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(Review)

Advances in Natural Products application for Diabetes Management: A Comprehensive Review (2010–2025)

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ABSTRACT

Herbal remedies have been widely used for management of several ailments in recent years in both developed and developing countries. Owing to their safety and efficacy, scientists paid a great attention to herbal products and/or blends in treating several health problems. Diabetes mellitus is one of the most crippling diseases with huge social, health, and economic consequences. Several phytochemical classes including alkaloids, flavonoids, and essential oils are bioactive ingredients widely distributed in herbal products with promising outcomes in diabetes management. The main aim of the current review is to introduce a holistic overview on medicinal plants used to treat diabetes mellitus from several perspectives: 1) Provide scientific data about the plants effective in diabetes control including the used organs, extracts, and the active phytochemicals. 2) possible mechanism of action of natural products in controlling diabetes. 3) The potential use of bioactive phytochemicals with antidiabetic properties. The vast array of this review can illustrate the value of herbal remedies for treatment of diabetes with possible application.

Keywords: Diabetes mellitus, medicinal plants, phytochemicals, herbal remedies; health value

1-Introduction

Diabetes mellitus is one of the most prevalent endocrine disorders that affect the body's ability to produce or utilize insulin [1]. Diabetes is a metabolic disorder characterized mainly by elevated blood sugar levels. Insulin, a hormone produced by the pancreas and aids in transferring circulatory glucose into the liver, muscle, and fat and utilized as fuel [2]. Insulin resistance is a major problem in which either pancreas not producing enough insulin or the cells not responding to insulin causing hyperglycemia[3]. Currently, 537 million adults (20-79 years) are living with diabetes. This number is predicted to increase to 643 million by 2030 and 783 million by 2045 [4]. Such rise in diabetic patients is due to an increase in sedentary lifestyle, consumption of energy-rich diet, and obesity [4]. Type II diabetes mellitus develops when the pancreas cannot produce enough insulin or when the body tissue becomes resistant to insulin and without insulin the body cannot process glucose resulting in too much sugar in the blood and not enough sugar in the body's cells [5]. This disturbance increases the risk of many disorders including obesity, hypertension, hyperuricemia, and dyslipidemia [6]. Only 5% of people with diabetes have type I diabetes, often known as juvenile diabetes, which is insulin dependent [7]. Reactive oxygen species (ROS cause oxidation of nucleic acids, Lipids, and proteins within cells. Research and empirical data have demonstrated that ROS production escalates in both forms of diabetes and that oxidative stress plays a significant role in the establishment of diabetes, mainly by oxidation, nonenzymatic protein glycation, and oxidative breakdown of glycated proteins[8]. Increased reactive oxygen species (ROS) such as endoplasmic reticulum stress and mitochondrial superoxide in endothelial cells, coupled with a decrease in antioxidant defense mechanisms, cause lipid peroxidation, cellular and enzyme damage, and ultimately lead to the onset and progression of insulin resistance and hyperglycemia [9]. Management of diabetes depends on several protocols including prescribed medications, follow a strict diet, and exercise regimen to regulate blood glucose levels [10]. Investigating alternative therapy modalities is becoming more popular, even if pharmaceutical medicines remain the cornerstone of diabetic care. Because they are made from a variety of plant sources, herbal drugs have generated interest because of their potential anti-diabetic properties. Several phytochemicals classes including alkaloids, flavonoids, and essential oils are bioactive ingredients widely distributed in herbal products with promising outcomes in diabetes management [11]. Several mechanisms underlie the anti-diabetic effects of herbs products. The major mechanisms of natural products role in diabetes control include, alteration of glucose metabolism (including inhibition of α –amylase, β –galactosidase, α–glucosidase, or renal glucose reabsorption), improvement in digestion along with a reduction in blood sugar and urea, stimulation of insulin secretion, induction of glycogenesis and hepatic glycolysis, prevention of pathological conversion of starch to glucose, or by protective effect on the β cells [12]. The protective properties of flavonoids, a broad class of secondary metabolites widely distributed in plants, against diabetes has been conducted extensively. Flavonoids compounds including quercetin, kaempferol, and rutin were reported for their antidiabetic potential owing to their antioxidant properties, enhance insulin production, and enhance the absorption of glucose; these actions assist control of blood sugar levels and reduce the likelihood of complications related to diabetes [13, 14]. Furthermore, essential oils have been reported for their antidiabetic effects. Cinnamon essential oil, mainly cinnamon aldehyde revealed antidiabetic effects via inhibition of key enzymes involved in glucose metabolism, promotes glucose absorption, and raises insulin sensitivity [11]. Moreover, alkaloids have shown promise in the management of diabetes. For instance, berberine, an alkaloid presents in numerous plants, such as *Coptis chinensis* and *Berberis* spp., has been extensively studied for its potential to prevent diabetes. Berberine has been found to modulate glucose metabolism, regulate insulin sensitivity, and reduce inflammatory responses associated with diabetes [15]. The main goal of the current review is to introduce an overview on the role of medicinal plants and their bioactive phytochemicals in treatment of diabetes and mechanisms of actions underlying such effects as well as future perspectives in diabetes.

