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Mode of Action of Anti-diabetic Phyto-Compounds Present in Traditional Indian Plants: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author DJ collected the literature cited here and wrote the first draft of the manuscript. Authors KB and NS arranged the final manuscript and refined as per the journal guidelines. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The traditionally used plants having therapeutically potent phyto-chemicals are known to have a great potential in the treatment of various ailments including the non-communicable ones like obesity, diabetes, hypertension, heart diseases etc. Diabetes is a serious metabolic disorder affecting a large number of population worldwide. Despite the great efforts made to understand and manage this disorder, its prevalence is increasing unabatedly which creates an upsurging demand for some other approach than conventional medicines. The use of many traditional plants with anti-diabetic potential is being considered as an alternate strategy, which is cost-effective and has less side effects. This paper reviews the accumulated literature mainly for five Indian herbs having anti-diabetic activity and their proposed action of mechanism which has been scientifically tested. Phyto-compounds present in medicinal plants like gurmur (*Gymnema Sylvestre*), cinnamon (*Cinnamomum*), sea buckthorn (*Hippophae rhamnoides*), mulberry leaves (*Moraceae Plant*) and fenugreek (*Trigonella foenum-graecum*) have shown significant hypoglycemic potential in treating

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type 2 diabetes through several possible mechanisms. Gymnemic acid in gurmur can inhibit the intestinal glucose absorption, whereas cinnamaldehyde in cinnamon and palmitoleic acid in Sea buckthorn enhances glucose uptake. The compound 1-deoxynojirimycin found in mulberry leaves inhibits the enzymatic activity of α-glucosidase and diosgenin in Fenugreek has a role in the regeneration of pancreatic β-cells, thus showing the mechanism of their anti-diabetic action. The inclusion of these medicinal plants in daily dietaries can be looked upon as an alternate strategy towards controlling and managing blood glucose levels among people with diabetes.

Keywords: Traditional medicinal plants; phyto-compounds; diabetes mellitus; anti-diabetic action; hypoglycemic effect.

1. INTRODUCTION

The prevalence of non-communicable diseases such as diabetes and heart diseases due to urbanization and modern lifestyle has already overtaken the communicable diseases in terms of morbidity and mortality in India. These lifestyles related diseases are more linked with the way people live, their eating habits, physical inactivity as well as changing environmental factors [1]. The management and the treatment of these diseases inflict both direct and indirect costs over the community and also have a great impact on the quality of life of an individual. Disproportionate allocation of health resources among the communities worldwide puts a major burden on the health facilitators to provide a cost-effective approach. The patients are being prescribed therapies involving chemically synthesized drugs for almost entire life and most of the time show side effects like weight gain, gastro-intestinal disturbances etc [2]. Presently, the approach towards management of these non-communicable diseases is being shifted more towards traditional disease management strategies involving lifestyle modification and use of plant sources on regular basis, as they are economical and have fewer or no side effects.

Diabetes is the fastest growing health problem worldwide and is becoming a major health issue. According to International Diabetic Federation (IDF) [3] the disease has affected around 463 million adults (20-79 years) in 2019 worldwide and now it is expected to affect probably 700 million population by 2045. World Health Organization (WHO) has indicated that diabetes mellitus is one of the potential threats with Southeast Asians and Western pacific people being at the highest risk [4]. India is facing an uncertain future concerning the risk of diabetes [5]. About 8.9 per cent of Indian adult population is suffering from this disease [6]. One of the major contributors to this disease is our food habits and sedentary lifestyle. Despite the great efforts made to understand and manage diabetes, its prevalence is increasing unabatedly which creates the demand for an alternate cost-effective approach which can cater to the needs of even poor segment of the society.

India is proud to be rich in biodiversity possessing about 8% of the estimated biodiversity in the world with around 12600 species [7]. According to the World Health Organization (WHO) about 80 percent of the world's population has incorporated plant sources as medicinal agents in health care, because traditional plants are known to have diversity in their biological activities and drug-like properties. It is estimated that about 25 percent of all modern medicines directly or indirectly come from medicinal plants. From ancient time's alternate system of medicines like Ayurveda and Unani have been shown to have wide usage in India. Herbal preparations for controlling diabetes in Ayurveda such as decoctions (boiled extracts), *Swaras* (expressed juices), *Asav-Arisht* (fermented juices), and powder formulations are based on plant compounds [8]. Numerous traditional plant foods like neem, tulsi, mango leaves, curry leaves, cinnamon, fenugreek seeds, aloe vera, *Gymnema Sylvestre*, tea leaves, vijayasar, holy basil etc. are reported to possess the anti-diabetic activity. In addition to that, these plant foods also help to ameliorate diabetic complications [9]. However, a very little is known about the mechanism action of anti-diabetic molecules in these herbs whether by controlling the blood glucose absorption or by enhancing the activity of β-cells to produce more insulin. This review mainly focuses on traditional Indian plants having anti-diabetic potential in them and their mechanism of action in the treatment of diabetes mellitus (DM). This review article includes the action mechanism of phyto-compounds present in traditional Indian plants namely Gurmur (*Gymnema sylvestre),* Cinnamon (*Cinnamomum)*, Sea buckthorn (*Hippophae* *rhamnoides),* mulberry leaves (*Moraceae* Plant) and Fenugreek (*Trigonella foenum-graecum*) in the control of diabetes. This review may help future researchers in identifying a right plant molecule to treat DM and also in understanding their mechanism of action in control of the disease.

2. MECHANISMS ACTION OF ANTI-DIABETIC PHYTO-COMPOUNDS

Phyto-Compounds are biologically active compounds present naturally in plant foods are also known as plant bio-actives or secondary metabolites [10]. Generally, these include plant polyphenols like flavonoids, phenolic acids, polyphenolic amides and phyto-chemicals like phenols, terpenoids, nitrogen-containing alkaloids and sulfur-containing compounds [11]. These compounds are extra nutritional constituents that typically occur in small quantities in plants but appear to provide numerous beneficial health effects. The phyto-compounds present in plants like neem, tulsi, cinnamon, fenugreek seeds, aloe vera, gurmar, tea leaves, vijayasar and holy basil etc are known to possess the anti-diabetic activity. Other medicinal plants like turmeric, Indian pumpkin, *Salvadora persica L*, *Moringa oleifera Lam* also shown to have hypoglycaemic action [12].

