JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/44121

SHORT REVIEW

A Comprehensive Review on the Role of *Gymenma sylvestre* in Combating Diabetes-2

S. M. Bhatt* and Navneet Sharma

Biotechnology Department, IIMT University, Meerut – 250001, Uttar Pradesh, India; drsmbhatt@gmail.com

Abstract

The current review focuses on a detailed comprehensive role of *Gymnema sylvestre* (GS) and other herbs for their Ayurvedic impact in controlling blood sugar by releasing insulin from the pancreas in diabetic Type 2. *G. sylvestre* (GS) supplementation has also been seen to leave an impact on various cardiovascular risk factors and improves the lipid profile, blood pressure, anthropometric indices, and control of glycemia. Additionally, extracts of *Gymnema* have been shown to have an inhibitory impact on triglyceride accumulation in muscles and the liver, while reducing the buildup of fatty acids in the bloodstream, thus also reducing HB1C parameters. In the current review, we have also discussed information about Gymnemic acid structure isolation their sources, their clinical effects in diabetic control in Type 1 and Type 2, and clinical effects over the humans and mice signalling as immunomodulators.

Keywords: Gymnemic Acid, *Gymenma sylvestre Ayurvedic*, Immunomodulators, Nutraceuticals

1. Introduction

The 2019 IDF report provided an update indicating that China, India, and the USA reportedly had the highest number of people living with diabetes: 116.4 million, 77.0 million, and 31.0 million, respectively. This trend is projected to continue in 2030 and 2045, where China will remain, together with India, among the countries carrying the largest burden of diabetes[1] (Figure 1).

Diabetes Mellitus is a chronic metabolic disorder characterized by high blood sugar levels because of the inability of the body to either produce or use insulin. Insulin is the hormone produced by the pancreas that maintains the sugar level in blood by providing used-up energy to the parts of the body through the entry of glucose into the cells[2].

After COVID-19, the incidence of Diabetes Mellitus Type 2 (DM2T) is escalating at a rapid pace, making it a significant metabolic endocrine disorder with a global impact. The most recent estimates give a global prevalence of 537 million adults having diabetes in 2021, projected to rise to 783 million by 2045[3] (Figure 2). The state-wise details of diabetes are shown in Figure 3.

As per the report, there is a high risk of developing diabetes-2 type in survivors of Covid-19[1]. Patients without a prior history of diabetes have been reported to experience new-onset hyperglycemia and insulin resistance as a result of coronavirus COVID-19[3]. After the remission of COVID-19, cytokines and TNF-α continue to be elevated, potentially leading to beta cell impairment and insulin resistance the development, as a result, NDD (Newly Diagnosed Diabetes mellitus) develops.

The possible causes of diabetes have been identified as, it may be genetic, which is characterized by the immune system attacking pancreatic beta-cells and damaging most parts as in Type 1 Diabetes (T1D) or it can be associated with resistance to insulin as in Type 2 Diabetes (T2D). Environmental factors[4], which is also nowadays recognized as Lifestyle diseases, mainly because of pollution or plastic used for food packaging, unhealthy diet, lack of physical activity, stress, and exposure to enteroviruses, and artificial cosmetics[5] are all environmental factors that contribute to the development of both Type 1 and Type 2 diabetes[6-11] and is most common now. Other factors recently

*Author for correspondence

Article Received on: 21.05.2024 Revised on: 04.08.2024 Accepted on: 27.08.2024

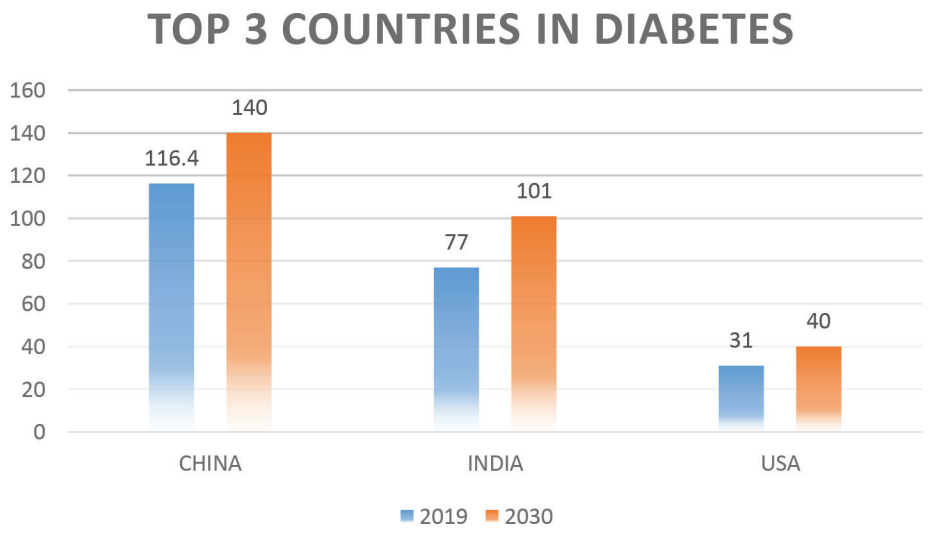

Figure 1. Current trend in Diabetes: 1 – China, 2 – India, 3 – USA, 2019 and 2030 data are shown in millions[1].

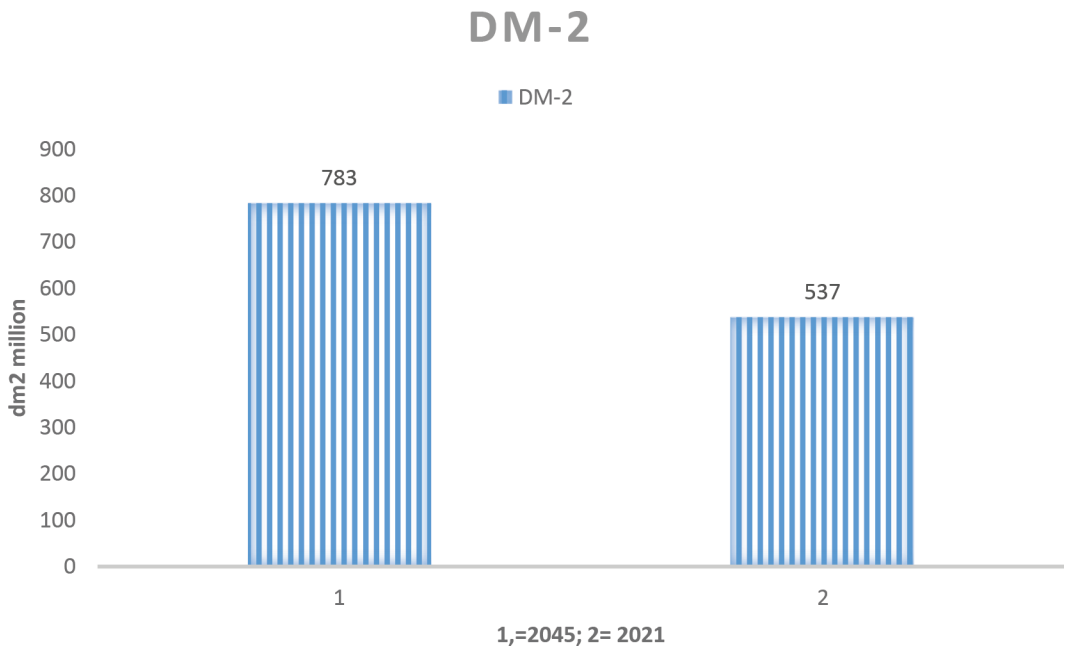

Figure 2. Global cases of DM2 I 2021 and 2045[3].

reported are epigenetics in nature[12], gut microbiome[13], and endocrine disruptors on the development and advancement of diabetes[14].