2-Role of medicinal plants in diabetes control

Many plant species are rich in bioactive phytochemicals that possess distinct pharmacological characteristics without any unfavorable side effects[16]. Communities in the developing nations have long held out hope for these plant-based remedies, and using inexpensive medicinal herbs rather than pharmaceuticals to manage diabetes is widespread there [11]. Various phytoconstituents having antidiabetic properties, such as terpenoids, saponins, flavonoids, carotenoids, alkaloids, and glycosides, were abundant in medicinal plants. The most prevalent is glucose metabolism alternation [11]. According to these most popular concepts, the main ways that medicinal herbs are used are to improve pancreatic function by raising insulin secretion or lowering intestinal glucose uptake. As a result, it is critical to use inhibitors that obstruct the digestive enzymes needed for macro element breakdown and absorption. The suppression of the enzymes that break down carbohydrates including pancreatic α-amylase (which breaks down polysaccharides into oligosaccharides and disaccharides) and α-glucosidase (which breaks down carbohydrates into monosaccharaides), may alleviate the issues with maintaining appropriate glycaemia [17]. According to reported research, terpenes, saponins, and polyphenols are the most important natural inhibitors widely distributed in antidiabetic plants. Several medicinal plants utilized worldwide and reported for their antihyperglycemic properties are covered in this overview and listed in **Table 1**. Moreover, several phytochemicals were reported for their antidiabetic effect and identified in different medicinal plants with antidiabetic capacity were listed in **Table 2**.

3- Quercetin

Flavonoids, a class of phenolic compounds with potent free radical scavengers and widely applied as potential treatments for diabetes mellitus [18]. The ability of flavonoids to transfer hydrogen or electrons free radicals, activate antioxidant enzymes, chelate metal catalysts, decrease α-tocopherol radicals, and inhibit oxidases is thought to be responsible for their protective actions in biological systems[18]. Oxidative stress is a consequence of both insulin resistance and hyperglycemia and can lead to a reduction in the effectiveness of insulin **Figure 1**. Research has demonstrated that the same route used by hyperglycemia also causes oxidative stress in the mitochondria due to hyperlipidemia [18]. According to studies, antioxidants were reported to enhance the activity of insulin. Several research had studied the possible effects of flavonoids in type II diabetes than in type I diabetes. It has been reported that flavonoids with potent antioxidant activity can help control diabetes mellitus. Antioxidants should be handed priority while treating diabetes mellitus due to their capacity to improve glucose metabolism and uptake and guard against the harmful consequences of hyperglycemia**.**

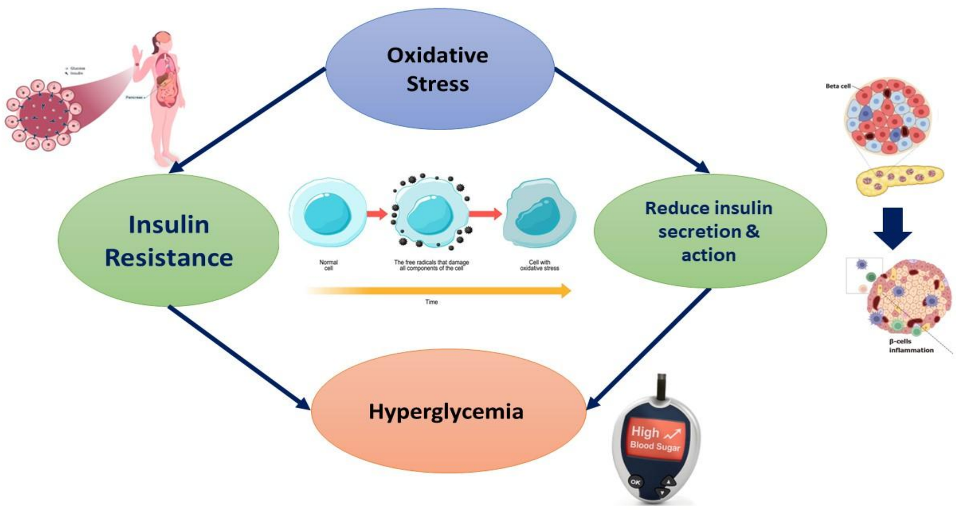


Figure 1. Role of oxidative stress in diabetes mellites.

Quercetin is a flavonoid that has been utilized extensively for the management of inflammatory and metabolic diseases due to its diverse pharmacological effects [19]. Quercetin has diverse effects as an antidiabetic which is illustrated in **Figure 2**. Quercetin was found to reduce the synthesis of vascular endothelial growth, which in turn inhibited the proliferation of high-glucose-induced cells *in vitro* on human retinal endothelial cells [13]. Additionally, *in vitro* settings, quercetin slowed down the onset of postprandial hyperglycemia and inhibited intestinal α glucosidase and pancreatic α amylase, reduced starch hydrolysis, and decreased the rate of glucose absorption [20]. Research carried out on streptozotocin (STZ)-induced diabetic rats has demonstrated quercetin's ability to lower blood glucose levels and enhance glucose tolerance [21]. Quercetin administration enhanced the reduction of plasma glucose level in type 2 diabetic rats. By inhibiting the Cytochrome P450 2E1 (CYP2E1) liver enzyme in diabetic mice, quercetin may be able to reduce diabetic liver oxidative damage [22]. It also reduces oxidative stress in the renal tissue of diabetics. In high-fat-fed obese mice, quercetin treatment reduced body weight, fat accumulation, hyperglycemia, dyslipidemia, and hyperinsulinemia [13, 22].

