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Review Article

Recent Advances in Phytoconstituent-Based Alpha Glucosidase Inhibitors and Therapeutic Potential for Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 Diabetes Mellitus is a chronic metabolic disorder characterized by insulin resistance and impaired glucose metabolism. Alpha-glucosidase inhibitors have emerged as a promising therapeutic approach to managing postprandial hyperglycemia by delaying carbohydrate digestion and glucose absorption. Phytoconstituent-based Alpha-glucosidase inhibitors, derived from medicinal plants, offer a natural alternative to synthetic drugs due to their enhanced efficacy and reduced side effects. Various plant extracts, including flavonoids, alkaloids, terpenoids, and phenolics, exhibit significant alpha-glucosidase inhibitory activity. Compounds such as quercetin, berberine, curcumin, and ginsenosides have demonstrated potent anti-diabetic effects by improving insulin sensitivity, reducing oxidative stress, and modulating inflammatory pathways. The therapeutic potential of these natural inhibitors extends beyond glycemic control, offering additional cardioprotective and neuroprotective benefits. However, challenges such as variability in bioavailability, standardization, and limited clinical trials hinder their widespread adoption. Advances in formulation techniques and bioenhancers can improve their therapeutic efficacy. Future research should focus on large-scale clinical trials to validate their efficacy and optimize dosage strategies. Integrating phytoconstituent-based Alpha-glucosidase inhibitors with conventional therapies may provide a holistic approach to diabetes management. This review highlights recent advancements in identifying and characterizing plant-derived Alpha-glucosidase inhibitors, their mechanisms of action, therapeutic benefits, and challenges in clinical application. With growing interest in natural remedies, phytoconstituent-based Alpha-glucosidase inhibitors hold significant promise in developing novel antidiabetic treatments with enhanced safety and effectiveness.

Keywords: Type 2 Diabetes Mellitus, Phytoconstituents, Alpha-glucosidase inhibitors, Antidiabetic therapy, Natural compounds, Insulin resistance.

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INTRODUCTION

Insulin resistance and reduced insulin production increase Blood Glucose Levels (BGL) and are characteristics of chronic metabolic Type 2 Diabetes Mellitus (T2DM). Effective management strategies are essential, while T2DM is becoming more prominent globally.[1] One therapy method is inhibiting alpha-glucosidase, an enzyme in the small intestinal tract that changes carbs into glucose. One common technique to help control T2DM is to block this enzyme to minimize postprandial hyperglycemia.[2] Using phytoconstituents, bioactive substances derived from plants as Alpha-Glucosidase Inhibitors (AGIs) have gained prominence in recent years. Because of their possible effectiveness and fewer adverse effects, these natural substances present a viable substitute for developed medications.[3] Numerous investigations into various plant extracts and their separated components indicate a significant inhibitory effect on alpha-glucosidase. These results demonstrate the phytoconstituents' medicinal potential in creating novel antidiabetic medicines.[4] This work aims to give a succinct overview of current developments in detecting and characterizing AGIs with plant-based constituents. Along with their methods of action and therapeutic potential, it will also cover the difficulties in developing and using them to treat T2DM.[5,6]

T2DM affects over 400 million people globally, and its prevalence is increasing rapidly. According to projections made by the International Diabetes Federation (IDF), 700 million persons worldwide will have diabetes by the year 2045.[7] Although the illness is more frequent in individuals over 45, children and teenagers are also receiving diagnoses for it regularly. T2DM is associated with various complications that significantly impact

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individuals' health and quality of life. One of the most significant side effects is cardiovascular illness, which includes an increased risk of heart attacks, strokes, and other cardiovascular disorders.[8]

Furthermore, individuals with T2DM typically have neuropathy or nerve damage, which is a debilitating condition that causes pain, tingling, and loss of sensation, particularly in the limbs. Another serious consequence is nephropathy, which is kidney damage that, if left untreated, can lead to chronic kidney disease and, eventually, renal failure. Retinopathy, the damage to blood vessels in the retina, poses a significant threat to vision and can lead to blindness if left untreated.[9] Furthermore, foot ulcers and infections, which can become so severe as to require amputations, result from impaired circulation and nerve loss.[10] To prevent or minimize the impacts on a patient's quality of life, T2DM patients must receive appropriate treatment and begin treatment as soon as feasible.[11]

