# **REVIEW ARTICLE**





# Gymnema and diabetes: A review on well-known and underexplored species

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#### **Abstract**

Diabetes mellitus, particularly type 2 diabetes (T2DM), has emerged as a major global health concern with over 800 million adults currently affected. This alarming increase more than a fourfold rise since 1990 underscores the urgent need for disease management and prevention. While pharmaceutical treatments, such as insulin and oral hypoglycemic agents are widely used, there is growing interest in herbal and natural therapies due to their affordability, availability and reduced incidence of side effects. Among these, species of the genus *Gymnema* have attracted considerable attention for their potent anti-diabetic properties. *Gymnema sylvestre*, the well-researched species has been traditionally used in Ayurvedic medicine for its ability to reduce sugar absorption, enhance insulin secretion and regenerate pancreatic beta cells. The presence of gymnemic acids, saponins and flavonoids contributes to its hypoglycemic effects. However, beyond *G. sylvestre*, several lesser-known *Gymnema* species, such as *G. montanum*, *G. latifolium* and *G. yunnanense* contain bioactive compounds with potential anti-diabetic effects yet remain largely unexplored. This review provides a comprehensive analysis of both well-established and lesser-known *Gymnema* species. It emphasizes the critical need for further pharmacological and clinical investigations to fully unlock the therapeutic benefits of these underutilized species.

Keywords: diabetes; gymnemic acid; Gymnema; underexplored

## Introduction

Gymnema spp. is a genus of medicinal plants belonging to the family Apocynaceae (commonly known as the milkweed family), under the subfamily Asclepiadoideae. The native distribution of this genus spans the tropical and subtropical Old World regions, extending to New Caledonia. As of 2025, the genus comprises 52 recognized species (Table 1) (1). Gymnema is a significant medicinal plant known for its anti-diabetic properties that has been used since ancient times and is commonly referred to as "sugar killer" (2). The plant possesses extensive medicinal, historical, ethnobotanical, traditional and economic significance across various medical systems, both in India and globally. India is a major supplier of Gymnema extract and Gymnema leaf powder in bulk for export. Many phytoconstituents such as gymnemic acid, berberine, curcumin, quercetin and resveratrol have demonstrated potential to combat diabetes and obesity by modulating glucose metabolism, enhancing insulin sensitivity and reducing oxidative stress (3). To ensure accurate species identification safe pharmaceutical use, Random Amplified Polymorphic DNA (RAPD) markers have been found more reliable compared to partial trnK gene sequencing (2).

Type 2 diabetes mellitus (T2DM) is a growing global health concern closely linked to the rise in obesity. Individuals with T2DM face a significantly increased risk of both microvascular and

macrovascular complications, including retinopathy, nephropathy, neuropathy and cardiovascular disease. These complications arise due to persistent hyperglycemia and factors related to insulin resistance, which are components of metabolic syndrome. The central issues in T2DM include reduced insulin sensitivity and inadequate insulin secretion (4).

Gymnema species, especially Gymnema sylvestre, have long been used in traditional medicine for their potential role in managing blood sugar levels and associated metabolic disorders. Their bioactive compounds, such as gymnemic acids (Fig. 1b) and deacyl gymnemic acid (Fig. 1a), may help regulate glucose metabolism by reducing intestinal glucose absorption and influencing insulin secretion. Research suggests that these compounds can enhance insulin sensitivity and promote insulin secretion, thereby contributing to improved glycemic control (5). While G. sylvestre is the most extensively studied species, others like G. lactiferum and G. montanum have also demonstrated potential antidiabetic effects. These species contain similar bioactive compounds, including saponins and gymnemic acids, which may support hypoglycemic activity. Although similar mechanisms are observed across different Gymnema species (Table 2), most studies have focused on G. sylvestre. More research is needed to compare the antidiabetic potential of other species and clarify their specific roles in metabolic ABHIRAMI ET AL 2

