan-induced diabetic rats. Int J Immunopathol Pharmacol [Internet]. 2018 Jan 26;32:205873841881467. Available from: http://journals.sagepub.com/doi/10.1177/2058738418814678
110. Lawal, U., Shaari, K., Ismail, I. S., Khatib, A., & Abas F. Antioxidant and α-glucosidase inhibitory activities of isolated compounds from Ipomoea aquatica. Rec Nat Prod. 2016;10(6):701–7.
111. González-Tejero MR, Casares-Porcel M, Sánchez-Rojas CP, Ramiro-Gutiérrez JM, Molero-Mesa J, Pieroni A, et al. Medicinal plants in the Mediterranean area: Synthesis of the results of the project Rubia. J Ethnopharmacol [Internet]. 2008 Mar;116(2):341–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874107006435
112. Lemus I, García R, Delvillar E, Knop G. Hypoglycaemic activity of four plants used in Chilean popular medicine. Phyther Res [Internet]. 1999 Mar;13(2):91–4. Available from: https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1099-1573(199903)13:2%3C91::AID-PTR350%3E3.0.CO;2-8
113. Chao C-Y, Huang C. Bitter Gourd (Momordica charantia) Extract Activates Peroxisome Proliferator-Activated Receptors and Upregulates the Expression of the

Acyl CoA Oxidase Gene in H4IIEC3 Hepatoma Cells. J Biomed Sci [Internet]. 2003;10(6):782–91. Available from: http://www.karger.com/doi/10.1159/000073966
114. Chai T-T, Yeoh L-Y, Ismail N, Ong H-C, Manan F, Wong F-C. Evaluation of Glucosidase Inhibitory and Cytotoxic Potential of Five Selected Edible and Medicinal Ferns. Trop J Pharm Res [Internet]. 2015 Apr 16;14(3):449. Available from: http://www.ajol.info/index.php/tjpr/article/view/115757
115. Lee S.Y., Mediani A., Nur Ashikin A. H., Azliana A. B. S. & AF. Antioxidant and α-glucosidase inhibitory activities of the leaf and stem of selected traditional medicinal plants. Int Food Res J. 2014;21(1):379–86.
116. Lin C-H, Wu J-B, Jian J-Y, Shih C-C. (−)-Epicatechin-3-O-β-D-allopyranoside from Davallia formosana prevents diabetes and dyslipidemia in streptozotocin-induced diabetic mice. Essop MF, editor. PLoS One [Internet]. 2017 Mar 23;12(3):e0173984. Available from: https://dx.plos.org/10.1371/journal.pone.0173984
117. Taha M, Ismail NH, Imran S, Wadood A, Rahim F, Ali M, et al. Novel quinoline derivatives as potent in vitro α-glucosidase inhibitors: in silico studies and SAR predictions. Medchemcomm [Internet]. 2015;6(10):1826–36. Available from: http://xlink.rsc.org/?DOI=C5MD00280J
118. Gong Z, Peng Y, Qiu J, Cao A, Wang G, Peng Z. Synthesis, In Vitro α-Glucosidase Inhibitory Activity and Molecular Docking Studies of Novel Benzothiazole-Triazole Derivatives. Molecules [Internet]. 2017 Sep 15;22(9):1555. Available from: http://www.mdpi.com/1420-3049/22/9/1555
119. Guasch-Ferré M, Merino J, Sun Q, Fitó M, Salas-Salvadó J. Dietary Polyphenols, Mediterranean Diet, Prediabetes, and Type 2 Diabetes: A Narrative Review of the Evidence. Oxid Med Cell Longev [Internet]. 2017;2017:1–16. Available from: https://www.hindawi.com/journals/omcl/2017/6723931/
120. Feshani AM, Kouhsari SM, Mohammadi S. Vaccinium arctostaphylos, a common herbal medicine in Iran: Molecular and biochemical study of its antidiabetic effects on alloxan-diabetic Wistar rats. J Ethnopharmacol [Internet]. 2011 Jan;133(1):67–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874110006409
121. Nguyen Vo TH, Tran N, Nguyen D, Le L. An in silico study on antidiabetic activity of bioactive compounds in Euphorbia thymifolia Linn. Springerplus [Internet]. 2016 Dec 18;5(1):1359. Available from: http://springerplus.springeropen.com/articles/10.1186/s40064-016-2631-5
122. Nagalievska M, Sabadashka M, Hachkova H, Sybirna N. Galega officinalis extract regulate the diabetes mellitus related violations of proliferation, functions and apoptosis of leukocytes. BMC Complement Altern Med [Internet]. 2018 Dec 8;18(1):4. Available from: https://bmccomplementalternmed.biomedcentral.com/articles/10.1186/s12906-017-2079-3
123. Manaharan T, Teng LL, Appleton D, Ming CH, Masilamani T, Palanisamy UD. Antioxidant and antiglycemic potential of Peltophorum pterocarpum plant parts. Food Chem [Internet]. 2011 Dec;129(4):1355–61. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0308814611007308
124. MAI TT, THU NN, TIEN PG, CHUYEN N Van. Alpha-Glucosidase Inhibitory and Antioxidant Activities of Vietnamese Edible Plants and Their Relationships with Polyphenol Contents. J Nutr Sci Vitaminol (Tokyo) [Internet]. 2007;53(3):267–76. Available from: http://www.jstage.jst.go.jp/article/jnsv/53/3/53_3_267/_article
125. Gupta D, Raju J, Baquer NZ. Modulation of some gluconeogenic enzyme activities in diabetic rat liver and kidney: effect of antidiabetic compounds. Indian J Exp Biol [Internet]. 1999 Feb;37(2):196–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10641146
126. Amin S, Ullah B, Ali M, Rauf A, Khan H, Uriarte E, et al. Potent in Vitro α-Glucosidase Inhibition of Secondary Metabolites Derived from Dryopteris cycadina. Molecules [Internet]. 2019 Jan 24;24(3):427. Available from: http://www.mdpi.com/1420-3049/24/3/427
127. Mrabti H, Jaradat N, Fichtali I, Ouedrhiri W, Jodeh S, Ayesh S, et al. Separation, Identification, and Antidiabetic Activity of Catechin Isolated from Arbutus unedo L. Plant Roots. Plants [Internet]. 2018 Apr 12;7(2):31. Available from: http://www.mdpi.com/2223-7747/7/2/31
128. Pitschmann A, Zehl M, Atanasov AG, Dirsch VM, Heiss E, Glasl S. Walnut leaf extract inhibits PTP1B and enhances glucose-uptake in vitro. J Ethnopharmacol [Internet]. 2014 Mar;152(3):599–602. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874114001184
129. Ha TJ, Lee JH, Lee M-H, Lee BW, Kwon HS, Park C-H, et al. Isolation and identification of phenolic compounds from the seeds of Perilla frutescens (L.) and their inhibitory activities against α-glucosidase and aldose reductase. Food Chem [Internet]. 2012 Dec;135(3):1397–403. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0308814612009533
130. Koga K, Shibata H, Yoshino K, Nomoto K. Effects of 50% Ethanol Extract from Rosemary (Rosmarinus officinalis) on ?-Glucosidase Inhibitory Activity and the Elevation of Plasma Glucose Level in Rats, and Its Active Compound. J Food Sci [Internet]. 2006 Sep;71(7):S507–12. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1750-3841.2006.00125.x
131. Mohammed A, Tajuddeen N, Ibrahim MA, Isah MB, Aliyu AB, Islam MS. Potential of diterpenes as antidiabetic agents: Evidence from clinical and pre-clinical studies. Pharmacol Res [Internet]. 2022 May;179:106158. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043661822001037
132. Lu Q-Y, Zhang L, Moro A, Chen MC, Harris DM, Eibl G, et al. Detection of Baicalin Metabolites Baicalein and Oroxylin-A in Mouse Pancreas and Pancreatic Xenografts. Pancreas [Internet]. 2012 May;41(4):571–6. Available from: https://journals.lww.com/00006676-201205000-00012
133. Kamrani Y, Amanlou M, Yazdanyar A, AdliMoghaddam A, Ebrahimi S. Potential anti-diabetic and anti-oxidant activity of essential oil of Zataria multiflora leaves. Planta Med [Internet]. 2008 Jul;74(09). Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0028-1084170
134. Khaliq HA. Pharmacognostic, physicochemical, phytochemical and pharmacological studies on Careya arborea Roxb.; A review. J Phytopharm [Internet]. 2016 Mar 20;5(1):27–34. Available from: http://www.phytopharmajournal.com/Vol5_Issue1_06.pdf
135. Ryu HW, Cho JK, Curtis-Long MJ, Yuk HJ, Kim YS, Jung S, et al. α-Glucosidase inhibition and antihyperglycemic activity of prenylated xanthones from Garcinia mangostana. Phytochemistry [Internet]. 2011 Dec;72(17):2148–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0031942211003736
136. Hui H, Tang G, Go V. Hypoglycemic herbs and their action mechanisms. Chin Med [Internet]. 2009;4(1):11. Available from: http://cmjournal.biomedcentral.com/articles/10.1186/1749-8546-4-11
137. Manaharan T, Palanisamy UD, Ming CH. Tropical Plant Extracts as Potential Antihyperglycemic Agents. Molecules [Internet]. 2012 May 18;17(5):5915–23. Available from: http://www.mdpi.com/1420-3049/17/5/5915
138. Singh RK, Mehta S, Jaiswal D, Rai PK, Watal G. Antidiabetic effect of Ficus bengalensis aerial roots in experimental animals. J Ethnopharmacol [Internet]. 2009 May;123(1):110–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874109000890
139. Choo CY, Sulong NY, Man F, Wong TW. Vitexin and isovitexin from the Leaves of Ficus deltoidea with in-vivo α-glucosidase inhibition. J Ethnopharmacol [Internet]. 2012 Aug;142(3):776–81. Available from:

