

Role of Plant-based Natural Products in the Treatment of Type 2 Diabetes

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Abstract

Diabetes mellitus is caused by the elevation of blood sugar levels and has become a serious health concern worldwide with the number of cases steadily increasing annually. Due to the increased side effects and costs associated with the use of conventional drugs, alternative treatment methods that use natural compounds from medicinal plants have been researched. This review summarizes the recent advances and discoveries of plant based natural compounds used for the treatment of Type 2 diabetes as well as their mechanisms of action, which include the inhibition of carbohydrate metabolizing enzymes, reducing oxidative stress, modifying the activity of the PPAR γ receptor, and modifying the activity of glucose transporters. We also describe the most prevalent classes of chemical compounds that have been shown to exhibit significant antidiabetic activity, thereby showing promise for development into novel drug molecules. These classes include polysaccharides, polyphenols, alkaloids, terpenes and quinones among others.

Keywords: T2D, Antidiabetic, Natural products, Medicinal plants, Drugs

INTRODUCTION

An Introduction to Diabetes and its Severity

Diabetes mellitus (DM) is a chronic metabolic condition that causes blood glucose levels to rise above normal thresholds. Although it is a treatable condition, research into this area has been steadily increasing due to the exponential rise in diabetes cases around the world. Recent estimates state that the number of people suffering from diabetes in 2019 was 463 million, reflecting a 62% increase during the last ten years. This number is predicted to increase to 578 million by 2030 based on the current trend. Diabetes is also among the top ten causes of death in adults [1]. The effects of diabetes have been crippling for the economies and healthcare providers of many developing countries with

factors like obesity, sedentary lifestyles, population growth, unhealthy diets and urbanization being main causes for the increase in patients.

Individuals with diabetes are prone to both macrovascular system complications such as cardiovascular diseases and microvascular system complications such as diabetic kidney disease and diabetic retinopathy. Diabetes is a multifactorial disease with both environmental and genetic arms [2]. A clear association is found between diabetes and periodontal disease, especially in uncontrolled diabetic patients. This association is said to be bidirectional as diabetes increases the risk of periodontal disease whereas poor glycemic regulation and increased severity of diabetic

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complications are a result of periodontal disease [3]. Another common complication of diabetes is diabetic foot ulcers or the diabetic foot. Diabetic patients face increased risk of lower limb amputations along with impaired wound healing. Recently, epidemiological evidence has suggested a strong correlation between diabetes and increased severity of nonalcoholic fatty liver disease (NAFLD). NAFLD can adversely increase the risk of diabetic complications such as cardiovascular disease (CVD), cardiomyopathy, cardiac arrhythmias and in particular, chronic kidney disease (CKD) [4]. Currently, many studies have shown that diabetes is an important comorbidity in patients with COVID-19 as it predisposes the severity of the disease *via* acute respiratory distress syndrome (ARDS), pulmonary and cardiac implications and ultimately increasing the mortality rates [5].

There exist many sub-classifications of diabetes, the main ones being Type 1, Type 2, gestational diabetes, neonatal diabetes, and steroid induced diabetes. Type 2 diabetes (T2D) is the key subtype comprising of 90-95% of the recorded cases [2]. Type 1 and Type 2 diabetes are caused by a lack of insulin production and/or lack of insulin action, respectively. Type 1 diabetes (T1D) could further be described as the autoimmune destruction of insulin secreting cells in the islets of Langerhans in the pancreas resulting in gradual decrease of insulin production until the available amounts are not sufficient to maintain normal blood sugar levels. T2D, on the other hand, is characterized by insulin resistance in the body, which leads to a reduction in glucose transport into the liver, muscle cells, and fat cells. T1D is mainly treated with exogenous insulin and oral hyperglycemic agents, while in contrast, T2D is treated with many different types of antidiabetic medications [6].

