Agriculture

A review on anti-diabetic activity of traditional medicinal plants from Jammu and Kashmir

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Abstract

Diabetes is a serious human ailment which afflicts various walks of life and raises concerns of health care industry in recent time. Instead of the availability of multiple treatment regimes for managing diabetes, the complications associated with it are still costly to be managed by available drugs. Natural products have been established by extensive research efforts for their anti-diabetic properties and emerge as potential sources for discovering new drugs. The preference is given for developing herbal formulations due to low cost and lesser side effects. There is still a great demand for developing new drugs of plant origin with anti-diabetic activities, due to the lack of scientific validation for majority of plant derived potential anti-diabetic agents. India is a vast reserve and a home of many medicinal plants with proven antidiabetic properties. In India, the state of Jammu and Kashmir due to wide range of elevations and diverse biogeography produce high diversity of vegetation especially in terms of medicinal plant wealth. Medicinal plants like *Berberis lyceum, Aegle marmelos, Artemisia sp, Allium sp, Tinospora cordifolia, Trigonella foenum,* etc. are the cultivars of Jammu and Karshmir with proven antidiabetic properties. In this review article, we reviewed the published studies describing the medicinal plants from Jammu and Kashmir for improving diabetes and associated complications. The detailed action mechanisms of phyto-active constituents of these medicinal plants are also described. However, the scientific validation of plant origin anti-diabetic drugs is required through in vitro and in vivo studies for their commercial exploitation.

Keywords: medicinal plants, diabetes, herbal drugs, natural products, jammu and kashmir, india

Introduction

Diabetes mellitus emerges as a serious threat to the health of mankind being most prevalent throughout the world. The disease is associated with the imbalance in the metabolism of protein, lipids and carbohydrates and is thus a complex and heterogeneous group of metabolic disorders predominantly hyperglycemia. WHO describe it as an a chronic disease which is caused by acquired or inherited deficiency in pancreas production of insulin thereby increasing the glucose concentration in the blood and damaging the systems of body particularly nerves and blood vessels (WHO, 2020). The recent data provided by International Diabetes Federation (IDF) Atlas highlights that among adults approximately 463 million people are currently diabetic and by 2030 the estimates will reach upto 578 million adults and by 2045 will reach 700 million (Diabetesatlas,2020). The inefficiency of therapeutic strategies makes diabetes mellitus management a global concern. The current therapeutic strategies centered on the use of either oral hypoglycaemic agents or/and insulin, however, the associated complications with these therapies, high cost, limited tolerability and side effects decreases their acceptance. For this possible reason now a days the common people are shifting from allopathic system to Ayurveda for management of diabetes.

The herbal drugs possessing multiple beneficial properties and enriched in many phytoconstituents have been used since ancient times for treating various diseases as medicines. As they are accomplished with natural occurrence, more efficacy and lesser side effects, the traditional herbal medicines are generally considered to be safe (Prabhakar, 2014). There is a long history in India for using medicinal plants to manage diabetes. Around 800 plants have been reported by World ethnobotanical information, to be used for controlling diabetes mellitus, of which the experimental proofs are available for only 410 plants for being anti-diabetic and for only 109 plants, the anti-diabetic mechanism is known (Prabhakar, 2014). Some Indian states like Jammu and Kashmir are the home for many important medicinal plants because of the presence of variable altitudes. The use of herbs for treating diabetes is considered more advantageous as they cause much lesser side-effects. These herbal medicines reduce the blood glucose level and protect β-cells from harmful effects of diabetic condition by acting through different mechanism (Jeeva and Sheebha, 2014).

The focus of this review is on the plants native of Jammu and Kashmir, India which are reported for their anti-diabetic activity in literature. An emphasis is given on the phytoconstituents and action mechanism of these plants implicated in managing diabetes (Table 1).