Dietary preferences and eating behaviours have a significant impact on the likelihood of developing diabetes and effectively controlling the disease. Eating behaviours have shown a significant impact on the likelihood of developing diabetes[15], such as poor dietary habits established during childhood[16], consumption of sugary beverages, fast food processed foods[17], the frequency of meals consumed, the quantity of food intake, how meals are consumed (e.g. skipping breakfast, snacking, or eating speed[18], all these factors play a major role in the development of various types of diabetes.

Moreover, personalized dietary plans, such as a 30% or 50% carbohydrate intake, can influence blood sugar management in individuals with Type 1 diabetes, where eating more vegetables and grains and less fats are linked to better results[19]. Nevertheless, although dietary interventions are effective, the number of people with diabetes is rising in the US, emphasizing

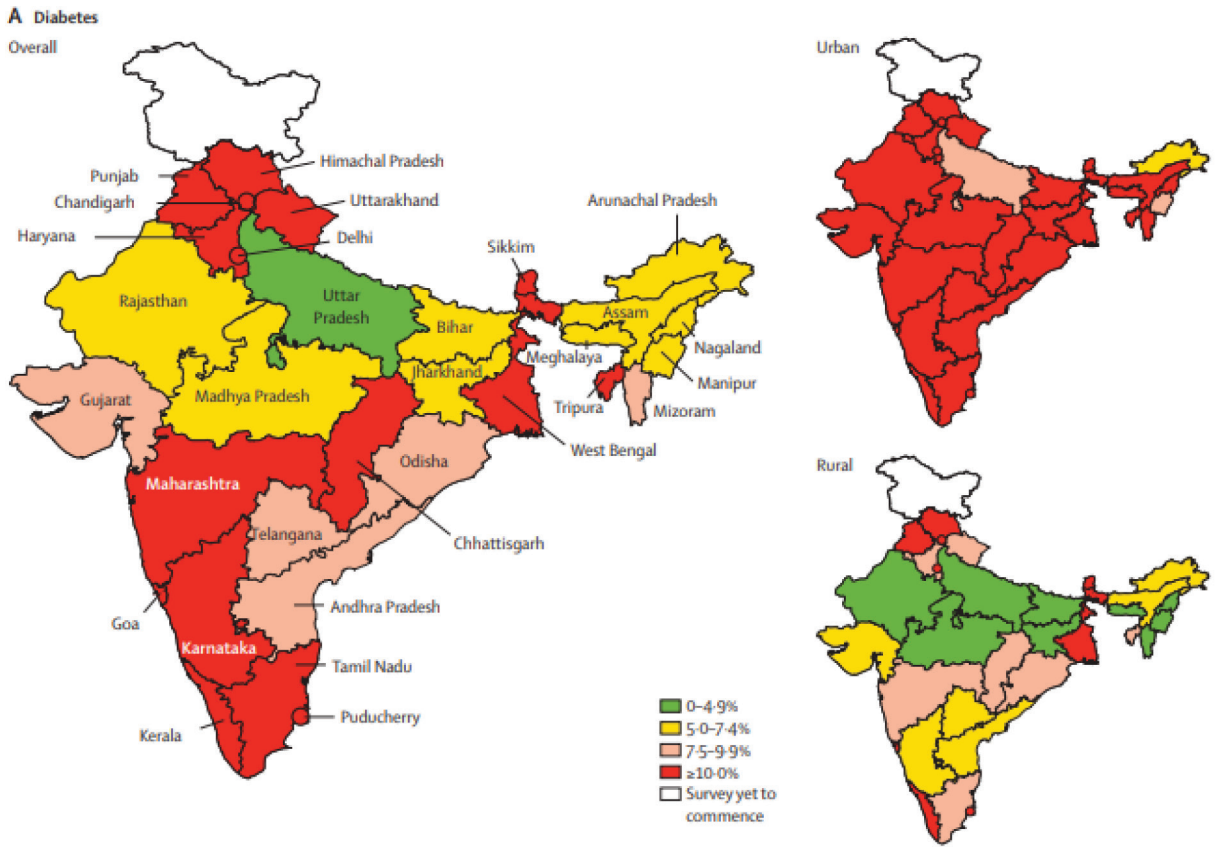

Figure 3. India state-wise report: Source of diabetes prevalence. Many red zones such as Maharashtra, West Bengal, Karnataka, Kerala, Chhattisgarh, Uttarakhand, Himachal Pradesh and Punjab have greater than 10% diabetic prevalence[30].

the need to address the deteriorating dietary control in individuals with diabetes[20]. Nurses and dietitians are crucial in educating patients about healthy eating and debunking common myths about diets to enhance diabetes results[21,22].

Combining strategies is essential for effective diabetes management. Establishing specialized diabetes teams within primary care facilities, like those in Canada, has the potential to improve patient access to education and support[23]. The use of continuous interstitial glucose monitoring systems, along with collaboration between various health professionals such as general practitioners, diabetologists, nurses, and dieticians, can lead to a noticeable enhancement in glycemic control[24]. Collaboration among healthcare providers from different professions is crucial, as inadequate communication can result in mistakes in diabetes treatment[25]. Furthermore, it is crucial to consider Social Determinants of Health (SDoH) when managing Type 2 diabetes, as health professionals stress the importance of integrating SDoH into individual clinical care for improved self-management and person-centred care[26]. By combining these methods, healthcare providers and individuals can collaborate to improve the prevention and management of diabetes.

2. Type of Diabetes

There are three varieties of diabetes distinguished as T1D, T2D and gestational diabetes.

2.1 Type 1 Diabetes (T1D)

Type 1 diabetes occurs when the pancreatic β-cells are destroyed by the self-immune system[27]. As a result, no insulin production occurs, which results in multiple insulin injections to manage the diabetes.

2.2 Type 2 Diabetes (T2D)

Type 2 is the most prevalent diabetes and occurs when a person's body becomes insulin resistant or does not

secrete sufficient insulin to meet the body's needs. In most cases, this type of diabetes goes along with lifestyle factors like obesity, lack of physical activity, or poor diet. Frequently, it can be successfully managed only by changes in lifestyle, including weight loss, regular exercise, and a healthy diet. There are, however, some who are prescribed oral medications or even insulin therapy to maintain their blood sugar levels[3]. Too high blood sugar that is over 200mg/dl is hyperglycemia. At the time of the diagnosis, women generally seem to carry a greater burden of the risk factors, with obesity showing up very dominantly in this Type 2 diabetes diagnosis[7].

Up-regulation of protein tyrosine phosphatase 1B is one of the main hallmarks of Type 2 Diabetes Mellitus and has been suggested to be a negative regulator of insulin signaling. Type 2 diabetes is a multifactorial disease that arises from a combination of genetic and environmental factors, featuring insulin resistance and a relative lack of insulin secretion.

2.3 How does the Insulin Signalling Pathway Regulate Diabetes and Obesity?

In its totality, insulin signalling represents intricate processes of insulin binding to its receptor on the surface of target cells. It leads to intracellular events that vertically prolong up to glucose uptake from blood into the cells. However, the upregulation of PTP1B in Type 2 Diabetes Mellitus disrupts this process. Insulin resistance comes out as yet another prime player in the causation of the disorder called Type 2 diabetes.

