A Review of Recent Investigations on Medicinal Herbs Possessing Anti-Diabetic Properties

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Abstract

Globally, the pervasiveness of chronic, non-communicable disease diabetes mellitus is growing by leaps and bounds. It is one of the major causes of premature morbidity and mortality worldwide. Almost 3.2 million people die of diabetes across the world every year. The worldwide prevalence of diabetes is 6.4% (corresponding to 285 million people); this varies from 10.2% in the Western Pacific to 3.8% in the African region and expected to grow up to 7.4% (439 million) of the adult population by 2030. In the last 20 years there has been a threefold increase in the prevalence of diabetes. It is estimated that there are 30 to 33 million diabetics in India now, and every fourth diabetic in the world today is an Indian. Indians are genetically more susceptible to diabetes and the WHO predicts the number of diabetics in India would go up to 80 million by 2030. WHO has also issued a warning that India is going to be the diabetes capital of the world with Chennai emerging as the diabetic capital of India. Many plants possessing hypoglycemic principles/properties are known to exist in nature. Also a large number of polyherbal formulations (PHF’s) derived from these plants are currently being prescribed as medicinal/dietary supplements for diabetes mellitus. Even the WHO (World Health Organization) approves the use of plant drugs for different diseases, including diabetes mellitus. However, these formulations lack proper standardization of the active constituents. There is an urgent need to address the issues of scientific authenticity about their efficacy, safety and their interaction with modern allopathic drugs. The paper reviews composition, active principles and pharmacological effects of some important plants which are widely used in commercially available herbal and polyherbal formulations and provides a detailed list of plants reported to possess potential anti-diabetic activity.

Keywords: Diabetes mellitus; diabetes management; polyherbal formulations; alternative medicine; anti-diabetic activity

Introduction

Diabetes mellitus is a major endocrine disorder affecting more than 10% population in the contemporary world [1]. India has the dubious distinction of having the largest number of people with diabetes. Its occurrence in more affluent societies is spectacular and of general concern [2]. It is a debilitating metabolic disorder and robs persons of their energy and vitality. Population-based surveys of 75 communities in 32 countries illustrate that diabetes is rare in communities in developing countries where a traditional lifestyle has been preserved. By contrast, some Arab, migrant Asian Indian, Chinese, and U.S. Hispanic communities that have undergone westernization and urbanization are at higher risk; in these populations, the prevalence of diabetes ranges from 14 to 20% (Table 1). Therefore, as considered previously it is no more a disease restricted to developed nations rather it is becoming the major health concern in developing nations (Figure 1 a & b). In spite of the introduction of the hypoglycemic agents, diabetes and related complications continue to be a major medical problem. Treatment of this disease with insulin and its derivatives is an invasive process and make the patients more susceptible to hypoglycemic episodes, premature atherosclerosis due to hyperinsulinemia, lipodystrophy [3]. Treatment with sulfonylureas may be associated with hypoglycemia, flatulence, weight gain, hyperinsulinemia, paresthesias, transient leukopenia, agranulocytosis, dementia and it is contraindicated in nursing mothers [4]. Biguanides may induce lactic acidosis, metallic taste, anorexia, vitamin B12 deficiency and are contraindicated in patients suffering from cardiovascular, respiratory [5], hepatic and renal diseases [6]. Meglitinide analogues given preprandially have been found to arouse dyspepsia, arthralgia in some patients and cautioned in hepatic disease [7]. Thiazolidinediones may cause plasma volume expansion, mild anemia, myalgia, hepatic dysfunction, may fail contraception therapy and is contraindicated in liver and congestive heart failure [8]. α-Glucosidase inhibitors, the mild option to overcome insulin resistance may lead to gastric discomfort mainly due to flatulence and diarrhea particularly after a high carbohydrate meal and may also interfere with iron absorption [9]. Moreover, literature reports quote gain in body weight, cataracts and macular degeneration during oral anti-diabetic treatment in some patients. Therefore, the need of the hour is to look for a treatment which not only checks the glucose levels in circulation system, but at the same time avoids the adverse effects associated with the currently available