Different parts of the plants have been focused for their anti-diabetic and anti-oxidant potential. The shreds of evidence accumulated from *in vivo* and *in vitro* investigations suggest that plant-bioactives have a significant function in prevention and management of type II diabetes through Insulin-dependent approaches including protection of pancreatic islet β-cell, reduction of β-cell apoptosis, promotion of β-cell proliferation, attenuation of oxidative stress, activation of insulin signaling, and stimulation of pancreas to secrete insulin and Insulin independent approaches including inhibition of glucose absorption, inhibition of digestive enzymes, modification of inflammation response and Inhibition of the formation of advanced glycation end products [8,13,14,15].

3. PLANTS WITH ANTI-DIABETIC POTENTIAL

3.1 Gurmur

Gurmur *(Gymnema sylvestre)* also known as Madhunashini (Fig. 1), is native product of Southern India, Africa, and the Middle East. Gymnema is traditionally being used as an anti-diabetic herb. It belongs to the periploca of woods in the Asclepediaceae family [16]. As the name 'Gurmur" means "sugar-destroying" was given because of its anti-sacharogenic property that suppresses the taste of sugar [17]. Its leaves are used for its acrid, thermogenic, anticancerous, anti-inflammatory properties but mainly used for its anti-diabetic potential. Insulinotropic activity is known for its essential chemical component "gymnemic acid" (Fig. 2), which is thought to increase secretion of insulin from the pancreas and promote the regeneration of islet cells [18]. Gymnemic acid also has different types from I to VII, IX out of which Type IV also known as GS_4 has an excellent role in controlling hyperglycemia among type I and type II patients [19].

Fig. 1. *Gymnema sylvestre* plant

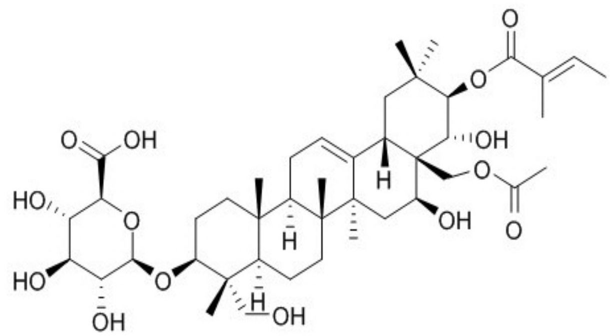

Fig. 2. Molecular structure of gymnemic acid

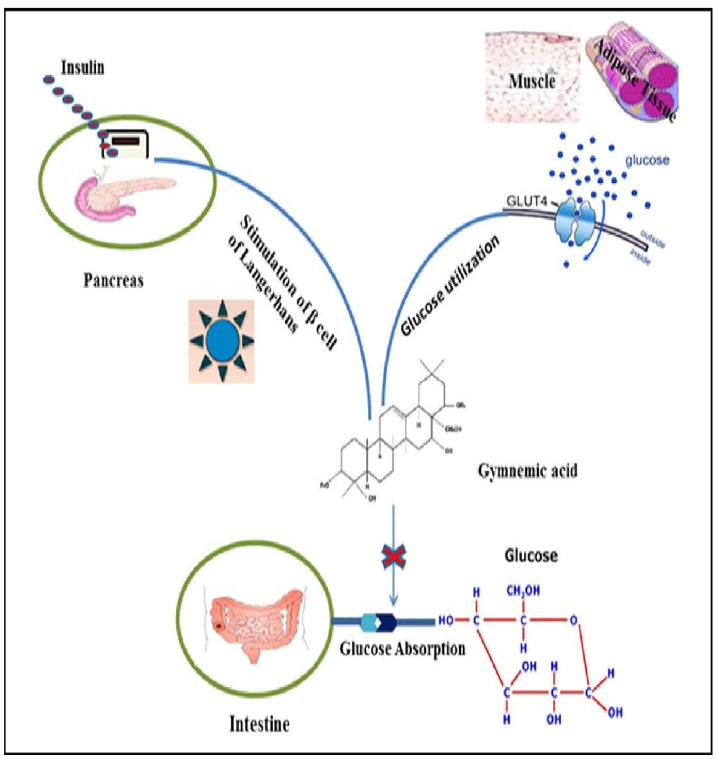

Fig. 3. Hypoglycemic mechanism of gymnemic acid

3.2 Mechanism of Action

G. sylvestre leaves exert its hypoglycaemic effect because gymnemic acid ($C_{4}0H_{68}O_{14}$) present in it, is a pentacyclic triterpenoid that exhibits anti-diabetic effect by suppressing the taste of sweetness, reduces the craving for sweet food, lowering the plasma glucose and insulin levels among diabetic patients and also known to inhibit intestinal glucose absorption [14,20]. Many experimental and clinical studies have documented the insulinotropic effect of the plant. A well explanatory mechanism process of gymnemic acid in its hypoglycemic effect has been reported in Fig. 3 [21].

Alcoholic extraction of *G. sylvestre* (GS) leaves produced a dose-dependent increase in insulin release from various β-cell lines like HIT T15, MIN6 and RINm5F. Insulin release depends upon the membrane permeability of beta cell lines [22]. There is a reverse relationship between GS extract and insulin secretion which is partially dependent on the presence of extracellular Ca^{2+} as GS extract increases the β-cell Ca^{2+} levels. This means even low concentrations of GS isolates stimulate insulin secretion *in vitro* without affecting the viability of β-cell. Water-soluble alcoholic extract of gymnema leaves has reported regenerating the β-cells in pancreatic islets of STZ-induced diabetic rats [4].