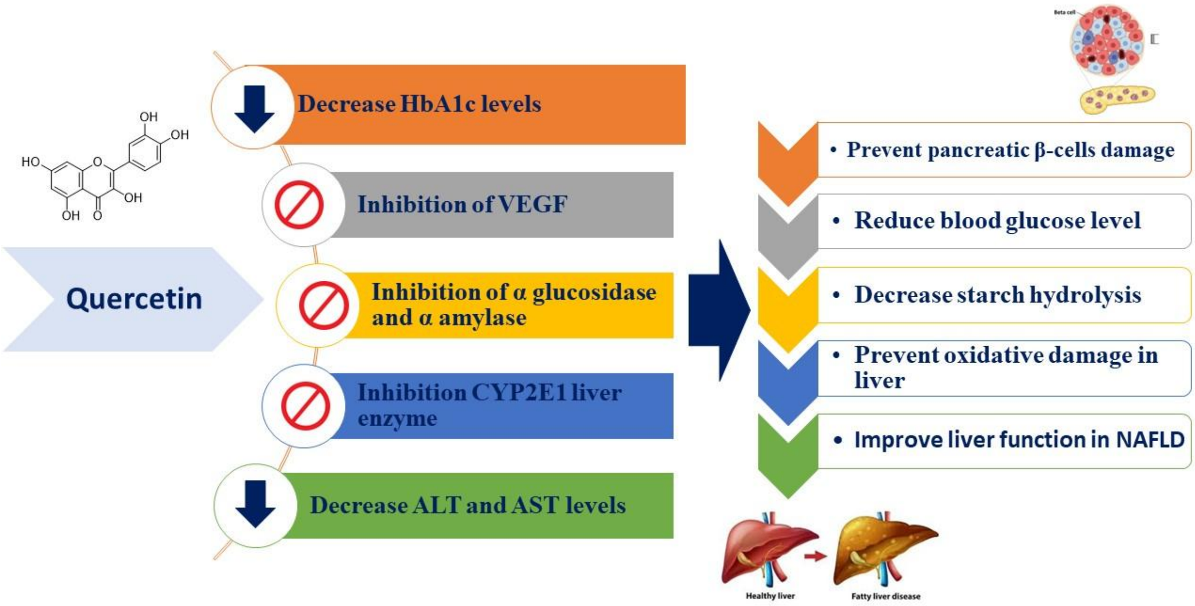


Figure 2. Mechanisms of action of quercetin in controlling diabetes mellitus.

4- Harmine

Among the plant phytochemicals, alkaloids are a diverse category of nitrogen-containing phytochemicals that have demonstrated various biological and pharmacological benefits [23].

Alkaloids are bitter substances that have been identified in 12,000 different sources throughout the past few decades. Approximately 14–20% of plant species contain alkaloids [24].

Harmine, a β-carboline alkaloid which is extracted from the seeds of the medicinal plant *Peganum harmala L.*, has been used for thousands of years. Harmine exhibits various pharmacological properties, including anticancer, antidiabetic, neuroprotective, and anti-inflammatory effects [25]. Worldwide, the prevalence of type 2 diabetes, obesity, and insulin resistance linked to obesity is rising quickly. Insulin resistance associated with obesity is lessened by PPARγ (peroxisome proliferator-activated receptor) agonists. Harmine inhibits the Wnt signaling pathway, which controls the expression of PPARγ [25]. Harmine inhibits the RAC1/MEK/ERK pathway, which essentially eliminates the obesity caused by high-fat diets. The risk of cognitive impairment is elevated with diabetes [26]. By blocking NLRP3 inflammasome activation and boosting the BDNF/TrkB signaling pathway, harmine not only significantly reduces the symptoms of diabetes but also lessens the cognitive impairment brought on by the disease [27]. Additionally, harmine is an effective DYRK1A inhibitor which promote β cell proliferation , improve blood glucose metabolism and as neuroprotective effect as showed in **Figure 3**[28].

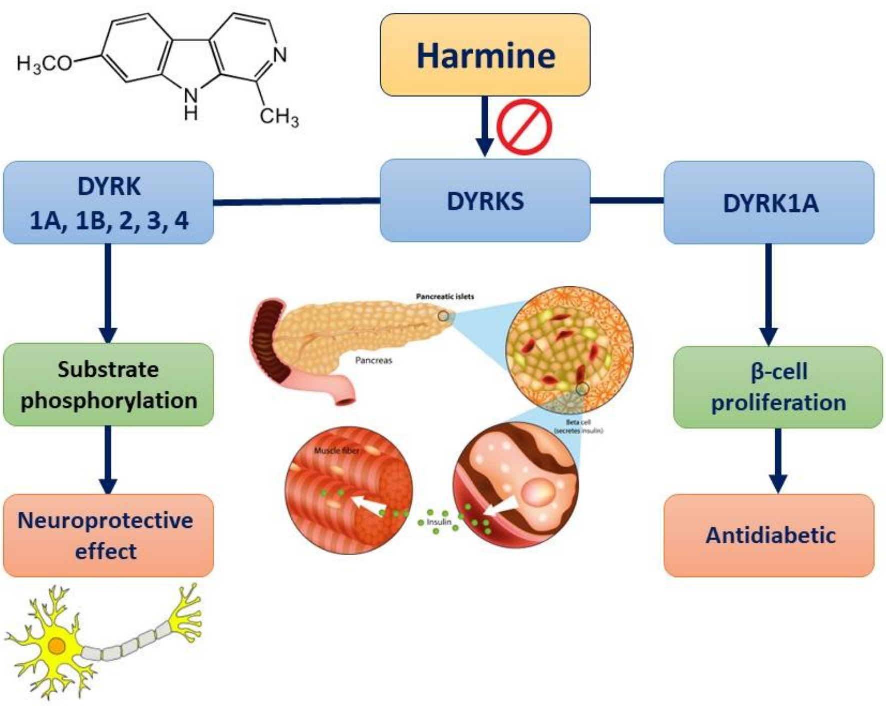


Figure 3. Mechanisms of the antidiabetic and neuroprotective effects of harmine

Table 1. Medicinal plants reported for treatment of diabetes with the effective extracts and possible mechanism of action