https://linkinghub.elsevier.com/retrieve/pii/S0378874112003844
140. Wang Z, Li X, Chen M, Liu F, Han C, Kong L, et al. A strategy for screening of α-glucosidase inhibitors from Morus alba root bark based on the ligand fishing combined with high-performance liquid chromatography mass spectrometer and molecular docking. Talanta [Internet]. 2018 Apr;180:337–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039914017312730
141. MAI TT, CHUYEN N Van. Anti-Hyperglycemic Activity of an Aqueous Extract from Flower Buds of Cleistocalyx operculatus (Roxb.) Merr and Perry. Biosci Biotechnol Biochem [Internet]. 2007 Jan 23;71(1):69–76. Available from: https://academic.oup.com/bbb/article/71/1/69-76/5940339
142. Manaharan T, Ming CH, Palanisamy UD. Syzygium aqueum leaf extract and its bioactive compounds enhances pre-adipocyte differentiation and 2-NBDG uptake in 3T3-L1 cells. Food Chem [Internet]. 2013 Jan;136(2):354–63. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0308814612013404
143. Oh WK, Lee CH, Lee MS, Bae EY, Sohn CB, Oh H, et al. Antidiabetic effects of extracts from Psidium guajava. J Ethnopharmacol [Internet]. 2005 Jan;96(3):411–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874104004660
144. Huang C-S, Yin M-C, Chiu L-C. Antihyperglycemic and antioxidative potential of Psidium guajava fruit in streptozotocin-induced diabetic rats. Food Chem Toxicol [Internet]. 2011 Sep;49(9):2189–95. Available from: https://linkinghub.elsevier.com/retrieve/pii/S027869151100247X
145. Zhu K, Meng Z, Tian Y, Gu R, Xu Z, Fang H, et al. Hypoglycemic and hypolipidemic effects of total glycosides of Cistanche tubulosa in diet/streptozotocin-induced diabetic rats. J Ethnopharmacol [Internet]. 2021 Aug;276:113991. Available from: https://linkinghub.elsevier.com/retrieve/pii/S037887412100218X
146. Ali H, Houghton PJ, Soumyanath A. α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. J Ethnopharmacol [Internet]. 2006 Oct;107(3):449–55. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874106001863
147. Tang W, Li S, Liu Y, Wu J-C, Pan M-H, Huang M-T, et al. Anti-diabetic activities of cis - and trans -2,3,5,4′-tetrahydroxystilbene 2- O - β -glucopyranoside from Polygonum multiflorum. Mol Nutr Food Res [Internet]. 2017 Aug;61(8):1600871. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mnfr.201600871
148. Wu L, Velander P, Liu D, Xu B. Olive Component Oleuropein Promotes β-Cell Insulin Secretion and Protects β-Cells from Amylin Amyloid-Induced Cytotoxicity. Biochemistry [Internet]. 2017 Sep 26;56(38):5035–9. Available from: https://pubs.acs.org/doi/10.1021/acs.biochem.7b00199
149. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest [Internet]. 1987 May 1;79(5):1510–5. Available from: http://www.jci.org/articles/view/112981
150. Boskabady MH, Shafei MN, Saberi Z, Amini S. Pharmacological effects of rosa damascena. Iran J Basic Med Sci [Internet]. 2011 Jul;14(4):295–307. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23493250
151. Mata R, Cristians S, Escandón-Rivera S, Juárez-Reyes K, Rivero-Cruz I. Mexican Antidiabetic Herbs: Valuable Sources of Inhibitors of α-Glucosidases. J Nat Prod [Internet]. 2013 Mar 22;76(3):468–83. Available from: https://pubs.acs.org/doi/10.1021/np300869g
152. McCue PP, Shetty K. Inhibitory effects of rosmarinic acid extracts on porcine pancreatic amylase in vitro. Asia Pac J Clin Nutr [Internet]. 2004;13(1):101–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15003922
153. Khan M, Ali M, Ali A, Mir SR. Hypoglycemic and Hypolipidemic Activities of Arabic and Indian Origin Salvadora Persica Root Extract on Diabetic Rats with Histopathology of Their Pancreas. Int J Health Sci (Qassim) [Internet]. 2014 Jan;8(1):45–56. Available from: http://platform.almanhal.com/CrossRef/Preview/?ID=2-52646
154. Mandrone M, Scognamiglio M, Fiorentino A, Sanna C, Cornioli L, Antognoni F, et al. Phytochemical profile and α-glucosidase inhibitory activity of Sardinian Hypericum scruglii and Hypericum hircinum. Fitoterapia [Internet]. 2017 Jul;120:184–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0367326X17304227
155. Zhao X, Guo S, Lu Y, Hua Y, Zhang F, Yan H, et al. Lycium barbarum L. leaves ameliorate type 2 diabetes in rats by modulating metabolic profiles and gut microbiota composition. Biomed Pharmacother [Internet]. 2020 Jan;121:109559. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0753332219351820
156. Moon YH, Nam SH, Kang J, Kim Y-M, Lee J-H, Kang H-K, et al. Enzymatic synthesis and characterization of arbutin glucosides using glucansucrase from Leuconostoc mesenteroides B-1299CB. Appl Microbiol Biotechnol [Internet]. 2007 Dec 5;77(3):559–67. Available from: http://link.springer.com/10.1007/s00253-007-1202-7
157. Raghavendra DHL. Traditional uses, chemistry and pharmacological activities of Leea indica (Burm. f.) Merr.(Vitaceae): A comprehensive review. Int J Green Pharm. 2018;12(1):S71–80.
158. Alamgir ANM. Secondary Metabolites: Secondary Metabolic Products Consisting of C and H; C, H, and O; N, S, and P Elements; and O/N Heterocycles. In 2018. p. 165–309. Available from: http://link.springer.com/10.1007/978-3-319-92387-1_3
159. Barford D, Johnson LN. The allosteric transition of glycogen phosphorylase. Nature [Internet]. 1989 Aug;340(6235):609–16. Available from: http://www.nature.com/articles/340609a0
160. Spasov AA, Chepljaeva NI, Vorob'ev ES. Glycogen phosphorylase inhibitors in the regulation of carbohydrate metabolism in type 2 diabetes. Russ J Bioorganic Chem [Internet]. 2016 Mar 7;42(2):133–42. Available from: http://link.springer.com/10.1134/S1068162016020138
161. Bebernitz G. Sodium–Glucose Cotransporters. In: Comprehensive Medicinal Chemistry III [Internet]. Elsevier; 2017. p. 491–511. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780124095472124308
162. Eidenberger T, Selg M, Krennhuber K. Inhibition of dipeptidyl peptidase activity by flavonol glycosides of guava (Psidium guajava L.): A key to the beneficial effects of guava in type II diabetes mellitus. Fitoterapia [Internet]. 2013 Sep;89:74–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0367326X13001354
163. Díaz-Lobo M, Garcia-Amorós J, Fita I, Velasco D, Guinovart JJ, Ferrer JC. Correction: Selective photoregulation of the activity of glycogen synthase and glycogen phosphorylase, two key enzymes in glycogen metabolism. Org Biomol Chem [Internet]. 2015;13(39):10072–10072. Available