Extract of *Gymnema sylvestre administere*d at 400mg/kg dose among to streptozotocin (STZ) induced diabetic rats for 40 days showed significant recovery of damaged β-cells in diabetic rats [2]. Lower molecular weight GS isolates have been reported to reduce blood glucose levels without altering the insulin sensitivity of target tissues in diabetic animal models [23]. On oral administration of GS extract in the amount of 1g/day for 60 consecutive days among type II diabetic patients induced a significant increase in circulating insulin and C-peptide which resulted in a significant reduction of fasting and post-prandial blood sugar levels [24]. Similarly, the intervention of gymnema leaf powder (6 gms in 3 divided doses for 1 month) showed blood glucose controlling potential [25].

GS extracts have also reported for increasing the regeneration of pancreatic islet cells to enhanced enzyme-mediated uptake of glucose. This process decreased glucose and fatty acid assimilation in the small intestine and interferes in the ability of receptors in the mouth and intestine to the sensation of sweetness. Gymnemic acid has been found to interact with glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a key enzyme in the glycolysis pathway [26]. The acyl moieties present in gymnemic acids play an important role in the GA-induced smearing of GAPDH and G3PDH and play an integral role in the anti-hyperglycemic activity of GA derivatives [23]. A moderate reduction in fasting blood glucose level (11%) and post-prandial blood glucose level (13%) of diabetic patients has been observed on the administration of 400mg of GS extract twice. Mild decrease (0.6-0.8%) in glycated hemoglobin (HbA1c) was also reported [27]. It has also reported that the combination of *Gymnema sylvestre* extract and hydroxycitric acid with niacin-bound chromium showed a significant reduction in weight and body mass index and promoted a healthy lipid profile [16].

3.3 Cinnamon

Cinnamon is the most frequently used spice in herbal remedies. The genus *Cinnamomum* consists of 250 species of aromatic evergreen trees and shrubs. The term *Cinnamomum* is derived from Greek *kinnamomon,* which means "sweet wood" (Fig. 4) [28]. The cinnamon of commerce is the dried inner stem-bark of a small evergreen tree, is native to tropical southern India and Srilanka. Mainly there are two types of cinnamon, common cinnamon (dalchini) or true cinnamon (*Cinnamomum zeylanicum*) and cassia (*Cinnamomum aromaticum*) [29]. Cinnamon is known for its anti-diabetic, anti-oxidant, anti-inflammatory and anti-bacterial properties [30,31]. Broadly monoterpenes, sesquiterpenes and phenylpropenes are the major volatile components present in all parts of cinnamon. Cinnamaldehyde (Fig. 5) and procyanidin are the main constituents in cinnamon bark oil showing anti-diabetic potential [32]. Extracts of C. cassia are reported to be superior to the extract of C. zeylanicum in insulin secretion and anti-diabetic potential [33].

Fig. 4. Cinnamon bark powder

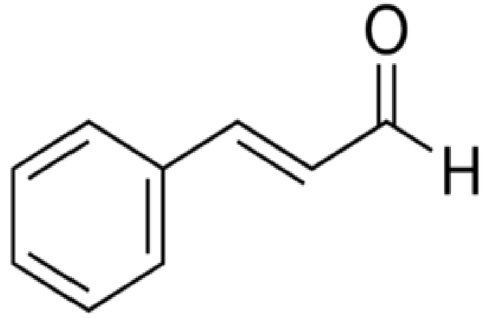

Fig. 5. Molecular structure of cinnamaldehyde

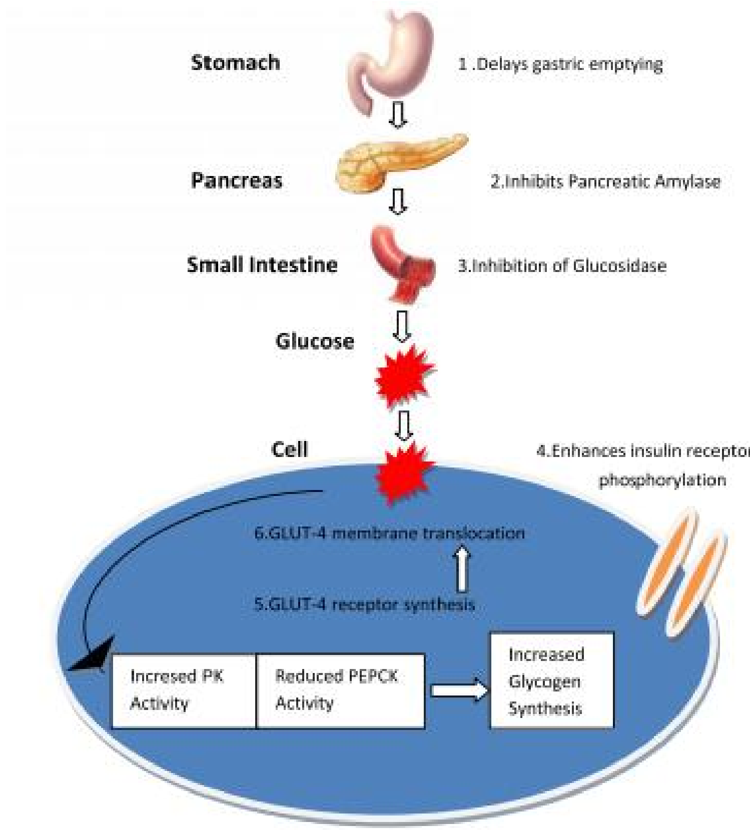

Fig. 6. Hypoglycemic mechanism of cinnamon

3.4 Mechanism of Action

Intake of cinnamon among type II diabetic subjects has shown modest decrease in blood glucose levels in the same order of magnitude as for metformin [34]. Cinnamaldehyde (CND) is the active compound of C. zeylanicum stem bark, has been shown to possess antihyperglycemic activity, inhibition of tumor cell proliferation, antioxidative and anti-inflammatory activities in suppressing nitric oxide production by LPS-stimulated macrophages [35]. As showed in Fig. 6 the chloroform extract of cinnamaldehyde (CND) induced in STZ treated diabetic rats (20 mg/kg) for 2 months showed an enhanced insulin release. The insulinotropic effect of CND was due to an increase in glucose uptake through glucose transporter (GLUT4) translocation in peripheral tissues [35]. CND treatment shows significant improvement in altered enzyme activities of pyruvate kinase (PK) and phosphoenol-pyruvate carboxykinase (PEPCK) and their mRNA expression levels, as these are major enzymes involved in glucose homeostasis [36].