Plant	Common name	Extract/ Part used	Result	Family	Reference
Allium sativum L.	Garlic	Aqueous/ Bulb	-*In vitro* stimulate insulin secretion from beta cells isolated from healthy rats - Reduce in the hyperglycemic status of diabetic animal - Inhibition glycogen-metabolizing enzymes	Liliaceae	[29, 30]
Aloe vera	Barbados aloe	Ethanolic/ Leaves	-Decrease Glycosylated hemoglobin	Liliaceae	[31, 32]
Aegle marmelos	Golden apple	Aqueous, ethanolic/Leaves, Seed, Fruit	- Increase glucose tolerance -Increase insulin sensitivity	Rutaceae	[7, 33]
Asparagus officinalis	Wild Asparagus	Stem	- In vivo, improves glucose tolerance. - Increase insulin secretion	Asparagaceae	[34, 35]
Brassica oleracea	Cabbage	Ethanolic Acetic Acid/ Seed	- In vivo, decrease of blood glucose level and glycosylated hemoglobin	Brassicaceae	[36]
Berberis lyceum		Methanol/ Root	- In vivo, decrease of blood glucose level and glycosylated hemoglobin.	Berberidaceae	[15, 37]

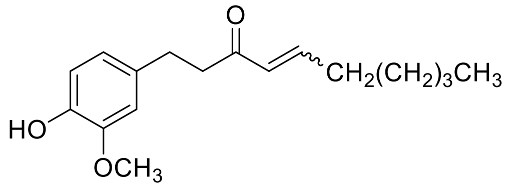
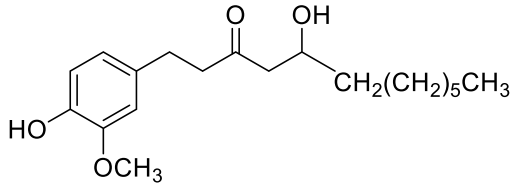
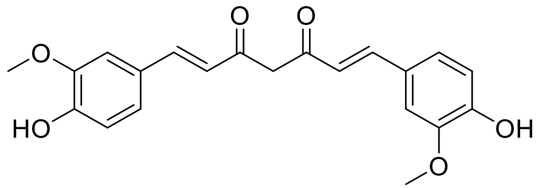
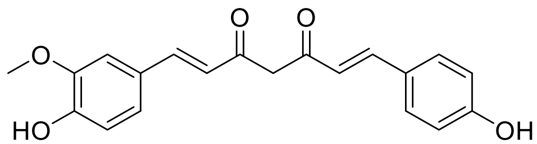
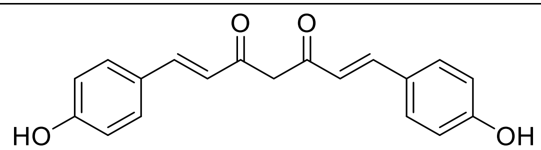
			- Increase insulin sensitivity and increase insulin-stimulated glucose uptake		
Curcuma longa	Turmeric	Aqueous/Rhizome	-Lower the blood sugar -Delay the occurrence of diabetes-induced neurodegenerative complications	Zingberaceae	[38-40]
Citrus genus	Orange / Lemon / Mandarin	Fruit	Increase the production and the release of insulin from the islet cells -Decrease the intestinal glucose absorption.	Rutaceae	[41, 42]
Coptis chinensis		Methanol /Rhizome	- Inhibition of the aldose reductase (AR)	Ranunculaceae	[15, 43]
Eucommia ulmoides	gutta-percha tree	Leaves	- Glycation inhibitors	Eucommiaceae	[44]
Ludwigia stolonifera		Ethyl acetate extract/ aerial parts	- In vitro, inhibition of α glycosidase	Onagraceae	[45]
Lagerstroemia speciosa	Banaba	Leaves	- Glucose transport-stimulating activity	Lythraceae	[30, 46]
Murraya koenigii	Curry Patta	Petroleum ether & methanolic /leaves	-*In vivo*, prevent the destruction of b cells of islets in the pancreas -*In vitro*, α-amylase inhibitor	Rutaceae	[15, 47-50]