The development of T2DM is influenced by several risk factors, including lifestyle, genetic, and demographic variables. Genetics are relevant since an individual's chance of developing T2DM is considerably raised if there is a family history of the condition.[12] Due to the direct correlation between excess body weight and insulin resistance, obesity, especially central obesity, is another significant risk factor.[13] This problem is further exacerbated by sedentary lives, as the onset of T2DM is closely linked to physical inactivity. Eating patterns have a significant impact as well; diets heavy in processed foods, sweets, and bad fats are strongly associated with the onset of diabetes. Age and ethnicity are other significant factors to consider. The risk of T2DM rises with age, and some ethnic groups, South Asians, African Americans, and Hispanics, for example, are more prone to the illness. Together, these elements draw attention to the complex nature of T2DM risk and underscore the necessity of an all-encompassing strategy for treatment and prevention.[14]

The quality of life and patient outcomes have greatly improved due to recent developments in T2DM care. Continuous Glucose Monitoring (CGM) systems allow for more precise insulin administration adjustments, significantly improving glycemic control and making real-time blood glucose readings feasible.[15] Another significant advancement in insulin delivery technology is the creation of the artificial pancreas. This closed-loop device automates insulin administration based on CGM to maintain a more stable BGL. With treatment approaches increasingly customized to each patient based on their genetic, environmental, and lifestyle characteristics, precision medicine is also progressing in treating diabetes. This leads to more individualized and successful management techniques.[16]

Furthermore, telemedicine has shown to be a handy tool, particularly during the COVID-19 epidemic, by facilitating virtual consultations and remote monitoring, which have increased access to diabetic treatment and allowed for ongoing management even under challenging situations. Together, these scientific and technical developments point to a hopeful future for the battle against T2DM.[17] Because of their wide range of pharmacological characteristics, phytoconstituents bioactive substances found in plants are essential to creating new drugs. Due to their numerous therapeutic benefits, these natural substances have long been the basis of both conventional and alternative medicine. Numerous pharmacological properties, including antidiabetic, anti-inflammatory, antioxidant, antibacterial, and anticancer effects, are displayed by phytoconstituents.[18] Their variety indicates they are excellent candidates for creating novel medications to address a range of illnesses. Numerous phytoconstituents are used as model compounds in pharmacological research. Scientists separate and alter these organic substances to enhance their effectiveness, durability, and bioavailability, creating novel pharmaceuticals.[19,20]

Pathophysiology of T2DM

Reduced insulin production and resistance are characteristics of T2DM, a complex metabolic illness. In the pathophysiology of T2DM, genetic, environmental, and psychological variables combine intricately to produce chronic hyperglycemia.[21]

Insulin-Resistance

T2DM is indicated by insulin resistance, a condition in which cells become less sensitive to the hormone insulin, which is required to absorb glucose. The liver, fat, and muscular tissues exhibit the most resistance. Muscle cells diminished capacity to absorb and use glucose is caused by insulin resistance, which increases BGL. Insulin often inhibits the liver's ability to produce glucose.[22] However, with T2DM, this inhibition is lessened, which raises the outflow of glucose from the liver and leads to hyperglycemia. Higher levels of pro-inflammatory cytokines and free fatty acids are released by insulin-resistant adipose tissue, exacerbating insulin resistance in other tissues.[23]

Beta-cell Dysfunction

Insulin resistance is countered by the pancreas producing more insulin. The Langerhans' islets eventually develop an abnormality that prevents them from releasing enough insulin to maintain the BGL within typical values. Numerous causes contribute to this beta-cell dysfunction, such as chronic inflammation, glucotoxicity, and lipotoxicity. Genetic predisposition also significantly influences the reduction of beta-cell function.[24]

Incretin Effect

Insulin production from the pancreas is enhanced by incretins, hormones produced from the stomach in response to food consumption. One example of such a hormone is glucagon-Like Peptide-1 (GLP-1). In T2DM, the incretin action is reduced, leading to insufficient insulin released postprandially. This

contributes to the overall hyperglycemia observed in T2DM patients.[25]

Glucagon Secretion

Apart from insulin dysregulation, incorrect glucagon secretion is another feature of T2DM. The pancreatic alpha cells that generate glucagon stimulate the liver to secrete more glucose. Glucagon production is frequently increased in T2DM, which increases hepatic glucose output and leads to hyperglycemia.[26]

Role of Adipokines and Inflammation

Adipose tissue, especially visceral fat, releases adipokines, hormones produced by fat cells, and pro-inflammatory cytokines, which are crucial to the pathophysiology of T2DM. Adipokines like leptin and adiponectin influence insulin susceptibility, whereas cytokines like Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α). Insulin resistance and beta-cell dysfunction in T2DM are caused mainly by this low-grade, persistent inflammation.[27]

Genetic and Epigenetic Factors

Numerous genes related to beta-cell function, insulin action, and synthesis contribute to a genetic predisposition that is important in the development of T2DM. Epigenetic modifications, which are differences in gene expression without altering the structure of DNA, also impact T2DM. Environmental variables, including nutrition, exercise, and pollutant exposure, can affect these alterations.[28]