It is a state whereby cells of the body become resistant to the effects of insulin, hence the increase in the level of glucose in the blood. Genetic factors and environmental factors may bring about this type of resistance. Genetic change may result in impairment of the response of the body to insulin. Environmental factors, for instance, obesity, overeating, and reduction of activities can cause one to be resistant to insulin.

3. Gymnemic Acid as a Positive Regulator of Insulin Signalling

PTP1B acts either as a negative regulator for insulin signalling or as a dephosphorylating enzyme of key proteins in the pathway for insulin signalling. One of its primary targets is the insulin receptor itself. By dephosphorylating the insulin receptor, PTP1B reduces its activity and impairs the downstream signalling events. Many good reviews are available on detailed aspects of this[28].

Among all the tyrosine phosphatases, PTP1B is considered to be quite well characterized, and it serves as both an important negative and positive modulator for most of the signal transduction pathways. The direct regulation of both the insulin receptor and the leptin receptor by PTP1B was good enough to make it an ideal potential therapeutic target for intervention against Type 2 diabetes and obesity. Furthermore, PTP1B also dephosphorylates Insulin Receptor Substrates (IRS), which are proteins that transmit signals from the insulin receptor to downstream signalling molecules. Dephosphorylation of IRS by PTP1B inhibits their ability to activate downstream signalling pathways, further compromising insulin signalling[29].

Up-regulation of PTP1B in Type 2 Diabetes Mellitus: Desensitization to insulin effects is caused by the increased concentration of PTP1B, whereby the body cells become less responsive to the effects of insulin. This is followed by reduced glucose uptake into the cells and increased blood glucose levels.

Elucidation of the role of PTP1B in Type 2 Diabetes Mellitus has opened up new avenues for therapeutic interventions. Hence, PTP1B inhibitors were developed as a potential therapy for the treatment of Diabetes Mellitus. These inhibitors prevent the activity of PTP1B in people with Type 2 Diabetes Mellitus and hence can reinstate insulin signalling by improving glucose uptake.

In summary, PTP1B is upregulated as a negative regulator of insulin signalling in Type 2 Diabetes Mellitus. It has been considered that overactive PTP1B perturbs insulin signalling, resulting in insulin resistance and thereby increasing blood glucose. Targeting PTP1B has become one of the potential therapeutic strategies to treat Type 2 Diabetes Mellitus[29].

4. Factors in the Development of Diabetes 2

Another environmental factor related to the development of T2D is physical inactivity. Inactivity can precipitate events such as weight gain, insulin resistance, and defects in glucose metabolism. Regular

exercise improves insulin sensitivity and maintains a healthy weight, hence reducing the risk of developing diabetes[5]. Other environmental factors or plastic used for food packaging, unhealthy diet, lack of physical activity, stress, and exposure to enteroviruses, and artificial cosmetics[5] are all environmental factors that contribute to the development of both Type 1 and Type 2 diabetes[6-11] also contribute to virtually all aspects of the pathogenesis of T2D.

Other causes of Type 2 diabetes also include stress. Going for a longer period under stress might lead to hormonal misbalance, increased inflammation and high blood glucose levels—physiological responses that could promote the development of insulin resistance and, hence, progress toward diabetes.

Finally, ageing is a natural risk factor for the development of Type 2 diabetes. As one gets older, the gradually declining body begins to produce lower amounts of insulin and finally uses less insulin than at younger ages. This means, that age-related decline in insulin function, coupled with genetic and environmental risk factors accumulated throughout one's lifetime, predisposes one to suffer from diabetes. Hence, finally, Type 2 diabetes represents a multifactorial disease whose pathogenesis is owing to the interacting genetic components of compromised insulin secretion and insulin resistance combined with various environmental factors, such as the plastic used for food packaging, unhealthy diet, lack of physical activity, stress, and exposure to enteroviruses, and artificial cosmetics[5].

Type 2 diabetes results from genetic predisposition. Genetic studies identified the susceptibility genes involved in this disease a

nd regulate insulin secretion, action, and glucose metabolism[31].

Alterations in genes can lead to impaired insulin production or reduced effectiveness of insulin in the body, making individuals more prone to developing diabetes.

4.1 Gestational Diabetes

Gestational diabetes is a carbohydrate intolerance. It is an illness that starts during pregnancy, mainly due to hormonal changes, and often clears up on its own after childbirth. The placenta produces many hormones during pregnancy, which can interfere with the body's effectiveness in using insulin. A woman who has had gestational diabetes runs an increased risk for the future development of type-2 diabetes.

If not controlled, diabetes can cause complications in the cardiovascular system, kidneys, nerves, and the eyes. That is why patients with this disorder must regularly measure their blood sugar levels, follow a healthy diet, exercise regularly, and take other prescribed medications as directed to avoid or manage these possible complications.

Other key components of the management of diabetes incorporate self-management education and support programs, which could help patients learn to take better care of their diseases and enhance their quality of life. In this article, we have discussed various herbal plant uses in curbing diabetes 1 and diabetes 2.

5. *Gymnema sylvestre* R. Br. as a Source of Remedy to Diabetes

In the Asclepiadaceae family, *Gymnema sylvestre* R. Br. is a globally recognized and distributed herb. Its leaves (Figure 4) are extensively utilized in Indian proprietary medicines for managing diabetes - 1 and 2 and acting as a diuretic[11].

Gymnema sylvestre, also known as *Gurmar*, has anti-diabetic properties[33]. It is known for its multifaceted approach to maintaining healthy blood sugar and supporting pancreas function[33]. The Sanskrit name for the plant is *Madhunashini***,** which is widely recognized for its ability to treat diabetes and its main component is gurmarin. According to studies, it normalizes blood sugar levels, strongly supports weight loss,

Figure 4. Plant of *Gymenma sylvestria* Br.

and significantly improves insulin sensitivity. These additional properties make gurmarin a multifunctional peptide with significant potential in the field of nutrition and health[34]. *Gymnema* is native to S. China, India and Sri Lanka.

5.1 Bioactive Components *Gymnema*

Many studies show that the phytochemical composition of *Gymnema* in methanolic extraction contains flavonoids, alkaloids, total phenol, saponins, and tannins. In the case of *Gymnema*, flavonoids are 8.56 ± 0.50 mg/g, alkaloids - 13.84 ± 0.67 mg/g, total phenol 1.98 ± 0.50 mg/g, saponins - 23.85 ± 0.35 mg/g, and tannins - 16.00 ± 0.34 mg/g[13] (Figure 5). It was revealed in the study on rats that the extract and fractions decreased body weight when administered at various doses of 300 and 600 mg/kg BW. The very doses were found to have a significant, $p<0.05$, impact on levels of some biochemical indices like aspartate transaminases, alanine transaminase, and alkaline phosphates[35].

The composition of *G. sylvestre was* analyzed by Murakami *et al.*[36] which reported that Gymnemic acid is the main constituents. The plant's bioactive component mainly consists of a collection of acids known as gymnemic acids[37] (Figure 6). Gymnemic acids, found in the leaves and extracts, are the primary bioactive components that engage with taste receptors on the tongue, resulting in a temporary suppression of sweetness perception. Besides this gymnemic acid has been used in different metabolic disorders such as bone regeneration[38], on liver and kidney functioning: *in vivo* study[39], improvement of lipid metabolic profile in diabetic 2 patients[40], in polycystic ovarian syndrome[41].