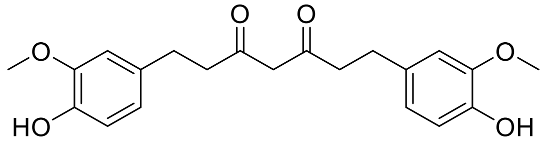
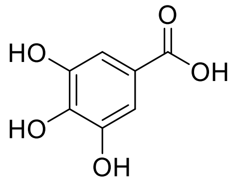
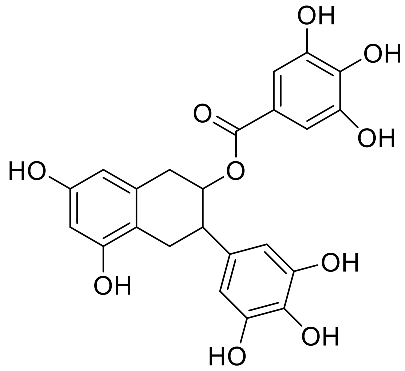
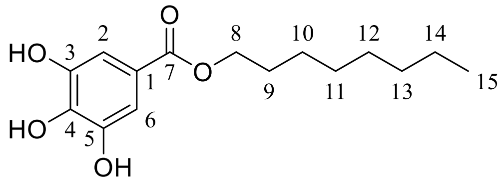
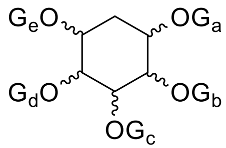
			- In vivo, reduce of glucose level		
Manikara indica		Methanolic/Leaves	-In vitro, inhibition with an IC_{50} of 4.6 μM against porcine lens aldose reductase.	Sapotaceae	[51]
Nigella glandulifera		Petroleum ether/ Seed	- Inhibitory effect of protein tyrosine phosphatase 1B (PTP1B), PTP1B indicated a negative regulator of the insulin signaling pathway in vitro.	Ranunculaceae	[15, 52]
Nigella sativa	Black seed	Whole plant	- significant fall in fasting blood glucose, blood glucose level 2h postprandial, glycated hemoglobin, and insulin resistance, and a rise in serum insulin	Ranunculaceae	[7, 53]
Ocimum sanctum L	Holy Basil	Ethanolic / leaves	Reduction absorption of glucose from gastrointestinal tract	Lamiaceae	[30, 54]
Phyllanthus emblica	Indian gooseberry	Methanolic / Fruit	Decrease in blood glucose and urine sugar levels, with a considerable rise in plasma insulin and hemoglobin levels.	Phyllanthaceae	[55, 56]

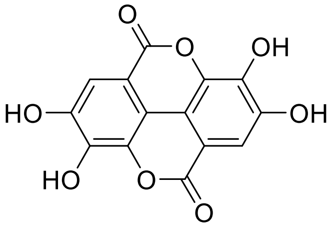
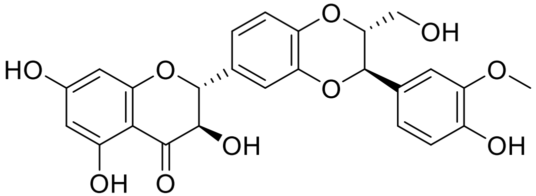
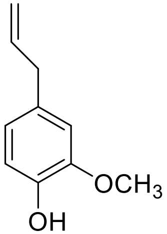
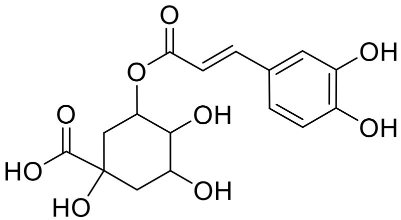
Peganum harmala		Hydroalcoholic extract /Seeds	- In vivo, decreased blood glucose level in normal and diabetic rats. - Enhance insulin secretion from residual pancreatic β-cells from diabetic rats	Nitrariaceae	[57]
Rosmarinus officinalis	Rosemary	Ethanol/ Leaves	- In vivo, lowered blood glucose level and increased serum insulin concentration in alloxan-diabetic rabbits	Labiatae	[58, 59]
Salacia chinensis		Aqueous methanolic/ Stem	-Inhibition of α glycosidase	Celastraceae	[44, 60, 61]
Silybum marianum	Milk thistle	Seeds	- Inhibitory effect of protein tyrosine phosphatase 1B (PTP1B) - Inhibition of α glycosidase - Improving the glycemic profile	Asteraceae	[62, 63]
Terminalia chebula, T. belerica, and Phyllanthus emblica	Triphala	Methanolic / Fruit	- Reduce the blood sugar level in normal and in alloxan diabetic rats significantly within 4 hr.	Combretaceae, and Phyllanthaceae	[64]
Tinospora cordifolia		Methanol & $CHCl_3$/ stem	- Mediated through insulin dependent pathway and by up	Menispermaceae	[15, 65, 66]

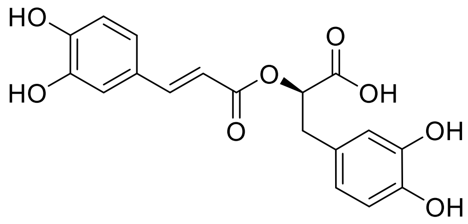
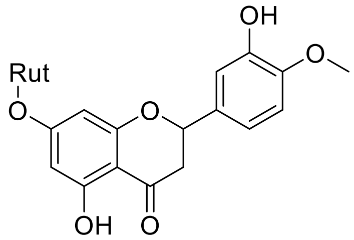
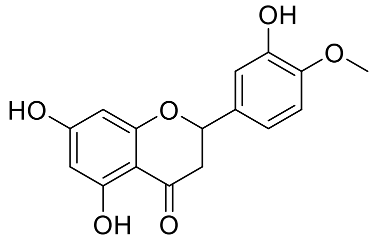
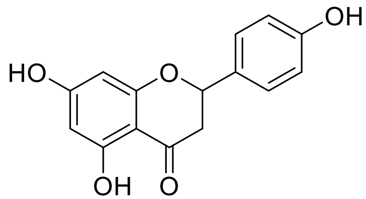
			regulating Glut-4 and PPAR expression. - stimulates insulin secretion by blocking ATP-sensitive K^+ channels (K^+-ATP channels) of the β cell membrane		
Tecoma stans	Yellow elder	Diethyl ether/NH_3/ Leaves	- Potent stimulating effect on the basal glucose uptake rate	Bignoniaceae	[15, 67]
Vaccinium simulatum	Blueberry	Fruit	-Regulate glucose metabolism in the body - improve insulin sensitivity in animal models of diabetes	Ericaceae	[68, 69]
Zingiber officinale Roscoe	Ginger	Bulb	-Increase insulin level -Decrease fasting glucose level	Zingberaceae	[11, 30]

