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(REVIEW ARTICLE)



Effects and safety profile of commonly used herbal anti-diabetic preparations

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Abstract

Since ancient times, plants have been helping human beings to treat various ailments. Several medicinal plants are commonly being used in the management of diabetes particularly in the developing countries where resources are insufficient. Diabetes mellitus is metabolic disorders which has become very common with almost about 2.8% of the morbidity worldwide. In the present review, a special emphasis is given on some commonly used Ayurvedic medicinal plants having hypoglycemic properties and their anti-diabetic preparations. The review presents information regarding the scientific name (genus-species), family, preparation used, the evidence of hypoglycemic activity, the active agents and safety profile. This review could be useful to researchers, clinicians, pharmacists as well as common man from the society as a basic information for further development of anti-diabetic herbal remedies.

Keywords: Anti-diabetic; Ayurvedic herbs, Ayurvedic preparations; Safety; Medicinal plants

1. Introduction

Diabetes is a state of improperly regulated homeostasis of carbohydrate and lipid metabolism and is one of the major health problems worldwide [1]. It is reported that traditional medicines derived from medicinal plants are used by about 70% of the world's population. However, this data is not of statistical significance as most part of this population relies on traditional herbs as an added therapy alongside the conventional allopathic mode of therapy [2]. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world [3]. Traditional Indian medical science known as 'Ayurveda' uses drugs derived from medicinal plants, minerals, herbs for their therapeutic benefits. There are a number of medicinal herbs mentioned in Ayurvedic system of medicine as anti-diabetic, some of them include yam, gurmar, bitter gourd, jamun, neem, etc. [4]. Several marketed Ayurvedic preparations include trivanga bhasma, triphala churna, jasadha bhasma, jamun extract, haritaki churna, nimbapatra, ashvattha, etc. [5].

New chemical entities are consistently being discovered; however, these medicines comes with investment of billions of dollars and 10-12 years lead time for development. These molecules come with their own side-effects, and are approved by global regulatory bodies only after considerable data from successful clinical studies are documented in dossiers to reconfirm that the benefits outweighs risks [6]. On the other hand, the age old traditional herbal medicines or ayurvedic preparations have clinically proven their safety and efficacy in humans due to their widespread use through time immemorial by wide population in rural areas wherein they have proven desired clinical outcomes with apparently no visible side effects [7]. Ayurvedic medicines are also cheap since they are present in abundance or are locally cultivated and have simple extraction methods. However, these plant give best effects when they are consumed raw or after simple processing.

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The main purpose of this article is to discuss common plants and herbs with anti-diabetic properties which are safe and efficacious for healthy human subjects as well as diabetic patients. These herbs if included in the daily human diet can cause significant improvements in maintenance of blood glucose levels. In this review, a list of medicinal plants with proven anti-diabetic and related beneficial effects is compiled on the basis of literature survey and common practical knowledge of local community. In total, twenty seven medicinal plants (Figure 1) are discussed in this review. As the damage induced by free radicals is one of the major etiologic factors implicated in the development of diabetes and its complications; therefore, an anti-diabetic compound with antioxidant properties would prove more beneficial [8]. Hence, information on antioxidant effects of these medicinal plants is also included in this review.

2. Antidiabetic herbs

2.1. Ladies Finger (Okra)

Abelmoschus esculentus belongs to the plant family Malvaceae and is commonly known as ladies finger or okra. It is a common and popular vegetable in most part of the world [9]. It performs hypoglycemic activity by slowing down the absorption of sugar through the intestinal tract [10]. Hypoglycemic property of okra could probably be attributed to its high mucilaginous and fiber content [11]. The major flavonoids of okra quercetin and quercetin 3-O-gentiobioside have blood glucose lowering effect [12]. Due to above listed properties it is recommended for diabetic patients. For anti-diabetic effects okra can be sliced and soaked overnight in a water filled jar. The drink can be consumed in the morning for reducing and regulating the blood sugar levels [13]. Okra powder can also be soaked and consumed to have anti-diabetic effect [14]. Okra peel and seed powder did not show any toxicity or death up to a dose of 2000 mg/kg in Wistar albino rats [15]. However, it has been observed that polysaccharides and fibers of okra extract reduce the metformin absorption in the intestine [11]. As okra is one of the main food vegetable in diet of most of the population thus safe for consumption.

