An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

ANTI-DIABETIC CHEMICAL CONSTITUENTS ISOLATED FROM TRADITIONAL MEDICINAL PLANTS

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ARTICLE INFO

Article history:

Received: 28 April 2016
Revised: 10 May 2016
Accepted: 18 May 2016

Key words:

Diabetes Mellitus;
Traditional Medicine Plant;
Bioactive Compound

ABSTRACT

The rapidly increasing amount of diabetes mellitus cases has posed serious threats to human health worldwide. The control and treatment of diabetes and its complications mainly depend on the chemicals of biochemical agents; however, cases involving individuals who recovered completely from diabetes have not been reported yet. With distinct traditional medical opinions and natural medicines mainly originating from herbs, traditional medicinal plants have been used effectively in clinical applications, and are potential treatments for diabetes mellitus and its complications. Chemical and pharmacological studies have also shown that numerous bioactive compounds are found in medicinal plants; these compounds can be used to treat diabetes. The present study reviews and describes natural bioactive compounds from plants with anti diabetic activities and their pharmacological properties. It is important to consider traditional medical therapeutics and natural medicine for the treatment of diabetes mellitus and its complications.

INTRODUCTION:

Diabetes mellitus, one of the most common endocrine, metabolic disorders, has resulted in significant morbidity and mortality because of micro vascular and macro-vascular complications [1].

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There are two types of diabetes, namely, type 1 and type 2. Type 1, or insulin-dependent diabetes mellitus (IDDM), accounts for 5% to 10% of diabetes cases, with type 1 the body does not produce any insulin. Individuals with type 1 diabetes need daily insulin injection to stay alive. Type 2, or non-insulin-dependent diabetes mellitus, accounts for 90% to 95% of diabetes cases, and with type 2, the body fails to produce enough insulin or properly use it. According to the World Health Organization [2], the diabetic population willlikely increase to 300 million individuals or more by 2025. Currently, the available therapies for diabetes include insulin and various oral anti-diabetic agents, such as sulfonylureas, biguanides, and glinides. Many of these agents elicit serious adverse effects; there-

fore, the search for effective and safe hypoglycemic agents is an important area of investigation.Various medicinal plants are used to treat diabetes; these plants have also been used empirically in anti-diabetic and anti-hyperlipidemic remedies. Hence, these plants are considered valuable alternative medicine because of fewer side effects and low costs. Some of these medicinal plants induce pancreatic beta cell regeneration, and insulin release, and prevent insulin resistance [3]. Hyperglycaemia is involved in the aetiology of diabetic complications. Hyperglycemic herbs increase insulin secretion and enhance glucose production from the liver [4]. Insulin and oral hypoglycemic agents, such as sulfonylureas and biguanides, are the major factors in disease management, but effective anti-diabetic agents should be further enhanced. Chemical and pharmacological studies have shown that numerous bioactive compounds are available in natural plants. These compounds include polysaccharides, terpenoids, flavonoids, sterols, alkaloids, and other compounds frequently implicated in anti-diabetic activities [5].

Anti-diabetic chemical constituents isolated from traditional medicinal plants

1. TERPENOIDS

Numerous compounds isolated from medicinal plants exhibit anti-diabetic activities. For example, triterpenoid saponins are promising compounds that can be used to develop new drugs for the treatment of diabetes. Ginsenoside, senticoside A, boussingoside, and momordin are triterpenoids extracted from *Boussingaultia baselloides* [6].

Kikyosaponin, timosaponin, 3,6,9-trihydroxyurs-12-en-28-oic acid, and 2,3-dihydroxyurs-12-en-28-oic acid are triterpenoids extracted from *Eriobotrya japonica* [7]. Moreover, oleanolic acid, tormentic acid, and ursolic acid are triterpenoids extracted from *Ligustrum lucidum* [8], *Eriobtrya japonica* [9], and *Punica granatum* [10], respectively. Gymnemagenin, gymnemasaponin, gymnemic acid, and gymnemosides are triterpenoids extracted from *Cornus officinalis* . Diterpenoids and sesquiterpenoids include stevioside, salvin, salvicin, and salvifolin, which are found in *Salvia japonica* Thunb [11]. Monoterpenoids mainly include iridoid glycosides, such as catalpol and rehmannioside A, B, C, and D extracted from *Rehmannia glutinosa* [12].