Gymnemic acid is a triterpenoid saponin and is the primary active compound responsible for the plant's pharmacological effects which is a secondary metabolite produced (Figure 6) Gymnemic acid is the main component of the *G. sylvestre*[42].

Gymnema, a medicinal plant native to India and Africa, is known for its unique set of 9 closely associated acidic glycosides. These glycosides, including gymnemic acids A, B, C, and D, are the most significant compounds found in *Gymnema*.

The pharmacological properties of this secondary metabolite are numerous: nephroprotection, hypoglycemia, antioxidant, antimicrobial, and

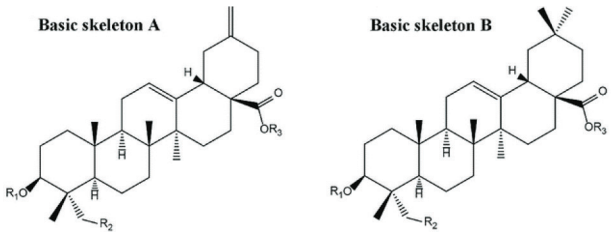

Figure 6. The basic skeleton of triterpene saponin A and B.

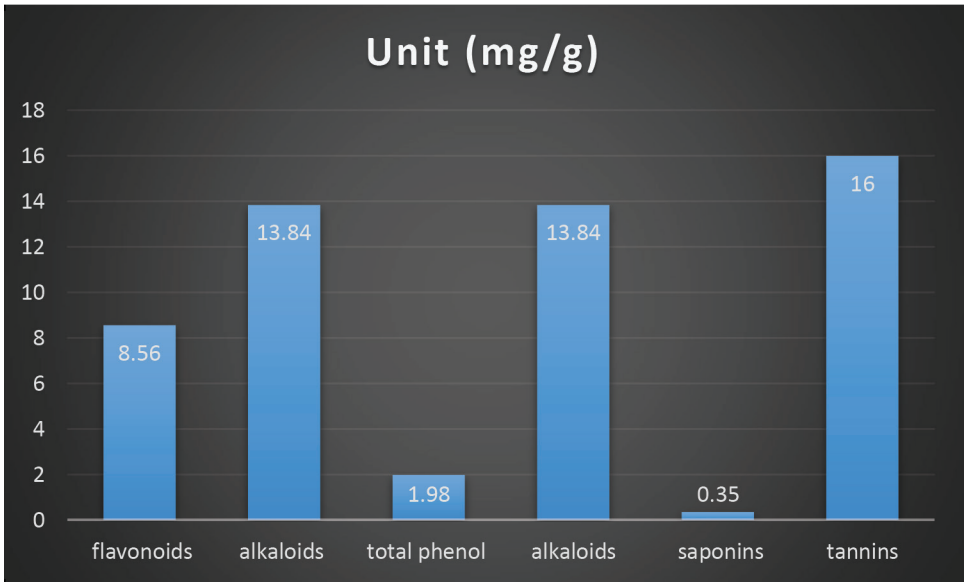

Figure 5. *Gymnema sylvestre* analysis for bioactive components such as flavonoids alkaloids total phenol saponins and tannins.

anti-inflammatory activities. Recently, much attention has been paid to *Gymnema*, with minimal side effects and high efficacy in the treatment of diabetes; it seems to be one of the largest used herbal medicines for the cure of diabetes[43]. Consequently, pharmaceutical companies have excessively exploited the plant's biomass in the wild to extract gymnemic acid.

The bitter test of *G. sylvestre* is due to the presence of Saponin, which is a triterpenoid glycoside that comes out when it is boiled in water. *G. sylvestre* triterpene saponins are known as gymnemic acids, *Gymnema* saponins, and a polypeptide, gurmarin[22]. This has been a medicinal plant in the treatment of diabetes and other disorders. The active ingredients of this herb inhibit the absorption of glucose and reduce cravings for sweet foods due to gymnemic acids. However, further studies are required to establish its efficacy and possible side effects[44].

5.2 Therapeutic Effect of Different Secondary Metabolites Present in *Gymnema*[32]

In addition to its sweet taste-suppressing properties, gurmarin derived from *G. sylvestre* has also been found to possess other potential health benefits. Some of them are predicted in Table 1.

The major chemical constituents of *G. sylvestre* include a group of triterpenoid saponins called gymnemic acids, which have been reported to possess anti-diabetic activity in the extracts[2]. Besides, gymnemic acids have been reported to exert beneficial influences on the kidney microvasculature and anti-angiogenic activities related to the expression of VEGF protein in STZ-induced diabetic rats. In addition, gymnemic acid exhibited antidiabetic, antilipidemic, and anti-inflammatory activities.

5.3 Medicinal Uses of *G. sylvestre* in Treatment of Diabetes

Gymnema sylvester has long been recognized for its therapeutic potential and is highly valued in Ayurvedic medicine. Numerous studies have demonstrated the ability of *G. sylvester* leaf extracts to reduce hyperglycemia in humans, diabetic rabbits and rats.

Gymnema sylvestre has been reported to be used against both Type 1 and 2 diabetes mellitus, but it has also been applied in various other diseases—for example, according to some studies, it has neuroprotective effects and it is supposed to help in the regeneration of pancreatic β-cells[44]. It has also been found to exhibit strong anti-diabetic properties and an anti-saccharin flavouring effect[57]. The plant has also been shown to inhibit α-glucosidase activity, further supporting its potential in glycemic control[58]. Furthermore, *G. sylvestre* has been reported to possess normoglycemic and hypolipidemic activities, making it a potential candidate for diabetes management. Its insulinotropic activity and ability to improve glucose tolerance have also been documented, indicating its potential to stimulate insulin secretion and synthesis[2]. *G. sylvestre* has strong anti-diabetic properties and has been applied in folk medicine in India since ancient times[59].

Table 1. Medicinal activities of *Gymnema*

1	α-Amylase and α-glucosidase inhibitor from *Gymnema* extract (methanol exts).	Leaves/stem	45
2	The antidiabetic activity was studied in alloxan-induced diabetic rats.	Oral polyherbal suspension is for antidiabetic activity.	46,47
3	Antioxidant activity of *Gymnema*.		48
4	Anti-inflammatory		49
5	Anti-obesity		50
6	Anti cancerous		51
7	Immunomodulatory effect		52
8	Analgesic activity		53
9	As potent nutraceuticals for various metabolic disorders.		54
10	Treatment of Type 2 diabetes mellitus.		55
11	Lymphocyte differentiations.		56

Gymnema sylvestre plant contains Gymnemic acid as its main active chemical constituent. This plant is known for its beneficial effects on digestion, inflammation, diuresis, hypoglycemia, and helminthiasis. It has been traditionally used also for treating leucoderma, dyspepsia, jaundice, constipation, haemorrhoids, asthma, cardiopathy, and bronchitis. Given this, extensive literature reviews have been made out on various pharmacological activities of the plant, including antidiabetic, antiobesity, hypolipidemic, antimicrobial, free radical scavenging, and anti-inflammatory effects.