Table 1: List of plants n'ative to Jammu and Kashmir innmanagement and treatment of diabetes

S. No.	Plant	Family	Part used	Phytochemicals	Mechanism of action	Reference
1.	*Aegle marmelos*	Rutaceae	Shoot and leaves	Scopoletin, Aegelin, Sitosterol	• Increase peripheral glucose utilization • Hepatic glycolysis correction • Decreasing the gluconeogenic formation	Upadhya *et al*., 2004; Nigam and Nambiar,2019
2.	*Allium Species*	Amaryllidaceae	Onion	Quercetin, Quercetin-4′-O-glucoside	• α-amylase activity inhibition • α-glucosidase inhibition • Inhibit GLUT2	Jaiswal and Rizvi, 2017; Schulze *et al*., 2015
3	*Artemisia species*	Asteraceae	Shoot and leaves	Thujyl alcohol, α- -and ß-Thujones, Cadinene, Azulenes,	• Insulin-sensitizing action • Activate adenosine monophosphate-activated protein kinase • Increased free glucose transporter	Daradka and Abas, 2014; Issa and Hussen Bule, 2015
4	*Berberis lycium*	Berberidaceae	Leaves, fruits and roots	Berberine	• Up-regulate signaling from insulin receptor • Blood lipid regulation • Reduce inflammatory responses	Cao and Su, 2019
5	*Catharanthus roseus*	Apocynaceae	Twigs and leaves	Vindoline	• Stimulation of β cell • Antioxidant activity • Decreased caspase 9 expressions	Oguntibeju *et al*., 2019
6	*Malus domestica*	Rosaceae	Fruit	Quercetin	• Delay intestinal glucose absorption	Boyer and Liu, 2004
7	*Mimosa pudica*	Fabaceae	stem and roots	Mimosine	• Free radical scavenging activity (antioxidative) • Inhibiting activities of α-glucosidase and α-amylase	Tunna *et al*., 2015; Sutrisna *et al*., 2015
8	*Syzygium cumini*	Myrtaceae	fruits, leaves and seeds	anthocyanins, glucoside, ellagic acid, isoquercetin, kaemferol and myrecetin	• Maltase and α-glucosidase inhibiting activity • Stimulated insulin release from cells of Langerhans	Shinde *et al*., 2008; Sharma *et al*., 2011
9	*Tinospora cordifolia*	Menispermaceae	Stem	Berberine, Tembetarine, Palmatine, Tinosporin, Magnoflorine	• Inhibit the activity of α-glucosidase enzyme and glycolysis • Ameliorate the activity of GLUT1/GLUT3 transporters • Inhibit gluconeogenesis • Exert insulin releasing/insulin sensitizing effects	Chougale *et al*., 2009; Patel *et al*., 2011; Joladarashi *et al*., 2014
10	*Trigonella foenum*	Fabaceae	Seeds	Trigonelline	• Stimulating insulin secretion • Increase pancreatic β cell's regeneration • Inhibiting glycogen synthase kinase activity • Inhibit GLUT-4 translocation	Zhou *et al*., 2011; Maurya *et al*., 2014; Roshana *et al*., 2018

Aegle marmelos

Aegle marmelos is also known as Bael or Billipatra in India and had been in use since prehistoric or Vedic times for treating various medical ailments. The beneficial effects of the plant has been described by Charak in an ancient medical-treatise called Charak Samhita where they called it as "Rasayana" for its beneficial effects in curing diseases. The plant especially shoots and leaves are also used in Indonesia as green vegetable. The antihyperglycemic effects of the leaf extract of *Aegle marmelos* are well known. The anti-diabetic effects of *Aegle marmelos* are also well reported in Ayurvdic, Siddha and Unani system of medicine in India, Bangladesh and Sri Laka (Miyazaki *et al*., 2007).

Significant improvement in blood glucose level was observed after orally feeding the leaf extract of *Aegle marmelos* (250-500 mg/Kg body weight) for one to two months to hyperglycemic glucose fed rats (Rathore, 2009). Oral administration of the leaf extract of *Aegle marmelos* for 14 consecutive days at doses 50, 70, 90and 100 mg/kg body weight was also found to induce hypoglycemic effect in both female and male Wistar rats. No acute toxicity as well as high level of drug safety was observed with the leaf extract of *Aegle marmelos* (Sachdeva *et al*., 2001). The observed hypoglycemic effects of *Aegle marmelos* are due to the increase in peripheral glucose utilization, hepatic glycolysis correction and decreasing the gluconeogenic formation (Upadhya *et al*., 2004). The supplemention of *Aegle marmelos* juice (20 g/100ml) in a randomized control trial for 60 days was also showed to improve all biochemical parameters in type 2 diabetes mellitus subjects. The phytoactive components like scopoletin, aegelin and sitosterol can be possibly responsible for management of diabetes (Nigam and Nambiar, 2019).