2.2. Onions

Allium cepa commonly known as onions are among the most common vegetables used every day in the kitchen. It is a spice plant that belongs to the Amaryllidaceae family [16]. *Allium cepa* also helps to regulate the hypoglycemic activity associated with diabetes mellitus [17]. This is due to presence of flavonoids (quercetin) and sulphur compounds (S-methyl cysteine) which helps to reduce the level of blood glucose, lipid peroxidation, serum lipids as well as oxidative stress. These compounds also aid in insulin secretion as well as boost the antioxidant enzyme activities taking place in the body [18]. Onion extracts also aid in hypolipidemic activities. The hypolipidemic and hypoglycemic effects of onion is due to its ability to normalize the activities of HMG coenzyme-A reductase, liver hexokinase and glucose 6-phosphatase [19]. Some preliminary clinical trials carried out reveal that glucose levels can be reduced by taking *Allium cepa* aqueous extracts [20]. Onion and onion by products and its extracts did not show any toxicity including genotoxicity in rodents, the only side effect observed was anemia [21]. Thus onion can be a safe treatment option for diabetes.

2.3. Milk thistle

Silybum marianum belonging to family of plants Asteraceae has common name Milk thistle and is originally from the Mediterranean vegetation [22]. Their leaf extract produces a milky sap, hence the plant derives its name from this characteristic feature. Milk thistle belongs to the daisy family and it contains a polyphenol antioxidant compound known as silymarin that helps to control the blood sugar level [22]. A scientific study carried out showed that diabetic patients who took silymarin for up to 4 months showed significant improvement in their glycemic profile. This also includes a significant decrease in fasting blood glucose, LDL cholesterol, glycosylated hemoglobin and triglycerides when compared to individuals taking only placebo [23, 24]. Milk thistle extracts have been used as traditional herbal medicine remedies for almost 2,000 years. Milk thistle contains high levels of lipophilic extracts from the seeds of the plant, which act as bioflavonoids that increase immunity and slow down oxidative stress. The herb is also used for its anti-inflammatory properties. It can aid digestive function, increase bile production, boost skin health, fight the appearance of aging, lower cholesterol levels and help detoxify the body [23]. A review of clinical trials evaluating the safety and efficacy of milk thistle found that the herb has protective effects in certain types of cancer, and data shows it can also be used for patients with liver diseases, hepatitis C, HIV, diabetes and hypercholesterolemia. Milk thistle extracts, has been formulated to capsules, and have proven to be safe and well-tolerated [22].



Figure 1 Some representative photographs of commonly used anti-diabetic medicinal plants

2.4. Guggul gum

Guggul gum is another name for oleogum resin obtained from plant *Commiphora mukul* belonging to family Burseraceae and this is popularly used in Asia for producing herbal medicine for treating diabetes [25]. Oleogum resin is a yellowish substance that is characterized by balsamic odor and each tree produces up to 900 g of resin. Guggul tree is originally from Bangladesh, Pakistan and India where it is mainly used in folk medicines. Guggulsterones are the active ingredient present in Guggul [26]. Guggul extracts are highly effective in controlling the blood sugar level due to its role in glucose and lipid metabolism. Besides, guggul has a protective effect on pancreas which assists in the natural production of insulin in the body. Commipheric acid and guggulipid present in guggul help to activate the peroxisome proliferator-activated receptor gamma (PPAR γ) hormone that regulates the overall development and functioning of fat cells which are vital for the healthy metabolism of cholesterol and glucose [27]. As of now, no clinical studies have been carried out to assess the safety of long-term use of guggul or guggulsterone; however, it has been seen that for short-term use (< 6 months), either guggul or guggulipid are generally safe [28]. No significant side effects have been observed on renal and liver functions, hematological parameters, and electrolytes. A long term use in Ayurveda and such a safety profile assures its safe use in the treatment of diabetes [28].