The cinnamon extract was also shown to have insulin receptor-mediated response through its tetrameric protein consisting of two identical extracellular α-subunits that bind insulin as well as two identical transmembrane β-subunits that have intracellular tyrosine kinase activity [37]. Insulin binds to the α-subunit of the receptor and the β-subunit tyrosine kinase gets activated, resulting in autophosphorylation of β-subunit tyrosine residues ultimately, the process increases insulin sensitivity [38]. Cinnamtannin B1, a proanthocyanidin isolated from the stem bark of Ceylon cinnamon, activates the phosphorylation of the insulin receptor β-subunit on adipocytes as well as other insulin receptors [39]. The inhibitory effect is mainly attributed to anti-glycation activity of its phenolic components [15].

A randomized control trial conducted over 60 diabetic patients were provided with different doses (1,3 and 6 g) of cinnamon showed significant decrease in fasting blood glucose level (18 to 29%) and total cholesterol level (12-26%) at the end of 40 days trail [40]. A study showed a dose-dependent, reversible inhibitory effect of cinnamon extract on α glucosidase activity reported that the enzyme remains intact even after the removal of inhibitor, thus probably decrease the risk of hypoglycemia due to chronic malabsorption of carbohydrate [12]. In vitro evaluation of methyl-hydroxyl chalcone polymer (MHCP), active ingredient have shown to increase the GLUT4 myc (master regulator of cell cycle) translocation by 1.5 and 2 fold on the cell surface of L6-GLUT4myc cells when treated with 62 and 125 μg/ml of cinnamon extract respectively [41].

3.5 Sea Buckthorn

Hippophae rhamnoides commonly known as sea buckthorn (SBT) (Fig. 7) is a mountainous shrub widely spread in the region of Eastern Asia and Russia. In India, mainly found in the Himalayan region, therefore also known as “Himalayan Berry”. Sea buckthorn is a deciduous shrub used in various life-saving drugs and health tonics, as it contains a variety of essential fatty acids and antioxidants including vitamin C, vitamin E, anthocyanins, carotenoids, organic acids, dietary minerals, β-sitosterol, polyphenolic acids and palmitoleic acid (Fig. 8) [42,43]. In the last few decades, SBT has gained worldwide recognition for its potential bioactive compounds as the fruit oil of SBT was used to protect people from nuclear radiation from an explosion at a nuclear plant at Chernobyl, Ukraine in 1986 [44]. SBT fruit extracts, fruit oil, seed oil, and leaf extracts have been reported for several pharmacological activities, such as anti-oxidant, immune-modulatory, anti-inflammatory, anti-cancer, anti-diabetic and anti-ulcer potential [45].