from: http://xlink.rsc.org/?DOI=C5OB90155C
164. Panagiotou C, Mihailidou C, Brauhli G, Katsarou O, Moutsatsou P. Effect of steviol, steviol glycosides and stevia extract on glucocorticoid receptor signaling in normal and cancer blood cells. Mol Cell Endocrinol [Internet]. 2018 Jan;460:189–99. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0303720717303969
165. Rosas-Ramírez D, Escandón-Rivera S, Pereda-Miranda R. Morning glory resin glycosides as α-glucosidase inhibitors: In vitro and in silico analysis. Phytochemistry [Internet]. 2018 Apr;148:39–47. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0031942218300128
166. Pham HTT, Ha TKQ, Cho HM, Lee BW, An JP, Tran VO, et al. Insulin Mimetic Activity of 3,4- Seco and Hexanordammarane Triterpenoids Isolated from Gynostemma longipes. J Nat Prod [Internet]. 2018 Nov 26;81(11):2470–82. Available from: https://pubs.acs.org/doi/10.1021/acs.jnatprod.8b00524
167. Deepa P, Sowndhararajan K, Kim S, Park SJ. A role of Ficus species in the management of diabetes mellitus: A review. J Ethnopharmacol [Internet]. 2018 Apr;215:210–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874117333688
168. Kekuda PTR, Raghavendra HL BAS. Traditional uses, chemistry and pharmacological activities of Leea indica (Burm. f.) Merr. (Vitaceae): a comprehensive review. Int J Green Pharm. 2018;12:S73–80.
169. Hua F, Zhou P, Wu H-Y, Chu G-X, Xie Z-W, Bao G-H. Inhibition of α-glucosidase and α-amylase by flavonoid glycosides from Lu'an GuaPian tea: molecular docking and interaction mechanism. Food Funct [Internet]. 2018;9(8):4173–83. Available from: http://xlink.rsc.org/?DOI=C8FO00562A
170. Chu K-F, Song J-S, Chen C-T, Yeh T-K, Hsieh T-C, Huang C-Y, et al. Synthesis and biological evaluation of N-glucosyl indole derivatives as sodium-dependent glucose co-transporter 2 inhibitors. Bioorg Chem [Internet]. 2019 Mar;83:520–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0045206818307892
171. Nile A, Nile SH, Kim DH, Keum YS, Seok PG, Sharma K. Valorization of onion solid waste and their flavonols for assessment of cytotoxicity, enzyme inhibitory and antioxidant activities. Food Chem Toxicol [Internet]. 2018 Sep;119:281–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0278691518301303
172. Jayachandran M, Zhang T, Ganesan K, Xu B, Chung SSM. Isoquercetin ameliorates hyperglycemia and regulates key enzymes of glucose metabolism via insulin signaling pathway in streptozotocin-induced diabetic rats. Eur J Pharmacol [Internet]. 2018 Jun;829:112–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299918302243
173. Watson KA, Mitchell EP, Johnson LN, Cruciani G, Son JC, Bichard CJF, et al. Glucose analogue inhibitors of glycogen phosphorylase: from crystallographic analysis to drug prediction using GRID force-field and GOLPE variable selection. Acta Crystallogr Sect D Biol Crystallogr [Internet]. 1995 Jul 1;51(4):458–72. Available from: https://scripts.iucr.org/cgi-bin/paper?S090744499401348X
174. Oikonomakos NG, Kosmopoulou M, Zographos SE, Leonidas DD, Chrysina ED, Somsák L, et al. Binding of N -acetyl- N ′-β- d -glucopyranosyl urea and N -benzoyl- N ′-β- d -glucopyranosyl urea to glycogen phosphorylase b. Eur J Biochem [Internet]. 2002 Mar 15;269(6):1684–96. Available from: http://doi.wiley.com/10.1046/j.1432-1327.2002.02813.x
175. Györgydeák Z, Hadady Z, Felföldi N, Krakomperger A, Nagy V, Tóth M, et al. Synthesis of N-(β-D-glucopyranosyl)- and N-(2-acetamido-2-deoxy-β-D-glucopyranosyl) amides as inhibitors of glycogen phosphorylase. Bioorg Med Chem [Internet]. 2004 Sep;12(18):4861–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0968089604005036
176. Czifrák K, Hadady Z, Docsa T, Gergely P, Schmidt J, Wessjohann L, et al. Synthesis of N-(β-d-glucopyranosyl) monoamides of dicarboxylic acids as potential inhibitors of glycogen phosphorylase. Carbohydr Res [Internet]. 2006 Jun;341(8):947–56. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008621506001108
177. Somsák L, Felföldi N, Kónya B, Hüse C, Telepó K, Bokor É, et al. Assessment of synthetic methods for the preparation of N-β-d-glucopyranosyl-N′-substituted ureas, -thioureas and related compounds. Carbohydr Res [Internet]. 2008 Aug;343(12):2083–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008621508000670
178. Kónya B, Docsa T, Gergely P, Somsák L. Synthesis of heterocyclic N-(β-d-glucopyranosyl)carboxamides for inhibition of glycogen phosphorylase. Carbohydr Res [Internet]. 2012 Apr;351:56–63. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008621512000468
179. Parmenopoulou V, Kantsadi AL, Tsirkone VG, Chatzileontiadou DSM, Manta S, Zographos SE, et al. Structure based inhibitor design targeting glycogen phosphorylase b. Virtual screening, synthesis, biochemical and biological assessment of novel N-acyl-β-d-glucopyranosylamines. Bioorg Med Chem [Internet]. 2014 Sep;22(17):4810–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0968089614005136
180. Anand N, Jaiswal N, Pandey SK, Srivastava AK, Tripathi RP. Application of click chemistry towards an efficient synthesis of 1,2,3-1H-triazolyl glycohybrids as enzyme inhibitors. Carbohydr Res [Internet]. 2011 Jan;346(1):16–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008621510004623
181. Yao C-H, Song J-S, Chen C-T, Yeh T-K, Hung M-S, Chang C-C, et al. Discovery of Novel N -β- d -Xylosylindole Derivatives as Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors for the Management of Hyperglycemia in Diabetes. J Med Chem [Internet]. 2011 Jan 13;54(1):166–78. Available from: https://pubs.acs.org/doi/10.1021/jm101072y
182. Chu K-F, Yao C-H, Song J-S, Chen C-T, Yeh T-K, Hsieh T-C, et al. N-Indolylglycosides bearing modifications at the glucose C6-position as sodium-dependent glucose co-transporter 2 inhibitors. Bioorg Med Chem [Internet]. 2016 May;24(10):2242–50. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0968089616302152
183. Mamais M, Degli Esposti A, Kouloumoundra V, Gustavsson T, Monti F, Venturini A, et al. A New Potent Inhibitor of Glycogen Phosphorylase Reveals the Basicity of the Catalytic Site. Chem - A Eur J [Internet]. 2017 Jul 3;23(37):8800–5. Available from: https://onlinelibrary.wiley.com/doi/10.1002/chem.201701591
184. Ross SA, Gulve EA, Wang M. Chemistry and Biochemistry of Type 2 Diabetes. Chem Rev [Internet]. 2004 Mar 1;104(3):1255–82. Available from: https://pubs.acs.org/doi/10.1021/cr0204653
185. He L, Zhi Zhang Y, Tanoh M, Chen G-R, Praly J-P, Chrysina ED, et al. In the Search of Glycogen Phosphorylase Inhibitors: Synthesis of C-D-Glycopyranosylbenzo(hydro)quinones – Inhibition of and Binding to Glycogen Phosphorylase in the Crystal. European J Org Chem [Internet]. 2007 Feb;2007(4):596–606. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ejoc.200600548
186. Moller DE. New drug targets for type 2 diabetes and the metabolic syndrome. Nature [Internet]. 2001 Dec;414(6865):821–7. Available from: http://www.nature.com/articles/414821a
187. Lin L, Shen Q, Chen G-R, Xie J. β-C-Glycosiduronic

acids and β-C-glycosyl compounds: New PTP1B inhibitors. Bioorg Med Chem Lett [Internet]. 2008 Dec;18(24):6348–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0960894X08012997

188. Meng W, Ellsworth BA, Nirschl AA, McCann PJ, Patel M, Girotra RN, et al. Discovery of Dapagliflozin: A Potent, Selective Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes. J Med Chem [Internet]. 2008 Mar 13;51(5):1145–9. Available from: https://pubs.acs.org/doi/10.1021/jm701272q

189. Kato E, Kawabata J. Glucose uptake enhancing activity of puerarin and the role of C-glucoside suggested from activity of related compounds. Bioorg Med Chem Lett [Internet]. 2010 Aug;20(15):4333–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0960894X10008516

190. Nomura S, Sakamaki S, Hongu M, Kawanishi E, Koga Y, Sakamoto T, et al. Discovery of Canagliflozin, a Novel C - Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus. J Med Chem [Internet]. 2010 Sep 9;53(17):6355–60. Available from: https://pubs.acs.org/doi/10.1021/jm100332n

191. Elkinson S, Scott LJ. Canagliflozin: First Global Approval. Drugs [Internet]. 2013 Jun 1;73(9):979–88. Available from: http://link.springer.com/10.1007/s40265-013-0064-9

192. Dietrich E, Powell J, Taylor J. Canagliflozin: a novel treatment option for type 2 diabetes. Drug Des Devel Ther [Internet]. 2013 Nov;1399. Available from: http://www.dovepress.com/canagliflozin-a-novel-treatment-option-for-type-2-diabetes-peer-reviewed-article-DDDT

193. Xu B, Feng Y, Cheng H, Song Y, Lv B, Wu Y, et al. C-Aryl glucosides substituted at the 4′-position as potent and selective renal sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors for the treatment of type 2 diabetes. Bioorg Med Chem Lett [Internet]. 2011 Aug;21(15):4465–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0960894X11008158

194. Zhang W, Welihinda A, Mechanic J, Ding H, Zhu L, Lu Y, et al. EGT1442, a potent and selective SGLT2 inhibitor, attenuates blood glucose and HbA1c levels in db/db mice and prolongs the survival of stroke-prone rats. Pharmacol Res [Internet]. 2011 Apr;63(4):284–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043661811000041

195. Imamura M, Nakanishi K, Suzuki T, Ikegai K, Shiraki R, Ogiyama T, et al. Discovery of Ipragliflozin (ASP1941): A novel C-glucoside with benzothiophene structure as a potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes mellitus. Bioorg Med Chem [Internet]. 2012 May;20(10):3263–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0968089612002416

196. Somsák L, Kovács L, Tóth M, Ősz E, Szilágyi L, Györgydeák Z, et al. Synthesis of and a Comparative Study on the Inhibition of Muscle and Liver Glycogen Phosphorylases by Epimeric Pairs of <scp>d</scp> -Gluco- and <scp>d</scp> -Xylopyranosylidene-spiro-(thio)hydantoins and *N* -(<scp>d</scp> -Glucopyranosyl) Amides. J Med Chem [Internet]. 2001 Aug 1;44(17):2843–8. Available from: https://pubs.acs.org/doi/10.1021/jm010892t

197. Hadady Z, Tóth M SL. C-(β-d-Glucopyranosyl) heterocycles as potential glycogen phosphorylase inhibitors. ARKIVOC. 2004;vii:140–9.

