

ETHNOPHARMACOLOGICAL INSIGHTS INTO DIABETES MANAGEMENT: EXPLORING MEDICINAL FLORA OF SHIVALIK RANGE OF HIMALAYA IN UTTARAKHAND



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Diabetes mellitus is a chronic metabolic disorder which is commonly found life-threatening disease and it continuously reducing the life expectancy. It is characterized by hyperglycaemia (raised blood sugar level) resulting from defects in insulin secretion, action, or both. Since thousands of years, medicinal plants are being used by our ancestors for the prevention, treatment or even cure the diabetes mellitus. Utilization of these herbal plants is increasing rapidly last two to three decades due to their lesser toxicity and cost effectiveness property as compared to synthetic drugs. In this review, approximately 30 medicinal plants were described which are native to India and traditionally used by the people living in shivalik range of Himalaya in Uttarakhand (specially Dehradun & Haridwar) for the treatment of diabetes mellitus. The data about these plants was collected from science direct, PubMed, web of science, scopus, mdpi, google scholar and different other search engines and websites. This review was conferred in a systematic way as it includes botanical name, family, vernacular name, parts used and pharmacological uses of plants in a tabulated form. There are various scientific evidences behind the uses of some medicinal plants which have been mentioned along with the summary of individual medicinal plant. In this review, all the plants and herbs are easily available in these regions of Uttarakhand and local people traditionally uses these plants as vegetable, seasoning, flavouring and usually consume as a part of their diet. There are some limitations of phytotherapy which limit it to completely replace the allopathic therapy as less bioavailability, less rate of absorption and slow rate of dissolution. But by using various advanced dosage forms (phytosomes, neosomes, liposomes, nanoparticles, nanobubbles, nano diamonds, nanosphere etc.) and method of delivery (various invasive and non-invasive methods) which can bypass these all problems associated with the potency and efficacy of phytochemicals.

KEYWORDS: *diabetes mellitus, medicinal plants, hyperglycaemia, ayurveda therapy, shivalik range of Himalaya.*

ЭТНОФАРМАКОЛОГИЧЕСКИЕ АСПЕКТЫ УПРАВЛЕНИЯ САХАРНЫМ ДИАБЕТОМ: ИССЛЕДОВАНИЕ ЛЕКАРСТВЕННОЙ ФЛОРЫ ШИВАЛИКСКОГО ХРЕБТА ГИМАЛАЕВ В УТТАРАКХАНДЕ

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Сахарный диабет (СД) — это хроническое метаболическое расстройство, которое часто приводит к угрожающим жизни заболеваниям и постоянно снижает ожидаемую продолжительность жизни. Он характеризуется гипергликемией, возникающей в результате нарушения секреции инсулина, его действия или того и другого. На протяжении тысячелетий наши предки использовали лекарственные растения для профилактики, лечения или даже излечения СД. В последние два-три десятилетия использование этих травяных растений стремительно возросло благодаря их меньшей токсичности и экономической эффективности по сравнению с синтетическими препаратами. В этом обзоре описано около 30 лекарственных растений, которые являются родными для Индии и традиционно используются жителями Шиваликского хребта Гималаев в Уттаракханде (особенно в Дехрадуне и Харидваре) для лечения СД. Данные о этих растениях были собраны из Science Direct, PubMed, Web of Science, Scopus, MDPI, Google Scholar и других поисковых систем и веб-сайтов. Обзор представлен в систематизированном виде, включая ботаническое название, семью, народные названия, используемые части и фармакологическое применение растений в табличной форме. Имеются различные научные доказательства применения некоторых лекарственных растений, которые также упоминаются вместе с кратким описанием каждого из них. Все растения и травы, рассмотренные в этом обзоре, легко доступны в этих районах Уттаракханды, и местные жители традиционно используют их как овощи, приправы и ароматизаторы, обычно включая в свой рацион. Существуют некоторые ограничения фитотерапии, которые не позволяют ей полностью заменить аллопатическую терапию, такие как низкая биодоступность, медленная скорость абсорбции и медленная скорость растворения. Однако с использованием различных современных лекарственных форм (фитосомы, неосомы, липосомы, наночастицы, нанопузырьки, наноалмазы, нанополлимеры и т. д.) и методов доставки (различные инвазивные и неинвазивные методы), можно обойти все проблемы, связанные с потенциальностью и эффективностью фитохимических веществ.

КЛЮЧЕВЫЕ СЛОВА: *сахарный диабет; лекарственные растения; гипергликемия; аюрведическая терапия; Шиваликские Гималаи.*