Fig. 7. Sea buckthorn fruit plant

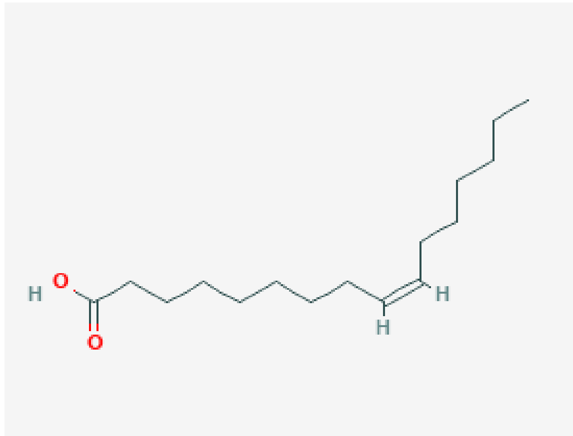

Fig. 8. Molecular structure of palmitoleic acid

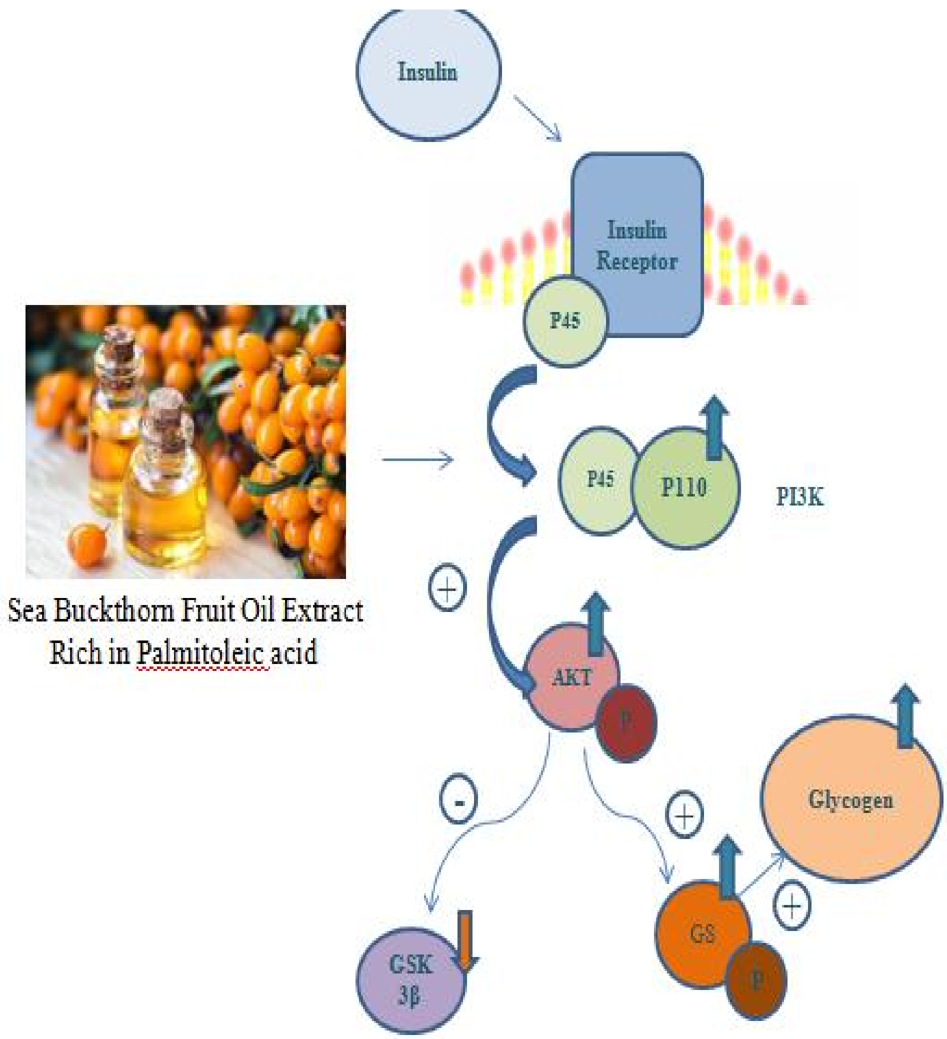

Fig. 9. Hypoglycemic mechanism of palmitoleic acid

3.6 Mechanism of Action

Palmitoleic acid (POA) a monounsaturated fatty acid, displays the potential to regulate various physiological processes, such as blood glucose metabolism, metabolic syndrome and the inflammatory response [46,47,48]. Sea buckthorn fruit oil is rich in palmitoleic acid, which is expected to be the major contributor of its hypoglycemic potential. In addition to improving glucose homeostasis and insulin resistance, Palmitoleic acid has been reported to enhance the Akt (Protein Kinase B) activation and increases plasma membrane GLUT1 and GLUT4 protein contents through AMPK or MAPK signaling pathways in skeletal muscle and adipocytes [49]. SBT fruit oil extract has shown as shown in Fig. 9, a dose-dependent increase in the glucose uptake [50] in IRHepG2 cells at the concentration of 400µg. SBT fruit oil extract promoted the expression of phosphatidylinositol-3-kinase (PI3K) and glycogen synthesis (GS) while inhibited the expression of glycogen synthesis kinase-3β (GSK-3β).

A dose-dependent decrease in blood glucose levels along with improved pancreatic tissue and β cell regeneration has also been reported among STZ induced diabetic rats after oral administration of SBT at two doses (1 and 2 ml/kg), for 3 weeks [51]. Aqueous extract of SBT seed residue showed a significant hypoglycemic effect among rat models with a reduction in the serum insulin levels of the diabetic control rats lowered by 43.59% than those of the normal control rats and the serum insulin concentrations in the residue supplemented diabetic rats were not affected significantly after the treatment period [52]. SBT administration has also decreased HbA1c levels and improved glucose tolerance in diabetic rats. Concentrated dioxide-extracted berries of sea buckthorn suppressed the post-prandial peak insulin response, though stabilizes the post-prandial hyperglycemic effect [53]. L-type Ca^{2+} channel-mediated insulin release from pancreatic β cell of rats has been reported which also neutralizes the ROS (Reactive Oxygen Species) produced through hyperglycemia [54]. Flavones extracts from the sea buckthorn plant has shown to improve insulin sensitivity by suppressing the elevated hyper-insulinemia and dyslipidemia among sucrose fed rats [55].

Apart from hypoglycemia, Sea buckthorn has lipid-lowering properties as reported to decrease the triglyceride levels in diabetic rats so it has been considered as an alternate process in the prevention of diabetic complications through improving dyslipidemia [56]. Reduced glutathione (GSH) could protect the cells from the toxic effects of reactive oxygen species or peroxidative damage *in vivo* and therefore contribute to the elimination of organic peroxides and foreign oxidative substances [57,58]. Aqueous extract of SBT has shown to decrease the activity of serum glutathione disulfide (GSSG-R) and the level of serum reduced GSH, whereas there was a notable increase in the activity of serum SOD (superoxide-dismutase) in STZ induced diabetic rats [52].

3.7 Mulberry Leaves

Mulberry (*Morus*) belongs to the Moraceae plant family and includes several species, such as the black mulberry (*M. nigra*), red mulberry (*M. rubra*), and white mulberry (*M. alba)* are distributed in tropical, subtropical regions throughout the world. However, the majority of plants can be found in Asian countries like China, Japan, Korea, and India [59]. Mulberry is a multi-functional plant, being an excellent source of nutrients and phytochemicals, now a day's recognized as a functional food [60]. Traditionally usage of various parts of the mulberry tree including root bark, leaves and fruits can be seen in the treatment of fever, cough, hyperlipidemia, hypertension and hyperglycemia [61]. Mulberry leaves (Fig. 10) are of *M. alba* has traditional usage to feed silkworms and also used in traditional Chinese and Thai medicine to treat diabetes [62]. The main active ingredients in mulberry leaves are flavones, polysaccharides and alkaloids and 1-deoxynojirimycin (DNJ) (Fig. 11) [63,64].

