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Review Article

Therapeutic Applications of Phytochemicals for Treatment of Diabetes Mellitus and Future Scope: An Overview

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ABSTRACT

Diabetes mellitus is a multifaceted metabolic syndrome that is typified by hyperglycemia of long duration due to the inadequate production or action of insulin. Due to the high expenses of synthetic drugs, coupled with their unwanted effects, increasing interest has been generated to turn to phytochemicals bioactive principles obtained from plants to treat diabetes. Recent research has highlighted the therapeutic potential of several phytochemicals, including alkaloids, glycosides, polysaccharides, terpenoids, polyphenols and flavonoids, for their anti-hyperglycemic, anti-hyper lipidemic, anti-inflammatory, antioxidant, and insulinotropic activity. Further studies need to focus on unmasking the molecular mechanisms of these compounds, performing large-scale clinical trials, improving bioavailability, and opening up the prospects of combination therapy. This article presents an extensive review of the complex features of diabetes mellitus pathobiology and the multimodal therapeutic actions of phytochemicals in discussing the present status and future outlook of these interventions.

Keywords: Diabetes Mellitus, Phytochemicals, Antidiabetic, Phytomedicines.

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INTRODUCTION

Prevalence estimates for diabetes, derived from a model that incorporates data from 1990-2017, indicate that it will reach 7079 per 100,000 in 2030 and 7862 per 100,000 in 2040 on a worldwide scale.[1] Type 1 diabetes affects 1.2 million people worldwide, and the International Diabetes Federation (IDF) reports that more than half of all diabetics go undetected, mostly in Africa, South and Southeast Asia, and the Western Pacific.[2] Japanese preventative programs, the Indian Diabetes Preventative Programme (IDPP) in India, and the Da Qing trials in China all found that LSM (lifestyle modification) altering their eating and exercise habits, which leads to significant weight loss in the obese and overweight prevented T2DM with minimum weight loss.[3] Metabolic risks, pharmacological accessibility, and diagnostics were among the five objectives for diabetes that the World Health Organization's Global Compact for Diabetic Control put out in 2022 with the aim of achieving by 2030.[4] There is a long history of using plants as a medicine source, and about 800 species have been identified as having possible anti-diabetic effects. The synthetic hypoglycemic medicines hefty price tag and potential adverse effects might be to blame. The World Health Organisation has recommended using common plant therapies for diabetes testing since they are effective, non-toxic, and have little or no adverse effects.[5] Diabetes mellitus herbals include alkaloids, glycosides, flavonoids, saponins have been used to treat a variety of complications in diabetic patients, including retinopathy, peripheral neuropathy, insulin-dependent and non-insulin-dependent diabetes, and more.

This article gives a general outline of the causes of diabetes, with an emphasis on how oxidative stress, hyperglycemia, and disruptions in glucose metabolism all contribute to the development of the disease. The study delves into the ways in which phytochemicals and their components can restore or change the disturbed balance of glucose metabolism, leading to various therapeutic benefits in the management of diabetes mellitus. Additionally, it delves into the current state and potential future of these medicinal substances.

Phytochemical in the management of DM

Alkaloids

Alkaloids help reduce postprandial glucose levels and treat by inhibiting carbohydrate-metabolizing enzymes like α-amylase and α-glucosidase. The small intestine produces glucose from the carbs in our diet through the action of α-glucosidase. Preventing postprandial hyperglycemia, a major cause of chronic diabetes and its complications, can be achieved by blocking the αglucosidase.[6] Starch is converted into glucose and maltose by the α amylase enzyme found in the salivary glands. Effective treatment for type 2 diabetes is thought to involve blocking α-amylase. In addition,

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the regeneration of pancreatic β-cells and insulin secretion are processes in which some alkaloids participate, leading to an improvement in overall glycaemic management (Tables 1 and 2).[7]

Flavonoids

The pharmacologically active chemicals known as flavonoids have hypoglycemic action and are found in numerous plants. Anthocyanins and Catechins are the two main types of flavonoids; some of these have been found to improve glucose and oxidative metabolism in diabetics.[19] Anthocyanins found in berries and blueberries may have the ability to ward against obesity and Type 2 Diabetic Mellitus (T2DM). They may decrease glucose absorption by delaying its release from the stomach, according to most *in vitro* investigation.[20]

Steroids and Terpenoids

In both plants and animals, the well-known triterpenes-numbering over four thousand-are steroid precursors that originate in the mevalonic acid pathway. While some exist as glycosides or in specific structures, the vast majority are in their free form.[26] The hypoglycemic effects of the pentacyclic triterpenoid Gymnemic acid IV, which is extracted from the leaves of the *Gymnema sylvestre* plant, are due to its ability to decrease blood glucose levels, increase insulin secretion by pancreatic beta cells, and limit glucose uptake in muscles.[27]

Glycosides

Plant glycosides are naturally occurring compounds categorized based on different structural features. They are primarily classified into four major groups.