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>People suffering from diabetes (in millions)</th>
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<tbody>
<tr>
<td></td>
<td>2000</td>
</tr>
<tr>
<td>India</td>
<td>31.7</td>
</tr>
<tr>
<td>South East Asia</td>
<td>22.3</td>
</tr>
<tr>
<td>Middle East Asia</td>
<td>20.0</td>
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<tr>
<td>China</td>
<td>20.8</td>
</tr>
<tr>
<td>Europe</td>
<td>28.3</td>
</tr>
<tr>
<td>United States and Canada</td>
<td>19.7</td>
</tr>
<tr>
<td>Latin America and The Caribbean</td>
<td>13.3</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>7.1</td>
</tr>
<tr>
<td>Australia</td>
<td>0.9</td>
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Table 1: Prevalence of diabetes: Estimated number of people region wise for the year 2000 and 2030.
commercially available herbal and PHFs and provides an exhaustive list of plants with potential anti-diabetic activity.

**Plants possessing hypoglycemic activity**

The judicious and liberal use of medicinal plants in treatment of various human diseases has always been supported by the ancient medicinal literature worldwide. The growing interest of researchers in traditional medicine has led to discovery and establishment of biological activity of many potent phytochemicals possessing hypoglycemic activity (e.g. glycosides, flavonoides, terpenes, steroidal saponins, alkaloids, polysaccharides). The use of fresh fruit juice of *karela* (momordica), seeds of *methi* (fenugreek), *jaman* (black plum) seed powder, leaves of *gurmar* (gymnema) are some examples of the home remedies for diabetes which are being practiced since ages. More recently these natural remedies are being formulated as PHFs and prescribed in conjunction with the allopathic drugs. Table 2 (Shown as supplementary) enlists some polyherbal and herbal anti-diabetic formulations currently available in the Indian and international market. More than 400 plants have been incorporated in approximately 700 recipes which are used to treat diabetes mellitus in almost two thirds of the world population [12]. Extensive literature survey suggests that in the past ten years a large number of plants have been investigated for their hypoglycaemic potential. Table 3 (Shown as supplementary) enlists some of the important plants with potential anti-diabetic activity. Botanical source, active principles and pharmacological activities and mechanism of action of some of the important plants (Figure 2) which are widely used in commercially available polyherbal formulations are described below:

Gymnema is a woody plant found in tropical forests of India and Africa, biologically known as *Gymnema sylvestre* from family Asclepiadaceae, commonly called the milkweed family. It is commonly known as “gurmar”. The major bioactive constituents of *gymnema* are a group of oleanane type triterpenoid saponins known as gymnemic acids (gymnemosides) [178]. The active principles (gymnemic acids) show selective anesthetic effect on the sweet taste buds [179]. It has been reported to be an effective anti-diabetic agent in lowering blood sugar in both type I and type II diabetes. It also acts as a hepatoprotective, hypolipidemic, antiatherosclerotic, stomachic, diuretic, refrigerant, astringent and tonic. Experimental studies on rats showed comparable anti-hyperglycemic effect to that of tolbutamide. *Gymnema*’s anti-diabetic activity appears to be due to a combination of mechanisms. It increases the activity of enzymes responsible for glucose uptake and utilization, and inhibits peripheral utilization of glucose by somatotrophin and corticoteraphin [180]. Plant extracts have also been found to inhibit epinephrine-induced and corticosteroid-induced hyperglycemia [102]. The drug influences the disturbed carbohydrate metabolism in hyperglycemic animals by limiting the carbohydrate turnover and thus inhibiting the vicious cycle of hyperglycemia. Investigations in streptozotocin treated rats indicate that this plant brings about blood glucose homeostasis through increased serum insulin levels provided by repair/regeneration of endocrine pancreas [181]. Further clinical trials in patients with insulin dependent diabetes mellitus also suggest that it acts by regeneration of residual β-cells in insulin dependent diabetes mellitus and is insulinitropic [182]. It is also one of the chief ingredients of ayurvedic preparations being sold as a remedy to treat diabetes mellitus available as Madhumehari Yog (Shree Baidyanath Ayurved Bhavan Private Limited, Jhansi, India), Diabecon® (Himalaya Herbal Healthcare®, Makali, Bangalore, India) and Amree plus (Aimil Pharmaceuticals (India) Limited).