**Table 1.** The 52 recognized *Gymnema* sp. as of 2025 (POWO) (1)

Table .	. The 52 recognized Gyn	nnema sp. as of 2025 (POWO)	
S.No	Species	Homotypic Synonym	Origin
1	G. acuminatum	Cynanchum acuminatum	Assam to Peninsula Malaysia
2	G. albidum	Tylophora albida	Lesser Sunda Island
3	G. albiflorum	<u>-</u>	Vietnam
4	G. calycinum	-	Philippines
5	G. chalmersii	-	New Guinea
6	G. cumingii	-	Philippines
ŭ	0. cag	Bidaria cuspidate	·····p····cs
7	G. cuspidatum	Cynanchum cuspidatum Marsdenia cuspidate	India, Sri Lanka
		Gymnema mohanramii var.	
8	G. decaisneanum	decaisneanum Gymnema sylvestre var. decaisneanum	India, Myanmar
9	G. dissitiflorum	Marsdenia decaisneana Marsdenia dissitiflora	Malaya
10	G. elegans	Bidaria elegans Marsdenia elegans	India
11	G. erectum	Bidaria erecta	Northern Territory, Western Australia
12	G. foetidum	Marsdenia angustata Bidaria foetida	China South-Central, Vietnam
13	G. geminatum	Marsdenia geminata	· · · · · · · · · · · · · · · · · · ·
	9	=	New Guinea, Northern Territory, Queensland, Western Australia
14	G. glabrum	Marsdenia ianturneri	Bangladesh, Myanmar
15	G. graniticola	Marsdenia graniticola Marsdenia craibii	Western Australia
16	G. griffithii G. hainanense		Myanmar, Thailand, Vietnam
17		Bidaria hainanensis	Hainan New Guinne
18	G. hamatum	Marsdenia hamata	New Guinea
19	G. hirtum	Marsdenia hirta	Malaya
20	G. indicum	Bidaria indica Gymnema montanum Marsdenia indica	India
		Bidaria	
21	G. inodorum	inodora Cynanchum inodorum Marsdenia inodora Parsonsia inodora	Andaman Island, Assam, Bangladesh, Borneo, China South-Central, China Southeast, East Himalaya, Hainan, India, Jawa, Malaya, Myanmar, Nepal, Philippines, Thailand, Vietnam, West Himalaya
22	G. javanicum	Marsdenia vajanicum	Jawa
23	G. lacei	Bidaria lacei Marsdenia lacei	Myanmar
24	G. lactiferum	Asclepiaslactifera Marsdenia lactifera	Assam, Borneo, India, Malaya, Myanmar, Sri Lanka, Sumatera
25	G. latifolium_	Bidaria latifolia Marsdenia wightii	Andaman Island, Assam, Bangladesh, China South-Central, China Southeast, East Himalaya, India, Myanmar, Nicobar Island, Thailand, Vietnam
26	G. littorale	Marsdenia littoralis	Jawa
27	G. longipedicellatum	Marsdenia longipedicellata	Queensland
28	G. longiretinaculatum	Bidaria longiretinaculata	China South-Central
29	G. lushaiense	Marsdenia lushaiensis	Assam
30	G. macranthum	Marsdenia hookeri	East Himalaya
31	G. macrothyrsa	-	Sulawesi
32	G. maingayi	Marsdenia forsteri	Malaya, Myanmar, Thailand
33	G. mariae	-	Philippines
		Marsdenia	••
34	G. molle	lakshminarasimhanii Asclepias montana	Bangladesh, Myanmar
35	G. montanum	Bidaria montana Periploca montana	India
36	G. muelleri	Marsdenia muelleri	Northern Territory, Queensland
37	G. pachyglossum	Marsdenia pachyglossa	Philippines
38	G. piperi	-	Philippines
39	G. pleiadenium	Marsdenia pleiadenia	New South Wales, Queensland, Western Australia
40	G. recurvifolium	Gongronema recurvifolium	New Guinea
41	G. rivulare	Marsdenia rivularis	New Guinea
42	G. rotundatum	Marsdenia sylvestris	Sri Lanka
		Mursuemu sylvestris	
43	G. schlechterianum	-	Philippines
44 45	G. spirei_	Maradania atramina a	Laos
45	G. stramineum	Marsdenia straminea	Queensland
46	G. suborbiculare	Marsdenia suborbicularis Marsdenia sylvestris	New Guinea, Queensland Angola, Assam, Bangladesh, Benin, Botswana, Burkina, Burundi, Cambodia, Cameroon, Cape Provinces, Caprivi Strip, Central African Republic, Chad, China South-Central, China Southeast, Comoros, Congo, Eritrea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Hainan, India, Ivory Coast, Kenya, KwaZulu-Natal,
47	G. sylvestre	Periploca sylvestris	Nansei-shoto, Niger, Nigeria, Northern Provinces, Northern Territory, Queensland, Rwanda, Saudi Arabia, Senegal, Sri Lanka, Sudan, Taiwan, Tanzania, Togo, Uganda, Vietnam, Western Australia, Yemen, Zambia, Zaïre, Zimbabwe