INTRODUCTION

In India, the WHO estimates that there are 77 million adults (those over the age of 18) who have type II diabetes and another 25 million prediabetics who are at risk of developing this condition in near future [1]. And according to a report by Sanyukta Kanwal that was published in Statista, more than 74 million Indians had been diagnosed with diabetes as of 2021, and that number is projected to increase to more than 124 million by 2045 [2]. Whereas as per 10th IDF Diabetes Atlas, there are 536.6 million peoples suffering with diabetes in the world till 2021 and this data will increase up to 783.2 million in 2045 [3]. Data may vary study to study but all the study concluded it surely that diabetes is a big matter of concern. For a number of reasons, we have decided to review the native Indian flora as a potential source of glucose-lowering compounds. First of all, native populations in focused area have a long history of using herbal medicine, and they frequently have extensive knowledge of therapeutic herbs and their uses. Second, investigating the local flora is consistent with the ideas of ethnopharmacology, which stresses the study of traditional medical practices in search of possible therapeutic advantages. For systematic literature review, we employed a systematic approach to search, evaluate, and select references for this review. Firstly, we have conducted comprehensive literature searches using electronic databases such as Web of Science, Scopus, Science direct, PubMed, PubMed central, mdpi, Google Scholar, and relevant botanical databases. Keywords related to ethnopharmacology, diabetes management, medicinal plants, and dun & duar of Uttarakhand located under shivalik range of Himalaya (specially Dehradun & Haridwar) were utilized to ensure a thorough search. Although, literatures for above places are merely available in these databases but reviewed plants and herbs are easily cultivated and available in this region and most of these herbs/plants are the part of their diet as seasonal, vegetables and foods. The inclusion criteria for literatures involved a critical re-

view of the identified references to ensure that only high-quality and pertinent studies were incorporated into the review. High blood sugar levels (hyperglycaemia) caused by inefficiency in insulin secretion, action, or both characterize diabetes mellitus or DM, a chronic metabolic disease. DM became one of the most serious, common and life-threatening disease and this is continuously reducing the life expectancy [4]. Type 1 diabetes is an autoimmune disease that results in a lack of insulin when the body's immune system mistakenly targets and kills the pancreatic cells responsible for making it. Contrarily, insulin resistance, a condition in which the body's cells become resistant to insulin and the pancreas fails to produce enough insulin to make up for it, is what causes Type 2 diabetes. Increased thirst, frequent urination, blurred vision, exhaustion, and slowly healing wounds are all signs of diabetes [5–7]. Serious complications from uncontrolled diabetes might include kidney failure, cardiovascular disease, neuropathy, and retinopathy etc. [1, 8]. Type-II diabetes mellitus (T-II DM) is a growing concern in India and even in worldwide, where sedentary lifestyles, unhealthy eating habits, and genetic predisposition have led to an increase in the incidence of T-II DM [7, 8]. Due to their efficiency and lack of adverse effects, plant-based treatments have gained popularity for the treatment of T-II DM last two to three decades. In this article, we'll provide an overview of the plants that are frequently uses to treat T-II DM. The basic type and causes of diabetes mellitus are represented diagrammatically by figure 1.

The purpose of this review is to shed light on the abundance of ethnopharmacological knowledge that exists in this part of India and explore the possibility of using native medicinal plants to provide complementary or alternative treatments for the management of diabetes. The review's goal is to expand the knowledge of traditional medicine and its use within contemporary healthcare, especially in combating towards diabetes and its complications, by gathering and assessing these insights.

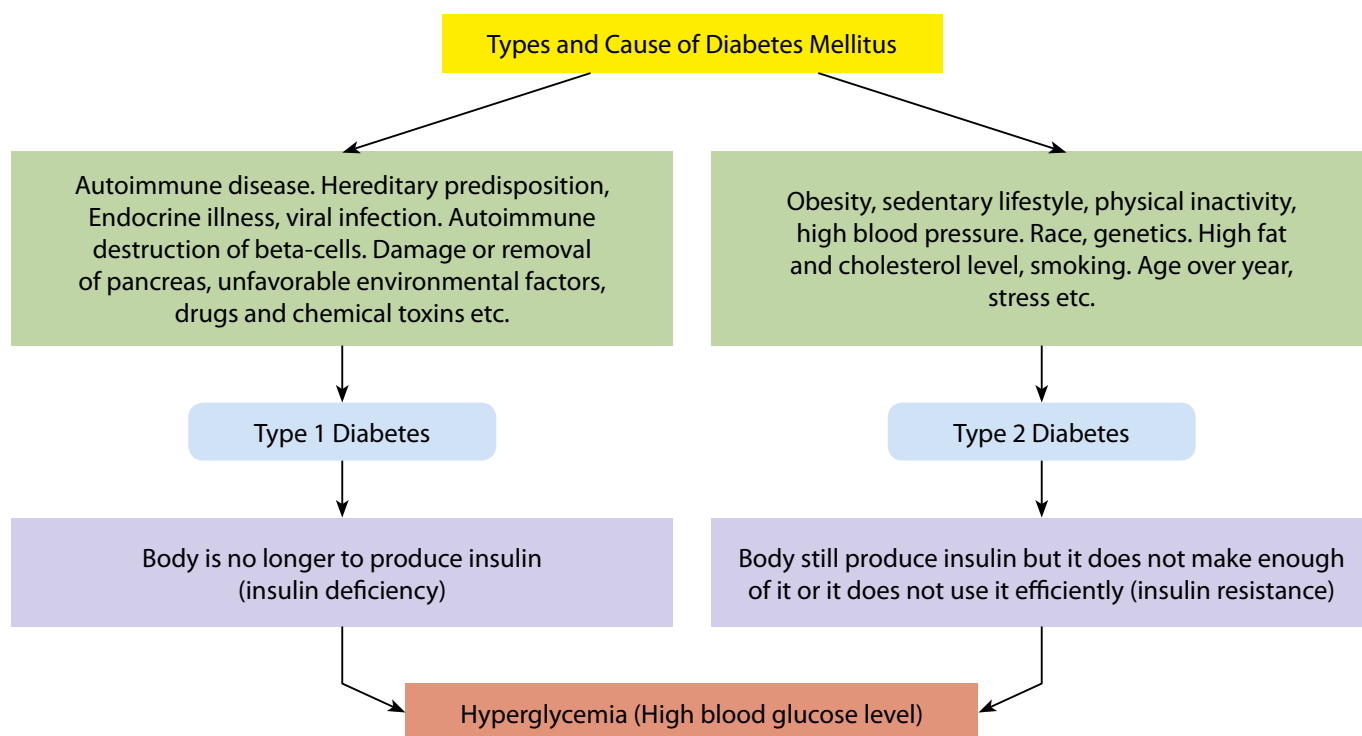


Figure 1. Basic types and Causes of Diabetes mellitus.