Ginsenoside R_{g2}

Panax ginseng C.A. Meyer (Araliaceae) is well known as a good tonic for health with two dimensional regulation of blood glucose (lowers hyperglycemia and raises hypoglycaemia, does not influence normal blood glucose). The extract of all parts of ginseng (the roots, stems, leaves and fruits) shows anti-hyperglycemic effects [13]. Ginsenoside R_{g2} was isolated and experimentally or clinically confirmed to be bioactive for anti-diabetes or/and diabetic complications (Figure1). The mechanism of action of these saponins involves regulating the activity of enzymes related to glucose metabolism directly or indirectly in rats with streptozotocin-induced diabetes [14].

Oleanolic acid and ursolic acid

The ursolic acid extract of the pulps of *Cornus officinalis* Sieb (Cornaceae) displayed anti-diabetic activity towards streptozotocin-induced diabetic rats (Figure 2). The Oleanolic acid (Figure 3) extract of *Momordica cochinchinensis* Sperengel (Cucurbitaceae) was responsible for decreasing postprandial plasma glucose and the insulin level of non-insulin dependent diabetic rats . An additional effect of ursolic acid and Oleanolic acid is the decrease in the amount of water consumption and urine volume in diabetic rats [15].

Tormentic acid

The hypoglycemic activity of tormentic acid that was extracted from *Poterium ancistroides* Desf (Rosaceae) was determined in nor-rnoglycemic, hyperglycemic, and streptozotocin-induced diabetic rats [16]. This principle reduces the fasting plasma glucose level with a corresponding increase in circulating insulin levels. Furthermore, glucose tolerance was improved by increasing insulin secretory responses to glucose. Conversely, tormentic acid did not change insulin and glucose levels in streptozotocin-induced diabetic rats (Figure 4). These effects were compared with those of glibenclamide, these results suggest that tormentic acid had a similar effect to glibenclamide in the body, in which insulin secretion from the islets of Langerhans is increased [17].

Gymnemic acid

Gymnema sylvestre (Retz.) Schylt (Asclrpiadaceae) leaves have been traditionally used as a medicine for diabetes care. There are many reports about the action and active constituents of Gymnema sylvestre [18]. The main constituent of gymnema is possibly gymnemic acid, which is a mixture of at least 17 different saponins. Gymnemic acid formulations have also been used against obesity . This anti-obesity property was attributed to the ability of gymnemic acids to delay glucose absorption in the blood. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. These mo-

lecules fill the receptor locations on the taste buds, thereby preventing its activation by sugar molecules present in food; as such,sugar craving was curbed. Similarly, gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine; thus, sugar molecule absorption in the intestine is prevented, resulting in low blood sugar levels [19].

Studies have described several possible mechanisms by which leaves, particularly gymnemic acids, elicited hypoglycemic effects. For example, in these studies, insulin secretion increased. The regeneration of islet cells was promoted , and therefore, glucose utilization increased. The activities of enzymes responsible for glucose utilization via insulin-dependent pathways and phosphorylase activity were possibly increased; furthermore, gluconeogenic enzymes and sorbitol dehydrogenase decreased. The inhibition of glucose absorption from the intestine was also triggered, but the exact action remains unknown [20] (Figure 5).