48	G. thorelii	-	Laos
49	G. tricholepis	Marsdenia tricholepis	New Caledonia, New Guinea, Queensland
50	G. trinerve	Bidaria trinervis Marsdenia trinervis	Northern Territory, Western Australia
51	G. uncarioides	-	Philippines
52	G. yunnanense	Bidaria yunnanensis Marsdenia banqlayunnanensis	Bangladesh, China South-Central, China Southeast, Vietnam

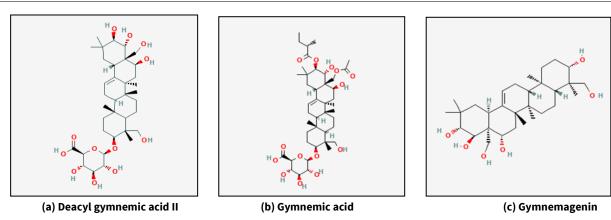


Fig. 1. Chemical structures of (a) Deacyl gymnemic acid II, (b) Gymnemic acid and (c) Gymnemagenin.

Table 2. Comparative summary for Gymnema species

Species	Key Bioactive Compounds	Traditional Uses	Modern Pharmacological Activities
G. sylvestre	Gymnemic acids, gymnemagenin, saponins, flavonoids	Gurmar ("sugar killer"), used in Ayurveda	Anti-diabetic, anti-obesity, hypolipidemic, antioxidant, antimicrobial
G. montanum	Gallic acid, quercetin, gymnemic acids	Used in folklore medicine for diabetes	Enhances insulin secretion, improves lipid profile, antihyperglycemic, cardioprotective
G. inodorum	Gymnemic acids, saponins, flavonoids	Rheumatic arthritis, gout	α-glucosidase inhibition, antioxidant, anti- inflammatory, antidiabetic
G. khandalense	High phenolic content	No recorded traditional uses (rare/ endemic)	Antioxidant, anti-inflammatory, potential antidiabetic
G. latifolium	Flavonoids, phenolics, terpenoids, glycosides	Indigenous herbal remedies	Antioxidant, α-glucosidase inhibition, stabilizes insulin ( <i>in silico</i> & <i>in vitro</i> )
G. lactiferum	Gymnemic acid	Tea and raw leaf use in Sri Lanka for diabetes	Lowers HbA1c, BP, LDL, triglycerides; supports weight loss
G. yunnanense	Steroidal aglycons, glycosides	Less documented	Enhances glucose tolerance, weight control, strong anti-hyperglycemic potential

regulation.

According to the WHO, a global target has been set to halt the rise of diabetes and obesity by 2025. Currently, approximately 830 million people live with diabetes, the majority of diabetes cases occur in low- and middle-income countries, where more than half of those affected do not receive adequate treatment due to limited access, high costs, or poor quality of care (6). In diabetes, the liver shows increased activity of glucose-6phosphatase (G6Pase) and decreased hexokinase activity. Elevated G6Pase activity contributes to the production of NADPH, which is essential for fatty acid synthesis from carbohydrates. Even when glycolysis slows down, the pentose phosphate pathway (PPP) remains active, ensuring a continuous supply of NADPH. This metabolic shift promotes lipid accumulation and insulin resistance, key factors in diabetes progression. Understanding these alterations can help in diabetes management by targeting metabolic pathways to regulate glucose production, enhance glucose utilization and reduce lipid synthesis, thereby improving overall glucose homeostasis (7).

## Gymnema sylvestre

G. sylvestre, a well-known species mostly found in India. Commonly referred to as "Gurmar", miracle fruit and sugar killer. The leaf is the primary plant part used for medicinal purposes. When the leaves are chewed, they momentarily impair the tongue's capacity to detect sweetness (8, 9).