3.8 Mechanism of Action

A single administration of mulberry leaves have shown to suppress the peak level and the incremental area under the curve (iAUC) of glucose excursion, after the carbohydrate loading [65,66]. While, long-term administration of mulberry leaves have shown to normalize the levels of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fructosamine and insulin indexes of diabetic animals to nearly normal values [67]. 1-deoxynojirimycin (DNJ) is regarded as the most potent anti-hyperglycaemic compound of mulberry leaves. As DNJ and glucose have similar structures, it can competitively block the active site of polysaccharide-degrading enzymes in the digestive tract. In vitro studies demonstrated the inhibitory effect of a DNJ-concentrated fraction against enzymes in the a-glucosidase class and the strongest inhibition was seen on sucrose enzyme) which ultimately inhibits the glucose digestion and absorption [66,68]. The main active ingredients apart from DNJ, in mulberry leaves, are flavones, polysaccharides, and alkaloids. The hypoglycemic effect of alkaloids is due to polyhydroxy alkaloids, known as α- glycosidase inhibitors which inhibit the α-glucosidase in the small intestine [69,70]. Hot water extract of mulberry leaves have shown a significant inhibitory effect against α-glucosidases, sucrase and maltase enzymes in Caco-2 cell culture and considered to have the potential to be consumed as antidiabetic herb tea [62].

Apart from hypoglycemic effect mulberry leaves active components have shown (in Fig. 12) protective effect on liver and kidney injury in db/db mice through insulin receptor and TGF-β/Smads signaling pathway which improve insulin resistance and oxidative stress-induced renal fibrosis [63].

As the administration of mulberry leaf polysaccharides and alkaloids showed a significant decrease in fasting blood glucose levels and the ratio of mALB/Cre (microalbumin/creatinine) in urine decreased and improved the renal cystic epithelial thickening. Mulberry leaf flavones and alkaloids also possessed a significant effect on reducing the levels of ALT (alanine aminotransferase) and AST (aspartate amino-transferase). Mulberry may inhibit kidney injury by inhibiting the expression of connective tissue growth factor (CTGF) and related genes [71]. Flavonoids of mulberry leaves have been reported to decrease the free fatty acid levels, increase the glucose consumption, levels of adiponectin and leptin in a dose-dependent manner [72]. Mulberry leaf extracts flavonoids alleviated the glycolipid metabolic abnormalities in 3T3-L1 adipocytes IR model, and the effect was associated with the activation of IRS1/PI3K/AKT pathway, the suppression of FAS, and the up-regulation of membrane transfer capacity of GLUT4 [73].

Fig. 10. Mulberry leaves

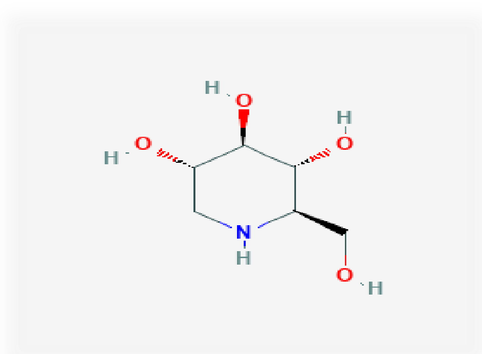

Fig. 11. Molecular structure of 1-deoxynojirimycin

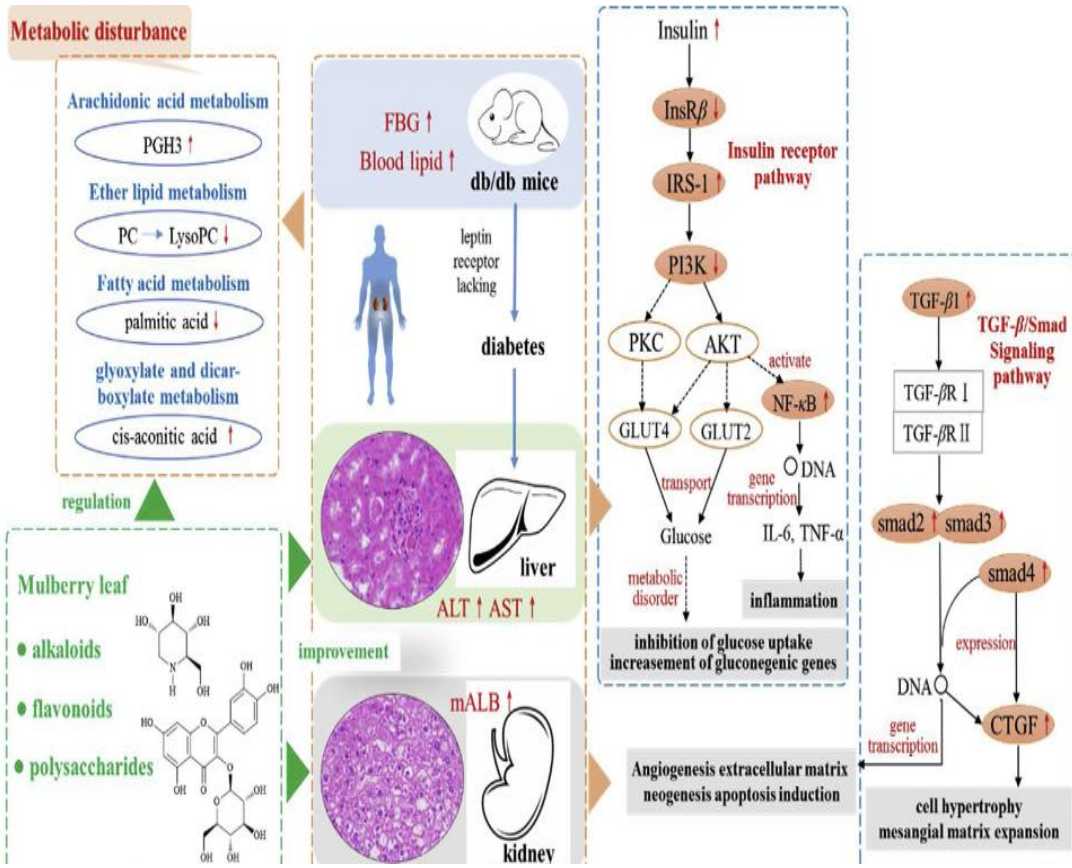

Fig. 12. Hypoglycemic mechanism of mulberry leaf alkaloids, flavones and polysaccharides