2. POLYSACCHARIDES

Polysaccharides are polymeric carbohydrate molecules composed of monosaccharide units bound together by glycoside linkages. Natural polysaccharide is an important class of biological polymers with general formula $(CH_2O)_n$ in which n is three or more. Their functions in living organisms and metabolic pathways have been identified and defined and include intestinal digestion, hepatic glycogen breakdown, lysosomal catabolism of glycoconjugates, and maturation of the sugar chains in glycoproteins [21]. In recent years, many types of polysaccharides have been isolated from traditional medicinal plants used to treat diabetes, Additionally, many polysaccharides from plants and epiphytes have been reported to be effective in protecting against pancreatic islets damage in diabetes [22]. Most of these polysaccharides, such as panaxan, laminaran, coixan, pachymaran, anemarn, moran, lithospeman,trichosan, saciharan, ephedran, abelmosan, and atractan, elicit beneficial effects [23].

Panaxans A and B

Various hypoglycemic and insulin-like principles have been observed in compounds isolated from roots of *Panax ginseng* Meyer (Araliaceae). These compounds include various glycans, designated as panaxans A to P, and ginsenoside Rb1. Some compounds exhibit antilipolytic activities; for example, adenosine, a carboxylic acid and peptide with a molecular weight of 1,400, can inhibit catecholamine-induced lipolysis in rat epididymal fat pads [24]. Two hypoglycemic fractions, DPG-3-2 and EPG-3-2 isolated from *P. ginseng* by Kimura et al. in 1981, demonstrated a hypoglycemic effect on EPG-3-2 in alloxan-induced diabetic mice [25].

Coixan

A water extract of the oriental crude drug "yokuinin" from the seed of *Coix lachryma jobi* (Poaceae) produces a marked hypoglycemic action when the drug is administered to mice [26]. After fractionation activity is completed, three glycans, namely; coixans A, B, and C, are isolated. These components elicited remarkable hypoglycemic effects in normal and hyperglycemic mice treated with alloxan [26].

Moran

An aqueous methanol extract of the oriental crude drug "sohakuhi" from root barks of *Morus alba* (Moraceae) markedly reduced plasma sugar level in mice [27]. An activity-guided fractionation of the extract produces a glycoprotein called moran A, which elicited remarkable hypoglycemic effects in normal and alloxan-induced hyperglycemic mice [27].

Trichosan

The non-dialyzable portion of the water extract of the oriental crude drug "Karokon" from the roots of *Trichosanthes kirilowii* reducds plasma glucose levels in mice. An activity-guided fractionation of this non-dialyzable portion produces five glycans: trichosans A, B, C, D, and E; these compounds showed hypoglycemic activities in normal mice. Trichosan A, the main glycan, also exhibited anti-diabetic activity in alloxan-induced hyperglycemic mice [28].

Glycans-Ephedran

An aqueous methanol/water extract of the bark of *Ephedra distachya* from Ephedraceae causes transient hyperglycemia and long-term hypoglycemia in mice. The activity-guided fractionation of this extract produces five glycans-ephedrans A, B, C, D, and E; these compounds displayed significant hypoglycemic effects in normal and alloxan-induced hyperglycemic mice .

Atractan

Atractylodes japonica koidzumi form the Compositae family is an herbal medicine that is traditionally used in East Asia for treatment of obesity and its related complications [29]. In recent years, several pharmacological activities, such as anti-obesity [30], anti-inflammatory [31], gastroprotective [32] and anti-oxidant effects of this plant have been reporte. The anti-diabetic activity of this plant was demonstrated via i.p administration of various doses of atractans A, B, and C extracted from the rhizome of *Atractylodes japonica koidzumi* in normal and alloxan-treated diabetic mice. These glycans had a significant hypoglycemic effect in normal and diabetic mice .