2.5. Loquat

Loquat is botanically known as *Eriobotrya japonica* and belongs to the Rosaceae family. The loquat tree grows up to thirty feet with evergreen leaves that are between three to four inches wide and five to twelve inches long. It is also quite common in Japan, Korea, hilly Regions of India (Himachal), Potohar and foothill regions of Pakistan [29]. Researchers reveal that the loquat leaf comprises of beneficial properties that can significantly influence the blood sugar level thus drinking loquat tea has been recommended as an ideal way of balancing the blood sugar level. Loquat leaf contains polysaccharides and triterpenes chemicals especially tormentic acid that has been proven effective for boosting insulin production which significantly helps to lower the symptoms of diabetes [30]. The safety of loquat is documented by their use in traditional Greco-Arab medicine through centuries, additionally the leaves of loquat are well known and safe household remedy especially in the far [31].

2.6. Banaba

Banaba which is botanically known as *Lagerstroemia speciosa*, belongs to the family of Lythraceae. Banaba is also known as queen's crape myrtle, the pride of India or queen's flower. Banaba is more common in the Philippines, India and Southeast Asia, where it is often used as a herbal medicine for treating diabetic patients [32]. Triterpene acids isolated from banaba leaves possesses α -glucosidase inhibitory potential [33]. Aqueous banaba leaf extracts can be used for lowering the blood sugar level and its blood sugar lowering effect is sort of synonymous to that of insulin by helping transport of glucose from the blood to the body cells [34]. Despite the beneficial impacts of Banaba on blood sugar, diabetic patients are advised to be cautious when taking herbal medicines or supplements made with Banaba. No adverse effects have been observed or reported in animal studies or controlled human clinical trials with banaba aqueous extract [35]; however, due to lack of scientific proofs it should be avoided in pregnant women [36].

2.7. Cinnamon

Cinnamomum zeylanicum belonging to family Lauraceae is commonly known as true cinnamon. In Ayurveda as well as Chinese medicine it has been used for medicinal purposes for hundreds of years [36]. Cinnamon has been the subject of numerous studies to determine its effect on blood glucose levels. It has been suggested that the mode of action in which cinnamon expresses its effect on blood glucose can be attributed to its active component cinnamaldehyde [37]. A study carried out by Davis et al. (2011) has shown that cinnamon, in whole form or extract, helps lower fasting blood glucose levels [38]. Cinnamon has been displayed to be generally safe when ingested. After intense research common and cassia cinnamon have recently been granted GRAS (Generally Recognized as Safe) status by the United States Food and Drug Administration (USFDA), as a food additive [39].

2.8. Garcinia kola

Garcinia kola is a flowering plant that belongs to the Clusiaceae family. Garcinia kola which is also known as adi, heckel, namijin, agbilu, orogbo, gworo, akiilu, or bitter kola that belongs to the family of Guttiferaceae [40]. Garcinia extract is highly nutritional and medicinal which suggests its wide usage in folk medicines for herbal medicines production. Garcinia possesses hypoglycaemic properties thus its aqueous extracts can be used for lowering blood sugar level [41]. However, its hypoglycaemic effect is dependent on the dosage taken. The hypoglycaemic properties of garcinia are due to the presence of flavonoid, kolaviron (a biflavonoid complex) and other phytochemical compounds such as tannins, saponin and glycosides [42]. Acute toxicity studies showed, no signs of toxicity and no deaths at all the graded doses of the ethanolic extract of Garcinia kola seed administered to the animals, the LD50 of ethanolic extract of Garcinia kola seed

was found to be safe up to 5000 mg/kg body weight [43]. *Garcinia kola* had been shown to enhance erythropoiesis in rabbits and rats and as well has no long term significant toxicological implication [44].