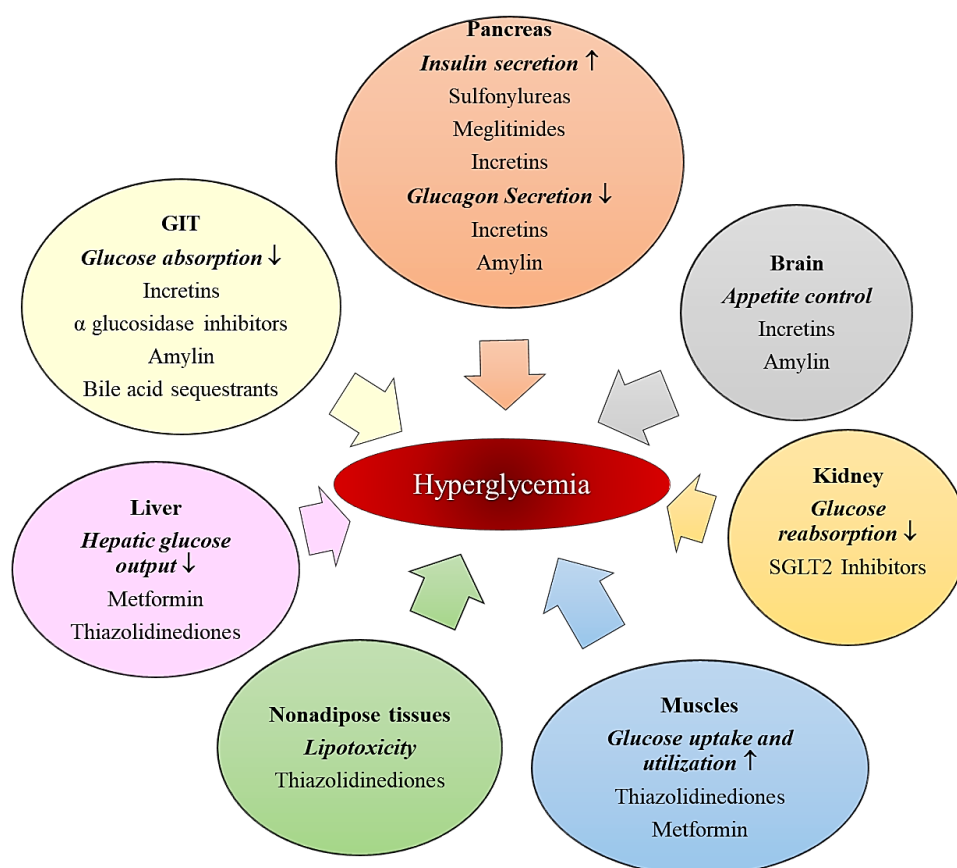


Figure 1. Mechanisms of common synthetic antidiabetic medications and their sites of action.

There are a variety of drug classes used to treat T2D (Figure 1), these include mainly biguanides, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, meglitinides, dipeptidyl-peptidase IV inhibitors and incretin-based therapies [7]. They are all effective to different degrees in the treatment

and management of the disease but as of yet, there is no permanent cure for this condition. However, the limitations of the synthetic drugs due to their “one drug-one target” mechanism and many undesirable side effects including weight gain, cardiovascular risk, and gastrointestinal troubles, there is a rapidly increasing demand for more effective, non-toxic treatment options [8]. Further, the long-term treatments that are required due to the lifelong duration of the disease and the high cost associated with the synthetic production of chemical-based drugs, have led the research in this area to find alternative, sustainable and affordable options for the treatment of diabetes.

Importance of Plant-based Natural Products

Plant-based natural products are organic chemical compounds with a distinct pharmacological activity, usually found within various parts of the plant body. They are regarded to be biologically insignificant in most cases as a vast majority of natural products are in fact secondary metabolites. That is, they do not directly contribute to the normal growth and development of the organism and are generally considered to be non-essential bioactive compounds.

Natural products perform a variety of uniquely important functions, which enable plants to thrive in their respective living eco-systems. Certain plants employ a vast array of natural products (alkaloids, terpenoids, phenylpropanoids, etc.) to improve their disease resistance and provide protection against microbial infections, insect attacks, and animal predation. Natural products have become a fundamental research area for organic chemists throughout the world due to their potential to be utilized industrially as dyes, drugs, perfumes, and oils. Development of new drugs, antibiotics, and pesticides are some of the more heavily focused study areas related to natural products.

Natural products exhibit a broad spectrum of properties that can be easily manipulated to suit our various necessities as required. These plant-based natural products (alkaloids, terpenoids, polyphenols, etc.) act as very good growth promoters, antimicrobial agents, immunostimulants, antioxidants, antivirals, and are also known to show excellent anti-diabetic properties in some cases [9].

Since this review discusses the anti-diabetic properties of natural products, it is essential to further evaluate the medical importance concerning their mode of action towards diabetes mellitus. The most common method is by reducing the blood glucose level. This minimizes the necessity of clinically injecting insulin. Some compounds are also capable of naturally controlling the insulin resistance of the body, while others can regulate insulin secretion. However, the safest mode with the least risk of side effects is the regulation of glucose absorption. This method limits the amount of glucose absorbed into the body from the food consumed [9].

Different plant parts are used in the treatment of T2D. While leaves (*Azadirachta indica* A.juss, *Mangifera indica* Linn., *Eucalyptus globulus* Labill, *Camellia sinensis*, *Ocimum sanctum* Linn.) are the most commonly used part, roots (*Withania somnifera* Dunal, *Pandanus odoratus* Linn.), stems (*Amaranthus spinosus* Linn., *Coscinium fenestratum* Calebr), seeds (*Trigonella foenum graecum*, *Punica granatum* Linn.), fruits (*Embellica officinalis* Gaertn., *Momordica charantia* Linn.), barks (*Croton cajucara* Benth), and flowers (*Musa sapientum* Linn., *Gentiana olivieri* Griseb.) have also been used according to reports. In some cases, the entire plant (*Anacardium occidentale* Linn., *Aloe vera* Tourn. ex. Linn., *Bixa orellana* L.) is used to treat the disease [10].