Beyond its antidiabetic properties, the plant exhibits strong antidiabetic activity by inhibiting key carbohydrate-digesting enzymes, thereby reducing glucose absorption and helping to regulate postprandial blood sugar levels. Additionally, it enhances insulin secretion from pancreatic β-cells and improves glucose-stimulated insulin release more effectively than the standard antidiabetic drug glibenclamide. These combined mechanisms suggest that G. sylvestre could be a valuable natural therapeutic for diabetes management, particularly in controlling blood glucose levels and supporting insulin function. Its potential role in modulating triglycerides also warrants further investigation to establish its broader metabolic benefits. However, it is important to clarify that this refers not to dietary triglycerides, but to an active fraction enriched with gymnemic acids. The active fraction previously referred to as triglycerides were identified as a mixture of gymnemic acids, specifically gymnemic acids I, IV and VII, which are recognized for their antidiabetic properties and their role in inhibiting glucose absorption. Additionally, the presence of Gymnemagenin (Fig. 1c), a triterpenoid aglycone, was confirmed. Gymnemagenin plays a crucial role as the aglycone of gymnemic acids, contributing to their overall biological activity and effectiveness in glucose metabolism regulation (10). Gymnemic acid was found not only in the leaves but also in the shoot tips, internodes, nodes, flowers, roots and seeds. Additionally, its concentration in the

ABHIRAMI ET AL 4

leaves varied significantly, with young leaves containing a higher amount compared to middle-aged and older leaves (11).

The antidiabetic potential of the hydroalcoholic extract of G. sylvestre has been attributed to several mechanisms. It significantly inhibits intestinal glucose absorption, with a maximum inhibition of 76.25 % at a concentration of 100 µg/mL, suggesting interference with glucose transporters or uptake in the intestinal lining. Additionally, the extract enhances glucose uptake in skeletal muscle, showing a 28.6 % increase at the same concentration, which may facilitate glucose utilization and help regulate blood sugar levels. Furthermore, in silico studies have shown that gymnemic acid and deacyl gymnemic acid interact favorably with proteins involved in glucose metabolism and transport, potentially enhancing their functional activities. The extract also exhibits antioxidant properties by scavenging free radicals, which may reduce oxidative stress associated with diabetes. These findings highlight the extract's therapeutic potential, particularly through its bioactive components for the development of phytopharmaceuticals targeting diabetes management (12). Beyond its antidiabetic properties G. sylvestre has demonstrated antimicrobial, antiobesity, free radical scavenging, hypolipidaemic and anti-inflammatory activities (13), further supporting its broad therapeutic potential.

## Gymnema montanum

G. montanum leaf extract can be a natural support for diabetes management. It is effective in lowering high blood sugar by enhancing insulin secretion and improving glucose uptake in peripheral tissues (14). It also helps lower lipid levels, primarily due to the presence of bioactive compounds such as gallic acid and quercetin. This suggests that it could serve as a potential alternative or supplement to standard medications like glibenclamide, especially for individuals who prefer herbal treatments (15, 16). The leaves help to restore the normal activities of hexokinase and G6Pase, balancing carbohydrate metabolism and reducing blood fat levels. This leads to lower levels of triglycerides (TG), total cholesterol (TC), bad cholesterol and free fatty acids. The ability of G. montanum to lower LDL cholesterol may help reduce the risk of heart disease, a major concern in diabetes. By reducing these, it may help to lower the risk of coronary heart disease, a major cause of mortality in diabetic patients (7, 16). Comparing the effects of G. montanum with glibenclamide highlights the potential of the plant as an effective alternative or complementary treatment for diabetes, particularly in managing lipid profiles (16). Further exploration of G. montanum is warranted as a potential source for developing new antihyperglycemic antihyperlipidemic agents is warranted. This research could lead to the discovery of more effective drugs with fewer side effects compared to existing treatments (15). Incorporating G. montanum extracts into dietary practices or as nutraceutical supplements may offer significant public health benefits, especially in populations with high diabetes prevalence (16).

#### Gymnema inodorum

*G. inodorum* is a native edible leafy plant found in Chiang Mai Province, Northern Thailand. Unlike *G. sylvestre*, it neither suppress sweetness nor exhibits bitterness (17, 18). This plant