3. FLAVONOIDS

Flavonoids are polyphenolic compounds that contain 15 carbon atoms, and they are the most numerous of the phenolics. They are found throughout the plant kingdom. They are present in high concentrations in the epidermis of leaves and the skin of fruits and have important and varied roles as secondary metabolites. In plants, flavonoids are involved in such diverse processes as UV protection, pigmentation, stimulation of nitrogen-fixing nodules and disease resistance [33]. Some flavonoids have been isolated from medicinal plants to treat diabetes. Most of these flavonoids improve the function of β-cells of the pancreatic islets [34] . Some examples of flavonoids include kakonein, 7-(6-O-malonyl-Dglucopyranosyloxy)-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, flavones C-glycoside, icariin, neomyrtillin, sappanchalcone, caesalpin P,3-deoxysappanone, protosappanin A, brazilin, swerchirin from *Swertia chirayita* (Roxb ex-Flem) Karst, and hyperin from *Tilia cordata* Mill [35].

Swerchirin

The *Swertia* species includes medicinal plants that belongs to the family Gentiaceae, which includes taxonomically informative molecules such as iridoids, xanthones, mangiferin and C-glucoflavones [36]. However, among the various species of Swertia**,** *Swertia chirayita Roxb* is known for its pharmacological aspect for diabetes, for example, xanthone has been isolated from the hexane fraction of the leaf of *Swertia chirayita Roxb* and identified as 1,8-dihydroxy-3,S-dimethoxyxanthone (swerchirin) (Figure 6), which elicits a very significant blood sugar reducing effect in fasted, fed, glucose-loaded, and tolbutamide-pretreated albino rat models .

Kola flavanone

Garcinia Kola is cultivated worldwide, and various extracts of the plant have been used traditionally for ailments such as laryngitis, cough and liver diseases. Recently, kolaviron has been isolated as a defatted ethanol extract from the seeds of Gracinia kola in a mixture of three compounds- Gracinia biflavonoid GB1, GB2 and kola flavanone [37].

The antioxidant and scavenging properties of kolaviron have also demonstrated non-toxic effect in vitro and in vivo [38]. It is generally consumed and plays an important role in traditional medicine. However, the anti-diabetic effects of orally administered kola flavonone leaf in various doses include significant hypoglycemic effects on normal and alloxan-induced diabetes mice [38]. (Figure 7).

Bellidifolin

The genus *Swertia* (Gentianaceae) comprises approximately 80 species among which 30 are well known as the folk traditional medicines [39]. Chemical in vestigations of the genus Swertia have resulted in various phytochemical compounds such as; Swertiamarin, mangiferin, swertianolin and bellidifolin that were used for treatment of liver diseases [40]. Compounds such as bellidifolin and, methylbellidifolin of *Swertia japonica* (Gentianaceae) have showed a potent and dose-dependent hypoglycemic effect in streptozotocin-induced diabetic rats after both i.p and p.o administration [38] (Figure 8).

Leucocyanidin

Ficus bengalensis L. (Moraceae) is a large evergreen tree with aerial roots. The medicinal properties of this plant have been described in the literature of traditional systems of medicine, including ayurveda, siddha, unani and homeopathy [40] . Bioactive compounds isolated from various parts of the plant are effective in the treatment of various ailments including dysentery, diarrhea, diabetes, piles, rheumatism, leucorrhea and menorrhagia, two flavonoids namely 5,70dimethyl ether of leucopelargonidin-3-O-α-L rhamnoside and 5,3`-dimethyl ether of leucocyanidin 3-O-α-D galactosyl cellobioside have been reported [41]. The leaves of these plants are used in traditional medicine to manage diabetes mellitus. The leucocyanidin fraction of this plant also elicits a hypoglycemic effect in fasted normal rats; this drug has also been used to treat hyperglycemia induced by the effects of alloxan rats [41] (Figure 9).

(-)-Epicatechin

The fraction extracts of the bark of *Pterocarpus marsupium Roxb.* (Leguminosae) displayed a hypoglycemic effect in the treatment of diabetes mellitus (DM). The active hypoglycemic principal of the bark is (-)-epicatechin (Figure 10) [32]. Furthermore, the hypoglycemic effects of this compound are due to the regeneration of β cells in the pancreatic islets of alloxan-induced diabetic rats.