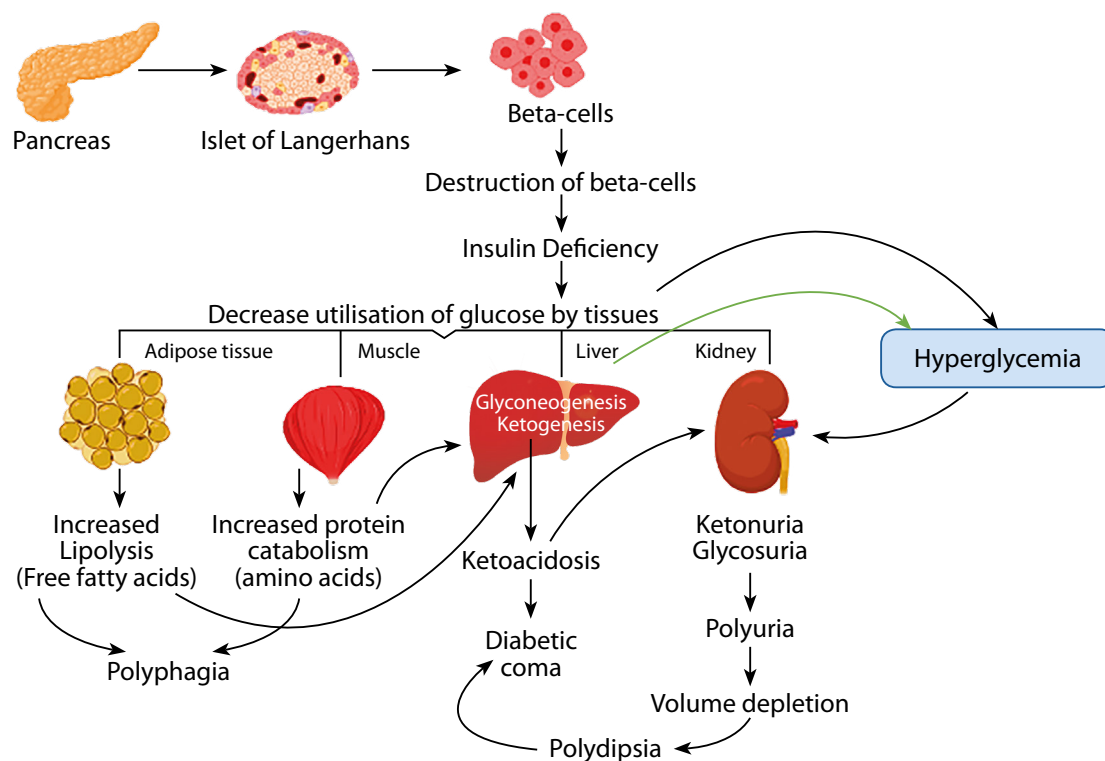


Figure 2. Pathophysiology of Diabetes Mellitus

PATHOPHYSIOLOGY OF DIABETES MELLITUS

Hyperglycaemia, or elevated blood sugar levels, is an indicator of diabetes mellitus, a long-term metabolic condition caused by deficiencies in insulin secretion, activity, or both. An autoimmune process causes the pancreatic beta cells to be destroyed in T-I DM, resulting in an absolute insulin deficiency. In T-II DM, the development of insulin resistance and relative insulin shortage is caused by a confluence of genetic and environmental variables, including as obesity, physical inactivity, and ageing [7, 9]. Insulin resistance is the result of reduced glucose absorption and utilisation by target tissues, including muscle, the liver, and adipose tissue. Insulin resistance is brought on by a combination of impaired insulin signalling and post-receptor abnormalities. In response, the pancreas compensates by producing more insulin, which initially maintains normoglycemia but eventually leads to beta cell exhaustion and failure [5]. The hyperglycaemia of diabetes leads to a range of systemic complications affecting various organs and tissues including macrovascular problems like cardiovascular disease, stroke, and peripheral vascular disease as well as microvascular complications like retinopathy, nephropathy, and neuropathy [5, 10].

Advanced glycation end products, oxidative stress, inflammation, and altered signalling pathways serve as the underlying mechanisms of these problems, which result in endothelial dysfunction, tissue damage, and organ failure [7]. In conclusion, the pathophysiology of diabetes is complex and multifactorial, involving a range of genetic, environmental, and metabolic factors, as well as intricate interactions between various organs and tissues. Understanding these mechanisms is essential for developing effective prevention and treatment strategies for this growing global health problem. The pathophysiology of diabetes mellitus has been diagrammatically represented by figure 2.