Based on the sugar moiety (glycones)

Apiosides, galactosides, glucosides, fructosides, rhamnosides, rutinosides, and xylosides.

Based on the non-sugar moiety (aglycones)

Alcoholic glycosides, anthraquinone glycosides, coumarin glycosides, chromone glycosides, cyanogenic glycosides, flavonoid glycosides, iridoid glycosides, phenolic glycosides, steroidal or cardiac glycosides, saponin glycosides, steviol glycosides, and thio glycosides

Based on the number of saccharide units

Monodesmosides, bidesmosides, or tridesmosides.

Based on the glycosidic bond

O-glycosides, C-glycosides, N-glycosides, and S-glycosides.

This multiclassification is an indicator of structural diversity and functional diversity of plant glycosides in nature making it useful for the diabetes management.[32]

Regulation of Protein Targets for the Treatment of Diabetes

The treatment of T2DM is chiefly concerned with the precise control of protein targets that are critical to the progression of disease. Phytochemicals of a broad array have been found to have the ability to modify the epigenome. These molecules are especially appealing in therapeutic situations because they have low toxicity and good safety profiles despite continuous, long-term treatment.[41] Moreover, this section will include the results of relevant clinical studies, establishing the efficacy and usefulness of these phytochemicals in T2DM management.

Impaired carbohydrate metabolism and hyperglycemia

Glucose metabolism is the body's single most affected system and requires attention with regards management followed by the complete usage of glucose stored in cells, which is used to create energy. Any lapse, therefore, in the distinct glucose metabolic pathway would commence with impaired glucose metabolism, development of excess blood sugar and in time could lead to diabetes mellitus.[42] One of the main actions of insulin is to enhance overall glucose disposal, and this is achieved through stimulating the uptake of glucose in the target tissues carried out by insulin-sensitive Glucose Transporter (GLUT-4). Besides, GLUT-4 is the key facilitator that preserves euglycemia within the body. Glucose-stimulated release of insulin and insulin-directed glucose metabolism are therefore, the key balancing component in maintaining euglycemic status in the blood.[43]

Hyperglycemia-induced oxidative stress and diabetic complications

Hyperglycemia-induced activation of Protein Kinase-C (PK-C) isoforms, augmented production of advanced glycation end products, and enhanced glucose flux through aldose reductase pathways are among the established biochemical mechanisms of hyperglycemia-induced tissue/organ damage.[44] But the idea that these metabolic pathways have their own independent origin has some revisions and postulated a single integrative hypothesis (Figure 1) which connects these mechanisms by which an increase in the levels of glucose potentiates endothelial ROS generation by various mechanisms.[45] ROS increases the production of TNF-α expression and there by increases oxidative stress. TNF-α can cause insulin resistance through a reduction in autophosphorylation of insulin receptor, transformation of insulin receptor substrate-1 to an inhibitor of insulin receptor tyrosine kinase activity, reduction in GLUT-4 transporter in muscle cells.[46]

Adipocytes treated with TNF become insulin-resistant, as insulin fails to stimulate hexose transport. This has been proven due to down-regulation in the expression of GLUT4. Antioxidants and polyphenolic compounds have been found to scavenge free radicals, lower oxidative stress and inhibit the expression of TNF-α.[47]

Numerous approaches of phytomedicines in combating diabetic disorders

Diabetes in recent years has resulted in tremendous progress in regimen for the treatment of this disease. This section gives a composite overview of the multiple target beneficial effects of the plant medicines/phytochemicals.

Glucose absorption

Tea polyphenolics have been reported to inhibit α-amylase and sucrase, and have been shown to be the principle substance for suppressing PPHG. Furthermore, these polyphenolics also inhibit glucose transport across the intestine by inhibiting sodium glucose co-transporter-1 (S-GLUT-1). catechin, (-) epicatechin, (-) epigallocatechin and epicatechin gallate, isoflavones from soybeans, polyphenolic compounds, tannic acid, chlorogenic acid, crude saponin fractions from *Gymnema sylvestre* and other saponins from several plant extracts have been shown to possess potent S-GLUT-1-mediated inhibition of glucose and antihyperglycemic activity.[48] The manipulation of S-GLUT-1-mediated transport along with α-amylase and α-glucosidase inhibitory activity by plant phenolics helps in the control and management of hyperglycemia.