Quercetin

Quercetin is able to inhibit bimolecular oxidation and can alter antioxidant defence pathways in vivo and in vitro [42]. Quercetin is present in many plants that are used for the treatment of diabetes, and it is often a major constituent of the medicinal activity of plants. It has been shown in experimental studies to have numerous protective effects on the body . Additionally, oxidative damage has been implicated in the etiology of diabetic complications and quercetin may have a therapeutic role in the amelioration of those

complications [25]. The quercetin (Figure 11) of the *Baubinia purpurea* L. (Leguminosae) leaf exhibit anti diabetic activities on insulin release and $^{45}Ca^{2+}$ handling in the Langerhans cells of rats. Insulin release was enhanced by approximately 44% to 47% when these islets were exposed to quercetin, naringenin, and chrysin. Quercetin inhibits the $^{45}Ca^{2+}$ efflux in the presence and absence of extracellular Ca^{2+}. This result suggests that stimulatory compounds, such as quercetin, may partially affect insulin release by changing Ca^{+2} metabolism [25].

4. INSULIN-LINKE COMPOUNDS

These substances produce an excellent effect for treating diabetes. Some of these substances include p-insulin such as bitter ground polypeptide from *Momordica charatia* L. of the Cucurbitaceae family, and ginseng glycopeptides and α-methylenecyclopropylglycin of *Litchi sinensis Sons* (Sapindaceae) [37]. Protein has been shown to reduce serum insulin, insulin resistance, hyperglycemia, body weight, hyperlipidemia, and hyperinsulinemia, which are disease components of obesity and diabetes. For example, insulin and glucagon secretion from the pancreas was reported with the intake of soy proteins, which is rich in arginine and glycine Additionally, a decrease in cholesterol due to a decreased of insulin-glucagon ratio caused by arginine and glycine in the soy protein effect has also been reported [44].

5. ALKALOIDS

One of the most common definitions of an alkaloid state that it is "a nitrogenous base of plant origin having marked physiological action". All alkaloids contain one or more nitrogen atoms, which is also true of proteins. A few compounds, such as berberin, anisodamine, vindoline, vindolinine, leurosine and hanfangchin A from plants, have been isolated to treat diabetes and elicit excellent effects [45].

Berberine

Berberine from *Coptis chinensis Fanch* leaf (Ranunculaceae) has been reported as a major component of this plant and, that was elicited a hypoglycemic effect in normal, alloxan-diabetic, and spontaneously diabetic KK mice. Berberin also antagonizes the hypoglycemic effect induced by IP injection of glucose or adrenaline in normal mice. As a result, the serum cholesterol level of mice fed with a high-cholesterol diet decreased and the aggregation of rabbit platelets *in vitro* was inhibited [46] (Figure 12).

Vindoline vindolinine, leurosine, and hanfangchin A

Catharantbus roseus (Apocynaceae) is a wild shrub known for its anti diabetic activities and is a source of indole alkaloids used in the treatment of cancer and hypertension [45]. Hypoglycemic activity was observed for catharanthine, leurosine, lochnerine, tetrahydroalstonine, vindoline, and vindolinine. At 100 mg/kg administered orally, leurosine sulfate and vindolinine hydrochloride showed a greater hypoglycemic effect tolbutamide [47] (Figure 13, 14).

6. STEROLS

Charantin

Momordica charantia L., (*Cucurbitaceae*) has been used as a treatment for diabetes for thousands of years. Currently, unripe fruits, seeds and aerial parts of *Momordica charantia* Linn. are widely used as vegetables and phytomedicine in various parts of the world to treat diabetes. Multiple compounds have been isolated from *Momordica charantia* (karela) fruit, seeds, and vines: saponins (sitosterol and stigmastadienol glucosides), proteins (p-insulin), steroidal glycosides (momordicines and momordicosides), and pyrimidine nucleoside (vicine). If administered by i.p to normal rabbits, sitosterol and stigmastadienol glucosides produce a gradual but significant decrease in blood sugar level. Pancreatectomy reduces but not abolishes the hypoglycemic effect of charantin (mixture of sitosterol and stigmastadienol glucosides) [48] (Figure15).