Allium species

Allium cepa also known as onion was found to possess potent free radical scavenging activity (IC50= 4.49±0.59 µg/ml) and anti-glycalting potential (IC50= 16.8±5.0 µg/ml) in a study comparing 25 herbs (Kim and Kim, 2003). The outer layers of onions were also found to possess potent α-amylase activity inhibition and rat intestinal α-glucosidase inhibition activity (IC50 values 1.27 mg/ml) (Jaiswal and Rizvi, 2017). The extract of onion was found to inhibit in concentration-

dependent manner the expression of both glucose transporter 2 (GLUT2) and sodium-glucose linked transporter (SGLT1) in Xenopus laevis oocytes where the onion flavonols aglycone quercetin and quercetin-4′-O-glucoside were found responsible for highest suppression of GLUT2 and SGLT1 (Schulze *et al*., 2015). The ethanolic *Allium cepa* extract increases the GLUT4 mediated glucose uptake in dose dependent manner in L6 myotubes by exerting insulin like activities like increasing Akt, insulin receptor substrate-1, and insulin receptor-β phosphorylation as well as GLUT 4 translocation to the cell surface (Gautam *et al*., 2015).

The hypoglycemic activity of onion and its phyto-constituents have been evidenced in multiple studies. A significant reduction in blood glucose level was observed in sucrose fed (2 g/Kg) male Sprague-Dawley rats after feeding them with onion skin ethanolic extract or an active phyto-constituent of onion, quercetin (both 0.5 g/kg); the effect is comparable to acarbose. A significant decrease in serum glucose levels as well as levels of TG, TC, LDL, ALP, AST and ALT along with increased HDL levels was observed in alloxan induced diabetic rats treated with *Allium cepa* aqueous extract for 21 days (100, 300 and 600 mg/kg daily doses (Ikechukwu and Ifeanyi, 2016). The supplementation of red onion extract as well as quercetin in C57BL/6J mice kept for 9 weeks on high-fat diet induced an augmentation of the expression of NT-PGC-1α and reduction in PGC-1α promoter methylation (Devarshi *et al*., 2017). Improved performance of reproductive system was observed in diabetic rats (streptozotocin induced) after orally feeding *Allium cepa* ethanolic seed-extract (200 mg/kg/day for 4 weeks (Fallah *et al*., 2017).

Artemisia species

In different animal diabetic models like high fat diet induced, alloxan induced or streptozotocin induced diabetic rats, the alcoholic as well as aqueous Artemisia species extract have been demonstrated to significantly induce hypoglycemic effect which is comparable to known hypoglycemic drugs like metformin, glibenclamide and repaglinide (Daradka and Abas, 2014). Among the different species of Artemesia, *Artemisia herba-alba* showed the maximum potency to decrease serum levels of glucose and produced only mild side-effects as compared to synthetic hypoglycemic drugs. The observed significant hypoglycemic activity have been credited to the presence of different phytoactive constituents like thujyl alcohol, α- -and ß-thujones, cadinene, azulenes, bisabolene, pinene, sabinene, and phellandrene in different species of Artemisia (Issa and Hussen Bule, 2015). Although the action mechanisms of these components in reducing blood glucose levels are not well defined but the presence of thujone which is the major phyto component of these group of plants, has been known to induce insulin-sensitizing action and thus hypothesized to be majorly responsible for reducing the levels of blood glucose. Thujone was also found to activate adenosine monophosphate-activated protein kinase and thereby increased free glucose transporter (insulin stimulated) (Daradka and Abas, 2014).

Berberis lycium

The inhabitants of Himalayan region have been using *B. lycium* Royle for treating diabetes and related disorders since traditional times. The leaves and fruits of *B. lycium* have been used to treat diabetes in Pakistan and south west region of Iran. Its roots soaked in water are also reported to be used for treating diabetes. The aqueous extract of *B. lycium* roots showed an antihyperlipidemic effect (Zain-Ul-Abidin *et al*., 2018). The alleviation of lipid profile and hyperglycemia have been observed in diabetic patients by leaf extract of *B. lycium*. The reduction in serum levels of glucose was also observed in both diabetic as well as normal rats by *B. lycium* root extract (Hussain *et al*., 2017).