Bitter melon also known as karela, bitter gourd, bitter apple,
bitter cucumber and karolla, is a vegetable cultivated in tropical areas. Botanically it is known as *Mormordica charantia* and belongs to family Cucurbitaceae. The fruits and seeds of this plant are been reported to exert hypoglycemic effect in animals and human subjects [183]. It has been taken for centuries as a part of diet. It contains several chemical constituents, including the glycosides (mormordin and charantin) and alkaloid (mormordin). It also contains an insulin-like polypeptide called Polypeptide-P [184]. Polypeptide-P has been designated as the 'plant insulin which lowers blood sugar levels when injected subcutaneously gerbilis, langurs and diabetic patients [185]. Another hypoglycemic principle charantin a sartor saponin found in the fruit of the plant is reported to be more potent than the drug tolbutamide [186]. It probably acts through an extrapancreatic mechanism such as improving glucose tolerance, promoting peripheral glucose utilization, decrease blood glucose synthesis through depression of the enzymes glucose-6-phosphatase, fructose-1, and 6 bisphosphatase and enhance glucose oxidation by enzyme glucose-6-phosphate dehydrogenase pathway [187]. Experimental studies in streptozotocin induced diabetic rats indicate that fruit juice of this plant may help in renewal/repair of partially destroyed β-cells [188]. Other reports demonstrate that fruit juice of bitter melon helps in prevention of diabetic cataract [189] and renal damage [190]. It is available in pure powder form (Himalaya Herbal Healthcare®, Makali, Bangalore, India) and is one of components of Diasulain (Danish Medicine and Chemical Company) and Divya Madhu Nashini Vati & Divya Madhukalp Vati (Swami Ramdev’s Divya Pharmacy, Haridwar, India).

*Azadirachta indica* (neem) belongs to family Meliaceae. In common language it is also known as margosa, nimb, nima, nimbatiktam, arishtha, praneem. The active ingredients are concentrated in seed oil, bark and leaves of this plant. Mainly leaf extracts and seeds are used to treat diabetes. The chief components present in neem oil extracted from seed are nimbim, nimbinin, and nimbidin respectively [191]. The seeds also contain a complex secondary metabolite azadirachtin. The leaves contain nimbin, nimbinene, 6-desactynlhimbinene, nimbandiol, nimbolide and quercetin. Leaves are also reported to contain β-sitosterol, n-hexacosanol and nonacosane [192]. Neem leaf extract and seed improves the blood circulation by dilating the blood vessels [193] and also helpful in reducing the requirement for insulin by 60-70%, however, the glucose levels remain intact [194]. Oral doses of neem leaf extracts significantly reduce insulin requirements for insulin dependent diabetes and have also been scientifically proved to be effective in treating and preventing diabetes [195]. The possible mechanism of anti-hyperglycemic effect of azadiractha leaf extract was found to be reduction in peripheral utilization of glucose and suppression of glycogenolysis effect due to epinephrine action [196]. The water soluble portion of the alcoholic extract of the leaves was found to possess a significant blood sugar lowering effect in glucose-fed and adrenaline-induced hyperglycemic rats. Treatment with ethanolic extract of leaves of neem is reported to ameliorate pancreatic islet lesions in streptozotocin induced diabetes [197]. According to a research report the blood sugar lowering capacity of extract of *Azadirachta* was more pronounced as compared to other antidiabetic plants like *Catharanthus*, *Gymnema* and *Ocinum* [198]. It is currently marketed by Himalaya Herbal Healthcare®, Makali, Bangalore, India as Neem capsules, Neem Guard® (Goodcare Pharma Private Limited, Calcutta, India), Pancreatic tonic- glycinoprin (US Botanicals, California, US) and Diabet Guard™ Granules and Capsules (Goodcare Pharma Private Limited, Calcutta, India).