Comparison of Natural Product Therapies Against Synthetic Medications

Synthetic medicines began to take the place of natural medicines with the advancement of technology in the fields of chemistry. Synthetic medicines are produced in the laboratory using various approaches, based on either lead compounds isolated from nature or molecular modeling studies.

The structural complexity of natural products distinguishes them from synthetic medicines. The efficacy of natural products by molecular target efficiency and selectivity is linked to the intricacy of their well-organized three-dimensional chemical and steric structures. Usually, these compounds are so complex that it would be very challenging for them to be synthesized in a laboratory as therapeutic candidates. Despite the fact that natural products are less potent than synthetic drugs in some circumstances, they are less toxic or have fewer adverse effects than synthetic drug-based treatments [11]. The use of natural products in traditional medicine and ethnopharmacology may provide insights regarding their efficacy and safety. Moreover, natural products in treatment of diseases are used as mixtures of compounds that consist of more than one type of natural product, minerals, and vitamins; therefore, they show additional benefits in contrast to synthetic medicines. Natural products are also less expensive to use than synthetic medications because medicinal plants are widely available. The high expense of synthetic pharmaceuticals is exacerbated by the costs of drug research, development, and marketing. Plant-based medications have moderate levels of pharmacological activity and the exact amounts in which they should be consumed is still not known. However, if we manage to find the exact doses required and develop them simultaneously in both experimental and clinical contexts the efficacy can be improved.

When compared to synthetic medicines, natural products typically have a higher molecular mass, a larger number of sp^3 carbon atoms and oxygen atoms but fewer nitrogen and halogen atoms, higher numbers of H-bond acceptors and donors, lower octanol-water partition coefficients (higher hydrophilicity), and greater molecular rigidity. However, to be compatible with Lipinski's rule of five to achieve a specific structure-function relationship, natural products need to be structurally optimized [12]. Furthermore, having an extensive understanding of a drug candidate compound and its molecular target is very beneficial for the drug development process. Identifying the particular bioactive compounds of interest and their mechanism of action for natural compounds is still challenging and time-consuming [13]. Besides, ecological and legal constraints, particularly laws governing plant access and benefit-sharing, along with patentability concerns by local authorities in native countries, have a significant impact on plants as a source of drug development [13].

Major Classes of Natural Products

A large number of diverse natural product classes with various subcategories that show anti-diabetic properties are present in plants. This review presents information about some of the most prevalent natural compound classes employed in the treatment of diabetes. They are polysaccharides, polyphenols, alkaloids, terpenoids and quinones. In addition to these major classes, information regarding other more commonly available natural compound classes would also be discussed. Out of these classes, only polysaccharides are considered to be primary metabolites. All the other classes belong to the secondary metabolites.

Terpenes

Terpenoids or terpenes are considered to be the largest group of organic compounds present in plants. They are made by the aggregation of two or more five-carbon building blocks and are commonly classified as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), and sesterterpenes (C_{25}), depending on the number of building blocks present. Terpenes are formed by the monomer isoprene (C_5H_8), which when joined together results in linear chains or rings (Figure 2) [14].

Terpenes are structurally diverse and can exist as hydrocarbons or oxygen containing compounds known as terpenoids. Terpenes and their derivatives have shown great promise as antidiabetic treatment options due to the multitargeting mechanisms of terpene compounds resulting in simultaneous action on different metabolic pathways. Terpenes usually improve glucose tolerance and insulin tolerance, while lowering the plasma glucose concentrations [15].

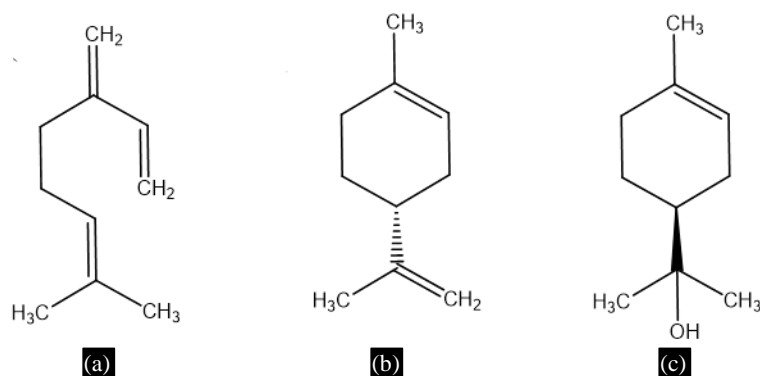


Figure 2. Chemical structures of (a) acyclic monoterpene; (b) cyclic monoterpene; and (c) monoterpenoid.