has been traditionally used for managing conditions such as rheumatic arthritis and gout (19). It is now recognized for its diverse pharmacological properties including antioxidant, antidiabetic and anti-inflammatory effects (20). The significant antidiabetic potential of is primarily attributed to its high content of gymnemic acids, saponins and flavonoids. These bioactive compounds play a crucial role in regulating blood glucose levels through multiple mechanisms. Gymnemic acids, the most abundant compounds in G. inodorum, are particularly known for their glucose-lowering effects by inhibiting glucose absorption in the intestinal tract (21). Additionally, crude saponin mixtures from plant were effective in maintaining stable blood sugar levels. It also demonstrates potent  $\alpha$ -glucosidase inhibitory activity, which helps slow carbohydrate digestion and glucose release into the bloodstream, thereby reducing postprandial hyperglycemia (22). Furthermore, ethanolic leaf extract of G. inodorum has been observed to modulate insulin resistance while exhibiting low cytotoxicity in cell-based studies, supporting its safety for therapeutic use. In addition to its effects on glucose metabolism, its antioxidant properties help protect pancreatic β-cells from oxidative stress-induced damage, further enhancing its antidiabetic benefits (23). Given its multifaceted pharmacological activities and favorable safety profile, G. inodorum holds considerable promise as a natural source for the development of novel antioxidant, antidiabetic and antiinflammatory therapeutics (20).

## Gymnema khandalense

This rare and endemic species, found exclusively in the Western Ghats of Maharashtra and Kerala, is notable for its rarity and specific habitat (24). It is a large climbing shrub with a mature corky stem about 6 cm in diameter. The young stem is tender, covered in small pores (lenticellate) and has fine hairs (pubescent). When cut, it releases milky white latex. The leaves are opposite, broadly elliptic-ovate, with a pointed tip and a flat base. They are leathery, densely hairy underneath and sparsely hairy on top, measuring 8-12.5 cm long and 5-8 cm wide. There are five or six pairs of lateral veins. The petiole is round, densely hairy and about 3-3.5 cm long. The flowers are slightly fragrant, small (0.8-1 cm) and grow in axillary clusters. The peduncle is about 1 cm long and the pedicel is around 0.7 cm. The calyx lobes are oblong, pointed, yellowishgreen and about 1-1.2 mm long, with hairy outer surfaces and edges. The yellow, bell-shaped corolla measures 3-3.5 mm in length and 1-1.2 mm in width, with fleshy, triangular lobes that are hairy inside and fringed along the edges (25).

Research has revealed that the roots of *G. khandalense* possess the highest total phenolic content among the four studied species (*G. sylvestre*, *G. hirsutum*, *G. elegans* and *G. khandalense*) based on phytochemical analysis of field-collected samples, suggesting significant medicinal potential. The high phenolic content in *G. khandalense* is crucial because phenolic compounds are known for their antioxidant and anti-inflammatory properties, which help regulate blood sugar levels. These compounds may enhance insulin secretion, improve glucose uptake by cells and inhibit carbohydrate-digesting enzymes, thereby reducing post-meal blood sugar spikes. This makes *G. khandalense* a promising candidate for developing natural antidiabetic treatments (24).

## Gymnema latifolium

G. latifolium is a synonym of the Indian endemic species G. kollimalayanum (26). The qualitative phytochemical analysis of Gymnema leaf aqueous extract confirmed the presence of phenols, flavonoids, terpenoids, saponins, glycosides, tannins and alkaloids. A quantitative study revealed a high flavonoid and phenolic content in the extract (27). The biological activity of flavonoids plays a crucial role in preventing lipid peroxidation, a key factor contributing to various diseases, including atherosclerosis, diabetes, hepatotoxicity, aging and inflammation (28). G. latifolium aqueous extract shows antioxidant properties in vitro. It can inhibit the α-glucosidase enzyme, which plays a key role in carbohydrate digestion and blood sugar regulation. Additionally, it helps stabilize insulin. In silico analysis confirmed that the active compounds in the extract can interact with human insulin and  $\alpha$ -glucosidase. Since the plant can reduce oxidative stress (by neutralizing harmful free radicals), help control blood sugar levels (by inhibiting α-glucosidase) and maintain insulin stability, it may have potential health benefits in managing type 2 diabetes mellitus (27).

## Gymnema lactiferum

G. lactiferum is a leafy vegetable that has been traditionally consumed. In Sri Lanka, diabetic patients chew the raw leaves. Due to the presence of gymnemic acid, the primary active compound in G. lactiferum, known for suppressing the taste of sweetness and potentially aiding in controlling blood sugar levels (29). Leaf powder of the plant did not show immediate blood sugar-lowering effects, but its long-term use gradually reduced fasting blood sugar (30). Tea made by dried leaves of the plant has been shown to significantly lower HbA1c levels in individuals with type 2 diabetes mellitus. HbA1c is a key marker of long-term blood sugar control and its reduction indicates better diabetes management (29). Additionally, the benefits of tea extend beyond blood sugar regulation. It also helps lower high blood pressure (hypertension), total cholesterol, low-density lipoprotein (LDL) cholesterol (often referred to as "bad" cholesterol) and triglycerides (TG) and also it supports weight loss, which is crucial for managing diabetes (29).