Glycoside

The genus *Xantium* (family Compoitae) is represented by 25 species in the world and, has been historically used as traditional herbal medicines in oriental countries. *Xanthium strumarium* L. is the principle species used to treat nasal sinusitis, headache, urticaria and arthritis. In various compounds of *Xanthium strumarium,* glycoside exhibits hypoglycemic activities at a dose of 1 mg/kg to 5 mg/kg IV in laboratory animals [49].

7. MISCELLANEOUS

Compounds with a sulfur bond, such as allicin and allyl propyl disulfide, 3-hydroxy-3-methylglutaric acid from *Tillandsia usneoides*, sodium oxalocetate from *Euonyrnus alantus* (Thunb.) Sied., and edyson from the leaf of *Morus alba* L. are examples of active compounds with varied structures that decrease blood glucose in streptozotocin induced rats [50].

Allicin and allyl propyl disulfide

Onion bulbs have been used as dietary supplements for the traditional treatment of diabetes in Asia, Europe, and the Middle East. Onions reduce free fatty acid concentrations in healthy subjects, Diphenylamine elicits hypoglycemic effects at a dose of 10 mg/kg in hyperglycemic rabbits. Diphenylamine is a more potent hypoglycemic agent than ibutamide. In an *in vitro* study, S-methyl L-cysteine sulfoxide (SMCS)

elicited an insulin secretagogue effect on pancreatic cells in moderately diabetic rats. Additionally, the antioxidant properties of a sulfoxide group and a possible lipotropic effect of a labile methyl group present in SMCS may be involved in the anti-diabetic effect. Allyl propyl disulfide and diallyl oxide (allicin) are active compounds in normal and alloxan-diabetic animals and patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM), and they possibly function by competing with insulin [51] (Figure 16).

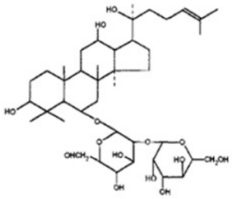

Figure 1. Ginsenoside R_{g2} (From *Panax ginseng*)[14]

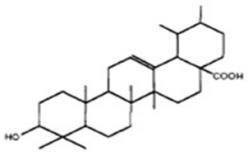

Figure 2. Ursolic acid (From *Cornus officinalis*) [15]

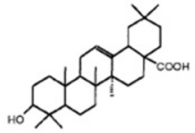

Figure 3: Oleanolic acid (From *Momordica cochinchinensis* Sperengel)

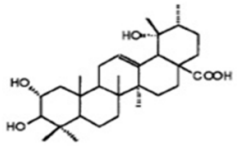

Figure 4. Tormentic acid (From *Poterium ancistroides*) [16]

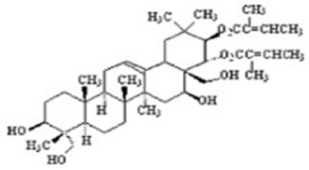

Figure 5. Gymnemic acid V (From *Gymnema sylvestre*) [20]

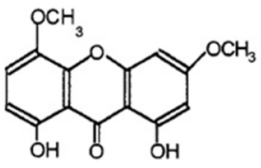

Figure 6. Swerchirin (From *Swertia chirayita Roxb*) [36]

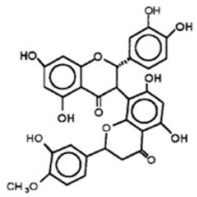

Figure 7. Kolaflavanone (From *Garcinia kola* Hook F.) [37]

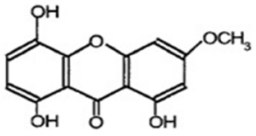

Figure 8. Bellidifolin (From *Swertia japonica*) [38]