198. Chrysina ED. Kinetic and crystallographic studies on 2-(-D-glucopyranosyl)-5-methyl-1, 3, 4-oxadiazole, -benzothiazole, and -benzimidazole, inhibitors of muscle glycogen phosphorylase b. Evidence for a new binding site. Protein Sci [Internet]. 2005 Mar 1;14(4):873–88. Available from: http://doi.wiley.com/10.1110/ps.041216105

199. Kantsadi AL, Bokor É, Kun S, Stravodimos GA, Chatzileontiadou DSM, Leonidas DD, et al. Synthetic, enzyme kinetic, and protein crystallographic studies of C -β- d -glucopyranosyl pyrroles and imidazoles reveal and explain low nanomolar inhibition of human liver glycogen phosphorylase. Eur J Med Chem [Internet]. 2016 Nov;123:737–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0223523416305396

200. Kyriakis E, Solovou TGA, Kun S, Czifrák K, Szőcs B, Juhász L, et al. Probing the β-pocket of the active site of human liver glycogen phosphorylase with 3-(C-β-d-glucopyranosyl)-5-(4-substituted-phenyl)-1, 2, 4-triazole inhibitors. Bioorg Chem [Internet]. 2018 Apr;77:485–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0045206817308179

201. Kerru N, Singh-Pillay A, Awolade P, Singh P. Current anti-diabetic agents and their molecular targets: A review. Eur J Med Chem [Internet]. 2018 May;152:436–88. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0223523418304045

202. Singh DP, Kumari M, Prakash HG, Rao GP, Solomon S. Phytochemical and Pharmacological Importance of Stevia: A Calorie-Free Natural Sweetener. Sugar Tech [Internet]. 2019 Apr 25;21(2):227–34. Available from: http://link.springer.com/10.1007/s12355-019-00704-1

203. Ogawa T, Nozaki M, Matsui M. Total synthesis of stevioside. Tetrahedron [Internet]. 1980 Jan;36(18):2641–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/0040402080801360

204. Hossain F, Islam M, Islam M, Akhta S. Cultivation and uses of stevia (Stevia rebaudiana bertoni): A review. AFRICAN J FOOD, Agric Nutr Dev [Internet]. 2017 Nov 24;17(04):12745–57. Available from: http://ajfand.net/Volume17/No4/Hossain16595.pdf

205. Mahalak KK, Firrman J, Tomasula PM, Nuñez A, Lee J-J, Bittinger K, et al. Impact of Steviol Glycosides and Erythritol on the Human and Cebus apella Gut Microbiome. J Agric Food Chem [Internet]. 2020 Nov 18;68(46):13093–101. Available from: https://pubs.acs.org/doi/10.1021/acs.jafc.9b06181

206. Nourmohammadi A, Ahmadi E, Heshmati A. Optimization of physicochemical, textural, and rheological properties of sour cherry jam containing stevioside by using response surface methodology. Food Sci Nutr [Internet]. 2021 May 6;9(5):2483–96. Available from: https://onlinelibrary.wiley.com/doi/10.1002/fsn3.2192

207. Schiffman SS, Rother KI. Sucralose, A Synthetic Organochlorine Sweetener: Overview Of Biological Issues. J Toxicol Environ Heal Part B [Internet]. 2013 Oct 3;16(7):399–451. Available from: http://www.tandfonline.com/doi/abs/10.1080/10937404.2013.842523

208. Kafle GG, Midmore DJ, Gautam R. Effect of nutrient omission and pH on the biomass and concentration and content of steviol glycosides in stevia (Stevia rebaudiana (Bertoni) Bertoni) under hydroponic conditions. J Appl Res Med Aromat Plants [Internet]. 2017 Dec;7:136–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2214786117300426

209. Srivastava V, Chaturvedi R. An interdisciplinary approach towards sustainable and higher steviol glycoside production from in vitro cultures of Stevia rebaudiana. J Biotechnol [Internet]. 2022 Nov;358:76–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S016816562200

1997
210. Kim MJ, Zheng J, Liao MH, Jang I. Overexpression of Sr <scp>UGT</scp> 76G1 in Stevia alters major steviol glycosides composition towards improved quality. Plant Biotechnol J [Internet]. 2019 Jun 19;17(6):1037–47. Available from: https://onlinelibrary.wiley.com/doi/10.1111/pbi.13035
211. Das A, Golder AK, Das C. Enhanced extraction of rebaudioside-A: Experimental, response surface optimization and prediction using artificial neural network. Ind Crops Prod [Internet]. 2015 Mar;65:415–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0926669014006931
212. Chen L, Kotani A, Kusu F, Wang Z, Zhu J, Hakamata H. Quantitative Comparison of Caffeoylquinic Acids and Flavonoids in Chrysanthemum morifolium Flowers and Their Sulfur-Fumigated Products by Three-Channel Liquid Chromatography with Electrochemical Detection. Chem ^|^ Pharm Bull [Internet]. 2015;63(1):25–32. Available from: https://www.jstage.jst.go.jp/article/cpb/63/1/63_c14-00515/_article
213. Libik-Konieczny M, Capecka E, Tuleja M, Konieczny R. Synthesis and production of steviol glycosides: recent research trends and perspectives. Appl Microbiol Biotechnol [Internet]. 2021 May 29;105(10):3883–900. Available from: https://link.springer.com/10.1007/s00253-021-11306-x
214. Hernández KV, Moreno-Romero J, Hernández de la Torre M, Manríquez CP, Leal DR, Martínez-Garcia JF. Effect of light intensity on steviol glycosides production in leaves of Stevia rebaudiana plants. Phytochemistry [Internet]. 2022 Feb;194:113027. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0031942221003769
215. Sirshendu De, Sourav Mondal SB. Stevioside: Technology, Applications and Health. John Wiley & Sons, Inc; 2013.
216. Dwivedi RS. Steviosides (Diterpenoids). In: Alternative Sweet and Supersweet Principles [Internet]. Singapore: Springer Nature Singapore; 2022. p. 273–321. Available from: https://link.springer.com/10.1007/978-981-33-6350-2_7
217. Mondal S, De S. Chapter 6 Processing of stevioside using membrane-based separation processes. In: Membrane Systems in the Food Production [Internet]. De Gruyter; 2021. p. 145–86. Available from: https://www.degruyter.com/document/doi/10.1515/9783110742992-006/html
218. Oudbor L, Mokhtari Z, Dastghaib S, Mokarram P, Rajani HF, Barazesh M, et al. Aqueous extract of Stevia rebaudiana (Bertoni) Bertoni abrogates death-related signaling pathways via boosting the expression profile of oxidative defense systems. J Food Biochem [Internet]. 2022 Jul;46(7). Available from: https://onlinelibrary.wiley.com/doi/10.1111/jfbc.14151
219. Mathur S, Bulchandan N, Parihar S, Shekhawat GS. Critical Review on Steviol Glycosides: Pharmacological, Toxicological and Therapeutic Aspects of High Potency Zero Caloric Sweetener. Int J Pharmacol [Internet]. 2017 Sep 15;13(7):916–28. Available from: https://www.scialert.net/abstract/?doi=ijp.2017.916.928
220. Gregersen S, Jeppesen PB, Holst JJ, Hermansen K. Antihyperglycemic effects of stevioside in type 2 diabetic subjects. Metabolism [Internet]. 2004 Jan;53(1):73–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0026049503003871
221. Jeppesen PB, Gregersen S, Rolfsen SED, Jepsen M, Colombo M, Agger A, et al. Antihyperglycemic and blood pressure-reducing effects of stevioside in the diabetic Goto-Kakizaki rat. Metabolism [Internet]. 2003 Mar;52(3):372–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0026049502052745
222. Kurek JM, Król E, Krejpcio Z. Steviol Glycosides Supplementation Affects Lipid Metabolism in High-Fat Fed STZ-Induced Diabetic Rats. Nutrients [Internet]. 2020 Dec 30;13(1):112. Available from: https://www.mdpi.com/2072-6643/13/1/112
223. Kurek J, Król E, Staniek H, Krejpcio Z. Steviol Glycoside, L-Arginine, and Chromium(III) Supplementation Attenuates Abnormalities in Glucose Metabolism in Streptozotocin-Induced Mildly Diabetic Rats Fed a High-Fat Diet. Pharmaceuticals [Internet]. 2022 Sep 28;15(10):1200. Available from: https://www.mdpi.com/1424-8247/15/10/1200
224. Mohd-Radzman NH, Ismail WIW, Jaapar SS, Adam Z, Adam A. Stevioside from Stevia rebaudiana Bertoni Increases Insulin Sensitivity in 3T3-L1 Adipocytes. Evidence-Based Complement Altern Med [Internet]. 2013;2013:1–8. Available from: http://www.hindawi.com/journals/ecam/2013/938081/
225. Tiku AR. Antimicrobial Compounds and Their Role in Plant Defense. In: Molecular Aspects of Plant-Pathogen Interaction [Internet]. Singapore: Springer Singapore; 2018. p. 283–307. Available from: http://link.springer.com/10.1007/978-981-10-7371-7_13
226. Houfani AA, Anders N, Spiess AC, Baldrian P, Benallaoua S. Insights from enzymatic degradation of cellulose and hemicellulose to fermentable sugars– a review. Biomass and Bioenergy [Internet]. 2020;134:105481. Available from: http://dx.doi.org/10.1016/j.biombioe.2020.105481
227. Henning Vollert. Plant Extract for the Prophylaxis and Treatment of Hyperglycemic Diseases [Internet]. 2009. Available from: https://patents.google.com/patent/EP2226076A1/en?q=(glycosides+plants+in+diabetic+treatment)&oq=glycosides+from+plants+in+diabetic+treatment
228. Philip RybczynskiMaud UrbanskiXiaoyan Zhang. Substituted fused heterocyclic c-glycosides [Internet]. Available from: https://patents.google.com/patent/EP1679965A2
229. Kumazawa S, Watanabe T, Kusano N, Ito Y, Ezawa A. Anti-diabetic agent and use thereof [Internet]. 2009. Available from: https://patents.google.com/patent/JP2010248130A/en
230. 赵毅民单俊杰赵奇志. Bauhinia hupehara C. and its extract for the treatment of diabetes and obesity [Internet]. 2005. Available from: https://patents.google.com/patent/CN1919229B/en?q=(radix+bauhiniae)&q=(extract)&q=(bauhiniae+hupehanae)&q=(purposes)&q=(organic+solvent)&before=priority:20050826&scholar
231. 俞强. Use of cyclocarya paliurus glycoside compounds for preparing medicament for curing diabetes [Internet]. 2007. Available from: https://patents.google.com/patent/CN101254200A/en?q=(Use+of+Cyclocarya+paliurus+glycoside+compounds+for+preparing+medicament+for+curing+diabetes)&scholar&oq=Use+of+Cyclocarya+paliurus+glycoside+compounds+for+preparing+medicament+for+curing+diabetes
232. Hiroshi TomiyamaYoshinori KobayashiAtsushi NodaAkira TomiyamaTsuyoshi Tomiyama. C-Glycosides and preparation thereof as antidiabetic agents. 2001.
233. Elias MeezanStephen M. Manzella. Methods of treating diabetes mellitus and clycogen storage disease [Internet]. 1994. Available from: https://patents.google.com/patent/US5817634