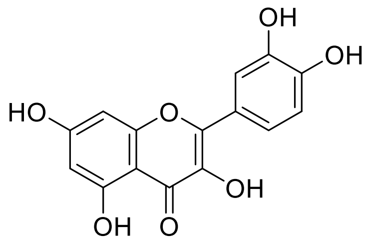
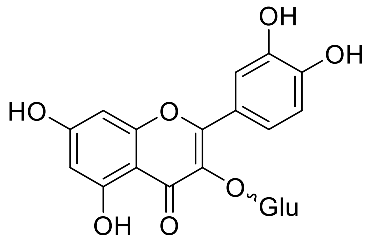
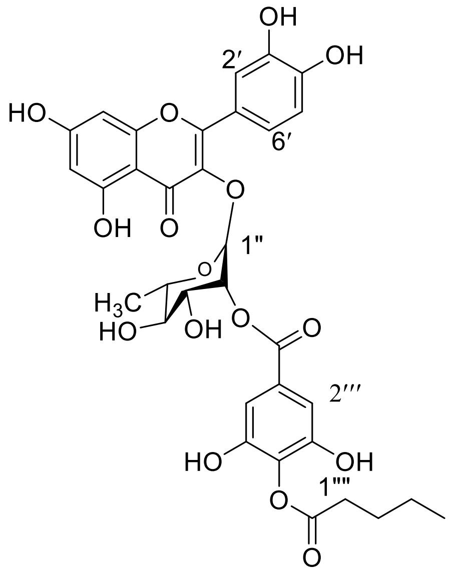
Table 2. Phytochemicals previously reported for their antidiabetic effects and their plant source

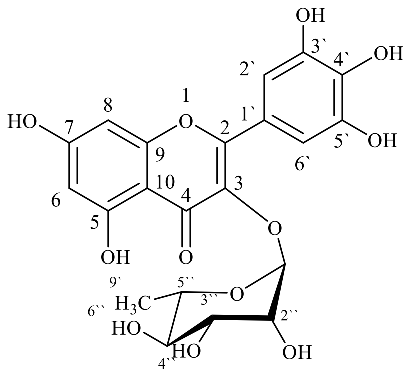
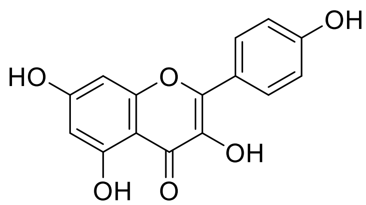
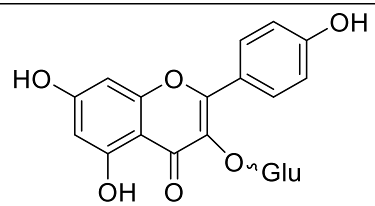
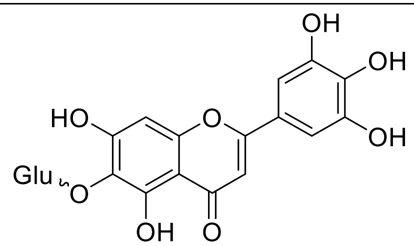
Compound	Structure	Plant	References
Phenolic compounds/derivatives			
Shogaol		Ginger	[11]
Gingerol		Ginger	[11]
Curcumin		Turmeric	[39 ,38]
Demethoxycurcumin		Turmeric	[39]
Bis-demethoxycurcumin		Turmeric	[38]

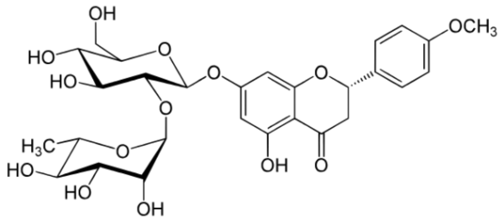
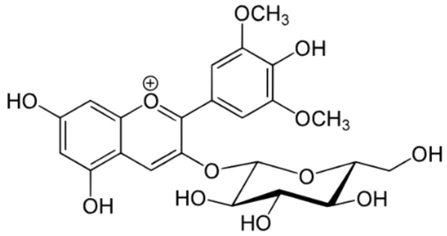
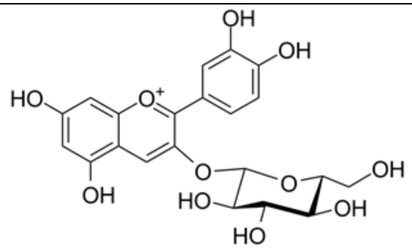
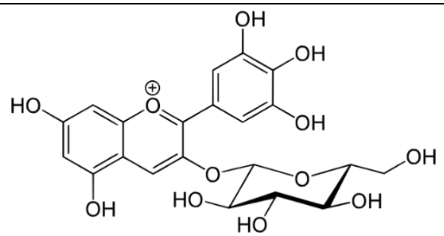
Tetrahydrocurcumin		Turmeric	[40]
Gallic acid		*Phyllanthus emblica* *T. belerica* *T. chebula*	[64 ,56 ,55]
Epigallocatechin Gallate		*Phyllanthus emblica*	[64]
Octylgallate		*Ludwigia stolonifera*	[45]
Gallotannins	 G=galloyl moeity	*Lagerstroemia speciosa*	[46]