SUMMARY OF SOME MEDICINAL PLANTS WITH A BRIEF DESCRIPTION

1. *Syzygium cumini*

S. cumini (Myrtaceae) is native to India and commonly known as Jamun and traditionally, it is considered as Holy tree and used as Antidiabetic herbs [11]. Jamun is also used as antihyperlipidemic, antiplaque, neuro-psychopharmacological, nephroprotective, radioprotective, antidiarrheal, antiarthritic, antipyretic, antifertility, antimicrobial, antioxidant, hepatoprotective and antiulcer etc. [12]. The antihyperglycemic potential of *S. cumini* is supported by a number of research studies. The effectiveness of jamun leaves in preventing «processes of oxidation, glycation, inflammation, and digestive enzyme catalysis» was examined in an investigation published in Journal of Ethnopharmacology. Researchers came to the conclusion that *S. cumini* had antioxidant and antiglycation features in addition to its capacity for inhibiting digestive enzymes [13]. In another study, investigator used aqueous extract of *S. cumini* to evaluate its antihyperlipidemic & antidyslipidemic pharmacological potential of it in diabetic rats. After giving 200 mg/kg per day and 400 mg/kg per day for 21 days, they observed a significant decrease in serum insulin levels. Aqueous extract of *S. cumini* also showed a significant reduction in insulin resistance and improvement in beta-cells' functions [14]. After critically study of many studies, it can be concluded as seeds and leaves of *S. cumini* have a great antidiabetic potential. Generally, peoples consumed jamun as a fruit and its low toxicity, clinically safe nature and easy availability makes it a prominent antidiabetic herb.

2. *Bauhinia variegata*

B. variegata (Fabaceae) is distributed all over the India including Uttarakhand and it is popularly called as Kachnar. Numerous phytochemicals, including glycosides, flavonoids,

saponins, kaempferol, tannins, and terpenoids, may be found in abundance in each part of this plant, which is why it is so well-known as a medicinal tree. Traditionally, it has been used to cure different diseases like diabetes mellitus, hyperlipidaemia etc. [15]. To confirm its antidiabetic effect, a study was conducted on STZ (streptozotocin) induced diabetic rats by administering ethanolic (EtOH) extract of Kachnar leaf (once daily for 21 days). At the end of study, investigator observed a significant reduction in blood glucose level at 400 mg/kg (highest dose) of EtOH extract of Kachnar leaf. Study also explored its antihyperlipidemic and antioxidant potential [16]. A comparative study between five medicinal plants also enlightened the antidiabetic activity of *B. variegata*. By doing in vitro evaluation of these five medicinal plants (*A. indica*/Neem, *B. variegata*/Kachnar, *Dalbergia sissoo*/Tahli, *Psidium guajava*/amrood and *S. cumini*/Jamun), authors concluded their findings as methanolic leaf extracts of kachnar and jamun exhibit better antidiabetic and antioxidant potential than remaining three medicinal plants [17]. Additionally, Kachnar could potentially induce mild gastric discomfort in individuals with a sensitive stomach. Large doses of Guggul may lead to adverse effects such as headaches, nausea, diarrhoea, hiccups, allergic reactions, skin and itching [15].

3. *Aegle marmelos*

A. marmelos (Rutaceae) is native to India and easily found in areas focused for review, it is commonly known as Bael which is considered holy by Hindus. Traditionally, its bark, leaves, stem, fruit and seeds have been used as medicinal herbs due to their various pharmacological significances. *A. marmelos* have antihyperglycemic effect, antiulcer, antidiarrheal, gastroprotective, antiviral, cardioprotective effects etc. [18]. There are a lot of scientific evidences which confirmed the antidiabetic potential of *A. cumini*. One of them is published in 'Journal of Food Biochemistry' and in this, the investigators used leaf extract of *A. cumini* (Alkaloid free hydroalcoholic) to investigate the antidiabetic potential of Bael. The findings of this study are significantly decreased blood sugar level, ameliorated state of dyslipidaemia, status of oxidative stress in diabetic mice. Even, authors found improved functions of pancreatic beta cells [19]. In a different study, the alcohol-based *A. cumini* leaf extract's potential to combat diabetes is investigated. Also, they have conducted its cytotoxicity study in vitro by using HepG2 cells. Finally, they came to the conclusion that *A. cumini* would be an exceptional restorative therapy for DM and related disorders [20].

4. *Azadirachta indica*

A. indica (Meliaceae), a plant native to India, is popularly called as nimba or neem in India. It is recognised to have antidiabetic, antipyretic, anti-inflammatory, and antibacterial effects and has a broad range of clinical relevance [21, 22]. There are a lot of scientific evidences about antidiabetic potential of Neem and one of them published in Journal of Ayurveda and Integrative Medicine investigated it on high fat diet induced diabetic rats. In this study, after giving diabetic rats 400 mg/kg of *A. indica* leaf extract for 30 days, researchers noticed the impairment in glucose tolerance, the insulin signalling system, glucose oxidation, and glycogen concentration. At the dose of leaf extract supplied,

researchers also observed normalisation in aberrant levels of blood sugar, serum insulin, insulin signalling molecules, and GLUT4 (glucose transporter type-4) proteins. Hence, after evaluating these findings, we can conclude it as *A. indica* exhibit a significant role in the management of T-II DM [23]. In various studies, it has been also observed that *A. indica* shows dose dependent toxicity on different animal model like mice, rats & hamster etc [24–28]. But mostly it adversely affects liver & kidney as in a study, investigators suggested that due to high concentration of nimbolide and nimbic acid, it causes hepatocyte degeneration [24–26]. Also, it had shown to give rise to skin allergens [25, 28].