It is anticipated therefore, that there are a number of ways to slow down glucose absorption in the small intestine: (a) through inhibition of digestive enzymes, (b) through inhibition of active transport of glucose through intestinal brush border membrane, and (c) through retardation of the gastric emptying rate of gastrointestinal content. Water-soluble dietary fibres, guar gum, pectin, plant-contained polysaccharides have been found to raise the viscosity of gastrointestinal content, which reduces the gastric emptying rate and slows/suppresses carbohydrate digestion and absorption.

Aldose reductase pathway inhibitors

Converting glucose to sorbitol is the job of aldose reductase. Diabetic problems include cataracts caused by intracellular sorbitol buildup in cells. Diabetes problems in experimental animals and human clinical trials have been ameliorated by aldose reductase inhibitors. Butein is a aldose reductase inhibitor for the treatment and prevention of diabetic problems, according to recent studies. Flavanone and flavonol glucosides extracted from the medicinal Brazillian plant *Myrcia multiflora*, which is often called "plant insulin," block aldose reductase and α-glucosidase and may have hypoglycemic effects in animals that develop diabetes due to alloxan.[49]

B-cell regeneration and insulin releasing activity

Conventionally, β-cells are selectively destroyed in experimental animals to induce diabetes using the drugs allloxan and Streptozotocin (STZ). Repairing damaged β-cells has proven to be an arduous endeavour. The epicatechin content of *Pterocarpus marsupium* was found to possess β-cell damage prevention and restoration properties when exposed to alloxan. Liquiritigenin and Pterosupin are two examples of the flavonoids found in *P. marsupium*; animal studies have shown that these phytochemicals have hypolipidemic effects. *Gymnema sylvestre* plant's extracts have been shown to have various effects related to their antidiabetic properties, including reducing the need for insulin (possibly by making more endogenous insulin available), improving the management of hyperlipidemia caused by diabetes,