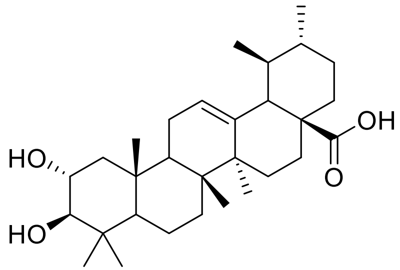
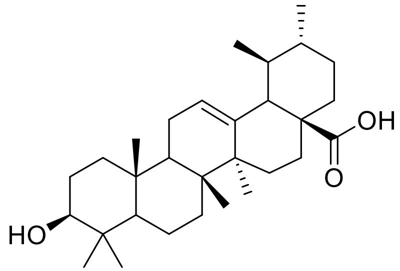
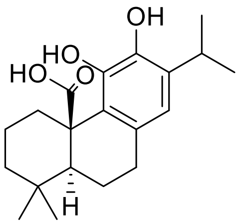
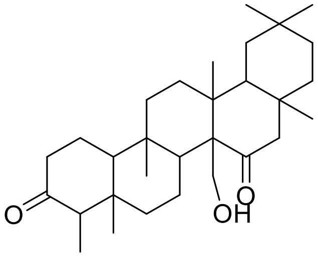
Ellagic acid		*Phyllanthus emblica* *T. belerica*	[64 ,56]
Silymarin		*Silybum marianum*	[62]
Eugenol		*Ocimum sanctum L*	[30]
Chlorogenic acid		Blueberry	[70]

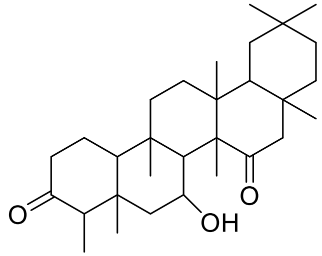
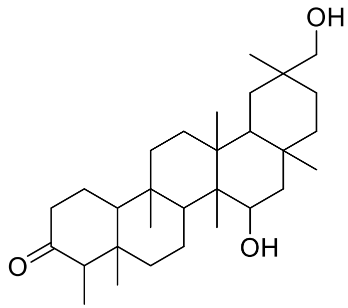
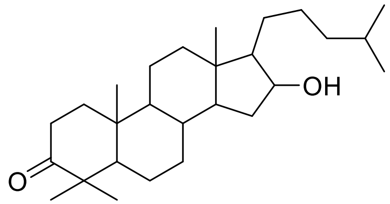
Rosmarinic acid		*Rosmarinus officinalis*	[58]
Flavonoid/derivatives			
Hesperidin		Citrus fruit	[42 ,41]
Hesperetin		Citrus fruit	[42]
Naringenin		Citrus fruit	[42 ,41]

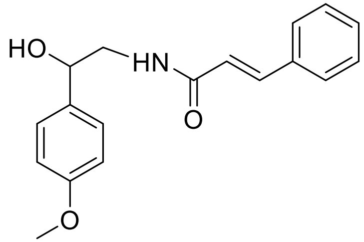
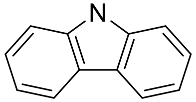
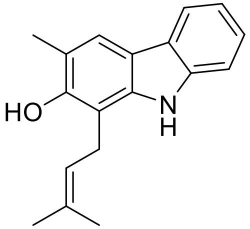
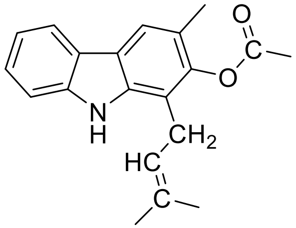
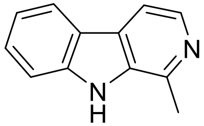
Quercetin		Citrus fruit *Piper nigrum* *Phyllanthus emblica Linn* *Silybum marianum* *Asparagus officinalis*	,42 ,34 ,13] [63 ,55
Quercetin 3-O-β-D-glucoside		*Eucommia ulmoides* *Ludwigia stolonifera*	[45 ,44]
Quercetin-3-O-α-L-rhamnoside- 2''-(4'''-O-n-pentanoyl)-gallate		*Ludwigia stolonifera*	[45]

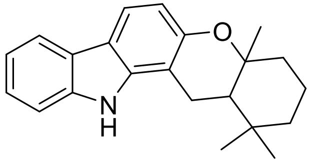
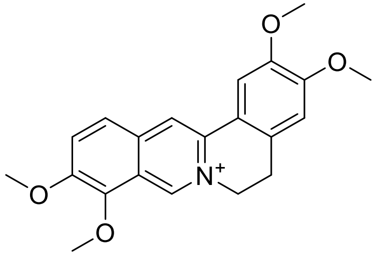
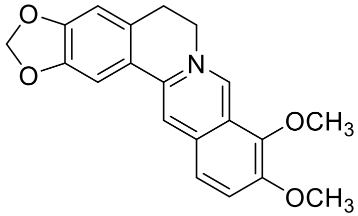
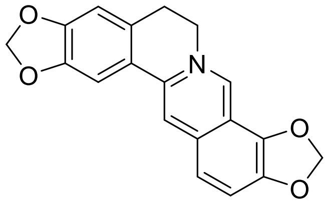
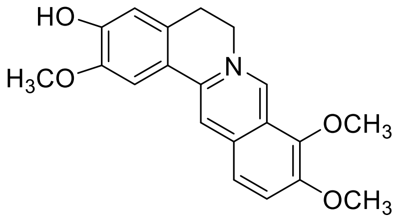
Myricetin -3-O- α-L-rhamnoside		*Ludwigia stolonifera*	[45]
Kaempferol		*Silybum marianum*	[63]
Kaempferol 3-O-β-D-glucoside		*Eucommia ulmoides*	[44]
Isoaffineyin		*Manikara indica*	[51 ,44]