5. *Momordica charantia*

M. charantia (Cucurbitaceae) is commonly called as Karela and traditionally, the people of these regions of India used it as an herbal medicine and vegetable. Other names for karela include bitter melon and bitter gourd. Karela has antidiabetic, anti-inflammatory, antibiotic and blood purifying properties. Various scientific studies showed that the fruit and leaves of karela has a great antidiabetic potential [29–32]. The electronic journal of biotechnology recently released a study on how *M. charantia* saponin (MCS) affected oxidative stress and the insulin signalling system in type II diabetic rats. Additionally, it was observed that MCS might lower fasting blood sugar levels and enhance rats' glucose tolerance, insulin sensitivity, and insulin content [30]. There are a lot of scientific evidences which provide the clarity about the antidiabetic and hypoglycaemic effects of karela or *M. charantia* [29]. Numerous toxicological investigations have illustrated those extracts from *M. charantia* may induce toxicity in various organs at different dosage levels [33–36]. Recently, a zebrafish study confirmed its teratogenic and cardiotoxic effects at specific doses [33]. Additionally, in 2020, Abdillah et al. documented hepatotoxic and nephrotoxic effects of *M. charantia* ethanolic extract over 28 days [34]. Further clarification of these reported toxicities on vital organs is necessary to establish a safe dosage for usage.

6. *Trigonella frenum-graecum*

T. frenum-graecum (Fabaceae) is commonly known as Methi or fenugreek and traditionally its seeds and leaves have been commonly used as seasoning and vegetable in all over India. Its seeds have antidiabetic, antihyperlipidemic, antidepressant, antianxiety, antioxidant as well as immunomodulating effects [37]. A randomized controlled clinical trial study investigated antidiabetic effect of fenugreek on diabetic patients. This study was conducted on 12 uncontrolled diabetic patients where investigator gave 2 gm methi per day to patients. After 12 weeks, investigator noticed a significant increment in fasting insulin level but insignificant reduction in fasting blood sugar level [38]. Another study was published in Journal of Diabetes Research which also investigated the antidiabetic effect of fenugreek seed powder. This study was performed on 114 newly diagnosed diabetic patients and investigator found pronounced effect in lipid metabolism in T-II diabetic patients without any side effects. Hence, it can be concluded as fenugreek may give new alternatives for the clinical management of T-II DM [39]. The potential side effects of methi and its various preparations have been investigated to identify possible adverse reactions. While major clinical trials assessing *Trigonella*'s use

as conventional or alternative herbal medicine are lacking, current knowledge of its side effects primarily stems from user-reported symptoms and animal studies, including stomach upset, diarrhoea, or bloating [40, 43]. Also, the intake of fenugreek seeds during pregnancy has been linked to a spectrum of congenital abnormalities, such as hydrocephalus, anencephaly, and spina bifida [41]. The findings of another study, indicate that exposing mice to a high dose of fenugreek seeds during prenatal development led to growth delays and changes in neurobehavioral performance after weaning [42]. However, the underlying molecular mechanisms behind these effects still require further investigation [43].

7. *Gymnema sylvestre*

Common names for *G. sylvestre* (Apocynaceae) are Gurmar and madhunashini. Historically, diseases like diabetes, arthritis, dental caries, anaemia, hypercholesterolemia, asthma, constipation, and others have been treated with the seeds and leaves of the Gurmar plant in Dehradun & Haridwar as well as whole Northern region of India. Gurmar has promising diabetes therapeutic potential since it has a favourable impact on blood sugar homeostasis, manages sugar cravings, and encourages pancreatic regeneration [44]. According to a study published in the Journal of Ethnopharmacology, 22 T-II DM patients taking conventional oral antidiabetic medications participated in the trial to determine the efficiency of an extract (GS4) from the leaves of Gurmar in lowering blood sugar levels. For a period of 18 to 20 months, 400 mg of GS4 was given daily as a complement to the usual oral anti-diabetic medications. Patients who underwent this therapy experienced a considerable decrease in their blood sugar levels, glycosylated haemoglobin and plasma proteins, as well as a reduction in the frequency and quantity of their regular antidiabetic medication. Out of the 22 T-II DM patients, 5 were able to discontinue using their traditional medications and maintain blood sugar homeostasis with GS4 alone. The presence of elevated insulin levels in the serum of T-II DM patients supports the assertion that these data also imply that the beta cells of the pancreas may be restored in T-II DM patients with GS4 supplementation [45]. There are not many numbers of literatures which declared *G. Sylvester* as toxic but, in some studies, its toxicity has been observed. Shiyovich et. al., (2010) reported a case of *G. sylvestre* induced liver injury (toxic hepatitis) [46] as well as Khare et. al., (1983) observed its hypoglycaemic effect on non-diabetic & diabetic patients [47].