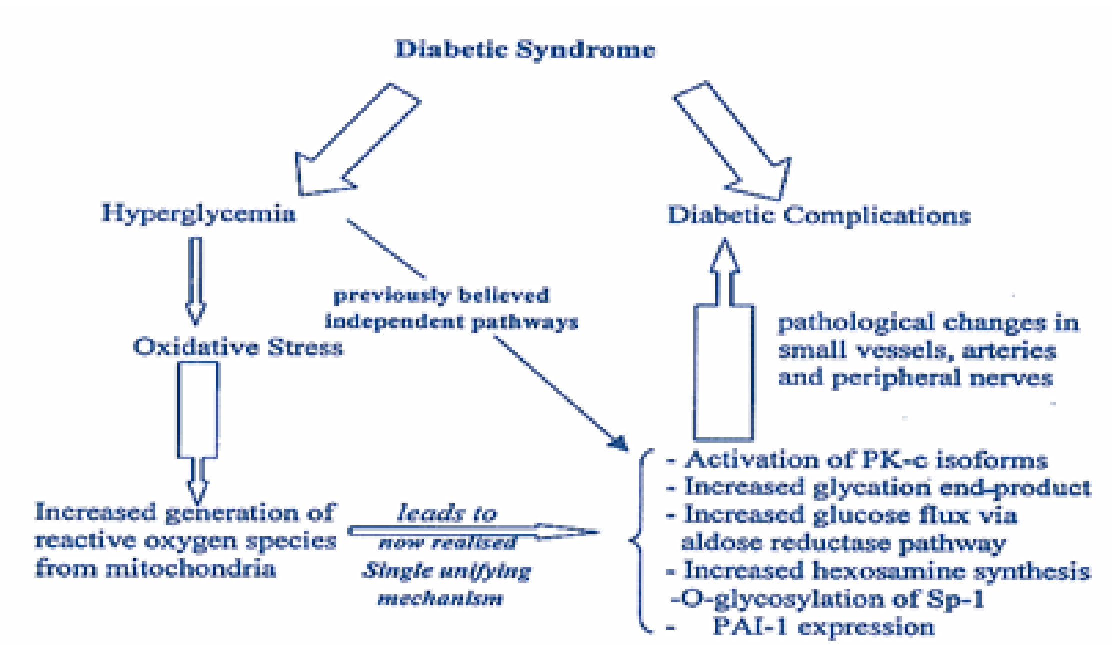


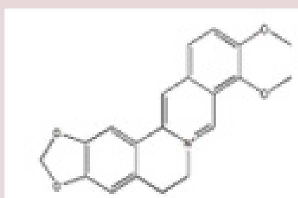
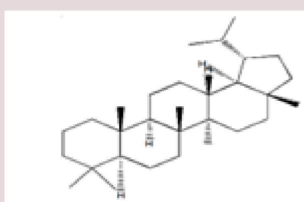
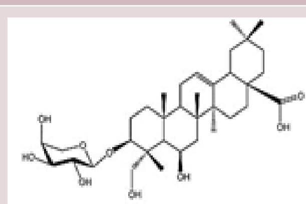
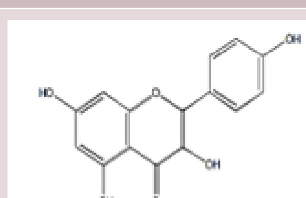
Figure 1: The Role of Oxidative Stress in Diabetes.

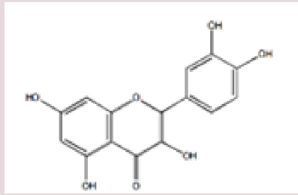
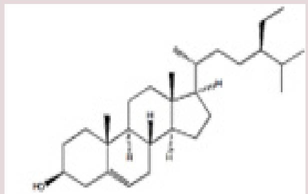
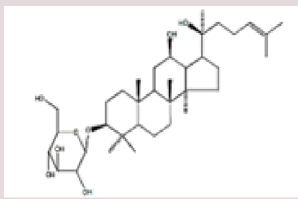
Table 1: Some important phytochemicals are in the management and treatment of type 2 diabetes mellitus.

Chemical Class	Phyto constituent(s)	Plant Source	Part Used	Mechanism of Action	References
Alkaloids	Berberine	*Berberis* spp., *Tinospora cordifolia*	Roots, Stem bark	Inhibits α-glucosidase; intestinal glucose transport.	[15]
	1-Deoxynojirimycin	Morus alba	seeds	Inhibits α-glucosidase and isomaltase.	[17]
	Mahanimbine	*Murraya koenigii*	leaves	↓ Blood glucose levels	[12]
	Cryptolepine	*Cryptolepis sanguinolenta*	Whole plant	Enhances insulin-mediated glucose disposal.	[14]
	Tecomine	*Tecoma stans*	Leaves	Stimulates glucose uptake.	[13]
	Trigonelline	*Trigonella foenum-graecum*	Seeds	Insulin mimetic	[9]
	Nigeglapine and Nigeglaquine	*Nigella glandulifera*	seed	activate the PI3K/Akt signalling pathway.	[10]
	Glycosin	*Rhizophora apiculate*	Whole plant	↓ Blood glucose levels	[11]
	Lupanine	*Lupinus perennis*	Whole plant	↑ Glucose-induced insulin secretion.	[16]
	Catharanthine, Vindoline	*Catharanthus roseus*	leaves	↓ Blood glucose in diabetic models.	[18]
	Palmatine,	*Coscinium fenestratum*	stem	Inhibit α-amylase	[8]
Glycosides	Kalopanax saponin A	*Kalopanax pictus*	Stem bark	inhibiting glucose absorption, increasing insulin secretion, modulating PPAR-γ,	[33]
	Myrciacitrins I-V	*Myrcia multiflora*	Leaves	Aldose reductase, α-glucosidase inhibition.	[34]
	pseudoprototimosaponin AIII	*Anemarrhena asphodeloides*	Rhizome	Inhibits gluconeogenesis/ glycogenolysis.	[35]
	bengalenoside	*Ficus benghalensis*	stem	Activate β-cell function.	[36]
	eupalitin 3-O-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside 1	*Sesuvium sesuvioides*	leaves	↓ Blood glucose levels	[37]
	3-O-alpja-L arabinopyrosyl-(1->2)-beta-D-glucopyranoside	*Eucommia ulmoides*	leaves	Block glycation activity.	[38]
	stevioside and rebaundioside A	*Stevia rebaudiana*	leaves	↑ Glucose uptake	[39]
	Kaempferitrin	*Bauhinia forficata*	Leaves	Stimulates glucose uptake GLUT4.	[40]
Flavonoids	Quercetin	*Chamaecostus cuspidatus*, others	Root, stem, leaves	Enhances insulin secretion; antioxidant	[24]
	liquiritin	*Glycyrrhizae radix*	Leaves	Attenuate glycation the RAGE/ NF-κB pathway.	[23]
	Rutin	*Multiple sources*	Various	Aldose reductase	[22]