5.4 Gymnemic Acid Therapeutic Effect

Gymnemic acid has been found to possess both anti-obesity and antidiabetic properties, making it a valuable tool in the fight against these conditions. It aids in weight reduction by inhibiting glucose absorption, thereby reducing the amount of sugar that is converted into fat. This mechanism not only helps in weight management but also contributes to the prevention and control of diabetes. In addition, it is reported to inhibit triglyceride accumulation in muscles and the liver by different components extracted from *Gymnema*. Triglycerides are a type of fat that can build up in these organs, leading to complications such as fatty liver disease. By inhibiting this accumulation, *Gymnema* extracts help maintain the health of these vital organs. Besides blocking the buildup of triglycerides, extracts from *Gymnema* also reduce the accumulation of bloodstream fatty acids. Large amounts of fatty acids can lead to conditions such as atherosclerosis, which is essentially the hardening and narrowing of arteries. By reducing the presence of these harmful substances in the bloodstream, *Gymnema* extracts help protect against cardiovascular diseases. *Gymnema inodorum* (GI) tea could help to prevent obesity by inhibiting adipocyte differentiation[50]. Gymnemic acid therapeutic effect has been given in Figure 7.

5.5 *Gymnema* Leaves as Anti-Diabetic Therapeutics

These glucose-lowering effects are believed to be attributed to increased insulin secretion. Furthermore, the methanolic extracts from the leaves and callus of *G. sylvestre* exhibited promising anti-diabetic activities through the regeneration of beta-cells. Although little research has been documented on the active agents in these extracts, aqueous-ethanolic extractions have resulted in two hopeful active fractions. One

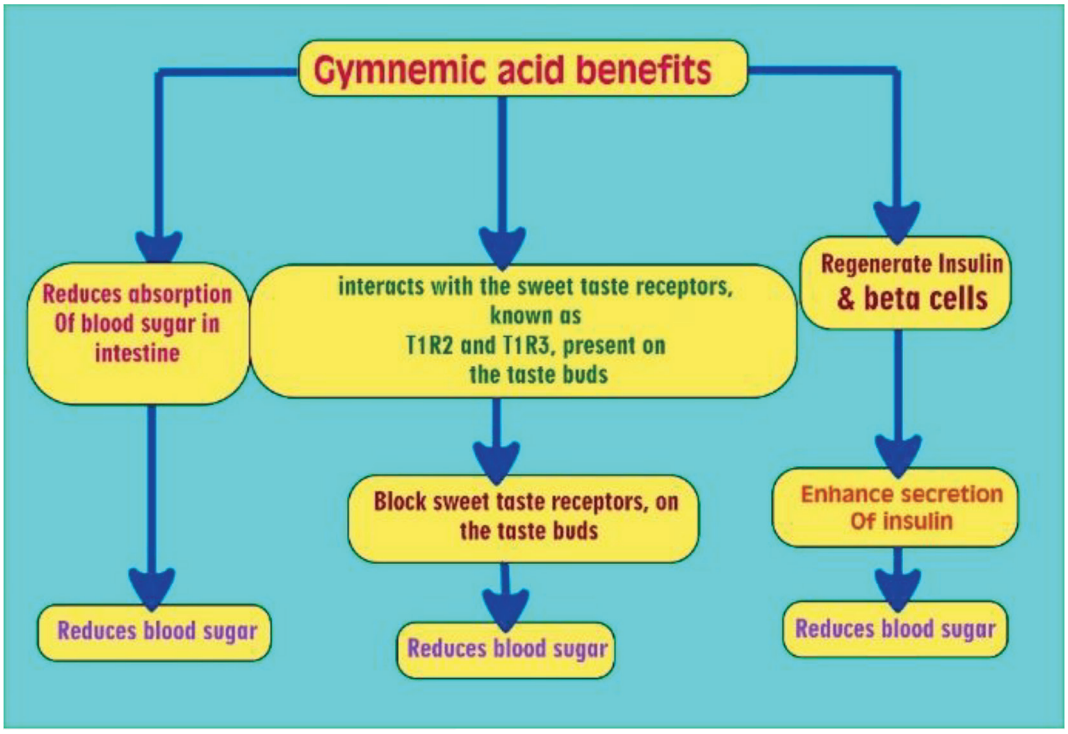

Figure 7. Gymnemic acid benefits.

fraction contains conduritol A, while another one—a mixture of acidic-soluble polyol-polyhydroxy cyclic compounds—contains an acid-insoluble triterpenoid saponin mixture called GS3 and GS4, glycemic acids.

The *Gymnema* leaf extract possesses various properties such as cough suppressant, diuretic, and laxative. However, these effects may be considered unfavourable when the extract is used for its intended purpose of lowering glucose levels in diabetes patients. Additionally, the peptide "Gurmarin" found in the extract has been discovered to disrupt the taste buds' ability to detect sweet and bitter flavours.

Some current reports indicate the potency of gymnemic acid formulations against obesity, most likely due to their ability to retard glucose absorption in the blood. Gymnemic acid molecules bind the taste buds receptor and also to absorptive outer layers of the intestine, thus blocking activation by sugar molecules in food and absorption of sugar molecules by the intestine, respectively. Since the atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules, they are known to suppress starving for sugar and result in lower blood sugar levels[60].

One of the bioactive constituents, gymnemic acid, is extensively studied in *G. sylvestre* for anti-diabetic activities. Among the major active constituents, a group of triterpenoid saponins known as gymnemic acids has been considered to be the active compounds responsible for the anti-diabetic properties of the extracts of *G. sylvestre*[2]. These gymnemic acids have been found to stimulate insulin release and synthesis, improve glucose tolerance, and have anti-inflammatory activities. In addition, they showed antidiabetic, antilipidemic, and anti-inflammatory activities[61]. Furthermore, gymnemic acids reportedly act by inhibiting the intestinal absorption of glucose and oleic acid[62]. Studies have also demonstrated the immunomodulatory properties of gymnemic acid, stimulating lymphocyte proliferation.

The presence of gymnemagenin and gymnemic acids in *G. sylvestre* extract has been recognized as being responsible for its antihyperglycemic effect[63]. Moreover, gymnemic acid, a structure of the saponin family of triterpene glycoside, which is present in the leaves of *G. sylvestre*, has been shown to exert potent anti-diabetic action[64]. Additionally, *G. sylvestre* extracts induced increased membrane permeability, thereby stimulating insulin release *in vitro*, this is a therapeutic potential for the treatment of noninsulin-dependent diabetes mellitus.

The 35-amino-acid peptide Gurmarin is a significant component found in *G. sylvestre* extract, identified for its sugar suppression action. This peptide has been shown to adhere to bitter and sweet taste receptors, temporarily inhibiting taste and thereby lowering sweet cravings. Furthermore, it is reported that gurmarin also inhibits calcium responses of cells expressing the sweet taste receptor protein in response to activation by sweetener-mediated means, T1R2/T1R3, thereby modulating sugar-feeding behaviour. Furthermore, gurmarin has been demonstrated to depress taste responses to sugars and saccharin sodium, indicating its potential to inhibit sweet taste. Moreover, gurmarin has been reported to prevent the absorption of sugary foods, thus contributing to glycemic control in Type 2 diabetes patients.

The presence of gurmarin in *G. sylvestre* extract aligns with its traditional use in managing Type 2 diabetes, as it contributes to the suppression of sweetness and sugar absorption. This supports the findings that *G. sylvestre* extract helps promote weight loss and controls blood sugar levels. The inhibitory result of gurmarin on sweet taste receptors and its ability to modulate sugar-feeding behaviour make it a promising candidate for further research in the management of diabetes and obesity.