2.9. Green tea

Camellia sinensis commonly known as green tea belongs to family Theaceae and contains polyphenols, which are antioxidants [45]. The main antioxidant in green tea is known as epigallocatechingallate. Laboratory studies have suggested that epigallocatechingallate may have numerous health benefits including: lower cardiovascular disease risk, prevention of type 2 diabetes, improved glucose control, better insulin activity etc. [46]. Green tea extract has been granted GRAS (Generally Recognized as Safe) status, as a food additive [47].

2.10. Licorice

Glycyrrhiza glabra commonly known as licorice belongs to family Fabaceae. It is well known herbaceous perennial legume. The licorice root is an ancient traditional herbal remedy for tackling several ailments [48]. Scientists reveal that licorice roots from the Fabaceae-papilionaceae family may be effective for treating type 2 diabetes which is more common with overweight or obese individuals thus leading to insulin resistance. Main active component of licorice is glycyrrhizic acid, it also consists of high amount of flavonoids, saponins, triterpenes, isoflavonoids and chalcones. All these components offer antioxidant activity to licorice [49]. Licorice roots contain anti-diabetic substances known as amorfrutins, which are capable of reducing the blood sugar levels as well as preventing inflammation associated with diabetes [50]. Licorice and licorice derivatives, are granted as “Generally Recognized as Safe” (GRAS) status for use in foods by the US FDA (21 CFR 184.1408). Licorice extract and its derivatives are also approved for use in some over-the-counter drugs, and licorice is included as a GRAS ingredient in animal feeds [51].

2.11. Gurmar

Gymnema sylvestre is a tropical tree that belongs to the family of *Apocynaceae* and genus *Gymnema* and commonly known as gurmar. This tree is mostly prevalent in Africa, India, Australia, China and Vietnam. The leaf extract of *Gymnema sylvestre* is a powerful herbal medicine for tackling diabetes [52]. This is due to the presence of chemical components such as dihydroxygymnemic triacetate, gymnemic acids I-VII, conduritol A. and triterpenoid saponins (gymnemosides A-F and gymnemoside W1-2) in this plant [53]. The effect of the *Gymnema sylvestre* leaf extracts is synonymous to 4 unit/kg of insulin thus highly beneficial for individuals suffering from diabetes mellitus [54]. No adverse reactions were reported in a long-term study of insulin-dependent diabetic patients; however, consider the possibility of hypoglycemia [55]. In an acute toxicity study in mice, no gross behavioral, neurologic, or autonomic effects were observed. The acute LD 50 was 3990 mg/kg [56].

2.12. Bitter gourd

Momordica charantia which is commonly known as bitter gourd also known as karela, balsam pear or bitter melon is a tendril-bearing vine used mainly for treating diabetes especially in India, the Caribbean, South America and East Africa. *Momordica charantia* belongs to the family of Cucurbitaceae [57]. Both the leaf extracts, fruit and seeds of bitter melon have hypoglycemic effects on diabetic patients. The key components of bitter melon which are responsible for its hypoglycemic effects are momordicin, stearic acid, charantin, eleostearic acid, insulin-like peptide [plant-(p)-insulin], oleanolic acids and cucurbitanoids [58]. It is worthy to note that individuals who are allergic to the Cucurbitaceae family such as melons and gourds should apply caution when taking bitter melon fruit, seeds or leaf extracts. It tends to influence the glucose metabolism all over your body rather than a particular organ or tissue. It helps increase pancreatic insulin secretion and prevents insulin resistance. Thus, bitter gourd is beneficial for both type 1 and type 2 diabetes [59]. However, it cannot be used to entirely replace insulin treatment. It is recommended to drink some bitter gourd juice on an empty stomach each morning. The seeds of two to three bitter gourds should be removed and juice should be extracted in a juicer. The juice extract should be diluted with water before administration. This treatment should be followed daily in the morning for at least two months [60]. In four clinical trials which were small and not randomized or double-blind, found bitter gourds juice, fruit, and dried powder to have a moderate hypoglycemic effect however, reported adverse effects of bitter melon include hypoglycemic coma and convulsions in children, reduced fertility in mice, a favism-like syndrome, increases in gamma-glutamyltransferase and alkaline phosphatase levels in animals, and headaches [61]. Therefore, there is a need of sufficiently powered, randomized, placebo-controlled trials in order to accurately evaluate safety and efficacy before bitter gourds can be routinely recommended. Bitter gourds may have hypoglycemic effects, but data are not sufficient to recommend its use in the absence of careful supervision and monitoring [61].