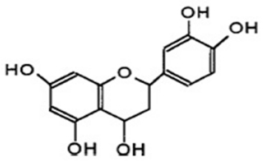

Figure 9. Leucocyanidin (From *Ficus bengalensis* L.) [41]

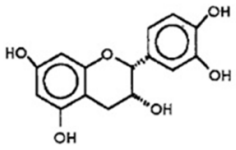

Figure 10.(-)-Epicatechin (From *Pterocarpus marsupium Roxb*) [32]

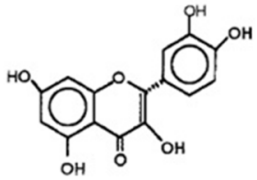

Figure 11. Quercetin (From *Baubinia purpurea* L.) [25]

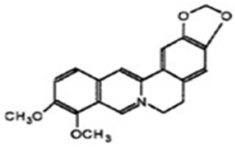

Figure 12. Berberine (From *Coptis chinensis*) [46, 48]

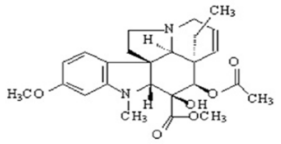

Figure 13. Vindoline vindolinine (From *Catharantbus roseus*) [47]

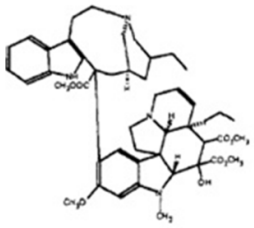

Figure 14. Leurosine (From *Catharantbus roseus*) [47]

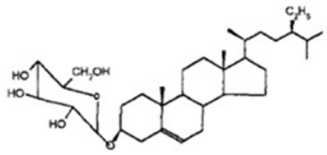

Figure 15. Stigmasta-D glucosides (From *Momordica charantia* L.) [51]

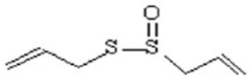

Figure 16. .Allicin (From *Tillandsia usneoides*) [96]

CONCLUSION

More than 1200 types of plants have been included in the treatment of diabetes mellitus, half as customary cures and half as exploratory substances contemplated for their hypoglycemic effects. More than 80% of these plants have demonstrated hyperglycemic activity in pharmacological studies. Data have also been presened to describe the underlying mechanisms, which are important for the bioassay-guided disengagement of potential hypoglycemic characteristics in *in vitro* and *in vivo* pharmacological assessment. Noteworthy advancements are being made in characterizing the bioactive compounds decrease the danger of major interminable illnesses and to identify the fundamental natural components that are responsible for their effects. The bioactive mixes are deductively assessed accordingly, and various bioactive mixes seem to have advantageous impacts. Based on the extensive database, there is sufficient proof to suggest an eating regimen high in sources rich in bioactive mixes. With the rise in diabetes mellitus cases in countries across populaces all through the world, the failure of treatments to control all the metabolic deformities of the disease and its results, and the substantial cost of current treatments indicated the need for advancing optional

techniques for diabetes treatment. The primary aim of this work was describe the phytochemical compounds from traditional medicinal plants related to treating diabetes complications. By discussing the data on viable techniques, this work can prompt both the advancement of indigenous natural assets as affordable sources of new hypoglycemic medications, and the revelation of novel hypoglycemic mixes that can serve as models for advanced hypoglycemic medication improvement.

ACKNOWLEDGEMENTS

This material is upon work supported by a grant number 304/PTEKIND/6312124 obtained from Universiti Sains Malaysia (USM). We also thank USM Fellowship.

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How to cite this article:

Leila Mousavi, Rabeta Mohd Salleh*, Vikneswaran Murugaiyah, Mohd Zaini Asmawi, Antidiabetic chemical constituents isolated from traditional medicinal plants, 7 (2): 3074 – 3083 (2016)