A mixture of triterpene glycosides is made to form Gymnemic acid isolated from the leaves of *G. sylvestre*. The plant extract has been under extensive research owing to its potential pharmacological properties. Leaves of *G. sylvestre* are the active ingredients, which are triterpene saponins belonging to the oleanane and dammarane series[65]. These saponins, including gymnemic acid, have been found to possess normoglycemic and hypolipidemic activity, stimulating insulin secretion without compromising β-cell viability[65]. Additionally, *G. sylvestre* leaf extract has been shown to have immunomodulatory effects, with a significant gymnemic acid content. In an animal study, the leaf extract of *G. sylvestre* improved the serum cholesterol and triglyceride levels by influencing lipid metabolism[66].

The potential beneficial effects of isolated triterpene glycoside fractions of *G. sylvestre* on blood sugar control have been investigated *in vitro*[67]. Moreover,

G. sylvestre has been found to contain more than 20 saponin glycosides, including gymnemic acid, and has been shown to possess anti-diabetic and antioxidant potential[2]. The active ingredient of *G. sylvestre*, gymnemic acid, was reportedly effective in exerting beneficial effects on vascular architecture and vascular endothelial growth factor in the kidney tissues of diabetic rats[68]. Furthermore, the isolation of gymnemic acid was characterized as a mixture of triterpene glycosides, among which gymnemic acid I, IV, VII, and gymnemagenin have shown great promise in diabetic treatment[69].

In the 2009 study by Liu *et al.*, the alcoholic extract of *G. sylvestre* (GS4) was tested for insulin secretion in islets of Langerhans and a variety of pancreatic β-cell lines. The results revealed that GS4 effectively stimulated insulin release from both β-cells and islets even without any additional stimulus. However, when 1mM EGTA was present, the GS4-induced insulin secretion was found to be inhibited[70].

Gymnemic acids are also attributed to suppress the sweet taste sensation in human beings, representing a mixture of triterpene glycosides isolated from *G. sylvestre*[67]. Apart from this, various gymnemic acids from GA I to GA XVIII have been reported from the leaves of *G. sylvestre*[67]. Furthermore, gymnemic acids have been found to have anti-inflammatory, anti-sweetener, and anti-diabetic activities[71].

6. Conclusion

The use of herbal products and secondary metabolites derived from traditional medicinal plants holds potential in the treatment of diabetes. However, it is crucial to conduct thorough studies to validate their effectiveness and safety. Large-scale clinical trials are necessary to determine the appropriate use and dosage of these natural preparations for diabetes management.

In conclusion, gymnemic acid, a compound isolated from *G. sylvestre*, has been found to possess various anti-diabetic properties, including antihyperglycemic, insulinotropic, and anti-inflammatory effects. These effects have been attributed to gymnemic acids and gymnemagenin present in the plant extract, which could perhaps form the basis for its potential therapeutic use in the management of diabetes.

7. Acknowledgement

The authors are thankful to the entire family of the Department of Biotechnology and Mr. Akash Philip for help during the revision.

8. References

1. Sentongo P, Zhang Y, Witmer L, Chinchilli VM, Ba DM. Association of COVID-19 with diabetes: A systematic review and meta-analysis. Sci Rep. 2022; 12(1):20191. https://doi.org/10.1038/s41598-022-24185-7
2. Laha S, Paul S. *Gymnema sylvestre* (Gurmar): A potent herb with anti-diabetic and antioxidant potential. Pharmacogn J. 2019, 11:201-6. https://doi.org/10.5530/pj.2019.11.33
3. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after COVID-19. Diabetologia. 2022; 65(6):949-54. https://doi.org/10.1007/s00125-022-05670-0
4. Beulens JWJ, Pinho MGM, Abreu TC, den Braver NR, Lam TM, Huss A, *et al.* Environmental risk factors of Type 2 diabetes-an exposome approach. Diabetologia. 2022; 65:263-74. https://doi.org/10.1007/s00125-021-05618-w
5. Fauziah M, Suhartono S, Widjanarko B, Gasem MH. Phthalates exposure as environmental risk factor for Type 2 diabetes mellitus. Int J Public Heal Sci. 2023; 12(1):172-80. https://doi.org/10.11591/ijphs.v12i1.22280
6. Alhowikan AM, AL-Ayadhi LY, Halepoto DM. Impact of environmental pollution, dietary factors and diabetes mellitus on Autism Spectrum Disorder (ASD). Pakistan J Med Sci. 2019; 35(4):1179-84. https://doi.org/10.12669/pjms.35.4.269
7. Öhlund M, Egenvall A, Fall T, Hansson-Hamlin H, Röcklinsberg H, Holst BS. Environmental risk factors for diabetes mellitus in cats. J Vet Intern Med. 2017; 31(1):29-35. https://doi.org/10.1111/jvim.14618
8. Zheng W, Chu J, Bambrick H, Wang N, Mengersen K, Guo X, *et al.* Impact of environmental factors on diabetes mortality: A comparison between inland and coastal areas. Sci Total Environ. 2023; 904:166335. https://doi.org/10.1016/j.scitotenv.2023.166335
9. Zorena K, Michalska M, Kurpas M, Jaskulak M, Murawska A, Rostami S. Environmental factors and the risk of developing Type 1 diabetes-old disease and new data. Biology. 2022; 11:608. https://doi.org/10.3390/biology11040608
10. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. Lancet. 2016; 387(10035):2340-8. https://doi.org/10.1016/S0140-6736(16)30507-4
11. Murea M, Ma L, Freedman BI. Genetic and environmental factors associated with Type 2 diabetes and diabetic vascular complications. Rev Diabet Stud. 2012; 9(1):6-22. https://doi.org/10.1900/RDS.2012.9.6