The use of terpenes from plants in diabetes has shown that it exerts its actions *via* a range of mechanisms including an insulin mimetic action, α -glucosidase and α -amylase inhibition, reduction of oxidative stress and hypolipidemic activity [16]. Diterpenes stevioside and steviol isolated from leaves of *Stevia rebaudiana* were found to increase the secretion of insulin in trials conducted on mouse islets and β cell lines INS1 in a dose dependent manner [17]. The triterpenes 25-dihydroxy-7 β -methoxycucurbita-5, 23 (E) diene and 3 β , 7 β , trihydroxy cucurbita-5, 23 (E) diene-19-al have been isolated from bitter melon and upon analysis were found to exhibit insulin sensitizing effects. In the presence of insulin in TNF α , both compounds increased the phosphorylation of IRS1 and protein kinase B [18].

The enzymes α -glucosidase and α -amylase are responsible for breaking down complex carbohydrates to absorbable monosaccharides, which is responsible for the sudden spike in post-prandial blood sugar levels. Inhibition of these enzymes might, to some extent, reduce this abrupt spike after meals, which is critical in the treatment of T2D [19]. Studies performed on essential oils isolated from *Hertia cheirifolia* have found that α -pinene (a monoterpene) shows a strong non-competitive inhibition of α -glucosidase with an IC₅₀ value of 0.24 ± 0.01 mg/mL [20]. Another study confirmed that purified fractions from *H. coronarium* rhizomes show significant activity against both α -glucosidase and α -amylase. The presence of terpenes was determined to be responsible for the activity of the fraction with the highest percent inhibition, as validated by HRLC-MS/MS. Diabetes progression can also give rise to various complications due to the oxidative stress caused by reactive oxygen species (ROS) [21]. Antioxidant compounds such as safranal, a terpene isolated from saffron, has demonstrated antioxidant activity in diabetic rats when administered intraperitoneally [22].

There has been evidence to suggest that reduction of plasma lipid levels in patients with T2D is beneficial in the reduction of insulin resistance [23]. Research performed on *Momordica charantia* has identified momordicoside, a triterpene, as a stimulator of glucose transporter 4 (GLUT4) translocation and function of AMP activated protein [24]. The alteration of the cellular distribution of the GLUT4 from the intracellular stores to the plasma membrane results in increased glucose uptake [25].

The majority of these plant derived terpene compounds have been used as antidiabetic treatments in traditional medicine. Subsequent studies on these compounds have revealed their mechanism of action and they have shown potential to develop new multitarget drugs to treat diabetes.

Polyphenolic Compounds

Polyphenols are a broad category of naturally occurring phytochemicals that have multiple phenol groups (Figure 3). They are plant secondary metabolites produced mostly by the shikimic acid pathway. There are four types of polyphenols: phenolic acids, flavonoids, stilbenes, and lignans. With

the development of phytochemical practices, these compounds have been highly utilized in different medicinal applications. Studies conducted on these chemicals strongly suggest that they have efficacy against the development of diabetes with fewer side effects. Prevention of glucose absorption, protection of pancreatic cell damage, increased insulin release and sensitivity, reduction of inflammation, modulation of the carbohydrate metabolism pathway, and regulation of insulin dependent and independent signaling pathways are among the mechanisms of polyphenol and phenolic compounds in controlling blood glucose of diabetic patients [26]. As a result, the scientific community has been very interested in the anti-diabetic properties of these polyphenolic chemicals. Due to their abundance in plants, polyphenolic compounds can be easily obtained from plant extracts.

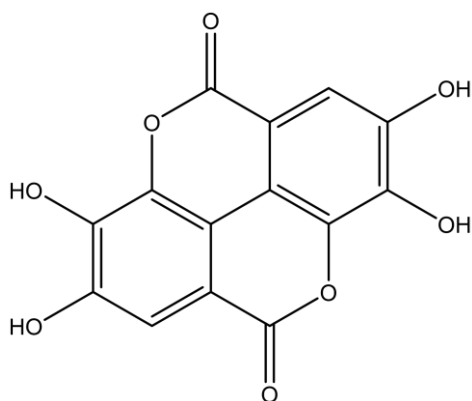


Figure 3. Typical chemical structure of a polyphenolic compound.

Cinnamon (*Cinnamomum verum*) is rich in secondary metabolite ingredients such as flavonoids. Caffeic acid, ferulic acid, syringic acid, ellagic acid, quercetin, α -tocopherol, catechol, pyrogallol p-hydroxybenzoic acid, p-coumaric acid, and gallic acid were the major polyphenolic constituents found in lyophilized water extracts and evaporated ethanolic extracts of cinnamon bark. On the cells lining the small intestine, α -amylase and α -glucosidase hydrolyze polysaccharides to monosaccharide units for absorption through the intestine. *In vitro* studies conducted have shown that the polyphenolic compounds have more affinity for α -amylase than for the α -glucosidase enzyme. It was also observed that these polyphenolic compounds extracted from cinnamon may have a relationship with improvement of anthropometric parameters, glycemic indices and lipid profiles of patients with T2D [27].