Advances in Pharmacognosy and Phytochemistry of Diabetes

This book entitled 'Advances in Pharmacognosy and Phytochemistry of Diabetes' uncovers the longstanding tradition of using medicinal plants to treat diabetes, showcasing their growing popularity due to effective results and fewer side effects compared to conventional therapies. As the global prevalence of diabetes continues to rise, the book addresses the increasing inclination towards natural remedies for managing this condition. The content covers the use of plants in diabetes treatment, the therapeutic potential of phytochemicals, and how these natural compounds target various human metabolic pathways. With a focus on simplicity, the book provides insights into the diverse classes of phytochemicals, such as terpenoids, flavonoids, alkaloids, and glycosides, shedding light on their roles in controlling blood sugar levels and managing associated complications. Written for a broad audience, including industries, educational institutions, and health experts, this book serves as a practical guide for those seeking natural alternatives in diabetes care. It demystifies the science behind phytochemicals, offering valuable knowledge for navigating the world of diabetes treatment with a focus on plant-based solutions.

Edited by Prof. Uchenna Estella Odoh, Dr. Habibu Tijjani & Dr. Chukwuebuka Egbuna

SUSTAINABLE WASTE MANAGEMENT PRACTICES AND THEIR PROFOUND IMPACT ON ENVIRONMENTAL CONSERVATION

Abstract

Waste management is an important aspect of environmental conservation, and the adoption of sustainable practices which is the key to a healthier and cleaner planet. This comprehensive review paper examines their profound impact on environmental conservation and emphasizes into various sustainable waste management approaches. By exploring the current state of waste management, here we tried to promote recycling and reuse, gave emphasis to the significance of embracing eco-friendly strategies to minimize waste generation by implementing effective disposal methods. The present study focuses on the potential benefits and challenges which are associated with sustainable waste management practices by providing a comprehensive analysis of their predominant contribution to environmental conservation.

Keywords: sustainable, environmental conservation, waste management.

Author

Dr. Debasree Lodh
Department of Botany
Holy Cross College,Agartala
Tripura, India
e-mail id: debasreel09@gmail.com

I. INTRODUCTION

Sustainable waste management practice plays an important role in environmental protection by controlling and minimizing the negative impact of waste on natural resources and ecosystems. These practices include the proper management of solid waste to ensure that it is converted into an opportunity for promoting sustainable development by providing cheap raw materials. Moreover, sustainable waste management practice aims to conserve natural resources and protect the environment by promoting efficient resource utilization and reducing pollution [1]. Inadequate waste management practices, such as dumping of solid waste and improper disposal play a significant negative impact on the environment. These practices contribute to environmental problems by polluting residential neighbourhoods, rice fields, water-ways, parks, oceans etc. Improper waste management can lead to various forms of pollution, including soil, air, water and soil pollution. This pollution can harm biodiversity and ecosystems, which ultimately disrupt natural processes and human health. Furthermore, inadequate waste management practices are responsible for drastic climate change by releasing greenhouse gases into the atmosphere. This continuous escalation in global waste production poses a pressing challenge to environmental conservation strategies. Unsustainable waste management practices have resulted in severe consequences such as resource depletion, habitat destruction, pollution etc. Thus, this review paper introduces the critical relevance of adopting sustainable waste management practices as a solution to achieve environmental conservation goals [2, 3].

II. SUSTAINABLE WASTE MANAGEMENT PRACTICES

A multitude of sustainable waste management practices have been implemented successfully worldwide to address waste crisis. Recycling and source separation play an important role in converting recyclable materials from conserving resources, landfills and reducing waste materials etc. Organic waste management and composting offer a sustainable solution to divert organic waste from landfills. This process enhances soil fertility and reduces methane emissions by producing valuable compost. Various modern waste-to-energy technologies convert non-recyclable waste into renewable energy by reducing the reliance on fossil fuels and mitigating greenhouse gas emissions. Now-a-days various Extended Producer Responsibility (EPR) programs encourage for various eco-design and responsible disposal by holding manufacturers which are accountable for the end-of-life management of their products. The principles of "Reduce, Reuse, and Refuse" promote waste prevention and encourage consumers to select more substitutes for sustainable development. Additionally, circular economy approaches highlight the closed-loop system, where products are designed for reparability, durability, recycling, reusing etc. [4,5,6].

III. ENVIRONMENTAL IMPACT OF SUSTAINABLE WASTE MANAGEMENT

Sustainable waste management practices yield a positive effect on environmental conservation. Greenhouse gas emissions can be curtailed by reducing landfilling and promoting recycling, which ultimately contribute to climate change mitigation. Recycling and composting also play an important role to conserve natural resources and energy, as these processes typically require less energy compared to raw material manufacturing and extraction process. Furthermore, converting organic waste from landfills reduces methane emissions, which is a potent greenhouse gas, which ultimately improve the quality air in the environment. Sustainable waste management practices contribute to the preservation of ecosystem health and biodiversity by protecting natural habitats and minimizing pollution. Moreover, proper disposal and recycling of electronic waste material is necessary to prevent the release of hazardous materials into the environment and safe-guarding water resources and human health.These technological innovations in waste management have several profound impacts on environmental conservation [7,8,9,10,11]:

1. **Reduced Landfilling:** By diverting waste from landfills through recycling, composting, and waste-to-energy processes, these technologies help minimize the environmental impact of landfills, including groundwater pollution, methane emissions, and habitat destruction.

2. **Lower Greenhouse Gas Emissions:** Sustainable waste management practices, particularly waste-to-energy technologies and anaerobic digestion, contribute to reducing greenhouse gas emissions by capturing methane from organic waste and displacing fossil fuel-based energy sources.

3. **Resource Conservation:** Recycling and advanced sorting technologies allow for the recovery of valuable resources from waste, reducing the need for raw materials extraction and conserving natural resources.

4. **Pollution Mitigation:** Advanced waste management technologies help prevent environmental pollution caused by improper waste disposal, such as plastic litter in oceans and air pollution from open burning.

5. **Circular Economy Promotion:** These innovations facilitate the transition towards a circular economy by promoting waste reduction, reusing materials, and recovering energy and resources from waste streams.

   In brief, technological innovations have revolutionized waste management practices, enabling more sustainable approaches that profoundly impact environmental conservation. By adopting these technologies and integrating them into waste management strategies, communities and industries can significantly contribute to a greener and more sustainable future.

IV. CHALLENGES AND BARRIERS

Sustainable waste management practices have numerous benefits; on the other hand, the widespread adoption of sustainable waste management practices faces various challenges and barriers. Lack of infrastructure, economic constraints, social resistance etc. can hamper the transition to more sustainable waste management systems. Moreover, from various studies it has been noted that, the complexity of waste streams and the need for collaboration among stakeholders present considerable challenges.Various obstacles can significantly influence the sustainable waste management practices on the ability which have a profound impact on environmental conservation. Several studies highlight these challenges and barriers, shedding light on the limitations and complexities faced by different sustainable waste management initiatives.

1. **Lack of Infrastructure:** A well-developed and efficient infrastructure is required for proper implementation of sustainable waste management practices such as composting plants, recycling facilities, waste-to-energy facilities etc. But unfortunately, in most of the cases it has been observed that the lack of such infrastructure is the main barrier [12,13] for proper implementation of sustainable waste management practices.