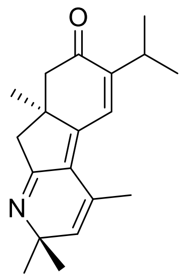
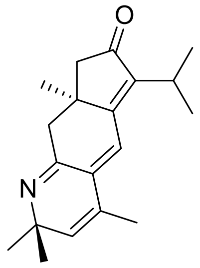
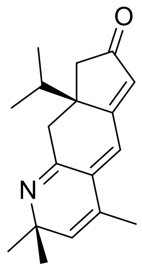
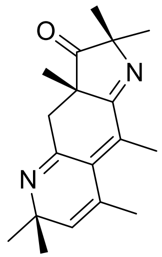
Poncirin		Citrus fruit	[42 ,41]
Anthocyanins			
Malvidin-3-O-glucoside		Blueberry	[68]
Cyanidin-3-glucoside		Blueberry	[68, 69]
Delphinidin-3-O-glucoside		Blueberry	[68]
Triterpenes/sterols			

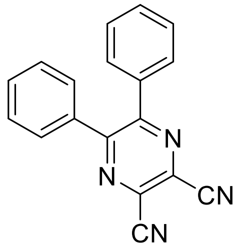
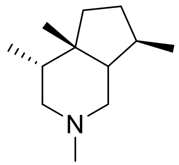
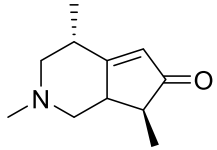
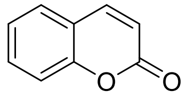
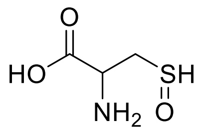
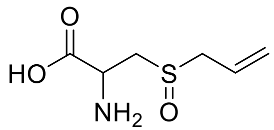
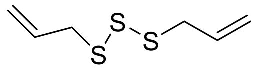
Corosolic acid		*Lagerstroemia speciosa*	[46]
Ursolic acid		*Rosmarinus officinalis*	[58]
Carnosic acid		*Rosmarinus officinalis*	[58]
Salasone A		*Salacia chinensis*	[60 ,44]

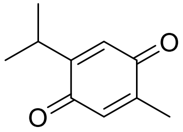
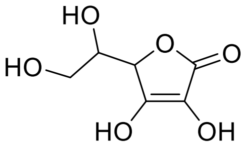
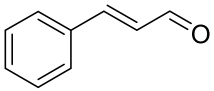
Salasone B		*Salacia chinensis*	[60 ,44]
Salasone C		*Salacia chinensis*	[60 ,44]
16-Hydroxy-4,4,10,13-tetramethyl17-(4-methyl-pentyl)-hexadecahydro-cyclopenta[a] phenanthren-3-one		*Ocimum sanctum L*	[71]
Miscellaneous			

Aegeline 2		*Aegle marmelos*	[33 ,7]
Carbazole		*Murraya koenigii*	[7]
Girinimbine		*Murraya koenigii*	[50 ,15]
Girinimbilylacetat		*Murraya koenigii*	[50 ,15]
Harmine		*Peganum harmala*	[72 ,57]

Bicyclomahanimbiline		*Murraya koenigii*	[50 ,15]
Palmatine		*Tinospora cordifolia* *Coptis chinensis*	[65 ,15]
Berberine		*Berberis lyceum* *Coptis chinensis*	[73 ,37 ,15]
Coptisine		*Coptis chinensis*	[43 ,15]
Jateorrhizine		*Coptis chinensis* *Tinospora cordifolia*	[66 ,43 ,15]

Nigelladine A		*Nigella glandulifera*	[52 ,15]
Nigelladine B		*Nigella glandulifera*	[52 ,15]
Nigelladine C		*Nigella glandulifera*	[52 ,15]
Nigellaquinomine		*Nigella glandulifera*	[52 ,15]

2,3-Dicyano -5,6-diphenyl pyrazine		*Brassica oleracea*	[36]
5β-Hydroxyskita-nthine		*Tecoma stans*	[67 ,15]
Tecomine		*Tecoma stans*	[67]
Coumarin		*Aegle marmelos*	[33 ,7]
Cysteine sulfoxide		Garlic	[29]
Alliin		Garlic	[29]
Diallyl trisulfide		Garlic	[29]

Thymoquinone		*Nigella sativa*	[7]
Ascorbic acid		Blueberry	[68]
Cinnamaldehyde		Cinnamon	[74]

5-Conclusion

Recently, scientists paid great attention to the potential of medicinal plants in the treatment of diabetes mellitus. This review includes an overview of the medicinal plants reported for their activity to control blood glucose level. Medicinal plants can control diabetes via several mechanisms including induction of the production and the release of insulin from the β-cells, decrease the intestinal glucose absorption by inhibition of digestion enzymes. Both *in vivo* and *in vitro* studies presented evidence-based results on the activity of natural phytochemicals in management of diabetes. Future studies are recommended to discover a novel phytochemical with antidiabetic potential and more in deep clinical studies are recommended to support pharmaceutical application of natural antidiabetic agents.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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