*Vinca rosea*, commonly known as sadabahar, baramasi, Madagascar periwinkle; botanically is *Catharanthus roseus* and belongs to family Apocynaceae. The plant is reported to contain over 70 alkaloids of the indole type. The aqueous extracts of flower and leaves produce blood glucose homeostasis reversed changes in carbohydrate, protein, and lipid metabolism, metabolic and pathologic changes. The leaf juice or hot water decoction of the flowers and leaves of the plant are used as a folk medicine for the treatment of diabetes [199]. A significant antihyperglycemic activity of the leaf alcholic extract [59], aqueous extract [200] and the dichloromethane-methanol extract of leaves and twigs [201] is also reported in laboratory animals. Fresh leaf juice of *C. roseus* has been reported to reduce blood glucose in normal and alloxan diabetic rabbits [202]. Literature survey reports hypoglycemic activity of vinca comparable to that of tolbutamide [201] and glibenclamide [202]. Another study shows that *Catharanthus* acts synergistically with fenugreek in reducing blood glucose levels [203]. The fresh leaf juice or leaf powder significantly reduced blood glucose level to almost normal level and also the levels of total cholesterol, triglycerides, low density lipoproteins (LDL) and very low density lipoproteins (VLDL) cholesterol and at the same time increased high density lipids (HDL) [200]. The antihyperglycemic action of *C. roseus* may be ascribed to increased plasma insulin concentration and insulin sensitivity due to the regeneration of pancreatic β-cells, which is probably due to the fact that the pancreas contains stable (quiescent) cells that have the capacity to regenerate [204,205]. Therefore, the surviving cells can proliferate to replace the lost cells. Phytochemicals such as flavonoids and alkaloids present in the *C. roseus* leaf powder may have protected the intact functional β-cells from further deterioration through oxidative stress [206]. The reduction in the levels of the LDL and VLDL could have resulted from the antioxidant effect of the fresh leaf juice whose phytochemical components include flavonoids [207]. Therefore, it can be said that *Vinca rosea* manifests its beneficial activity probably through enhanced insulin secretion, extrapancreatic mechanism, β-cell rejuvenation, regeneration and stimulation [208,209]. It is one of the components of Diabeta™ and Dyboss™ (Morpheme Remedies Private Limited, Panchkula, Haryana, India).

*Pterocarpus marsupium* (Indian Kino Tree) is a deciduous tree of the family Leguminosae. It is known as Vijaysar, Bijaka, Pitasa and Pitashalaka. Several polyphenolic compounds/flavonoids and their derivatives have been isolated from various parts of the plant [210]. The key chemical constituents include a diaryl propane derivative: propterol, a stilbene: pterostilbene, a hydroalcone: pterosipin, a benzoferanone: marsuparin, a flavanoid: liquiritigenin and a catechin: (-)-epicatechin. The first four are the main components of the heartwood, while (-)-epicatechin is found in the bark of the tree [211]. The phenolics, marsuparin, pterosipin, and, pterostilbene have been identified as the blood sugar lowering [212] and antihyperlipidemic components [213]. The heartwood of the tree is used to make tumblers/goblets/beakers which are filled with water and allowed to stand overnight to give 'Boojum water'. The positive activities of which against diabetes has been confirmed [170]. (-)-Epicatechin, its active principle, has been found to be insulinoenic, enhancing insulin release and conversion of proinsulin to insulin in vitro [214]. It restores the normal insulin production of the pancreas and stabilizes the normal sugar levels [215]. The extract of the bark of plant is found to prevent hyperglycemia, hyperglycemia and insulin resistance [216]. It may also lower blood sugar through an unrelated pathway of that of insulin making it useful in the treatment of both types of diabetics [217]. It is also reported to help regenerate, reverse the damage and repopulate the β-cells in the pancreas. Experimental studies in diabetic rats show that the plant extract also exhibited anti-cafarct effect [218]. It is one of the main ingredients of Diabecon® (Himalaya Herbal Healthcare®, Makali, Bangalore, India), Pancreatic tonic- glycinoprin
(US Botanicals, California, US), Diabeta™ and Dyboss™ (MorpHEME Remedies Private Limited, Panchkula, Haryana, India) and Epinsulin (Swastik Pharmaceuticals Formulation Private Limited, Varanasi, India).