The most bioactive compound found in *Berberis* species is Berberine which is a ammonium quaternary salt and belongs to alkaloids group benzylisoquinoline. Reports have suggested the effectiveness of Berberine against diabetes and related metabolic diseases (Wang H. *et al*., 2018). Berberine was found to improve metabolic disorders associated vascular remodeling and inflammation by inhibiting the activation of p38 MAPK, phosphorylation of ATF-2 and expression of MMP-2. The renal injury was also decreased and the weight of adipose tissue was diminished by Berberine's long-term treatment in hypertensive rats. The insulin receptor mediated signaling is upregulated which improved insulin-mediated vasodilatation in mesenteric arteries of diabetic rats. Regulation of blood lipid as well as glucose levels and reduced inflammatory responses were observed in patients with metabolic syndrome by Berberine administration (Cao and Su, 2019).

Catharanthus roseus

The plant of *Catharanthus roseus* has been used for managing and treating metabolic ailments like diabetes mellitus since ancient times (Kotakadi *et al*., 2013). This plant is enriched in indole alkaloids like vinblastine and vincristine which have also been successfully evaluated for anticancer therapy (Kotakadi *et al*., 2013). The alkaloid vindoline is mostly enriched in twigs or leaves of *C. roseus* and previous reports have demonstrated that its administration induced hypoglycemic effects in rats (Islam *et al*., 2009). Vindoline is also hypothesized to be the major component of *C. roseus* which is responsible for its antidiabetic activities (Islam *et al*., 2009). The mode of antidiabetic activity of vindoline is linked to the stimulation of β cell. The oral feeding of vindoline (20mg/Kg) to STZ (Streptozotocin) induced diabetic rats for 6 weeks was found to improve the ferric reducing antioxidant power in heart, reducing lipid peroxidation level and increasing SOD activity in kidneys. It also decreased caspase 9 expressions and restored renal parenchyma structure in diabetic rats (Oguntibeju *et al*., 2019).

Malus domestica

Malus domestica is also commonly known as Apple and is amongst the most nutrient-rich, culturally and economically significant fruit which is grown in temperate zones. The health benefits of apple are irreplaceable and they form important part of human nutrition, enriched in bioactive substances, increases immunity and stress resistance (Boyer and Liu, 2004). The enriched bioactive substances in apples which contributes to its health beneficial effects include polysaccharides, sterols, polyphenols, organic acids and pentacyclic triterpenes which are mainly enriched in the peel and pulp but vary in concentration (Padua *et al*., 2014).

The presence of high Quercetin amount in apples was found responsible for decreasing the risk of diabetes. The flavonoids enriched in apple juice were found to significantly decrease plasma glucose concentration and also affect the levels of hormones glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide and insulin which result in delaying intestinal glucose absorption (Boyer and Liu, 2004). The apple flavonoids from its peel were also found effective in cardiovascular disease and hypertension (Balasuriya and Rupasinghe, 2012).

Mimosa pudica

The ornamental plant *Mimosa pudica* is known specially for its nyctinastic and thigmonastic movements. The protective effect of *M. pudica* in various disorders like obesity, hepatitis, cancer, urinary infections and diabetes are also known. Mimosine an anticancer alkaloid is enriched in *M. pudica* along with other important secondary phytochemicals like flavonoids, steroids, tannins, glycosylflavones and triterpenes. These phytochemicals also impart to antidiabetic potential of *M. pudica*. The petroleum ether and ethanolic extract (600mg/Kg) of *M. pudica* leaves when fed for 7 days was found to significantly decrease the serum glucose level in alloxan (150mg/Kg body weight) induced diabetic rats (Sutar *et al*., 2009). The ethanolic extract (70%) of stem and roots of *M. pudica* also showed hypoglycemic effect and significantly lower the levels of blood glucose in Alloxan-induced diabetic rats when fed for 11 days (Sutrisna *et al*., 2015). The normalization of glucose level and body weight was observed in hyperglycemic rats (fructose fed rats) by crude methanol extract of *M. pudica* leaves. The histopathological studies of these rats revealed the recovery of liver damage and improvement in insulin levels by crude methanolic extract of *M. pudica* leaves (Sundaresan and Radhiga 2015). The methanolic extract of *M. pudica* was found to impart antidiabetic potential by free radical-scavenging activity (antioxidative) and inhibiting the activities of α-glucosidase and α-amylase (Tunna *et al*., 2014, 2015).