Recent research based on rambutan (*Nephelium lappaceum*) peel phenolic extracts demonstrated high antidiabetic activities *in vitro* and *in vivo*. Peel is a byproduct of the fruit. Results of the study showed that phenolic extracts from rambutan peel reduced the fasting blood glucose levels of diabetic mice. Glycogen content in mice liver was improved by the phenolic compounds present in the extract. This extract was rich in catechin and ellagic acid. Furthermore, these compounds can increase the activity of superoxide dismutase and glutathione peroxidase and reduce lipid peroxidation in diabetic mice [28].

Vernonia cinerea is a small plant which has been used in traditional Chinese medicines. A study conducted to investigate the antidiabetic property of this plant showed that the total phenolic content of *V. cinerea* leaf extract was found to consist of several polyphenolic compounds such as caffeoylquinic acid derivatives, phenolic acids, phenolic aldehydes, and flavonoids. Especially, caffeoylquinic acid derivatives were found to show antidiabetics effects by inhibiting the activity of α -amylase and α -glucosidase [29].

Haskap (*Lonicera caerulea*) berries contain mainly flavonoids as phenolic compounds. Many anthocyanin flavonoid compounds were found to be present in the dried samples and ethanolic

extracts of haskap berries. These compounds have shown antidiabetic activities by inhibiting α -amylase and α -glucosidase [30]. *Capparis spinosa* belongs to the family Capparaceae. Phytochemical analysis of extracts prepared from leaves, fresh buds and salty buds of the plant have shown the presence of flavonoids. The extracts were found to be rich in rutin, catechin, epicatechin and gallic acid. Blood glucose control observed following ingestion of *C.spinosa* plant parts has been attributed to these polyphenolic constituents [31]. Another study performed on *Dregea volubilis*, which is a large twining shrub growing in the southern and eastern regions of Asia have demonstrated similar results. Hydroalcoholic extracts of *D. volubilis* have shown antidiabetic properties and the liquid chromatography of the extracts showed the presence of gallic acid, ferulic acid, rutin, ellagic acid and quercetin as polyphenolic compounds. These phenols present in extracts of *D. volubilis* are thought to be responsible for its carbohydrate hydrolyzing enzyme inhibition activity [32].

Polysaccharides

Polysaccharides, which are structurally composed of homo or hetero monosaccharides joined by glycosidic linkages, are considered as one of the important macromolecules for all living species (Figure 4). They are mostly present in terrestrial plants, seaweeds, animals, fungi, and bacteria. Polysaccharides play an important role in a variety of physiological functions. Polysaccharides have been found to exhibit a wide range of pharmacological effects including antidiabetic, antioxidative, anticancer, antibacterial, anti-obesity, hypolipidemic, and hepatoprotective effects. The pharmacological effect of a bioactive polysaccharide is significantly determined by their chemical structure and configuration. These bioactive polysaccharides consist non-carbohydrate parts as well. These non-carbohydrate moieties are also important in exhibiting bioactivities. These compounds can act as antidiabetic agents by reducing postprandial glucose level *via* changing the small intestine transit time and preventing carbohydrate digestion by suppression of digestive enzymes [33].

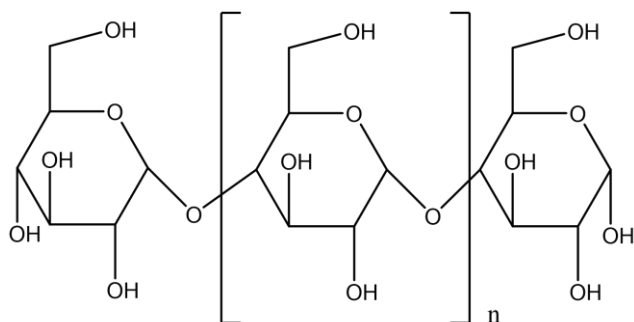


Figure 4. Typical chemical structure of a polysaccharide.

Blackcurrant (*Ribes nigrum*) is a plant which originates from Northern Europe and Asia. Studies carried out on degraded polysaccharides of blackcurrant showed that they have significant α -amylase and α -glucosidase inhibitory activity, where the lower molecular weight fractions possessing higher bioactivity [34].

Studies carried out on *Schinus terebinthifolius* and *Schinus molle* fruit extracts have also shown the presence of antidiabetic polysaccharides in the extract. *Schinus terebinthifolius* and *Schinus molle* are perennial woody plants belonging to the *Anacardiaceae* family, which are categorized under invasive plants in North America, Europe and parts of Asia. Therefore, exploitation of these plants may be a better source for mass consumption. From the α -amylase and α -glucosidase assays carried out on these plant extracts it was evident that they contain polysaccharides that have potential anti diabetic effect [35].