Chemical Class	Phyto constituent(s)	Plant Source	Part Used	Mechanism of Action	References
	Epigallocatechin gallate	*Camellia sinensis*	Leaves	Insulin receptor signaling mimic PI3K pathway.	[21]
	Genistein	*Glycine max* (Soy)	Seeds	PPAR agonist; improves lipid/ glucose metabolism.	[25]
Terpenoids and Steroids	Corosolic acid	*Lagerstroemia speciosa, Vitex* spp.	Leaves	Activates glucose transporters.	[30]
	Gymnemic acid IV	*Gymnema sylvestre*	Leaves	Inhibits glucose absorption; increases insulin.	[27]
	β-Sitosterol	*Azadirachta indica*	Leaves	Induces insulin secretion.	[29]
	Andrographolide	*Andrographis paniculata*	Whole plant	↑ β-endorphins, ↓ gluconeogenesis.	[28]
	Ganoderans A and B	*Ganoderma lucidum*	Fruit body	Stimulates insulin secretion.	[31]

Table 2: Structure of some phytochemicals used in treatment of type 2 diabetes mellitus.

Phytochemicals	Structure	Plant name	Part used
	Alkaloids		
Berberine		*Berberis* spp. *Tinospora cordifolia*	Stem-bark, roots
Lupanine		*Lupinus perennis*	Whole plant
	Glycosides		
Kalopanax		*Kalopanax pictus*	Stem bark
	Flavonoids		
Kaempferol		*Jindai soybean*	Leaves

Phytochemicals	Structure	Plant name	Part used
Quercetin		*Chamaecostus cuspidatus*	Root, stem, leaves
Terpenoids and steroids			
β-sitosterol		*Azadirachta indica*	leaves
Ginsenosides		*Panax species*	Rhizomes

lowering serum amylase activity, and improving β-cell function (as shown by higher serum C-peptide levels).[51]

Antioxidant defence

Many of the substances discussed in the text have recently had their antioxidant properties studied, Therefore, it seems that medicinal plant compounds, either alone or in combination, have a number of positive effects and the ability to provide a holistic therapeutic effect in complex diseases like diabetes and its complications, in addition to acting on carbohydrate's metabolic targets. Diabetes is similar to other chronic diseases and cell death caused by oxidative stress and the resulting tissue damage.[52] However, there is rapidly developing evidence supporting the use of antioxidants as a therapeutic tool in the treatment of diabetes and other serious diseases.

Present status and future prospects

There are still worries, even though there are a variety of medications available to control the illness, including sulphonylureas, biguanides, and glitazones. While glitazones like troglitazone and rosiglitazone work to reduce insulin resistance, they come with side effects such liver damage and an increased risk of heart disease, according to the UK Drug and Therapeutic Bulletin. Medicinal plants offer a promising platform for the development of new therapeutics due to their versatile and advantageous actions, which include modulating carbohydrate metabolism, restoring and preventing β-cell function, improving glucose uptake and utilisation, and exhibiting antioxidant properties.[53] A multi-modal approach utilising several medications is necessary to treat diabetes due to its complex aetiology. In order to maximise therapeutic efficiency while decreasing adverse effects, these preparations make use of synergistic and varied pharmacological effects derived from plants. Herbal remedies and preparations must be taken in light of their comprehensive therapeutic approach.[54]

CONCLUSION

Phytochemicals found in nature and extracted from a wide variety of plants have shown promising anti-diabetic effects via several different pathways. Among these, you can find measures to reduce harmful lipids, inflammation, oxidative stress, and insulin secretion, as well as to lower blood glucose levels. With the prevalence of diabetes on the rise around the world, these chemicals are gaining attention for their possible therapeutic use in diabetes management. Phytochemicals have many promising future applications in the treatment of diabetes. large-scale clinical trials are necessary to verify their efficacy in statistically valid groups. In order for these compounds to exert their therapeutic effects, optimising their bioavailability remains a crucial goal. In addition, there is great promise in developing personalised medicine methods according to individual patient profiles and combination therapies that incorporate phytochemicals with existing medications. Phytochemicals have the ability to completely change the way diabetes is treated if further research and development is done.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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