Syzygium cumini

S. cumini is also commonly called jambolan, jamun, black plum, Indian blackberry, java plum, Jamaica plum, Malabar plum, purple plum and damson plum. This species of the plant is generally found in Thailand, India, Madagaskar, Philippines, Africa, Caribbean and Tropical America. The fruits, leaves and seeds of *S. cumini* are known to possess multiple medicinal applications like improving reproductive dysfunction in, hypertriglyceridemia, cardiometabolic diseases and thrombotic disorders (Gaspar *et al*., 2020). The extract of S. cumini was also found to posses' potent maltase and α-glucosidase inhibiting activity (Shinde *et al*., 2008).

In diabetic rats the treatment with extract of *S. cumini* seed was found to exert a hypoglycemic effect which was also proven through oral glucose tolerance test (OGTT) in other diabetic animals (Proma *et al*., 2018). A significant reduction in the levels of blood fasting glucose was observed after oral administration of seed ethanolic extract of *S. cumini* (100mg/Kg) in alloxan-induced diabetes in rabbits. The normal morphology was observed in the aorta, liver and pancreas of treated animals by histopathological studies. The effectiveness and hyperglycemic activity of S. cumini extract was also observed in rats induced with diabetes by STZ injection (Sharma *et al*., 2008). The ethanolic extract of *S. cumini* was found to increase key enzyme activities of glycolytic enzymes and reduces gluconeogenesis. It also stimulated insulin release from cells of Langerhans and increased the content of glycogen in muscle and liver of treated animals (Sharma *et al*., 2011). The alleviation of diabetes associated secondary complications like nephropathy, neuropathy, peptic ulcer and gastropathy were observed by *S. cumini* extracts (Chaturvedi *et al*., 2009). The improvement in pancreatic function along with reduced hyperinsulinemia and glucose tolerance reversal was observed in monosodium L-glutamate-induced obese rats after receiving *S. cumini* leaves extract (500mg/Kg) for 30 days (Sanches *et al*., 2016). Decreased levels of fasting total cholesterol and triglycerides were also observed after treatment with *S. cumini* in alloxan-induced diabetic rats (Chagas *et al*., 2018). In clinical studies administration of S. cumini seed powder (12g) to 30 NIDDM patients for 3 months show moderate hypoglycemic effect (Sahana *et al*., 2010).

Tinospora cordifolia,

Tinospora cordifolia (family Menispermaceae), a herb native of India, Sri Lanka and Myanmar, has been reported for its anti-diabetic potential even in Ayurveda and is a constituent of various Ayurvedic formulations (Khare, 2008). The richness of phytochemicals especially alkaloids in *Tinospora cordifolia* like Berberine, Tembetarine, Palmatine, Tinosporin, Magnoflorine etc, are responsible for its anti-diabetic effects. The part of *Tinospora cordifolia* which is maximally investigated for its anti-diabetic activity is its stem. A significant reduction in blood fasting glucose was observed by *Tinospora cordifolia* methanolic extract in diabetic rats (STZ induced). Reports have also indicated the improvement in levels of C-peptide and insulin suggesting β cells regeneration in the pancreas. A polysaccharide isolated from *Tinospora cordifolia* stem's methanolic extract was also found to posses potent hypoglycemic activity and regenerate β-cell in STZ-induced diabetic rats (Rajalakshmi *et al*., 2016).

Tinospora cordifolia was found to inhibit the activity of α-glucosidase enzyme and glycolysis and this may be the possible action mechanism for its hypoglycemic activity (Chougale *et al*., 2009). *Tinospora cordifolia* stem's extract was found to stimulate glucose uptake on one hand and also ameliorate the activity of GLUT1/GLUT3 transporters to inhibit basal glucose uptake and thus exert hypoglycemic effect (Joladarashi *et al*., 2014). The alkaloid fraction of *Tinospora cordifolia* was found to inhibit gluconeogenesis and exert insulin releasing/insulin sensitizing effects, which may be the possible mechanism for its anti-diabetic activity (Patel *et al*., 2011).

Trigonella foenum

The common name of *Trigonella foenum* is fenugreek and is well known as an alternative therapy to treat diabetes. The herb is native of India and Northern African countries and has long usage history being also reported in Ayurveda for its anti-diabetic potential (Bahmani *et al*., 2016). The fenugreek seeds have been extensively studied for their richness in phytochemicals mainly alkaloids (36%), steroidal saponins, fibers and mucilage (Bahmani *et al*., 2016). The major phytoconstituent in fenugreek seed among alkaloids is

Trigonelline which is majorly responsible for the herb activity. Yamogenin and diosgenin are the enriched steroidal saponins constituting 0.1–2.2% and the mucilage is mostly a galactomannan (25–30%). Seeds are also enriched in a sapogenin peptide ester called Fenugreekine. 4-hydroxyisoleucine is a free amino acid enriched in the seeds of *Trigonella foenum* which have been reported for direct insulin stimulation (Roshana *et al*., 2018).