Certain polysaccharides extracted from plants have shown activity against advanced glycation end products. Wild walnut (*Juglans regia*), is a plant that is highly utilized in Chinese traditional medicine. *Diaphragma juglandis* is the dry wood diaphragm of walnut kernel, which is a byproduct of

walnut production. Therefore, use of these parts as medicines is sustainable since it is not required for any other process. Polysaccharides present in the extract of the dry wood diaphragm of walnut kernel showed antidiabetic activity by a dose-dependent inhibitory effect on α -glucosidase activity. These polysaccharides also showed inhibitory activities in formation of advanced glycation end products [36].

Momordica charantia commonly known as bitter gourd or bitter melon is a member of the Cucurbitaceae family and is a popular vegetable and use as a traditional remedy for diabetes all over the world. Polysaccharides are one of most common bioactive constituents found in bitter melon. Studies based on bitter melon powder extracts show that polysaccharides in the extract have anti-hyperlipidemic effects and provide relief of the diabetic complications and symptoms [37].

Legumes are rich in non-starch polysaccharides and have a low glycemic index. Hence, they are a particularly good food choice. Furthermore, cultivation of the legumes is important in nitrogen fixation of soil. Therefore, they are a very important choice of crops that can be used in agriculture. Polysaccharides prepared from six legumes: soybean (*Glycine max*), white kidney bean (*Phaseolus vulgaris*), red kidney bean (*Phaseolus vulgaris*), small black soybean (*Vicia faba*), field bean (*Lablab purpureus*) and lentils (*Lens culinaris*) were studied for their anti-diabetic activity. Studies based on streptozotocin-induced Type 2 diabetic mice showed that the high molecular weight polysaccharides extracted from these legumes have significant antidiabetic activity. Furthermore, these compounds have shown effects on body weight, fasting blood glucose levels, glycosylated serum protein level, and serum insulin levels [38].

Alkaloids

Alkaloids are a major group of secondary metabolites found in plants. They are basic compounds made up of heterocyclic nitrogen atoms (Figure 5). Alkaloids are found in about 14-20% of total plant species in the plant kingdom. The antidiabetic effect is one of the more prominent pharmacological effects elicited by alkaloid compounds. Alkaloid-containing herbal plants are utilized by the ayurvedic (herbal) medicine practitioners in many Asian countries like India, China, and Sri Lanka to treat patients with T2D. Their mode of action, as to exactly how they affect the disease, differs from one alkaloid to another.

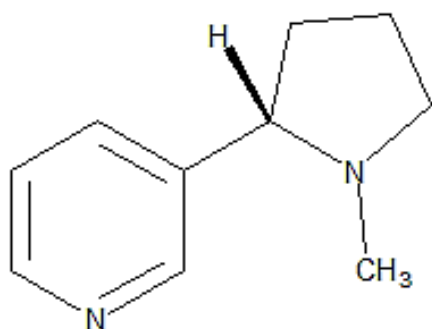


Figure 5. Chemical structure of a simple alkaloid.

Punarnavaine is an alkaloid compound that can be found within the entire plant of *Boerhaavia diffusa* L. (Punarnava) of the Nyctaginaceae family. It is capable of increasing the hexokinase enzyme activity and the plasma insulin level while decreasing the glucose-6-phosphatase and fructose bisphosphatase activity [39]. Ecliptin alkaloid is present in the leaves of *Eclipta alba* Linn. (Bhringraj) plant of the Compositae family. It decreases the activity of glucose-6-phosphatase and fructose-1, 6-bisphosphatase [40].

Canthin-6-one derivative is an alkaloid compound present in the roots of the *Aerva lanata* plant of the Amaranthaceae family. It is capable of regulating low levels of glucose in the blood [41].

Hunteria umbellata is responsible for the reduction of glutathione and glutathione-s-transferase activity, resulting in an overall decrease of the blood glucose level [42]. Alkaloids in the seed powder of *Brassica juncea* of the Brassicaceae family is able to greatly reduce the fasting serum glucose levels of humans [43].

Quinones

Quinones are chemicals with a benzoquinone chromophore made up of two carbonyl groups connected by two carbon-carbon double bonds. Benzoquinones, naphthoquinones and anthraquinones are the three main classes of quinones, with 1, 2, and 3 ring structures, respectively (Figure 6). The basic subunit of quinone compounds is benzoquinone even though it is the least common among the sub classes. Naphthoquinones are the second most common group of quinones found naturally, with over 120 sources studied. Anthraquinones are the most studied group, with over 700 compounds being investigated. Nearly half of these are derived solely from plants [44].