Tinospora cordifolia, (Gily) is also known by the common name Guduchi, it is herbaceous vine of family Menispermaceae. The active adaptogenic constituents are diterpene compounds including tinosporone, tinosporic acid, cordifoliosides A to E, syringen, the yellow alkaloid, berberine, giloin, and a glucosidal bitter principle as well as polysaccharides, including arabino-galactan polysaccharides [219,220]. The active principles are found to possess anticomplementary and immunomodulatory activities [221]. The oral administration of an aqueous root extract is reported to exert a significant reduction in blood glucose and brain lipids [222]; increase in body weight, total haemoglobin and hepatic hexokinase [223]. The roots extract also lowers hepatic glucose-6-phosphatase and serum acid phosphatase, alkaline phosphatase, and lactate dehydrogenase. Studies in rodents postulate that alcoholic or aqueous extracts of the plant decrease blood glucose and increase glucose tolerance [224]. The histological examination of pancreas has not revealed any evidence of regeneration of β-cells of islets of Langerhans and the possible mode of action of the plant is by interfering with glucose metabolism [225]. It is one of the components of the polyherbal formulations viz. Diacon® (Himalaya Herbal Healthcare®, Makali, Bangalore, India), Diabeta™ (MorpHEME Remedies Private Limited, Panchkula, Haryana, India), Diabet Guard capsules and granules® (Goodcare Pharma Private Limited, Calcutta, India).

Fenugreek is a plant in the family Fabaceae botanically known as Trigonella foenum graecum. Fenugreek, more often called ‘methi’ is used both as a herb and as a spice. Fenugreek, a common curry ingredient in Indian and Middle Eastern cuisine, has been shown to regulate blood sugar levels and increase good cholesterol while lowering total cholesterol. The main chemical components of fenugreek seeds include galactomannans, 4-hydroxyisoleucine [226], a pseudo alkaloid trigonelline, steroids like sitosterol, steroidal saponins like trigrogenin and gitogenin. Besides these linoleic and linolenic acid; g-lactone, sotolone (responsible for characteristic odor); diosgenin, trigocoumarin, trigomethylcoumarin, fibre and mucilage is also present [227]. Fenugreek seed in powder or germinated form exhibits anti-diabetic properties [228], hypocholesterolemic effect [229] and effect on thyroxine-induced hyperglycaemia [230]. Fenugreek seeds have been used as an oral insulin substitute, and seed extracts have been reported to lower blood glucose levels [231]. The anti-diabetic and the blood cholesterol lowering activity are linked to the fibre and galactomannan rich fraction present in the seed [227]. The insulinotropic and anti-diabetic properties of the drug are associated with amino acid 4-hydroxyisoleucine [231], which causes direct β-cell stimulation, delayed gastric emptying and inhibition of glucose transport [232]. Various animal studies demonstrate the glucose lowering effects of fenugreek [233]. Another study showed that defatted fraction of the seeds lowered blood glucose levels, plasma glucagons, somatostatin levels; carbohydrate-induced hyperglycaemia [234]. Also, reduction in cataract incidence has been reported in diabetic mice after treatment with extracts of seeds and leaves of the plant [218]. Galactomannans and saponins also contribute towards hypocholesterolemic activity [235]. Galactomannans decrease the uptake of bile acids, lower the blood and liver concentration of cholesterol and decrease hepatic cholesterol synthesis. It is commercially available as Fenure™ (Fenfur™, Panchkula, Haryana, India), Syndrex (Plethico Laboratories, Indore, India), Diabetan™ (Hamida™ Pharma, Lake Forest, California, US) and Fenugreek Plus (Metagenics, Gig Harbor, Washington, US).

Aloe vera a perennial, rosette forming plant belongs to family Liliaceae. It is also known as Indian aloe, Ghezkumari and Gwarpatha. It is rich in anthraquinones, saccharides, enzymes, vitamins, minerals, cholesterol etc. The principal constituents present in the leaves are barbaloin, chrysophanol glycoside and the aglycone, alo-emodin [236]. The phyto-sterols present in the aloe vera gel have been reported to possess anti-hyperglycemic activity which may have a long term blood glucose level control effect and would be useful for treatment of Type I and Type II diabetes mellitus [237]. Another study reports the presence of inorganic trace elements (vanadium, zinc, copper; manganese and traces of chromium) in aloe leaf gel possessing hypoglycemic property, probably through improvement in impaired glucose tolerance thereby indirectly contributing to management of diabetes [238]. An experimental report states hypoglycemic activity on insulin dependent and non-insulin dependent rats with the effectiveness being enhanced for non-insulin dependent rats in comparison to glibenclamide [239]. In another study it was observed that Aloe vera successfully reduced the blood sugar as well as the blood triglyceride levels [237]. In a group of patients who were not responding to glibenclamide were given to Aloe vera and a 48% reduction in blood sugar levels and a 52% reduction in triglycerides was observed [239]. It is present in the anti diabetic polyherbal formulations namely GlucoCare® and Diacon® (Himalaya Herbal Healthcare®, Makali, Bangalore, India).