8. *Ocimum sanctum*

O. tenuiflorum or *O. sanctum* (Lamiaceae) is native to Indian subcontinent and it can be easily found all over the India [48]. It is basically found in two variant that are Rama Tulsi or Sri Tulsi (green coloured leaves) and Krishna Tulsi (Purple coloured leaves) [49]. It considered as sacred plant by Hindus and it is commonly known as Tulsi or Holy basil. It contains more than 60 phytochemicals including steroids, phenols, phenyl propanoids, essential oils etc. and it is scientifically proven that it is used as antidiabetic, antioxidant, anticancer, antistress and anti-inflammatory etc. [48]. Numerous in vitro, in vivo, and clinical studies have been carried out to check *O. sanctum*'s antidiabetic efficacy. One of them is published in 'Caspian journal of Internal medicine' and in this, investiga-

tor used MeOH (methanolic) leaf extract of Tulsi to conduct the evaluation of IVIV (In vitro-In vivo) antidiabetic and antioxidant activity. The STZ-induced diabetic Wistar rat model was chosen by researchers for in vivo research, and suppression both α -amylase and α -glucosidase was used for in vitro research. Finally, researchers reported that diabetic wistar rats had significantly lower blood glucose levels and oxidative stress [50]. Three species of tulsi (*O. basilicum* L./Green Tulsi, *O. gratissimum* L./Jungli Tulsi, and *O. tenuiflorum*/Black Tulsi) have been found to have considerable anti-inflammatory and anti-diabetic potential in a comparative research [51]. Although tulsi is very spiritual plant in Sanatan Dharma and many peoples administering it on daily basis as herb for all diseases, but it can be toxic for any individuals as it can give rise to skin allergens as well as it is contraindicated with anti-coagulants and antiplatelets drugs [52, 53].

9. *Tinospora cordifolia*

T. cordifolia (Menispermaceae) is a native to India and traditionally, peoples used it as a medicinal plant. Giloy (*T. cordifolia*) exhibits antidiabetic, gastroprotective, antidiarrheal, anti-inflammatory, antioxidant and analgesic properties. Even many people believed that it has great potential in the treatment of typhoid, dengue and malarial fever as well as people used to drink its juice as an immunostimulant drink [54]. A scientific study regarding antidiabetic potential of Guduchi/Giloy has been published in Innovative food science and emerging technology states that phytochemicals of *T. cordifolia* have similar effect as insulin and antihyperglycemic property. And authors found that chloroform extract of Giloy shown highest hypoglycaemic activity as IC50-11.34mg/ml. There is an issue regarding its low bioavailability and poor stability which limits its antidiabetic potential but author used whey protein-based electro sprayed nanospheres and observed a tremendous increment (28.12%) in its activity. By using modern drug delivery systems as nanospheres, liposomes, neosomes, nanobubbles, nano diamonds etc., we can bypass its low bioavailability and low stability issues. After studying various research and review articles, we can conclude it as *T. cordifolia* has excellent hypoglycaemic potential and it can provide insulin mimicking effects [54–57]. Giloy is widely regarded as a safe botanical entity, with scant scientific literature documenting any potential toxicity. In a study conducted by Gupta & Sharma (2003) have shown that administering a 70% methanolic extract of *Tinospora cordifolia* stem orally can result in reduced sperm motility and density, decreased serum testosterone levels, as well as lowered protein, sialic acid, and glycogen contents. Additionally, this extract has been found to deplete vesicular fructose in the testes, ultimately leading to diminished male fertility in rat subjects [58].

10. *Allium sativum*

A. Sativum (Amaryllidaceae), a flowering plant is widely used for flavouring and seasoning purpose. There is a lot of human and animal studies which confirms that garlic has copious number of medicinal properties due to its sulphur containing phytochemicals. It shows antidiabetic effect, cardioprotective property, antimicrobial effect, anticancer, antioxidants and hypoglycaemic effects etc. Since last two decades, garlic became popular for its antidiabetic effect [59, 60].

In an investigation, authors compared antidiabetic effect of Garlic with glibenclamide (600 microgram/kg). Author gave garlic extract for 14 days via oral route to normal and STZ-induced rats and evaluated its effect on level of glucose, triglycerides, total cholesterol, AST and ALT. Investigator observed significant decrease in level of glucose, urea, uric acid, AST, creatinine, total cholesterol, triglyceride and concluded the study as garlic extract exhibit better antidiabetic effect than glibenclamide [61]. There are lot of scientific evidences published in various reputed international journals and reports that support the hypoglycaemic property of garlic [59–64]. Generally, garlic is used as a part of diet worldwide and its low toxicity, clinically safe and cost-effectiveness make it first choice as a complete solution for many ailments.

DISCUSSION & CONCLUSION

As it is already discussed that shivalik range of Himalaya (specially Dehradun & Haridwar) of Uttarakhand, India is highly rich in biodiversity of medicinal plants. Since thousands of years, these are used by local population to get relief from various diseases including diabetes. Various scientific studies have been cited in this review which confirms that these medicinal plants are the best alternative to allopathic medicines to treat or even cure the diabetes mellitus. These medicinal herbs have the potential to control the blood glucose level as well as increase the blood insulin level and repair the insulin secretory cells of pancreas. Botanical source, vernacular names and possible clinical significance of these medicinal plants are shown in table 1. All the findings of this

Table 1. List of traditional plants used to treat Diabetes Mellitus type 2.