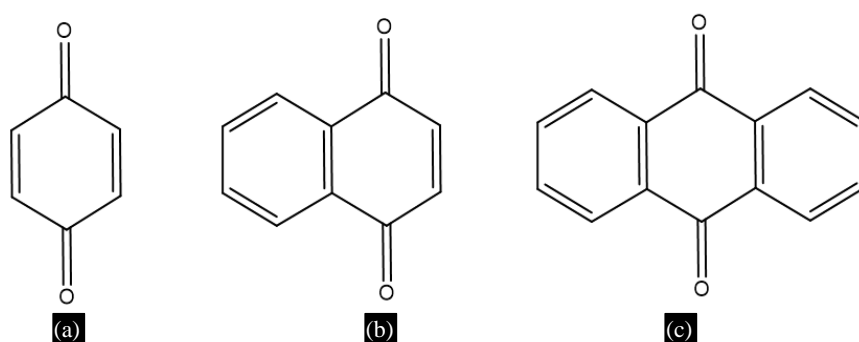


Figure 6. Typical chemical structures of (a) benzoquinone; (b) naphthoquinone; (c) anthraquinone.

Roots of *Averrhoa carambola*, which is a long-term plant, contain a benzoquinone BACR that shows antidiabetic effects via reduction of inflammation. This effect is resulting from inhibiting the toll like receptor 4 (TLR4) and nuclear factor kappa light chain enhancer of activated B cells (NF- κ B) signaling pathways as observed in diabetic induced rats [45]. Embelin is a para-benzoquinone present in *Embelia ribes* that shows α -glucosidase inhibition activity *in vitro* [46].

Emodin is a naturally occurring anthraquinone present in all parts of *Cassia occidentalis* [47]. The antidiabetic activity of emodin occurs by binding to peroxisome proliferator-activated receptor- γ found mostly in adipose tissues that is linked to adipocyte development and insulin sensitivity [48, 49]. Further, it inhibits the mitochondrial complex 1 while triggering AMP-activated protein kinase (AMPK). AMPK inactivation occurs in diabetes and activation of AMPK induces the cellular glucose uptake and inhibits the production of intracellular glucose [50]. It also acts by controlling the sterol regulatory element binding protein (SREBP) pathway. SREBP-1c is the primary transcription factor that insulin uses to control hepatic *de novo* lipogenesis [49]. Emodin can bind to the 11 β -hydroxysteroid dehydrogenase enzyme [51] and reduces its activity. Emodin regulates the blood glucose level by interacting with the glycogen synthase kinase-3 β enzyme to control glycogen metabolism [52] or the acetyl-CoA carboxylase enzyme to regulate fatty acid metabolism [53]. Emodin also can upregulate L-type calcium channels that could induce insulin release from pancreatic β cells [54]. As exemplified by much research, emodin is a good candidate to develop natural product-based antidiabetic drugs.

Salvia miltiorrhiza is a plant rich in tanshinones, an anthraquinone. Tanshinones can reduce the levels of proinflammatory cytokines and NF- κ B and serine 307 phosphorylation, which results in the reduction of insulin resistance *via* insulin receptor substrate-1 pathway in rats with T2D. Another anthraquinone, rhein isolated from *Rheum rhizoma* has induced insulin-stimulated glucose uptake and inhibited α -glucosidase and α -amylase activity [55].

Shikonin is a naphthoquinone, which is naturally occurring in *Lithospermum erythrorhizon* and has demonstrated antidiabetic activity [56]. Shikonin was also reported to regulate FABP4 and LPL gene expression which causes the accumulation of triglycerides, ultimately giving an anti-obesity effect in 3T3-L1 cell lines [57]. Rhinacanthin-C present in roots and leaves of *Rhinacanthus nasutus* [58] is also a naphthoquinone, which can inhibit α -glucosidase and stimulate glucose uptake in muscles and adipocytes through the mechanism of GLUT4 [59]. Plumbagin in root and wood of *Diospyros kaki* and the whole plant of *Plumbago zeylanica* showed its antidiabetic effect *via* regulation of serum and hepatic carbohydrate metabolizing enzymes including glucose-6-phosphatase, fructose-1, 6-bisphosphatase, and hexokinase [56].

Other Classes of Natural Products used in Diabetes Treatment

Apart from above mentioned natural product classes, other subclasses such as saponins, xanthenes and coumarins have also shown hypoglycemic activity (Figure 7). Saponins are naturally occurring surface-active glycosides [60]. Saponins can reduce the hyperglycemic state by restoring the insulin response [61], improving insulin signaling [62], increasing plasma insulin levels [63], expression of GLUT4 [64], inhibiting gluconeogenesis [65] and inhibiting α -glucosidase activity [60]. Furthermore, steroidal saponins from *Dioscorea polygonoides* are capable of significantly reducing plasma glucose levels and minimizing the activity of glucose-6-phosphatase in the liver [66].