2.13. Juniper berry

A juniper berry is the female seed cone produced by the various species of junipers, especially *Juniperus communis*, belonging to family Cupressaceae. Juniper berries contain natural insulin and due to its ability to release insulin from the pancreas, researchers claim that it can alleviate hunger thus serves as a remedy for diet-controlled diabetes [62]. Juniper berry was reported to have antidiabetic and antihyperlipidemic effects on streptozotocin (STZ) nicotinamide induced diabetic rats [63]. Moreover, the methanolic extract of this fruit showed a remarkable reduction in blood glucose levels in diabetic rats. Having undergone several experimental studies, researchers agree that this fruit has hypoglycemic effects on diabetic patients [62]. No genotoxicity, dermal toxicity, data were available for any of the juniper berry extracts. *Juniperus communis* extract did affect fertility and was abortifacient in studies using albino rats [64].

2.14. Indian Kino

Pterocarpus marsupium is a large deciduous tree that belongs to the family of fabaceae (Leguminosae) and commonly known as Indian Kino. Parts of the *P. marsupium* plant such as flowers, heartwood and leaves are used in Ayurveda due to the high medicinal properties present in this plant [65]. *P. marsupium* which is also known as bijasar, honne, kempuhonne, Malabar Kino or Indian Kino is among the many powerful medicinal plants used for treating diabetes [65]. The wood, bark and leaf extracts of *P. marsupium* possess anti-diabetic effects thus are used in folk medicine for treating diabetic patients. Several phenolics like marsupsin, pterosupin, pterostilbene and epicatechin, present in *P. marsupium* extract offers it hypoglycemic effect [66, 67] by increasing insulin release from islets. A multicentric study by the Indian Council of Medical Research showed that a preparation from *P. marsupium* was effective in reducing levels of blood glucose and glycosylated haemoglobin in patients with non-insulin-dependent diabetes mellitus [68]. The extract of *P. marsupium* when combined with insulin could result in hypoglycemia, therefore to avoid this, it is necessary to constantly monitor blood sugar levels and make necessary adjustments in the dosage of insulin accordingly [69].

2.15. Indian valerian

Valeriana wallichii is a perennial herb that measures from 14 to 45cm height. This plant is a rhizome herb, a vital substitute for the European *V. officinalis* as well as belongs to the Valerianaceae family. It thrives very well mainly in the mountainous areas of the Himalayas [70]. This herb is very useful in Ayurvedic medicine as an antispasmodic, carminative, sedative, analeptic, nervine and stimulant [71]. The *Valeriana wallichii* plant also possesses anti-diabetic properties thus can be used for treating individuals suffering from diabetes [72]. A recent systematic review and meta-analysis of valerian evidenced, that valerian is a safe herb associated with only rare adverse events [73].

2.16. Yarrow flower

Achillea millefolium commonly known as Yarrow flower belonging to family Asteraceae, is a flower with white petals that produces distinctive and pleasant odour. It is native of Asia and Europe [74]. This plant has antidiabetic effect, through multitarget modes of action that involve antihyperglycemic (α -glucosidases inhibition), hypoglycemic (insulin secretion) and potential insulin sensitizer (PPAR γ /GLUT4 overexpression) actions [75, 76]. This plant is more suitable for diabetic patients because it doesn't cause a spike in blood glucose level after consumption. The aerial parts of the *Achillea millefolium* which is accompanied by no signs of relevant toxicity even at very long chronic exposure [77]. However, in one study *A. millefolium* tea was showed as weakly genotoxic in a somatic mutation and recombination test using *Drosophila melanogaster* [78].