ALPHA-GLYCOSIDASE

An essential gastrointestinal enzyme critical to the cellular breakdown of carbohydrates is alpha-glucosidase. It catalyzes the hydrolysis of alpha-glucoside bonds in carbohydrates, which releases glucose and other simple sugars into the circulation and breaks down complicated sugars into simpler forms. This enzyme process, which predominantly takes place in the small intestine, assists in converting food carbs into energy that can be used.[29] Because of its essential function in the synthesis of glucose, alpha-glucosidase has been identified as a target for several diabetic drugs that block its function to slow down the digestion of carbohydrates and assist in controlling blood sugar levels in patients with T2DM. Improving dietary strategies and developing therapies for metabolic diseases requires a thorough understanding of alpha-glucosidase's function and management.[30]

Inhibitors of Alpha-Glucosidase

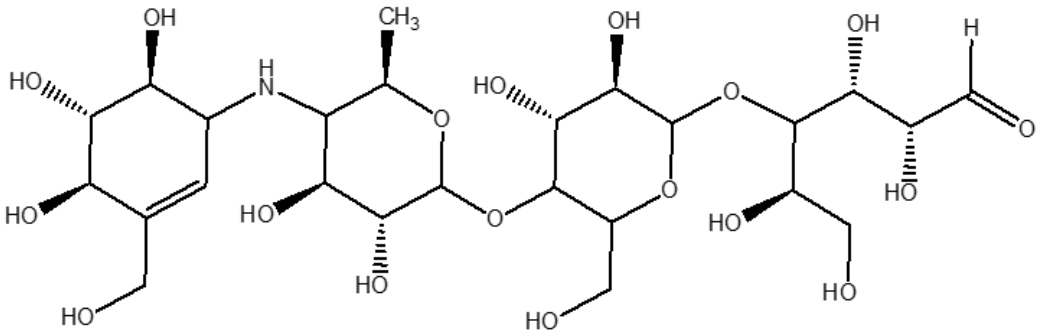
AGIs are a class of medicine used primarily to manage T2DM. These medications delay the intestinal digestion of carbs, which lowers the rate at which glucose reaches in the blood circulation after meals. These medicine work by inhibiting the action of alpha-glucosidase, a digestive enzyme that converts complex carbohydrates into simpler sugars, hence limiting postprandial increases in BGL.[31] Additionally to helping to lower total blood sugar levels, this technique may improve glycemic control. Acarbose, a synthetic AGI, delays carbohydrate digestion by inhibiting α-glucosidase enzymes but often causes gastrointestinal side effects. In contrast, natural AGIs may offer similar benefits with fewer adverse effects, making them promising alternatives. Common examples of AGIs include *Acarbose, miglitol, thymol, voglibose, carvacro*l, etc. They are frequently used with other antidiabetic medications to achieve ideal blood glucose control.[32]

Figures 1 to 5 illustrate the chemical structures of key alpha-glucosidase inhibitors, both synthetic and natural. Acarbose, shown in Figure 1, is a widely used synthetic inhibitor that delays carbohydrate digestion and absorption, thereby reducing postprandial blood glucose levels.[33] Figure 2 presents the structure of voglibose, another synthetic inhibitor that works by competitively inhibiting alpha-glucosidase enzymes, effectively managing type 2 diabetes mellitus.[34] Miglitol, depicted in Figure 3, is a sugar mimic that inhibits intestinal glucosidase activity, preventing rapid glucose absorption.[35] Figures 4 and 5 represent the structures of carvacrol and thymol, naturally occurring phenolic compounds with significant alpha-glucosidase inhibitory activity. These natural inhibitors, found in essential oils of various plants, contribute to lowering blood sugar levels and offer potential alternatives to synthetic drugs for diabetes management.[36]