Multiple studies have analyzed the anti-diabetic potential of *Trigonella foenum* extracts. Fenugreek seed's ethanolic extract was found to significantly decrease the levels of serum glucose, triacylglycerol, total cholesterol with an increase in levels of serum insulin in STZ induced diabetic rats (Eidia *et al*., 2007). Trigonelline was also found to induce hypoglycemic effect by strengthening the functions of pancreatic β cells and reducing the levels of blood glucose in alloxan induced diabetic rats. The herb's mode of action had been reported to be through stimulating insulin secretion by increasing pancreatic β cell's regeneration (Zhou *et al*., 2011). Trigonelline had also been reported to regulate the metabolism of glycogen by inhibiting glycogen synthase kinase activity and thus induces hypoglycemic effect. Trigonelline was also found to improve insulin signaling and enhance lipid/glucose hemostasis (Roshana *et al*., 2018). *Trigonella foenum* was also found to improve insulin resistance, inhibit GLUT-4 translocation and thus inhibit glucose uptake (Maurya *et al*., 2014).

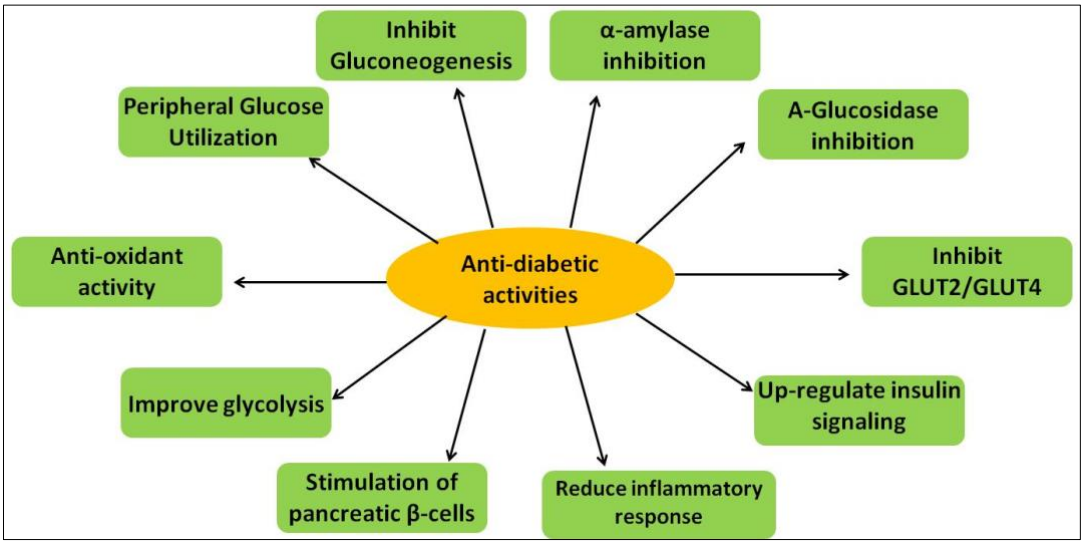

Fig 1: Various anti-diabetic activities of plants native to Jammu and Kashmir

Conclusion

Diabetes is still a major cause of mortality and morbidity worldwide instead of all the therapeutic developments. There is a need to investigate safer and effective anti-diabetic agents as the current available allopathic therapies are loaded with side effects. The ever-emerging role is played by ethno-botany and traditional medicine for treating and managing diabetes mellitus. This review highlighted the usefulness of plants native of Jammu and Kashmir, India for managing diabetes. Around 10 plants which possess anti-diabetic potential have been reviewed with respect to their phytochemistry and underlying anti-diabetic action mechanism. The richness of phytoconstituents in these plants are majorly responsible for their anti-diabetic potential through mechanisms like stimulating insulin secretion, pancreatic β cells regeneration, α-glucosidase inhibition etc (Figure 1). On the basis of this comprehensive overview the conclusion can be made that these plants and their phytoconstituents can be safer alternatives or can complement to available allopathic drugs. More in-depth investigations on these plants can lead to identification of potent anti-diabetic agents with lesser side effects.

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