Inclusion of the dried leaf powder of mulberry leaves (*Morus indica L.*) at 25% level in the diet of diabetic rats for 60 days showed a significant decrease in blood glucose level and glycosylated haemoglobin (HbA1c) with decreased activity of serum enzymes like lactate dehydrogenase, alkaline phosphatases, glutamate pyruvate transaminase (GPT) and glutamate oxaloacetate transaminase (GOT) [74]. Treatment with dried mulberry leaf powder at 25% of the diet of STZ induced rats for 8 weeks remarkably controlled hyperglycemia and glycosuria and showed reversed alterations in gluconeogenic substrates that significantly reduced the serum pyruvic and lactic acid levels [75]. Even the ethanolic extract of mulberry leaves showed a reduction in blood glucose levels of among diabetic Wistar rats after an oral dose of 400 mg/kg/ body weight/day. Furthermore, it was proved that the plant extract can restore the diminished number of β cells by increasing the amount of the mentioned components and sensitize the insulin receptor to insulin or by stimulating stem cells of the islets of Langerhans [76]. Evaluation of hypoglycemic effect of mulberry leaves among type 2 diabetic patients that the ingestion of 1 g of mulberry extract along with 75 g sucrose in 500 ml hot water remarkably reduces the blood glucose level over the first 120 min in the experimental group [77].

3.9 Fenugreek

Fenugreek (Trigonella foenum-graecum) (Fig. 13) is an annual herb belonging to leguminous family of Fabaceae, is native of western Asia and southeastern Europe [78]. It is used as a condiment in the Indian sub-continent and Mediterranean countries, commonly being known as methi [22]. Its seeds and leaves have been reported to have anti-diabetic and hypo-cholesterolemic potential [79]. The major bioactive compounds present in fenugreek seeds known for the anti-diabetic effect are diosgenin (3b-hydroxy-5-spirostene), 4-hydroxyisoleucine (Fig. 14) and soluble dietary fibers along with major alkaloid trigonelline [80].

Fig. 13. Fenugreek seeds

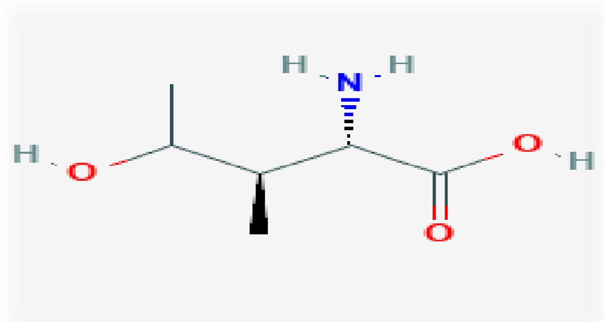

Fig. 14. Molecular structure of 4-hydroxyisoleucine

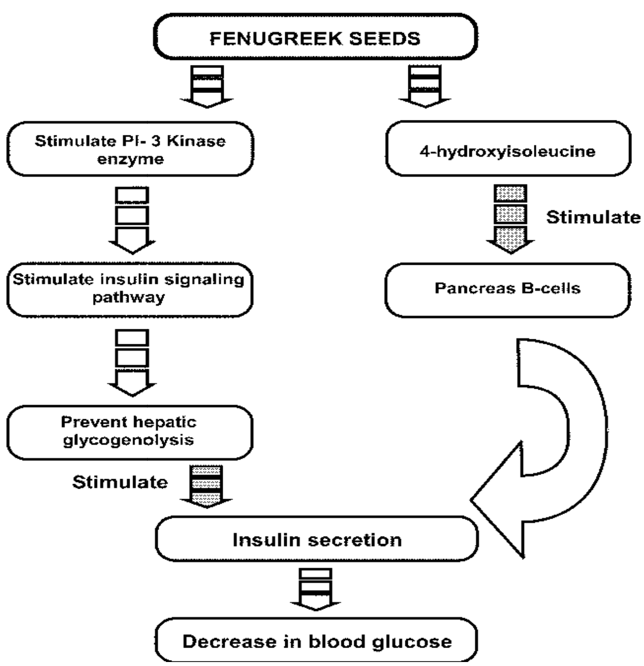

Fig. 15. Hypoglycemic mechanism of fenugreek seeds

3.10 Mechanism of Action

Fenugreek seed extracts have been reported to exhibit hypoglycemic potentials by producing a delay in gastric emptying time and suppresses the release of gastric inhibitory peptides and insulinotropic hormones [38,81]. Diosgenin, the major saponin aglycone has the potential to regenerate the pancreatic β cells thus stimulate insulin secretion and enhance the glucose uptake [82,83]. The majority of the free amino acid present in fenugreek is mainly, 4-hydroxyisolucine, which is the branched-chain amino acid derivative [84], which is known for glucose -dependent insulin secretion in vitro and in vivo [85]. Seeds of fenugreek have been reported to decrease insulin levels (7%) and increase insulin sensitivity (56%) along with the reported reduction in serum triglyceride levels up to 53% [86]. A study observed that administration of 4-hydroxyisolucine among diabetic rats for 6 days has shown to reduce the basal hyperglycemia levels and basal insulin levels resulting in improvement in glucose tolerance [87]. As shown in Fig. 15, it has been reviewed that 4-hydroxyisolucine stimulates insulin secretion from pancreatic β-cells, simultaneously seed compound stimulates the Pi-3 Kinase enzyme to promote insulin signaling pathway and prevent hepatic glyconeolysis as well as promote insulin secretion, ultimately lead to the hypoglycemic effect [13].