#### Gymnema yunnanense

Research has identified several bioactive compounds in G. yunnanense, including steroidal aglycons and glycosides, which contribute to its distinct chemical composition. Previous study (31) reported six steroidal aglycons in G. yunnanense, one of which was previously unknown, highlighting its unique phytochemical profile compared to other Gymnema species, such as G. sylvestre, which has been more extensively studied for its antidiabetic properties. Extracts of G. yunnanense have demonstrated significant potential in improving blood sugar control, enhancing glucose tolerance and supporting weight management key factors in diabetes care. Its strong antihyperglycemic effects may also help reduce reliance on conventional diabetes medications, making it a promising natural alternative or complementary treatment. Given the growing interest in herbal remedies over synthetic drugs, G. yunnanense holds potential as a valuable therapeutic option for diabetes management (32). Since G. yunnanense is less well

known compared to other species, further validation through studies in human models is necessary to confirm its medicinal potential.

## **Gymnema tingens**

G. tingens has long been used in Chinese folklore medicine for the treatment of rheumatism and polio, highlighting its traditional medicinal significance. Recently, four novel triterpenoid saponins, identified as Tigensides A-D (1-4), have been extracted from G. tingens. These compounds exhibit significant bioactivity, particularly in enhancing glucose uptake, with an increase ranging from 1.12 to 2.52 times. Given these findings, G. tingens shows strong potential for the development of novel antidiabetic agents (33). Its unique botanical characteristics include multicellular uniseriate trichomes, druses of calcium oxalate crystals and paracytic stomata. Physicochemical properties such as bulk density, ash value, specific gravity, pH and aqueous extractive value help in determining its quality. The plant contains key phytochemicals like alkaloids, phytosterols, saponins, flavonoids and tannins, contributing to its medicinal properties. Fluorescence analysis, which involves observing the color emitted by plant powder treated with various reagents under UV light, further confirms its distinct phytochemical composition. These findings establish baseline quality standards essential for ensuring the authenticity and efficacy of G. tingens preparations, supporting its use in herbal formulations for diabetes management and other therapeutic applications (34).

## **Future prospects**

Future studies should prioritize comprehensive phytochemical profiling, clinical trials and mechanistic investigations to validate the efficacy and safety of these underexplored species. Advances in biotechnology and metabolomics may facilitate the identification of novel bioactive compounds that enhance glucose metabolism and insulin sensitivity. The integration of *Gymnema* extracts into functional foods, nutraceuticals and pharmaceutical formulations presents another exciting avenue for diabetes management. Combining *Gymnema* with other herbal and synthetic antidiabetic agents could lead to synergistic effects, reducing reliance on conventional medications while minimizing side effects. Overall, the future of *Gymnema* research lies in unlocking the full therapeutic potential of both well-known and underexplored species, paving the way for innovative and sustainable diabetes treatments.

#### Conclusion

Gymnema species, particularly G. sylvestre, have long been recognized for their anti-diabetic properties, with extensive research supporting their ability to regulate blood sugar levels through multiple mechanisms. While G. sylvestre remains the most studied, other species such as G. montanum, G. latifolium and G. yunnanense also contain bioactive compounds with promising therapeutic potential. Despite their phytochemical and pharmacological significance, these lesser-known species remain largely underexplored. Expanding research on the diverse Gymnema species could lead to the discovery of novel, cost-effective treatments for diabetes, addressing the growing global burden of the disease. Future studies should focus on detailed pharmacological evaluations and clinical trials to

ABHIRAMI ET AL 6

validate their efficacy and safety, particularly for populations with limited access to conventional diabetes therapies. Unlocking the full potential of these underutilized plants may contribute to the development of more accessible and sustainable solutions for diabetes management.

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#### **Authors' contributions**

The first draft of the manuscript was written by VAA. MV provided guidance for overall correction and improvement. TS, SP, MK and GGK assisted with literature collection and formatting. All authors contributed equally to revising the manuscript and approved the final draft.

# **Compliance with ethical standards**

**Conflict of interest:** Authors do not have any conflict of interests to declare.

**Ethical issues:** None

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