S.No.	Botanical Name	Family	Vernacular name	Part used	Ethnopharmacological uses	Reference
1	<i>Gymnema sylvestre</i>	Apocynaceae	Gurmar, Madhunashini	Seed, Leaves	Antidiabetic, Antiarthritic, Dental carries, Antibiotic, Antimicrobial, Anti-inflammatory, Anticancer, Immunomodulator etc.	[31, 32]
2	<i>Momordica charantia</i>	Cucurbitaceae	Karela, Bitter melon	Seeds, Fruit	Antidiabetic, Anti-inflammatory, Antibiotic etc.	[24–27, 43]
3	<i>Azadirachta indica</i>	Meliaceae	Neem, Nimba	Seed, Leaves and Fruit	Antidiabetic, Antioxidants, Anti-inflammatory, Anticancer effects etc.	[21, 22]
4	<i>Trigonella frenum-graecum</i>	Fabaceae	Methi, Fenugreek	Seed, Leaves	Antidiabetic, Anti-hyperlipidemia, Antioxidants, neurological disorders etc.	[28, 30]
5	<i>Syzygium cumini</i>	Myrtaceae	Jamun, Jambul	Seed, Fruit	Antidiabetic, Antihyperlipidemic, Antiulcer, Hepatoprotective, Antiplatelet, Antipyretic, Antidiarrheal etc.	[11, 12]
6	<i>Terminalia chebula</i>	Combretaceae	Harad, Haritaki	Fruit, Bark	Antidiabetic, Gastroprotective, Antiparasitic, Hepatoprotective, Antioxidant, Antiaging etc.	[47, 48]
7	<i>Berberis aristata</i>	Berberidaceae	Daru Haldi, Daruharidra, Zarishk	Leaves, Wood	Antidiabetic, Cardiovascular complications, Oxidative stress, neurodegeneration, hepatic dysfunctions etc.	[32, 49]
8	<i>Allium sativum</i>	Amaryllidaceae	Lehsun, Garlic	Bulb, Leave	Antidiabetic, Cardiovascular diseases, common cold, cancer, Antimicrobial, Antiviral etc.	[50, 51]
9	<i>Aegle marmelos</i>	Rutaceae	Bael, Bilva, Wood Apple	Fruit, Leaves	Antidiabetic, Gastroprotective, Antidiarrheal, Radioprotective, Cardioprotective, Antimicrobial etc.	[52, 53]
10	<i>Nardostachys jatamansi</i>	Caprifoliaceae	Jatamansi, Muskroot	Whole Plant	Antidiabetic, Hepatoprotective, Anti-Parkinson, Hypoglycemic insecticidal, Anticancer, Anticonvulsant etc.	[54, 55]
11	<i>Acacia catechu</i>	Fabaceae	Katha, Khadir	Bark, Wood, Seed	Antidiabetic, Strong Antioxidant, Astringent, Antimicrobial, Immunomodulatory etc.	[56, 57]
12	<i>Bauhinia variegata</i>	Fabaceae	Kachnaar, Orchid tree	Flower	Antidiabetic, Antihyperlipidemic, Antioxidant	[15, 16]

S.No.	Botanical Name	Family	Vernacular name	Part used	Ethnopharmacological uses	Reference
13	<i>Piper longum</i>	Piperaceae	Pippalli	Fruit, Leaves, Root	Antidiabetic, Immunomodulatory, Insomnia, Dementia, Epilepsy Carminative etc.	[58–60]
14	<i>Ocimum sanctum</i>	Lamiaceae	Tulsi, Holy basil	Leaves, Wood	Antidiabetic, Antistress, Radioprotective, Anticough, leishmanicidal, Antioxidant, Anti-inflammatory etc.	[33, 61]
15	<i>Andrographis paniculate</i>	Acanthaceae	Kalmegh, King of Bitter	Leaves, Root	Antidiabetic, Antiviral, Jaundice, Anti-obesity, Anti-inflammatory, Anticancer etc.	[62, 63]
16	<i>Pterocarpus marsupium</i>	Faboideae	Vijaysar, Indian Kino	Heart Wood, Seeds	Antidiabetic, Analgesic, Anti-inflammatory, Hepatoprotective, Antifungal, Antioxidants etc.	[64, 65]
17	<i>Commiphora wightii</i>	Burseraceae	Guggul, Indian bdellium tree	Resin, Fruit	Antidiabetic, Cardioprotective, IBD, Ulcer, Arthritis etc.	[66–68]
18	<i>Boerhaavia diffusa</i>	Nyctaginaceae	Punarnava	Leaves, Flowers, Pollen	Antidiabetic, Anemia, Oedema, Expectorants, R.A., Anticonvulsants etc.	[69, 70]
19	<i>Casearia esculenta</i>	Salicaceae	Saptarangi	Root	Antidiabetic, Antihyperlipidemic, Anticaries activity, RFA, Hepatoprotective etc.	[71–73]
20	<i>Swertia chirata</i>	Gentianaceae	Chirayata	Whole plant	Antidiabetic, Bitter tonic, febrifuge, Antiperiodic, stomachic etc.	[74–76]
21	<i>Tinospora cordifolia</i>	Menispermaceae	Giloy, Guduchi	Leaves, Fruits	Antidiabetic, Antioxidant, Immunomodulatory, Anti-inflammatory, Anticancer etc.	[37, 38, 41, 42, 77]
22	<i>Lepidium sativum</i>	Brassicaceae	Chandraprabha, Haloon	Seed, Sprouts	Antidiabetic, Antidiarrheal, Antioxidant, Antiasthmatic, Bone fracture etc.	[78, 79]
23	<i>Phyllanthus emblica</i>	Phyllanthaceae	Amla	Fruits	Antidiabetic, Antiviral, Antifungal, Antiallergic, Antimicrobial etc.	[80, 81]
24	<i>Picrorhiza kurroa</i>	Plantaginaceae	Kutki	Leaves, Flower, Rhizome	Antidiabetic, Cardioprotective, Antimalarial, Immunomodulatory, Antimicrobial etc.	[82, 83]
25	<i>Cassia fistula</i>	Fabaceae	Amaltas	Stem Bark, Seed, Leaves	Antidiabetic, Antioxidant, Hepatoprotective, Antitumor, Antimicrobial, Anti-inflammatory etc.	[84–86]
26	<i>Butea monosperma</i>	Fabaceae	Palash	Flowers	Antidiabetic, Antioxidant, Anti-inflammatory, matrix metalloproteinase inhibitory activities etc.	[87, 88]
27	<i>Tribulus terrestris</i>	Zygophyllaceae	Gokharu	Fruits, Burs	Antidiabetic, Antiuro lithic, Anthelmintic, Antispasmodic, Anticariogenic activities etc.	[89, 90]
28	<i>Crocus sativus</i>	Iridaceae	Kesar, Saffron	Stigmas, Flower	Antidiabetic, pleotropic anti-inflammatory effects, neuroprotective, Antioxidants etc.	[91, 92]
29	<i>Zingiber officinale</i>	Zingiberaceae	Adrak, Ginger	Rhizome	Antidiabetic, Anticlotting, Anti-inflammatory, Analgesic etc.	[93–95]
30	<i>Withania somnifera</i>	Solanaceae	Ashwagandha, Indian Ginseng	Leaves, Root	Antidiabetic, Antihyperlipidemic, Oxidative stress, Immunomodulator etc.	[96, 97]