Apart from these effects, fenugreek seeds have also shown to enhance glycemic control by inhibition of lipid and carbohydrate hydrolyzing enzymes in the digestive system [88]. Galactomannan is known to reduce glucose uptake through acting as a physical barrier [89,90]. In the in vitro studies, oral administration of plant extract showed dose-dependent decrease in blood glucose level of diabetic rats [91]. A significant reduction in the fasting blood glucose level of diabetic rats was reported after the administration of 300 mg seed powder for 21 days. The reduction in the fasting blood glucose levels has been reported due to reverse activity of gluconeogenic, glycolytic, lipogenic enzymes in the liver and kidney of diabetic rats [92]. A meta-analysis on the effect of traditional herbal medicines highlighted that fenugreek consumption has improved glycated hemoglobin (HbA1c) levels among people with type II diabetes [93]. Similarly, the addition of 20g/day of fenugreek seeds for 16 weeks showed a significant decrease in postprandial glucose levels of type II diabetic patients [94].

Inclusion of fenugreek seed powder in the daily diet of diabetic patients improved the glucose tolerance and serum level of insulin [22]. Similarly, the administration of defatted seeds (25g for 3 weeks) produced significant improvement in glucose tolerance and also decreased serum cholesterol and 24-hour urinary glucose output [95]. Apart from these, the administration of fenugreek seeds has shown to have antioxidant activity [96], normalized the creatinine kinase activity in heart, reduced renal and hepatic glucose 6 phosphatase and fructose 1,6 biphosphatase enzyme activity [97]. In addition, seeds also showed the reduction in lipid-peroxidation and increased levels of GSH showing its potential to reduce diabetes-related complications.

The phyto-compounds present in above discussed traditional medicinal plants have shown to have anti-diabetic effect through various mechanisms. A summarized content of the plant's major phyto-compounds and their mode of action resulting in anti-diabetic effect have been discussed in Table 1.

Table 1. Major phyto-compounds and their mode of action for anti-diabetic effect

Traditional Medicinal Plant (Scientific Name)	Phyto-compounds with Anti-diabetic potential	Mode of Action	Reference
Gurmar (*Gymnema sylvestre*)	Gymnemic Acid	Suppresses the taste of sweetness reduces the craving for sweet food	[20]
		Inhibit intestinal glucose absorption	[14]
		Recovery of pancreatic β-cells and Increase release of insulin from β-cells	[22, 4, 2]
		Inhibtion of enzyme activity	[26, 23]

Traditional Medicinal Plant (Scientific Name)	Phyto-compounds with Anti-diabetic potential	Mode of Action	Reference
Cinnamon (*Cinnamomum*)	Cinnamaldehyde Cinnamtannin B1	Enhances insulin release and increases glucose uptake	[35]
		Alters activity of enzyme involved in glucose homeostasis	[36]
		Activates the phosphorylation of the insulin receptor β-subunit on adipocytes	[39]
		Anti-glycation activity	[15]
		Inhibitory effect in on α glucosidase activity	[12]
Sea Buckthorn (*Hippophae rhamnoides*)	Palmitoleic acid	Enhance the Akt activation and increases plasma membrane GLUT1 and GLUT4 protein contents through AMPK or MAPK signaling pathways in skeletal muscle and adipocytes	[49]
		Improves insulin resistance	[49]
		Increase glucose uptake by promoting expression of PI3K and glycogen synthesis and inhibits the expression of glycogen synthesis kinase-3β (GSK-3β)	[50]
		Regeneration of β –cells	[51]
Mulberry Leaves (*Morus*)	Flavones, Polysaccharides Alkaloids 1-deoxynojirimycin	Blocks the active site of polysaccharide-degrading enzymes in the digestive tract	[66, 68]
		Inhibits the α-glucosidase activity in the small intestine	[62, 69, 70]
		Increase the glucose consumption	[72]
		Regeneration of β –cells and improves insulin sensitivity	[76]
Fenugreek (Trigonella foenum-graecum)	Diosgenin 4-hydroxyisoleucine Galactomannan	Delays gastric emptying time	[38]
		Suppresses the release of gastric inhibitory peptides and insulinotropic hormones	[81]
		Regenerates pancreatic β cells thus stimulate insulin secretion and enhance the glucose uptake	[82, 83]
		Increase insulin sensitivity	[86]
		Stimulates the Pi-3 Kinase enzyme to promote insulin signaling pathway and	[13]

Traditional Medicinal Plant (Scientific Name)	Phyto-compounds with Anti-diabetic potential	Mode of Action	Reference
		promote insulin secretion	
		Inhibits activity of lipid and carbohydrate hydrolyzing enzymes in digestive system	[88]
		Galactomannan acts as physical barrier and reduce glucose uptake	[89, 90]

4. CONCLUSION

Plants have always been an important part of research in finding the new and alternate approach in the treatment of various human diseases without any side effects. Among hundreds of plants known for their anti-diabetic potential, only a few of them have been reported with scientific evidence in clinical and animal studies. India is facing the period of diabetic explosion, which makes it furthermore important to search the alternate approaches in its treatment other than conventional remedies. Various phyto-compounds present in these medicinal plants have a different degree of hypoglycemic effect. Some of them have shown potential anti-diabetic effects such as gymnemic acid present in *Gymnema sylvestre* can inhibit the intestinal glucose absorption [14]. Cinnamaldehyde in cinnamon 35 and palmitoleic acid in sea buckthorn have shown to enhance glucose uptake [50]. 1-deoxynojirimycin (DNJ) found in mulberry leaves have been reported to inhibit the enzymatic activity of α-glucosidase [63] and diosgenin in fenugreek has a role in the regeneration of pancreatic β-cells [83] thus showing their anti-diabetic potential.

Though the multifactorial pathogenicity of diabetes demands a multi-model therapeutic approach, the use of these ethno medical approaches is practical and cost-effective. Since ancient times we have been using various parts of some traditionally grown plants for the treatment and prevention of diabetes. In this paper, an overview the possible scientific mechanisms of action of the bioactive phyto-compounds in various plants to control the blood glucose level were presented. The understanding of the possible mechanism of action can help the future researchers in optimization and standardization of the dose of these phyto-compounds for controlling diabetes mellitus.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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