12. Tremblay J, Hamet P. Environmental and genetic contributions to diabetes. Metabolism. 2019; 100:153952. https://doi.org/10.1016/j.metabol.2019.153952
13. Bezirtzoglou E, Stavropoulou E, Kantartzi K, Tsigalou C, Voidarou C, Mitropoulou G, *et al*. Maintaining digestive health in diabetes: The role of the gut microbiome and the challenge of functional foods. Microorganisms. 2021; 9:1-26. https://doi.org/10.3390/microorganisms9030516
14. Hinault C, Caroli-Bosc P, Bost F, Chevalier N. Critical overview on endocrine disruptors in diabetes mellitus. Int J Mol Sci. 2023; 24:4537. https://doi.org/10.3390/ijms24054537
15. Dziewa M, Bańka B, Herbet M, Piątkowska-Chmiel I. Eating disorders and diabetes: Facing the dual challenge. Nutrients. 2023; 15(18):3955. https://doi.org/10.3390/nu15183955
16. Mahmood L, Flores-Barrantes P, Moreno LA, Manios Y, Gonzalez-Gil EM. The influence of parental dietary behaviors and practices on children's eating habits. Nutrients. 2021; 13:1138. https://doi.org/10.3390/nu13041138
17. Almutairi OO, Alhomaid TA, Alshuaibi AM, Alahmad RMA, Al Mardhamah NH, Alamri T. The influence of eating habits on Type 2 diabetes in Saudi Arabia: A systematic review. Cureus. 2023; 15(7):e42638. https://doi.org/10.7759/cureus.42638
18. Kudo A, Asahi K, Satoh H, Iseki K, Moriyama T, Yamagata K, *et al*. Fast eating is a strong risk factor for new-onset diabetes among the Japanese general population. Sci Rep. 2019; 9:8210. https://doi.org/10.1038/s41598-019-44477-9
19. Lejk A, Chrzanowski J, Cieślak A, Fendler W, Myśliwiec M. Effect of nutritional habits on the glycemic response to different carbohydrate diet in children with Type 1 diabetes mellitus. Nutrients. 2021; 13(11). https://doi.org/10.3390/nu13113815
20. Yuan S, He J, Wu S, Zhang R, Qiao Z, Bian X, *et al*. Trends in dietary patterns over the last decade and their association with long-term mortality in general US populations with undiagnosed and diagnosed diabetes. Nutr Diabetes. 2023; 13:5. https://doi.org/10.1038/s41387-023-00232-8
21. Boocock RC. Dietary management of adults with Type 2 diabetes and the role of the nurse. Nurs Stand. 2023; 38(3):57-61. https://doi.org/10.7748/ns.2023.e11960
22. Tan YQ, Tan ZE, Tan YL, How CH. Dietary advice in diabetes mellitus. Singapore Med J. 2023; 64(5):326-9. https://doi.org/10.4103/singaporemedj.SMJ-2022-004
23. Gucciardi E, Espin S, Morganti A, Dorado L. Exploring interprofessional collaboration during the integration of diabetes teams into primary care. BMC Fam Pract. 2016; 17(1). https://doi.org/10.1186/s12875-016-0407-1
24. Sola-Gazagnes A, Riveline JP. La mesure continue du glucose : Présent et avenir Mesure continue du glucose au long cours en 2012. Med des Mal Metab. 2012; 6(6):484-9. https://doi.org/10.1016/S1957-2557(12)70467-4
25. Afandi A, Candrayani M, Ardiana A, Fariasih C. Interprofessional collaboration in patients diabetes mellitus: A case study. J Kesehat Komunitas Indones. 2023; 3(1):126-36. https://doi.org/10.58545/jkki.v3i1.67
26. Frier A, Devine S, Barnett F, McBain-Rigg K, Dunning T. Incorporating social determinants of health into individual care - A multidisciplinary perspective of health professionals who work with people who have Type 2 diabetes. PLoS One. 2022; 17(8):e0271980. https://doi.org/10.1371/journal.pone.0271980
27. Harrison LC. Type 1 diabetes. Clinical immunology: Principles and practice. Sixth Edition; 2022. p. 909-18. https://doi.org/10.1016/B978-0-7020-8165-1.00071-X
28. Agrawal N, Dhakrey P, Pathak S. A comprehensive review on the research progress of PTP1B inhibitors as antidiabetics. Chem Biol Drug Des. 2023; 102:921-38. https://doi.org/10.1111/cbdd.14275
29. Obanda DN, Cefalu WT. Modulation of cellular insulin signalling and PTP1B effects by lipid metabolites in skeletal muscle cells. J Nutr Biochem. 2013; 24(8):1529-37. https://doi.org/10.1016/j.jnutbio.2012.12.014
30. Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, *et al*. Metabolic non-communicable disease health report of India: The ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023; 11(7):474-89. https://doi.org/10.1016/S2213-8587(23)00119-5
31. Liu X, Collister JA, Clifton L, Hunter DJ, Littlejohns TJ. Polygenic risk of prediabetes, undiagnosed diabetes, and incident Type 2 diabetes stratified by diabetes risk factors. J Endocr Soc. 2023; 7(4). https://doi.org/10.1210/jendso/bvad020
32. Khan F, Sarker MMR, Ming LC, Mohamed IN, Zhao C, Sheikh BY, *et al*. Comprehensive review on phytochemicals, pharmacological and clinical potentials of *Gymnema sylvestre*. Front Pharmacol. 2019; 10. https://doi.org/10.3389/fphar.2019.01223
33. Sai L. *Gymnema sylvestre* - An overview. World J Pharmaceutical Research. 2017; 6(10):191-195. https://doi.org/10.20959/wjpr201710-9267
34. Sigoillot M, Brockhoff A, Neiers F, Poirier N, Belloir C, Legrand P, *et al*. The crystal structure of gurmarin, a sweet taste-suppressing protein: Identification of the amino acid residues essential for inhibition. Chem Senses. 2018; 43(8):635-43. https://doi.org/10.1093/chemse/bjy054
35. Raji RO, Muhammad HL, Abubakar A, Maikai SS, Raji HF. Acute and sub-acute toxicity profile of crude extract and fractions of *Gymnema sylvestre*. Clin Phytoscience. 2021; 7:56. https://doi.org/10.1186/s40816-021-00290-4
36. Murakami N, Murakami T, Kadoya M, Matsuda H, Yamahara J, Yoshikawa M. New hypoglycemic constituents in gymnemic acid from *Gymnema sylvestre*. Chem Pharm Bull. 1996; 44(2):469-71. https://doi.org/10.1248/cpb.44.469