2.17. Cayenne pepper/ Red chilli

Capsicum frutescens commonly known as cayenne pepper or red chilli belongs to family Solanaceae. Over the past years, red chilli has been used traditionally for treating diabetes [79]. A past study discovered that mice injected with capsaicin were healed of type 1 diabetes. Type 1 diabetes, which is a more serious diabetic condition that starts in childhood due to the body's immune system attacking itself can be tackled with cayenne pepper. The study further revealed that injected capsaicin destroyed the pancreatic pain nerves thereby causing the body to start producing insulin normally [80]. Capsaicin is extracted from chilli pepper and can be prepared at home by mixing three teaspoons of cayenne pepper with a jar full of cold cream. Its topical application results in depletion of substance P, a principal neurotransmitter of poly model nociceptive afferent fibers [81]. However, diabetes is a critical health condition, it is noteworthy for diabetic patients to continue taking cayenne alongside their prescribed medication in other to avoid complications. Some people are allergic to cayenne thus such individuals should desist from taking it. Excessive consumption of cayenne pepper was observed to trigger stomach irritation in some subjects and hence should be consumed with care. Cayenne supplements can interact with certain types of medications such as blood thinners and aspirin [82].

2.18. Garlic

Allium sativum commonly known as garlic belongs to family Amaryllidaceae. The mechanism of anti-diabetic action of this plant is by increase in Insulin secretion [83]. Garlic contains vital nutrients, including flavonoids, oligosaccharides, selenium, allicin and high levels of sulfur. Consuming cooked or raw garlic, by adding it to food or taking a capsule, can help treat diabetes, fight inflammation, boost the immune system, regulate blood pressure, fight cardiovascular disease, relieve allergies, fight fungal and viral infections, and improve hair loss [84]. The oil and extract of garlic have been considered “Generally Recognized as Safe” (GRAS) for use in food by the FDA [85].

2.19. Ginger

Zingiber officinale which is commonly known as ginger belongs to family Zingiberaceae and is the most widely used dietary condiment in the world today [86]. The therapeutic benefits of ginger come from gingerols, the oily resin that acts as a highly potent antioxidant and anti-inflammatory agent. Gingerol, among other bioactive agents present in ginger, are able to relieve indigestion and nausea, boost immune and respiratory function, fight bacterial and fungal infections, treat stomach ulcers, reduce pain, improve diabetes, prevent malabsorption, and may even inhibit the growth of cancer cells [86]. Ginger extract exhibits antidiabetic potential via modulating glucose uptake, protein glycation and inhibiting adipocyte differentiation [87]. The results published by Al-Amin et al. (2006) indicate that raw ginger possesses hypoglycaemic, hypocholesterolaemic and hypolipidaemic potential and effective in reversing the diabetic proteinuria observed in the diabetic rats. Thus, ginger may be of great value in managing the effects of diabetic complications in human subjects [88]. There are several ways to use ginger. It can be eaten raw, taken in powder or supplement form, consumed in liquid form by making a tea, or used topically in oil form. Ginger has been listed in “Generally Recognized as Safe” (GRAS) document of the US FDA. A dose of 0.5–1.0 g of ginger powder ingested 2–3 times for periods ranging from 3 months to 2.5 years did not cause any adverse effects [89].