Abbreviations. DM: diabetes mellitus, RA: rheumatoid arthritis, IBD: inflammatory bowel disease, RFA: reproductive function activity, AST: aspartate aminotransferase, ALT: alanine aminotransferase

review suggests that individual plant mentioned above is capable to treat diabetes and if they are taken along with any medicines like metformin, glibenclamide etc., they show synergistic action on the diabetes mellitus and enhance the efficacy of that particular medicine. These all herbs like Giloy, Jamun, Neem, Methi, Karela, Gurmar, Lehsun etc. are easily found in whole northern region of India including Dehradun & Haridwar and local peoples of this region used these plants or herbs directly or indirectly to treat diabetes since thousands of years. Most of these discussed plants are used as vegetables, seasoning, flavouring and spices etc. Complications of diabetes mellitus result not only from high blood glucose and there are some other serious complications associated with diabetes like kidney failure, impairment in glucose tolerance, insulin signalling system, insulin sensitivity, glucose oxidation, and glycogen concentration, oxidative stress, obesity, liver dysfunction etc. Many literatures suggest that the people living with their traditional lifestyle are maintaining their fitness and health by using these traditional plants as a part of their diet but since last two or three decades, modernisation and urbanisation drastically affects their lifestyle and food patterns. This sedentary lifestyles, unhealthy eating habits, and genetic predisposition played a vital role in increment in the cases of diabetes mellitus in this region [116, 117]. With phytotherapy, there is a problem of their less bioavailability and rate of absorption. As compare to allopathic therapy, phytotherapy shows less potency and efficacy towards its targeted site and disease. But in the field of pharmaceuticals, there are various advanced dosage forms (phytosomes, neosomes, liposomes, nanoparticles, nanobubbles, nano diamonds, microsphere etc.) and method of delivery (various invasive and non-invasive methods) which can bypass these all problems associated with the potency and efficacy of phytochemicals [118–120]. Various superdisintegrants, advanced polymers and other excipients are available in the market which have capability to increase their bioavailability, rate of absorption, retention

time, contact time, rate of dissolution and disintegration etc. Although phytotherapy has very less toxic effect, but various toxicological evidences also confirm it that these herbs or plants can be a greater alternate to the existing medicines [121, 122]. If we see the trend, most of the researcher related to pharmacy field are doing investigation on phytochemicals and exploring their clinical significances. These all efforts indicate that phytotherapy has an excellent potential to treat or even cure these deadly diseases including diabetes mellitus. After reviewing many research and review articles, we can conclude it as mentioned plants or herbs have a great potential to prevent, treat and cure diabetes mellitus.

ABBREVIATIONS

DM: diabetes mellitus, **T-I:** type-I, **T-II:** type-II, **WHO:** world health organisation, **IDF:** international diabetes federation, **STZ:** streptozotocin, **EtOH:** ethanol, **MeOH:** methanol, **RA:** rheumatoid arthritis, **IBD:** inflammatory bowel disease, **RFA:** reproductive function activity, **HepG2:** human liver cancer cell line, **GLUT-4:** glucose transporter type-4, **MCS:** *Momordica charantia* saponin, **GS4:** *Gymnema sylvestre* extract, **IVIV:** In-vitro In-vivo, **AST:** aspartate aminotransferase, **ALT:** alanine aminotransferase.

ADDITIONAL INFORMATION

Participation of authors. Sachin Kumar – conceptualization, writing, original draft preparation; Ashok Kumar – supervision, study design; Junaid Tantray – literature survey, editing; Aman Shukla – writing, reviewing and editing.

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