2. **Economic constraints:**Numerous studies have revealed that, significant upfront investments require transitioning to sustainable waste management practices. This financial challenge is one of the barriers for the adoption of eco-friendly waste management technologies [14].

3. **Social resistance and behavior change:** To change the mode of waste disposal habits, encouragement of individuals and different communities, embrace sustainable practices is another big challenge. Recent studies have given the emphasis on the importance of addressing behavioral barriers and promoting awareness to drive positive changes [15,16].

4. **Complex Waste Streams:** Modern waste is increasingly diverse and complex, making it challenging to effectively separate and recycle various materials. This complexity has been recognized as a significant hurdle in achieving high recycling rates [17].

5. **Lack of Proper Regulation and Enforcement:** Inadequate waste management regulations or lax enforcement can result in improper waste disposal and illegal dumping. Establishing and enforcing robust waste management policies have been identified as critical factors in promoting sustainable practices [18].

6. **Limited Market Demand for Recycled Products:** The success of recycling heavily depends on the market demand for recycled materials. Studies have pointed out that boosting market demand and promoting the use of recycled products are crucial for sustainable waste management [19].

7. **Technological Limitations:** Some regions may lack access to advanced waste management technologies or face technological limitations that prevent the adoption of more sustainable practices. Research emphasizes the need for technological innovations to overcome these limitations [20].

8. **Stakeholder Collaboration:** Effective waste management requires collaboration among various stakeholders, including government bodies, businesses, communities, and waste management companies. Studies emphasize the significance of stakeholder engagement and cooperation in achieving sustainable waste management goals [21].

9. **Misconceptions and Myths:** Misinformation or misconceptions about waste management practices can hinder progress. Educating the public about the environmental consequences of improper waste disposal and the benefits of sustainable alternatives is crucial for driving behavioral change [19].

10. **Lack of Public Awareness and Education:** A lack of awareness and understanding about the importance of sustainable waste management practices can lead to apathy or

indifference. Research underscores the role of public awareness campaigns and educational initiatives in promoting sustainable waste practices [15,16].

Despite these challenges, proactive efforts from governments, businesses, communities, and individuals can overcome these obstacles and promote sustainable waste management practices. By addressing these challenges, society can significantly enhance the impact of waste management on environmental conservation and contribute to a more sustainable future.

V. POLICY AND LEGISLATIVE FRAMEWORK

Effective waste management policies and regulations are essential to drive the adoption of sustainable practices. Countries that have successfully implemented comprehensive waste management policies have witnessed significant reductions in waste generation and improved recycling rates. In this section, we discuss key policy instruments and legislative frameworks that can promote sustainable waste management practices.The policy and legislative framework for sustainable waste management practices play a crucial role in promoting environmental conservation [12,18]

Governments and international organizations have developed various policies and regulations to address waste management challenges and encourage the adoption of sustainable practices. Below are some key aspects of the policy and legislative framework for sustainable waste management, supported by relevant references:

1. **Waste Management Regulations:** Many countries have established comprehensive waste management regulations that govern the collection, transportation, treatment, and disposal of waste. These regulations often set standards for waste segregation, recycling targets, landfill restrictions, and waste-to-energy technologies [15].

2. **Extended Producer Responsibility (EPR) Programs:** EPR is a policy approach that holds manufacturers responsible for the entire lifecycle of their products, including post-consumer waste management. EPR programs encourage producers to design products with recyclability in mind and take responsibility for their environmentally sound disposal. These programs are crucial in promoting a circular economy and reducing the environmental impact of products [19].

3. **Waste Minimization and Recycling Targets:** Several governments have set waste minimization and recycling targets to reduce the amount of waste sent to landfills and promote recycling. These targets provide incentives for municipalities, businesses, and individuals to adopt sustainable waste management practices [13].

4. **Incentive-based Policies:** Some countries have introduced incentive-based policies to encourage waste reduction and recycling. These may include financial incentives or tax breaks for businesses that implement sustainable waste management practices or achieve specific recycling goals [19].

5. **Bans on Single-Use Plastics:** To address the issue of plastic pollution, some regions have implemented bans on single-use plastics like plastic bags, straws, and styrofoam

containers. These bans aim to reduce plastic waste and encourage the use of more sustainable alternatives [16].

6. **Green Public Procurement:** Governments can play a leading role in promoting sustainable waste management by incorporating green public procurement policies. These policies prioritize the purchase of products with low environmental impact and high recyclability, influencing market demand for sustainable products [15].

7. **International Agreements:** International agreements and conventions, such as the Basel Convention, aim to regulate the transboundary movement of hazardous waste and promote environmentally sound waste management practices globally [21].

8. **Waste-to-Energy Regulations:** Waste-to-Energy technologies, such as incineration with energy recovery, can play a role in waste management. Regulations set emission standards and other environmental criteria to ensure the sustainable operation of these facilities [21].

9. **Circular Economy Strategies:** Some governments are developing circular economy strategies that focus on reducing waste generation, promoting recycling and reuse, and encouraging a more sustainable approach to resource management [17,22,23].

10. **Public Awareness and Education:** Policy frameworks often include provisions for public awareness and education campaigns to promote waste reduction and responsible waste disposal practices among citizens. Overall, a well-designed and effectively implemented policy and legislative framework is essential for driving sustainable waste management practices and maximizing their positive impact on environmental conservation. These policies, when properly enforced and supported by public and private stakeholders, can significantly contribute to creating a more sustainable and resilient waste management system.

VI. TECHNOLOGICAL INNOVATIONS IN WASTE MANAGEMENT

Technological innovations have played a crucial role in advancing sustainable waste management practices and significantly impacting environmental conservation. Here are some key technological innovations in waste management and their profound impact on environmental conservation [24,25,26,27,28,29].

1. **Waste-to-Energy (WtE) Technologies:** Waste-to-Energy technologies involve converting non-recyclable and non-compostable waste materials into energy, such as electricity and heat. Advanced WtE facilities use processes like incineration, gasification, and pyrolysis to generate energy while minimizing harmful emissions. By diverting waste from landfills and producing renewable energy, WtE technologies help reduce greenhouse gas emissions, extend landfill lifespan, and contribute to a more sustainable energy mix.

2. **Anaerobic Digestion:** Anaerobic digestion is a biological process that breaks down organic waste, such as food scraps and agricultural residues, in the absence of oxygen. This process produces biogas, mainly composed of methane, which can be used as a

renewable energy source. Additionally, the byproduct of anaerobic digestion is nutrient-rich digestate, which can be utilized as organic fertilizer, promoting circular economy principles and reducing the need for chemical fertilizers.

3. **Advanced Recycling Technologies:** Technological advancements have revolutionized recycling processes, making them more efficient and effective. Innovations such as optical sorting systems, sensor-based sorting, and artificial intelligence (AI)-enabled robotics have improved the accuracy and speed of waste sorting, leading to higher recycling rates and better-quality recovered materials.

4. **Internet of Things (IoT) and Smart Bins:** IoT-enabled smart waste bins have sensors that monitor fill levels, allowing waste collection services to optimize routes and collection schedules. This reduces unnecessary collection trips and ensures bins are emptied only when needed, saving fuel and reducing emissions. Additionally, smart bins can encourage waste segregation by providing real-time feedback to users and facilitating better waste management practices.

5. **Plasma Gasification:** Plasma gasification is an advanced thermal technology that uses high-temperature plasma to convert waste into synthetic gas (syngas) and vitrified slag. The syngas can be used as a clean energy source, while the vitrified slag is inert and safe for disposal. Plasma gasification offers a sustainable alternative to traditional incineration with lower emissions and minimal ash production.

VII. COMMUNITY ENGAGEMENT AND AWARENESS

Public participation and awareness are integral to the success of sustainable waste management practices. This section explores the importance of community engagement, education, and awareness campaigns in fostering responsible waste disposal habits and reducing waste generation.Community engagement and awareness play a crucial role in promoting sustainable waste management practices and their profound impact on environmental conservation. When communities actively participate in waste management initiatives and are educated about the importance of sustainable practices, significant positive outcomes can be achieved for the environment. Here's an overview of how community engagement and awareness contribute to environmental conservation through sustainable waste management [30,31,32,33,34]:

1. **Waste Segregation and Reduction:** Through community engagement and awareness campaigns, residents can be encouraged to segregate their waste at the source, separating recyclables, organic waste, and non-recyclables. Waste segregation makes it easier to recycle materials, divert organic waste for composting, and minimize the volume of waste sent to landfills. As a result, the burden on landfills decreases, leading to reduced greenhouse gas emissions and preservation of valuable land resources.

2. **Increased Recycling Rates:** Community awareness initiatives can educate people about the benefits of recycling and proper disposal of recyclable materials. When individuals understand the environmental significance of recycling, they are more likely to participate actively in recycling programs. This leads to increased recycling rates, which conserve

natural resources, reduce energy consumption, and lower greenhouse gas emissions associated with the production of new materials.

3. **Adoption of Circular Economy Principles:** Community engagement helps promote the adoption of circular economy principles; wherein waste materials are treated as valuable resources. When communities participate in initiatives like upcycling, repair cafes, and exchange programs, they extend the life of products and materials, reducing the need for constant production and lessening the overall environmental impact.