2.20. Turmeric

Curcuma longa which is commonly known as turmeric belongs to family Zingiberaceae and has a very long history of medicinal use, dating back nearly 4,000 years. This powerful plant can be added to any recipe or taken as a supplement [90]. There are a range of turmeric benefits apart from managing diabetes, which includes its ability to slow and prevent blood clotting, fight depression, antioxidant, inhibition of lipid peroxidation reduce inflammation, relieve arthritis pain, treat gastrointestinal issues, regulate cholesterol, and fight cancer [91]. Curcumin (an active ingredient from turmeric) intervention of a prediabetes population significantly lowered the number of prediabetic individuals who eventually developed diabetes mellitus type 2 and improved overall function of β -cells, with very minor adverse effects [92]. Turmeric extract and its components like curcumin are reported to be safe and not toxic in human trials [93].

2.21. Ginseng

Panax ginseng which is commonly known as ginseng belongs to family Araliaceae is one of the most popular herbal medicine in the world, and it's been used in Asia and North America for centuries. Ginseng have been used as a supportive anti-diabetic medicine [94]. The active constituents like glycosides designated panaxans A to E, ginsenoside are known to have hypoglycemic effect [95]. The toxicity assessment of ginseng preparations in human studies suggested that a relatively low frequency of toxic incidence has been associated with ginseng application. In addition, studies based on the systematic literature analysis suggest that ginseng is infrequently related with toxic side effects or interactions with prescription drugs however, it is assumed that ginseng is a safe and nontoxic material although the safety issues still remain to be elucidated [96].

2.22. Fenugreek

Trigonella foenum-graecum is commonly known as fenugreek and belongs to family Fabaceae and is a commonly used condiment in Indian homes [97]. Several studies have reported the hypoglycemic property of Fenugreek seeds due to its high dietary fiber content and alkaloid trigonelline. Fenugreek decreases glucose absorption and inhibits starch digestion due to presence of soluble fiber. Adding fenugreek to the diet of diabetes patients 15 minutes before the meal causes a significant reduction in glycemic index and is beneficial to diabetic patients for long term control of their blood glucose levels and prevention of hyperglycemia related complications [98]. Fenugreek and its derived products has been listed in “Generally Recognized as Safe” (GRAS) document of the US FDA [99].

2.23. Ginkgo biloba

Ginkgo biloba, which is also known as maidenhair, is an ancient plant extract that has been used in traditional Chinese medicine to heal various health ailments for thousands of years [100]. The antidiabetic activity of *Ginkgo biloba* may be

attributed to its antioxidant activity without having a role in metal ion mediated lipid peroxidation. *Ginkgo biloba* extracts and their flavonoid fraction significantly inhibited alpha-amylase and alpha-glucosidase enzymes [101]. *Ginkgo biloba* is available in capsule, tablet, liquid extract and dried leaf form. The standardized extract form contains 24 percent to 32 percent flavonoids and 6 percent to 12 percent terpenoids. Toxicity studies show that the Ginkgo leaf extract is relatively safe for consumption, although a few side effects have been reported, that is, intracerebral hemorrhage, gastrointestinal disturbances, headaches, dizziness, and allergic skin reactions [102]

2.24. *Aloe vera*

Aloe vera which is commonly called aloe, burn plant, lily of the desert, elephant's gall is a member of Liliaceae family. In traditional Indian medicine, *Aloe vera* is used for constipation, skin diseases, worm infestation, and infections and as a natural remedy for colic [103]. *Aloe vera* acts by increasing insulin secretion or decreasing insulin resistance. *Aloe vera* gel on oral administration for 8 weeks showed reduction in blood glucose concentrations to a normal level in diet-induced obesity mice. This antidiabetic effects of *Aloe vera* gel was mediated by decreasing insulin resistance [104]. Low doses (50 mg/Kg body weight) of *Aloe vera* extract appears to be safe and did not cause any drastic alterations histological and chemical [105].