Xanthenes are oxygen-containing heterocyclic substances that can be found as secondary metabolites in the Guttiferae, Gentianaceae, Moraceae, Clusiaceae, and Polygalaceae families of higher plants. As reported by Santos et al., xanthenes including mangiferin 2, the most abundant natural glycosylate, has the capability to inhibit α -glucosidase enzyme [67].

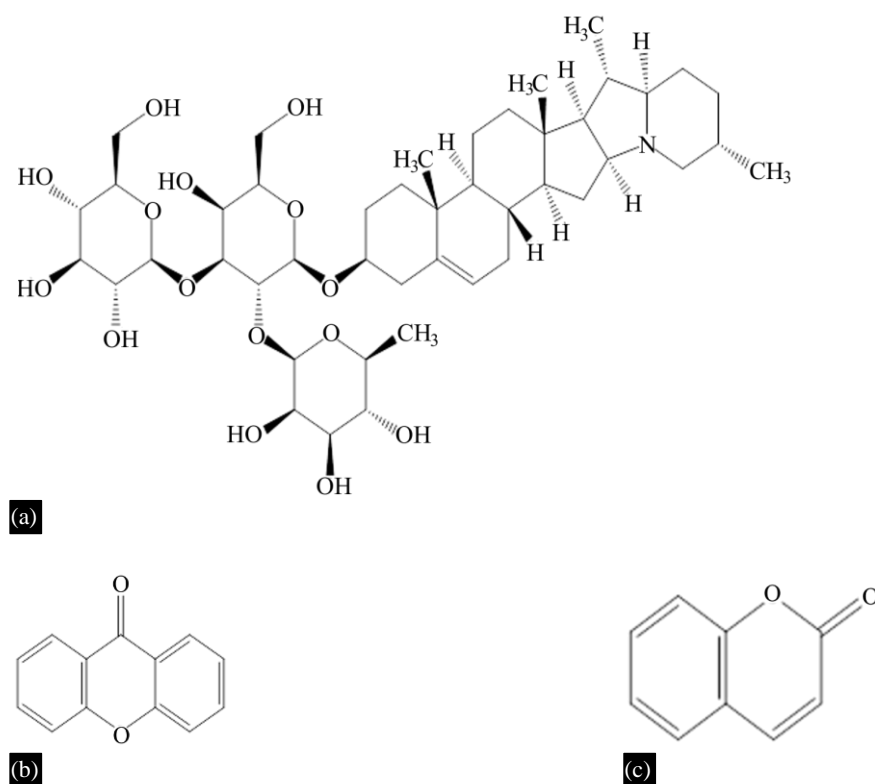


Figure 7. Typical chemical structures of (a) saponin; (b) xanthone; (c) coumarin.

Coumarins are natural phenolic compounds that are found in plant species. They have many therapeutic effects with a focus on anticoagulation and antithrombotic therapy for cardiovascular diseases. Though anticoagulation and antithrombotic therapy takes precedence, they are also known to

have significant anti-diabetic effects making them potential anti-diabetic agents. Because there seems to be a direct correlation between cardiovascular diseases and diabetes, potential treatment methods using coumarin compounds could have a greater therapeutic effect to general health of a diabetic patient. Umbelliferone is a simple coumarin compound extracted from the *Citrus aurantium* plant that is capable of lowering both the fasting blood glucose level and the amount of glycated hemoglobin type A1c (HbA1c) cells in the blood when treated *via* an oral pathway [68].

CONCLUSION

Potential antidiabetic properties of plant-based natural product classes including terpenes, polyphenols, polysaccharides, alkaloids and quinones, and their potential in treatments of T2D is discussed in this review. Antidiabetic therapeutic procedures employing natural products from plant materials permit several benefits to the patients' health over synthetic drug treatments: these plant products are more biocompatible and less toxic than the chemicals in synthetic drugs, resulting in minimal side effects. However, there is a limitation in the supply of natural products due to issues in mass production and destructive harvesting methods leading to resource exhaustion. To enable sustainable use of natural products as therapeutics, these limitations need to be addressed. Use of continuously growing parts for extractions can minimize destructive harvesting. Further, modern agricultural techniques including tissue culture, micropropagation and synthetic seed technologies can also be employed to improve the yield and reduce the space and cost required for cultivation of these plants in the long run.

A majority of the reported natural compounds reduce the glucose level in the body by direct interference with the gluconeogenesis metabolic pathway; mainly by interacting with the activity of various enzymes. Only a few natural compounds were found to interfere with the insulin synthetic pathways to elicit their antidiabetic properties. Despite the abundance of biochemical data available, there is still a lack of clinical trials on natural product medications. To establish these natural compounds as contemporary treatment methods, it is necessary to study their efficacy and safety in large randomized clinical trials.

Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

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