Stevia rebaudiana, commonly known as sweet leaf, sugarleaf, or simply stevia, belongs to the family Asteraceae and is widely grown for its sweet leaves. One of the main constituents of the extract is a diterpene glycoside, stevioside, which is known for its intense sweetness and has been applied as non-caloric sweetener in several countries [240]. The leaf extract of plant have been used for many years in the treatment of diabetes in South America [241]. Recently it has been established that both intravenous as well as oral administration of stevioside exerts antihyperglycemic, insulinotropic and glucagonostatic actions [242]. Stevioside and its aglucone steviol directly potentiate the glucose-stimulated insulin secretion, insulin utilization by decreased protein levels of phosphoryl pyruvate carboxykinase by slowing down gluconeogenesis [243]. Stevioside also possess blood pressure lowering properties [244] which can be used as an effective means of preventing diabetic macrovascular complications [242]. Therefore, a multifactorial approach combining blood glucose, blood pressure and lipid lowering would be most effective in treating diabetes and preventing diabetic complications [245]. Stevioside also results in reduction in postprandial blood glucose levels in Type II diabetic patients, indicating improvement in the glucose metabolism [240]. It is marketed as Stevia sweetener and Stevia Plus® by Nutricare Group, Bangladesh.

Turmeric, haldi, arishia, pasupu, haridra, kurkum are the common names for ‘The Indian Solid Gold’ curcumin. Botanically it is Curcuma longa belonging to the family Zingiberaceae. The dried powdered rhizomes of Curcuma, have extensively been used for centuries as a spice, food preservative, and a yellow colourant for food, drugs, and cosmetics [246]. Curcumin along with its mono- and bis-demethoxy derivatives, collectively called curcuminoids, constitute the major orange-yellow colouring matter and the biologically active constituents of turmeric. Besides curcuminoids, minor amounts of oils and resins are also present in curcumin. These include α-turmeron, β-turmeron, curlon, zingiberen. It is an important herb in most Ayurvedic treatments of diabetes as it lowers blood sugar, increases glucose metabolism and potentiates insulin activity more than three-folds.
The rhizome extract of the plant is shown to lower blood glucose in experimental, induced- diabetic rats [247]. It has also been observed that in type II diabetes, administration of curcumin reduced the blood sugar, hemoglobin, and glycosylated hemoglobin levels significantly in an alloxan-induced diabetic rat model [248]. Diabetic rats maintained on a curcumin diet for 8 weeks excreted less albumin, urea, creatinine and inorganic phosphorous. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creatinine and inorganic phosphorous in diabetic animals [249]. Several animal studies have demonstrated that curcumin can overcome insulin resistance and can delay cataract incidence in diabetic patients [250]. It is present in many polyherbal formulations viz. Diabecon® (Himalaya Herbal Healthcare®, Makali, Bangalore, India), Diabet Guard™ Graneules and Capsules (Goodcare Pharma Private Limited, Calcutta, India) and Diabetes™ (Morpheme Remedies Private Limited, Panchkula, Haryana, India).

**Summary**

It is estimated that by the year 2030 India will have nearly 22% of the world’s diabetic population. If not adequately managed, diabetes would result in a wide range of complications that have clinical, social and economic implications. Many plants are known to possess anti-diabetic properties. If the active plant constituents of these potential plants are isolated and quantified suitably formulated it would definitely be a positive contribution towards the management of diabetes. Natural phytochemicals can be relevant today only if these are tested within the framework of modern sciences and subjected to the rigorous criteria for quality, safety and efficacy. Further the commercialization of such delivery systems possessing safe phytochemicals will save the patients from the undue side effects caused by present allopathic anti-diabetics. The anti-diabetic therapy with the natural phytochemicals together with a balanced diet rich in carbohydrates and having lesser fat content and regular exercise would help in increasing insulin sensitivity and improve the life quality of a diabetic patient. The study of such medicines may offer a natural key to unlock a diabetologist’s pharmacy for the future.

**References**

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