37. Kanetkar P, Singhal R, Kamat M. *Gymnema sylvestre*: A memoir. J Clin Biochem Nutr. 2007; 41:77-81. https://doi.org/10.3164/jcbn.2007010
38. Joy S, Thomas NG. Gymnemic acid-conjugated gelatin scaffold for enhanced bone regeneration: A novel insight to tissue engineering. Biotechnol Appl Biochem. 2023; 70(5):1652-62. https://doi.org/10.1002/bab.2463
39. Nazim R, Choudhary AN, Meraj A, Tahir F, Sohail MT. Effect of *Gymnema sylvestre* extract on liver and kidney functioning: *In-vivo* study. Life Sci J. 2023; 20(9).
40. Nani A, Bertuzzi F, Meneghini E, Mion E, Pintaudi B. Combined inositols, α-lactalbumin, *Gymnema sylvestre* and zinc improve the lipid metabolic profile of patients with Type 2 diabetes mellitus: A randomized clinical trial. J Clin Med. 2023; 12(24):7650. https://doi.org/10.3390/jcm12247650
41. Pachiappan S, Ramalingam K, Balasubramanian A. Evaluation of *Gymnema sylvestre* R. Br. against letrozole induced polycystic ovarian syndrome in rats. Res J Pharm Technol. 2023; 16(1):385-90. https://doi.org/10.52711/0974-360X.2023.00066
42. Saneja A, Sharma C, Aneja KR, Pahwa R. *Gymnema sylvestre* (Gurmar): A review. Der Pharm. 2010; 2(1):275-84.
43. Aditi, Sharma L, More P, Ghangale G, Tare H. Effect of *Gymnema sylvestre* in the control of diabetes: A review. Int J Pharm Qual Assur. 2023; 14(1):214-19. https://doi.org/10.25258/ijpqa.14.1.37
44. Rajalakshmi A, Sumathy G. *Gymnema sylvestre*-a review. Indian J Forensic Med Toxicol. 2020; 14:1081-4.
45. Poongunran J, Perera H, Fernando W, Jayasinghe L, Sivakanesan R. α-Glucosidase and α-amylase inhibitory activities of nine Sri Lankan antidiabetic plants. Br J Pharm Res. 2015; 7(5):365-74. https://doi.org/10.9734/BJPR/2015/18645
46. Mahajan SM, Baviskar DT, Chaudhari P. Anti-diabetic activity of polyherbal formulation on alloxan induced diabetes. IOSR J Pharm Biol Sci. 2018; 13(1):1-6.
47. Islam A, Rebello L, Chepyala S. A review of anti-diabetic activity of *Gymnema sylvestre* and *Pterocarpus marsupium*: Special emphasis on its combination in 4DM. Int J Nat Sci. 2019; 3.
48. Keerthika R, Raghu S. Efficacy of *Gymnema sylvestre* as a potent antioxidant: An *in vitro* study. Ann Med Health Sci Res. 2021; 11:225-36.
49. Anjum, T., Hasan Z. *Gymnema sylvestre* plant used by peoples of Vidisha District for the treatment of diabetes. Int J Eng Sci Invent. 2013; 2(6):98-102.
50. Saiki P, Kawano Y, Ogi T, Klungsupya P, Muangman T, Phantanaprates W, *et al.* Purified gymnemic acids from *Gymnema inodorum* tea inhibit 3t3-l1 cell differentiation into adipocytes. Nutrients. 2020; 12(9):1-14. https://doi.org/10.3390/nu12092851
51. Packialakshmi B, Sowndriya SR. Anti-cancer effect of *Gymnema sylvestre* leaf extract against MG63, human osteosarcoma cell line - An *in vitro* analysis. Int J Curr Res Rev. 2019; 11(11):18-24. https://doi.org/10.31782/IJCRR.2019.11114
52. Singh VK, Dwivedi P, Chaudhary BR, Singh R. Immunomodulatory effect of *Gymnema sylvestre* (R. Br.) leaf extract: An *in vitro* study in rat model. PLoS One. 2015; 10(10). https://doi.org/10.1371/journal.pone.0139631
53. Lavanya D, Haldar A, Priya SC. Phytochemical screening, isolation and evaluation of analgesic activity on the leaves of *Gymnema sylvestre*. Indo Am J Pharm Res. 2014; 4(03):4-3.
54. Khan J, Sheoran S, Khan W, Panda BP. Metabolic differentiation and quantification of gymnemic acid in *Gymnema sylvestre* (Retz.) R. Br. ex Sm. leaf extract and its fermented products. Phytochem Anal. 2020; 31(4):488-500. https://doi.org/10.1002/pca.2912
55. Rajalakshmi A, Sumathy G. Histological studies on pancreatic tissue in high fat diet with low multiple dosage of streptozotocin induced Type 2 diabetes after *Gymnema sylvestre* administration. Indian J Public Heal Res Dev. 2019; 10(12):917-22. https://doi.org/10.37506/v10/i12/2019/ijphrd/192237
56. Singh VK, Dwivedi P, Chaudhary BR, Singh R. Gymnemic acid stimulates *in vitro* splenic lymphocyte proliferation. Phyther Res. 2016; 30(2):341-4. https://doi.org/10.1002/ptr.5514
57. Venkatesan H, Karthi SA. Hypoglycaemic effect of alcoholic extracts of the leaves of *Abroma Augusta* and *Gymnema sylvestre* plants in Type II diabetes mellitus patients. Indian J Public Heal Res Dev. 2020; 11(7):288-94.
58. Ranjan A, Singh RK, Khare S, Tripathi R, Pandey RK, Singh AK, *et al*. Characterization and evaluation of mycosterol secreted from endophytic strain of *Gymnema sylvestre* for inhibition of α-glucosidase activity. Sci Rep. 2019; 9(1):17302. https://doi.org/10.1038/s41598-019-53227-w
59. El-Aziz A, Hamdy A, M Attia AE-R, El Mallah MM. Study the effect of *Gurmmar* aqueous extract on oxidative stress of diabetic rats. Egypt J Nutr. 2018; 33(1):1-35. https://doi.org/10.21608/enj.2018.142708
60. Sahu NP, Mahato SB, Sarkar SK, Poddar G. Triterpenoid saponins from *Gymnema sylvestre*. Phytochem. 1996; 41(4):1181-5. https://doi.org/10.1016/0031-9422(95)00782-2
61. Sehajpal S, Saraswat R, Verma N. Pharmacognostical profile of *Gymnema sylvestre* and its anti-hyperglycemic activity. J Pharm Res Int. 2021; 33(58A):365-76. https://doi.org/10.9734/jpri/2021/v33i58A34128
62. Zhu X-M, Xie P, Di Y-T, Peng S-L, Ding L-S, Wang M-K. Two new triterpenoid saponins from *Gymnema sylvestre*. J Integr Plant Biol. 2008; 50(5):589-92. https://doi.org/10.1111/j.1744-7909.2008.00661.x

63. Myemba DT, Bwire GM, Sangeda RZ. Microbiological quality of selected local and imported non-sterile pharmaceutical products in Dar es Salaam, Tanzania. Infect Drug Resist. 2022; 15:2021-34. https://doi.org/10.2147/IDR.S355331
64. Karthikeyan, G., V. Ravindran, and J. Ramamurthy. "Prevalence of usage of stainless steel crown, strip crown and zirconia in anterior teeth for paediatric dental patients in different age groups." Int. J. Res. Pharm. Sci 11 (2020): 1511-1516.
65. Daisy P, Eliza J, Farook KAMM. A novel dihydroxy gymnemic triacetate isolated from *Gymnema sylvestre* possessing normoglycemic and hypolipidemic activity on STZ-induced diabetic rats. J Ethnopharmacol. 2009; 126(2):339-44. https://doi.org/10.1016/j.jep.2009.08.018
66. Shigematsu N, Asano R, Shimosaka M, Okazaki M. Effect of administration with the extract of *Gymnema sylvestre* R. Br leaves on lipid metabolism in rats. Biol Pharm Bull. 2001; 24(6):713-7. https://doi.org/10.1248/bpb.24.713
67. Shenoy RS, Prashanth KV, Manonmani HK. *In vitro* antidiabetic effects of isolated triterpene glycoside fraction from *Gymnema sylvestre*. Evidence-based Complement Altern Med. 2018. https://doi.org/10.1155/2018/7154702
68. Komolkriengkrai M, Jangchart R, Sandech N, Vongvatcharanon U, Khimmaktong W. Beneficial effects of gymnemic acid on three-dimensional vascular architecture and expression of vascular endothelial growth factor of intrarenal segmental and interlobar arteries in diabetic rat kidney. Funct Foods Heal Dis. 2022; 12(6):340-51. https://doi.org/10.31989/ffhd.v12i6.930
69. Shenoy RS, Nagendra HG, Manonmani HK, others. *In silico* evaluation of naturally isolated Triterpene Glycosides (TG) from *Gymnema sylvestre* towards diabetic treatment. Heliyon. 2021; 7(12):e08407. https://doi.org/10.1016/j.heliyon.2021.e08407
70. Liu B, Asare-Anane H, Al-Romaiyan A, Huang G, Amiel SA, Jones PM, *et al.* Characterisation of the insulinotropic activity of an aqueous extract of *Gymnema sylvestre* in mouse β-cells and human islets of Langerhans. Cell Physiol Biochem. 2009; 23(1-3):125-32. https://doi.org/10.1159/000204101
71. Venkatesan H, Karthi SA. Hypoglycaemic effect of alcoholic extracts of the leaves of *Abroma Augusta* and *Gymnema sylvestre* plants in Type II diabetes mellitus patients. Indian J Public Heal Res Dev. 2020; 11(7).