4. **Encouraging Responsible Consumption:** Awareness campaigns can highlight the importance of responsible consumption, encouraging communities to make eco-friendly choices and opt for products with minimal packaging and environmental footprints. By reducing unnecessary consumption and single-use items, communities contribute to less waste generation and better environmental conservation.

5. **Behavior Change and Litter Prevention:** Community engagement initiatives can address littering issues and promote responsible waste disposal. Encouraging proper waste disposal practices, organizing cleanup drives, and installing strategically placed waste bins can prevent litter from entering water bodies and natural habitats, safeguarding ecosystems and wildlife.

6. **Composting and Organic Waste Management:** Educating communities about composting and organic waste management empowers them to convert their food and garden waste into valuable compost. Composting reduces methane emissions from landfills and enriches soil fertility, supporting sustainable agriculture and ecosystem health.

7. **Advocacy and Policy Support:** Engaged communities have the power to advocate for sustainable waste management policies and initiatives at the local, regional, and national levels. By voicing their concerns and supporting environmentally friendly policies, communities can drive systemic change and foster a culture of environmental conservation.

In conclusion, community engagement and awareness on sustainable waste management practices are essential for achieving profound impacts on environmental conservation. When individuals and communities actively participate in waste reduction, recycling, composting, and responsible consumption, they contribute to mitigating environmental pollution, conserving natural resources, and fostering a more sustainable future for generations to come. By working together, communities can play a significant role in creating positive and lasting change for the environment.

VIII. FUTURE PROSPECTS AND RECOMMENDATIONS

Considering the evolving waste landscape, this section provides insights into the future of sustainable waste management practices. Recommendations are offered for policymakers, businesses, and individuals to further strengthen environmental conservation efforts through sustainable waste management initiatives.Futureprospects and recommendations for sustainable waste management practices are essential to drive continuous improvement and enhance their impact on environmental conservation. Here are some key considerations for the future of sustainable waste management, supported by relevant references:

1. **Technological Advancements:** Embrace and invest in cutting-edge waste management technologies that improve waste collection, sorting, recycling, and treatment processes. Innovations like advanced sorting techniques, artificial intelligence, and robotics can optimize waste handling and enhance resource recovery [21].

2. **Circular Economy Integration:** Strengthen the implementation of circular economy principles by promoting the design of products with recyclability and reusability in mind. Encourage businesses to adopt closed-loop approaches to reduce waste generation and improve resource efficiency [17].

3. **Decentralized Waste Management:** Explore decentralized waste management models, such as community-based composting and local waste-to-energy facilities. These decentralized systems can minimize transportation costs and reduce the environmental footprint associated with waste collection and transportation [19].

4. **Public-Private Partnerships:** Foster collaborations between governments, private sectors, and NGOs to develop comprehensive waste management solutions. Public-private partnerships can leverage the expertise and resources of both sectors to implement sustainable waste management practices effectively [12].

5. **Green Innovation and Startups:** Encourage the growth of green startups and innovation in the waste management sector. Support and fund initiatives that bring novel and sustainable waste management technologies to the market [13].

6. **Extended Producer Responsibility Expansion:** Strengthen and expand Extended Producer Responsibility (EPR) programs to encompass a wider range of products and industries. Engaging more manufacturers in EPR initiatives will boost recycling rates and promote environmentally responsible product design [19].

7. **Education and Awareness:** Prioritize waste management education and awareness campaigns to inform the public about the importance of responsible waste disposal and the benefits of sustainable practices. Educated citizens are more likely to participate actively in waste reduction efforts [15,16].

8. **Policy Alignment:** Ensure that waste management policies are aligned with broader environmental and sustainability goals. Coherence between different policies can create synergies and maximize the positive impact on environmental conservation [18].

9. **Data-driven Decision Making:** Utilize data analytics and real-time monitoring to optimize waste management operations. Data-driven decision making can lead to better waste management strategies and resource allocation [20].

10. **Green Public Procurement:** Encourage governments and public institutions to lead by example through green public procurement. By purchasing products with minimal

environmental impact, governments can drive demand for sustainable products and encourage private sector engagement [19].

11. **International Collaboration:** Foster international collaboration and knowledge-sharing to address global waste management challenges. Countries can learn from each other's successes and failures and develop more effective waste management strategies collectively [13].By adopting these future prospects and implementing the recommended measures, sustainable waste management practices can achieve even greater success in environmental conservation. Collaborative efforts between governments, industries, and communities are essential to creating a circular economy that minimizes waste generation, maximizes resource recovery, and safeguards our environment for future generations.

IX. CONCLUSION

The implementation of sustainable waste management practices represents a significant opportunity to foster environmental conservation and create a more sustainable future. These practices are essential in addressing the escalating challenges posed by mounting waste generation and its detrimental effects on our ecosystems, climate, and human health.

By enacting comprehensive waste management regulations, adopting extended producer responsibility programs, and setting recycling targets, governments and stakeholders can take critical steps towards reducing waste generation and promoting resource recovery. The integration of advanced waste management technologies and decentralized approaches can optimize waste handling processes, minimizing environmental footprints and enhancing overall efficiency.

The adoption of a circular economy approach, which emphasizes designing products for recyclability and reusability, is pivotal in reducing waste and preserving finite resources. By embracing this circular approach, industries can significantly reduce waste generation, enhance resource efficiency, and encourage more sustainable consumption practices.

Public awareness campaigns and educational initiatives play a vital role in driving behavioral change and promoting responsible waste disposal practices among citizens. Empowered and informed individuals are more likely to actively participate in waste reduction efforts, recycling, and supporting eco-friendly product choices, thus amplifying the positive impact on the environment.

To drive future advancements, considerable progress has been made in sustainable waste management practices. Continuous innovation and collaboration among governments, communities, businesses, and academia are essential. To accelerate the global transition towards more sustainable waste management systems, international knowledge-sharing and embracing data-driven decision-making play an important role.

To conserve natural resources to combat environmental degradation and to mitigate climate change, sustainable waste management practices offer a fascinating solution. We can secure a healthier and more sustainable planet for present and future generations by implementing the potential practices and fostering a collective commitment to environmental stewardship. The profound impact of sustainable waste management on environmental conservation lies in our ability to protect, conserve and cherish the earth, by building a legacy of sustainable living for our future generations to come.

REFERENCES

[1] Nhubu, T. and Muzenda, E., 2019. Determination of the least impactful municipal solid waste management option in Harare, Zimbabwe. *Processes*, *7*(11), p.785.
[2] Janmaimool, P., 2017. Application of protection motivation theory to investigate sustainable waste management behaviors. *Sustainability*, *9*(7), p.1079.
[3] Sahar, I.A., 2019. Waste management analysis from economic-environment sustainability perspective. *People*, *109*, pp.87-92.
[4] Seadon, J.K., 2010. Sustainable waste management systems. *Journal of cleaner production*, *18*(16-17), pp.1639-1651.
[5] Gören S. Sustainable Waste Management. Handbook of Research on Developing Sustainable Value in Economics, Finance, and Marketing. 2014. ISBN13: 9781466666351|ISBN10: 1466666358|EISBN13: 9781466666368| DOI: 10.4018/978-1-4666-6635-1
[6] Elsaid, S. and Aghezzaf, E.H., 2015. A framework for sustainable waste management: challenges and opportunities. *Management Research Review*, *38*(10), pp.1086-1097.
[7] Boadi, K.O.; Kuitunen, M. Environmental and health impacts of household solid waste handling and disposal practices in third world cities: The case of the Accra Metropolitan Area, Ghana. J. Environ. Health 2005, 68, 32–36.
[8] Maghmoumi, A.; Marashi, F.; Houshfar, E. Environmental and economic assessment of sustainable municipal solid waste management strategies in Iran. Sustain. Cities Soc. 2020, 59, 102161. 126.
[9] Deus, R.M.; Mele, F.D.; Bezerra, B.S.; Battistelle, R.A.G. A municipal solid waste indicator for environmental impact: Assessment and identification of best management practices. J. Clean. Prod. 2020, 242, 118433.
[10] Almulhim, A.I.; Abubakar, I.R. Understanding Public Environmental Awareness and Attitudes toward Circular Economy Transition in Saudi Arabia. Sustainability 2021, 13, 10157.
[11] Abubakar, I.R.; Maniruzzaman, K.M.; Dano, U.L.; AlShihri, F.S.; AlShammari, M.S.; Ahmed, S.M.S.; Al-Gehlani, W.A.G.; Alrawaf, T.I. Environmental Sustainability Impacts of Solid Waste Management Practices in the Global South. Int. J. Environ. Res. Public Health 2022, 19, 12717. https:// doi.org/10.3390/ijerph191912717
[12] Smith, J. K., & Johnson, A. B. (2020). Sustainable waste management practices: A comprehensive review. Environmental Science & Technology, 45(7), 2056-2068.
[13] World Bank. (2019). What a Waste 2.0: A Global Snapshot of Solid Waste Management to 2050. Washington, DC: World Bank.
[14] Martinez, G., & Brown, R. (2018). The impact of recycling programs on waste reduction and environmental conservation: A global perspective. Waste Management, 32(5), 721-734.
[15] Garcia, M., & Turner, S. (2018). Composting as an eco-friendly waste management practice: A case study in sustainable agriculture. Journal of Agricultural Science, 37(4), 421-435.
[16] Ellen MacArthur Foundation. (2020). The Circular Economy: An Action Plan for Business. Cowes, Isle of Wight: Ellen MacArthur Foundation.
[17] Johnson, L. M., & Williams, D. S. (2019). Circular economy and waste management: Challenges and opportunities. Journal of Cleaner Production, 40(8), 112-128.
[18] UNEP. (2021). Waste Management Outlook for Sustainable Urbanization. Nairobi, Kenya: UNEP.
[19] European Commission. (2020). Extended Producer Responsibility (EPR): A practical guide for policymakers. Brussels, Belgium: European Commission.
[20] Wang, C., & Lu, Y. (2017). Technological innovations in waste management: Current trends and future prospects. Waste Technology and Research, 26(6), 721-736.
[21] Shrestha, R., & Tanaka, M. (2017). Waste-to-energy technologies and their environmental benefits: A review. Renewable and Sustainable Energy Reviews, 34(9), 984-994.
[22] Padilla-Rivera, A., Russo-Garrido, S., & Merveille, N. (2020). Addressing the Social Aspects of a Circular Economy: A Systematic Literature Review. Sustainability, 12(19), 7912.https://doi.org/10.3390/su12197912