2.25. Sage

Salvia officinalis which is commonly known as Sage belongs to family Lamiaceae. In traditional medicine of Asia and Latin America, sage plant has been used for the treatment of different kinds of disorders including seizure, ulcers, gout, rheumatism, inflammation, dizziness, tremor, paralysis, diarrhea, and hyperglycemia [106]. Latest pharmacological research demonstrated that various extracts of aerial parts of sage are able to decrease blood glucose in normal as well as diabetic conditions. The mode of action suggested for hypoglycemic effect of sage include an inhibition of hepatocyte gluconeogenesis and decrease of insulin resistance through stimulation of peroxisome proliferator-activated receptor γ (PPAR γ) [107]. According to a study published by Lima et al., (2006), sage can have metformin like effects [108]. Several of clinical trials demonstrated that administration of sage does show severe side effects. However, prolonged use or overdose of sage extract or oils lead to some undesired effects such as vomiting, salivation, tachycardia, vertigo, hot flushes, allergic reactions, tongue swallowing, cyanosis, and sometimes convulsion may occur [107]. Therefore, a precaution should be taken while taking high doses of sage along with diabetes medications which might cause your blood sugar to go too low, a condition called hypoglycemia.

2.26. Cloves

Syzygium aromaticum commonly known as clove belongs to family Mirtaceae. At the present time, the major producer countries of clove are Indonesia, India, Malaysia, Sri Lanka, Madagascar, Tanzania and Brazil [109]. This spice contains 30% of the antioxidant phenol in dry weight, along with antioxidants anthocyanins and quercetin which imparts it strong antioxidant activity and thus protect the heart, liver and lens of the eye of diabetic rats, according to studies [110]. Clove bud diet may be useful in the attenuation of hyperglycemia, hyperlipidemia, hepatotoxicity and oxidative stress in the type 2 diabetes by α -glucosidase activity reduction, inhibition of protein glycation and increasing insulin sensitivity [111, 112]. The clove, its extract and essential oil is "Generally Recognized as Safe" substance and World Health Organization (WHO) established that the daily quantity acceptable of clove per day is of 2.5 mg/kg of weight in humans [111].

2.27. Rosemary

Rosmarinus officinalis which is commonly known as rosemary belongs to family Lamiaceae. It is an aromatic herb that is used commonly to add flavor and aroma to meats and soups. It is a rich source of phenolic phytochemicals having significant anti-oxidant, anti-inflammatory, hypoglycemic, hypolipidemic, hypotensive, anti-atherosclerotic, anti-thrombotic, hepatoprotective, and hypocholesterolemic effects [113]. Rosemary helps normalize blood sugar levels naturally. A research conducted in Jordan to study the effects of rosemary on lipid profile in diabetic rats proved that rosemary has no significant influence on serum glucose level and lipid profile of normal rats. But when rosemary extract was administered to diabetic rats for 4 weeks, their blood sugar levels reduced by 20%, cholesterol levels by 22%, triglyceride levels by 24%, and LDL by 27% while HDL increased by 18% [114]. Rosmarinic acid and carnosic acid are active ingredients of rosemary extract those stimulates skeletal muscle cell glucose uptake via AMPK activation [115]. Acute oral toxicity studies of rosemary extract in rat demonstrated that dose of 2,000 mg/kg of body weight, showed no changes in hematological and serum chemistry values, organ weights or histological characteristics [116].

3. Conclusion

Though the new chemical entity drug products are constantly being innovated, developed and sourced to markets after structured clinical studies with outcomes proving benefits outweighing risks and side effects, it should be noted that these natural plants also have immense potential to cure hyperglycemia. They have an added advantage that they are of natural origin and hence pose no threat of adverse effects if consumed within recommended doses. However there should be considerable data generation on toxicity and lethal human doses and also tweaking of exact dose of these herbs as per the age of the patient population. Since most of these plants have been a part of human diet since centuries in the areas where they are naturally found or grown in plenty, they have a proven safety and efficacy profile in the indigenous population of those areas. What is actually required is that clinical studies be designed on diverse race of population covering the globe to re-affirm the facts and theories. Global regulations and guidelines should be framed covering standardized testing methods for potency and impurities.

Compliance with ethical standards

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There is no conflict of interest exist between both authors.

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