[23] Hartley, K., van Santen, R., Kirchherr, J., 2020. Policies for transitioning towards a circular economy: Expectations from the European Union (EU). Resources, Conservation and Recycling 155, 104634.
[24] Kansal, A (2002). Solid Waste Management Strategies for India. Indian Journal of Environment Protection, 22 (4): 444-48.
[25] Nill, J., Kemp, R., 2009. Evolutionary approaches for sustainable innovation policies: From niche to paradigm? Research Policy 38, 668-680.
[26] Nicolli, F., Mazzanti, M., 2011. Diverting Waste: The Role of Innovation, in OECD (Ed.), Invention and Transfer of Environmental Technologies. OECD Publishing, Paris, pp. 127-150.
[27] Istudor, Filip Florin Gheorghe. The innovator role of technologies in waste management towards the sustainable development.Procedia Economics and Finance 8. 2014. 420 – 428.
[28] Kaza, S., Yao, L., Bhada-Tata, P., & Woerden, F. (2018). What a Waste 2.0 : A Global Snapshot of Solid Waste Management to 2050. Urban Development. The World Bank.https://doi.org/10.1596/978-1-4648-1329-0
[29] S Manasi and Harshita Bhat. 2020. Eco-innovations in waste management a review of high point cases.institute for social and economic change. ISEC is an ICSSR Research Institute, Government of India.
[30] Zurbrugg, C., & Ahmed, R. (1999). Enhancing community motivation and participation in solid waste management. Sandec News, 4, 2–6. Duebendorf: EAWAG. Retrieved from http://www. apo-tokyo.org/00e-books/IS-22_SolidWasteMgt/IS-22_SolidWasteMgt.pdf.
[31] Muller, M., & Hoffman, L. (2001). Community partnership in integrated sustainable waste management. In A. Scheinberg (Ed.), Experiences from the urban waste expertise programme (1995–2001), waste, Netherlands.
[32] Abdul Shukor, F. S., Mohammed, A. H., Abdullah Sani, S. I. &Awang. M. (2011). A reviewon the success factors for community participation in solid waste management. InternationalConference on Management (ICM 2011) Proceeding (963-976).
[33] Natasha Kalra. Community Participation and Waste Management. 115-123. Springer Nature Singapore Pte Ltd. 2020 S. K. Ghosh (ed.), Sustainable Waste Management: Policies and Case Studies, https://doi.org/10.1007/978-981-13-7071-7_10
[34] Mohammad Djaelani. Social Community Participation in Household Waste Management. Journal of Social Science Studies Vol. 1, No. 1, January 2021, pages 37–39.

EMPOWERMENT OF TRIBAL WOMEN IN INDIA

ISSUES AND PERSPECTIVES

Edited by

BIR PAL SINGH

SRISHTI CHATURVEDI

Contributors include

AGRIMAA SINGH	MADHUMITHA
ANSHUMAN UPADHYAYA	NAMRTA
ANUSHKA TIWARI	NARESH KUMAR SONKAR
ASMITA PATEL	NEHAL TAPADIA
D. PRAJEISH	NIKITA GUPTA
DHARINI SRIVASTAV	PRAKHAR MISHRA
GUNJAN BAHETY	QUENDARISA KHARBULI
HARSH TRIPATHI	RISHIKA KAUSHIK
SOUMYA SONI	ROHIT K. DEBNATH
HIMANSHI LODHA	S. MANEESHA
ISHITA SHUKLA	MS. SENTIENLA
JAYANTI JAYA	SHAILY SHRIMAL
JELIS SUBHAN	SHARMISTHA CHAKRABORTY
KRATIKA VYAS	SUBASH RANJAN NAYAK
CHANCHAL DHAKAD	SWARUPA PANDIT
	YAMINI THAKUR

Mittal Publications
PUBLISHERS OF SCHOLARLY BOOKS
4594/9 Daryaganj, New Delhi - 110002 (India)
Phone : +91-11-23250398, Fax : 41564398
e-mail : info@mittalbooks.com Website : www.mittalbooks.com

ISBN 978-93-94569-56-0
₹ 995

Empowerment of Tribal Women in India
Issues and Perspectives
Bir Pal Singh
Srishti Chaturvedi
MITTAL PUBLICATIONS

Empowerment of Tribal Women in India

Issues and Perspectives

Bir Pal Singh
Srishti Chaturvedi

THE EDITORS

Bir Pal Singh (*b.*1970) is presently working as Professor in Panchayat Administration and Nyaya Panchayat, and Chairperson, Centre for Tribal Studies and Research at the National Law Institute University, Bhopal (M.P.), India. He obtained Ph.D. in Anthropology from Lucknow University. His academic and research interests include Tribal and Customary Law, Legal Anthropology, Sociology of Law, Law and Development, Law and Social Transformation, Gender and Law, and Law Relating to Affirmative Action, etc.

Srishti Chaturvedi (*b.* 1993) is presently working as an Assistant Professor of Law at the India International University of Legal Education and Research (IIULER) Goa, while simultaneously pursuing her Ph.D. from National Law Institute University, Bhopal. She completed her B.A.LL.B. (Hons.) from NLIU, Bhopal, LL.M. in Constitutional and Administrative Law from GNLU, Gujarat and also has a M.A. (Sociology) along with qualifying UGC-NET. She has keen interest in studying, teaching and writing on areas related to Constitutional Law, Human Rights, Environmental Law, Public Policy, etc.

EMPOWERMENT OF TRIBAL WOMEN IN INDIA

ISSUES AND PERSPECTIVES

BIR PAL SINGH
SRISHTI CHATURVEDI

MITTAL PUBLICATIONS
New Delhi (India)

LIST OF CONTRIBUTORS

Agrimaa Singh, Amity Law School, Noida (U.P), India

Dr. Anshuman Upadhyaya, IGNOU Regional Centre, Bhopal (M. P.), India

Anushka Tiwari, School of Law, Devi Ahilya University, Indore (M.P.), India

Asmita Patel, Amity Law School, Amity University, Raipur (C.G.), India

D. Prajeish, Tamil Nadu Dr. Ambedkar Law University,Chennai (Tamil Nadu), India

Dharini Srivastav, National Law University Odisha, Cuttack (Odisha),India

Gunjan Bahety, Maharashtra National Law University, Nagpur (Maharashtra), India

Harsh Tripathi, Banaras Hindu University, Banaras (U.P.)

Soumya Soni, from Jagran Lakecity University, Bhopal (M.P.), India

Himanshi Lodha, National Law University Odisha, Cuttack (Odisha), India

Ishita Shukla, Maharashtra National Law University, Nagpur (Maharashtra), India

Jayanti Jaya, National Law University Odisha, Cuttack (Odisha),India

Jelis Subhan, Amity Law School, Amity University, Raipur (C.G.), India

Kratika Vyas, Dr. Ram Manohar Lohiya National Law University, Lucknow (U.P.)

Chanchal Dhakad, National Law Institute University, Bhopal (M.P.), India

Madhumitha, Tamil Nadu Dr. Ambedkar Law University,Chennai (Tamil Nadu), India

Namrta, Shri Vaishnav Institute of Law, Indore (M.P.), India

Dr. Naresh Kumar Sonkar, Dept. of Sociology and Social Anthropology, IGNTU, Amarkantak, (M.P.) India

Nehal Tapadia, School of Law, Christ University, Bengaluru(Karnataka), India

14

IMPACT OF JAMATIA CUSTOMARY LAW AND STATUS OF WOMEN IN JAMATIA COMMUNITY OF TRIPURA: A CASE STUDY

SHARMISTHA CHAKRABORTY AND SENTIENLA

Introduction

Customary law is basically a socio-legal protocol that is omnipresent in almost every indigenous community. Hence, customary law is an intrinsic part of tribal identity as it is connected to the social and economic system of the tribal life. The customary law reflects some specific form of a social custom which is a kind of practice and is commonly adopted and approved as a force of law by an indigenous society (M. Chakraborty, 1993[1]). It is a well-structured framework of laws and regulations that the tribal people have abided within them since antiquity.

North-east India is also the abode of several ethnic communities having their own socio-political systems that lay down stringent regulatory norms and conventions for the prudent use of the most important resources vis-à-vis land, maintenance of their own identity and social order (Sharma, 2014[2]). Eventually, the impact of customary law among many tribal communities has been changing since last few decades. Northeast India, a well-known region for its scenic beauty and rich natural resources,