MECHANISM OF ACTION

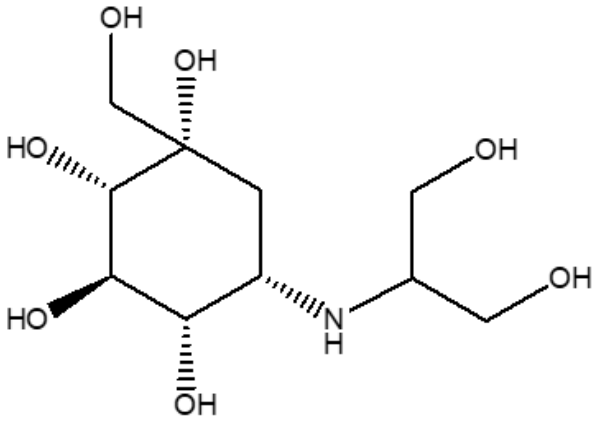
AGIs stop the small intestine from absorbing carbohydrates by competitively inhibiting the enzymes that convert complicated, nonabsorbable carbohydrates into simple, absorbing carbohydrates.[37] Enzymes that are involved include glucoamylase, sucrase, maltase, and isomaltase. By delaying the absorption of carbs, these inhibitors reduce the rise in blood glucose concentrations after a meal by approximately three mmol/L. Acarbose is the drug in this class that is most often used and studied.[38] Voglibose and miglitol are further agents. Acarbose is most effective against glucoamylase and inhibits α-amylase, maltase, sucrase, and dextranase. Remarkably, lactase, a β-glucosidase enzyme, is unaffected by Acarbose. Along with Acarbose, Voglibose is not FDA-approved in the USA but is approved in Japan. Both drugs have limited absorption from the gastrointestinal system, leading to low bioavailability and elimination, mainly in faeces. Miglitol is wholly absorbed in the gastrointestinal system and eliminated through the kidneys. The colon processes the sugar acarbose through metabolic processes, while the metabolism of miglitol and voglibose is little.[39]

In Figure 6 illustrated that the carbohydrate digestion and absorption occur in the small intestine, where amylase breaks down starch into simpler sugars. Enzymes like sucrase and lactase convert these sugars into glucose, fructose, and galactose for absorption. α-Glucosidase aids glucose release, while



Acarbose

Figure 1: Chemical structure of acarbose.



Voglibose

Figure 2: Chemical structure of voglibose.

drugs can inhibit this process, affecting blood sugar levels.[40] Salivary amylase in the mouth is the first step in the digestion of carbohydrates since it breaks down starch (amylose and amylopectin) into simpler sugars. The pancreas continues to break down amylose and amylopectin into disaccharides and smaller sugar units in the small intestine as food passes through the digestive tract.[41] In the small intestine, enzymes such as lactase, sucrase, and α-glucosidase are crucial for the further breakdown of carbohydrates. α-glucosidase breaks down starch into glucose, which is then absorbed by the body. Lactase breaks down saccharides into glucose and fructose and breaks down lactose into glucose and galactose.[42] The villi and microvilli found in the gut walls provide a significant surface area for absorption. Monosaccharides such as glucose, fructose, and galactose are transmitted through the intestinal barrier and into the circulation. These sugars are taken to the liver after absorption, where they undergo further processing to either store or provide energy.[43] Amylase breaks down carbs first, and then enzymes like lactase, sucrase, and α-glucosidase turn them into monosaccharides in the small intestine. Following absorption by the intestinal lining, these monosaccharides are either stored in the liver or used to create energy in the circulation.[44]

Table 1 highlights medicinal plants with alpha-glucosidase inhibitory activity, beneficial for managing T2DM. Various plant parts, including leaves, bark, fruits, and roots, contain bioactive compounds like flavonoids, triterpenoids, phenolic acids, and alkaloids that contribute to blood sugar reduction. Notable examples include *Momordica charantia* (charantin), *Syzygium cumini* (jamboline), *Curcuma longa* (curcumin), and *Gymnema sylvestre* (gymnemic acids), which exhibit strong hypoglycemic effects. Many commonly used spices and herbs, such as *Allium sativum, Cinnamomum verum,* and *Zingiber officinale*, also show promising antidiabetic properties. These plants offer a natural approach to diabetes management and hold potential for future therapeutic applications.[85,86]

RECENT ADVANCES IN PHYTOCONSTITUENT-BASED AGIS

Quercetin

Quercetin is an essential flavonoid found in a wide variety of fruits, vegetables, and grains that is used to treat T2DM. Due to its antioxidant qualities, it can lessen oxidative stress, which is a significant cause of T2DM. It has been demonstrated that quercetin increases insulin sensitivity by modifying signalling pathways related to glucose metabolism. Furthermore, it reduces inflammation by blocking pro-inflammatory cytokines, frequently high in individuals with diabetes.[87,88] Studies suggest that quercetin could be effective in lowering BGL by enhancing the uptake of glucose by muscle cells and reducing the production of glucose in the hepatocytes. Blocking the alpha-glucosidase and alpha-amylase enzymes also aids in controlling BGL after a meal. Quercetin also helps to mitigate dyslipidaemia, a significant

Table 1: Medicinal Plants that have AGIs Activity.

Sl. No.	Plant Name	family	Part Used	Chemical Constituent Responsible for Hypoglycemia	IC_{50} µg/mL	Effect on T2DM	References
1	*Hypericum ascyron* L.	Hypericaceae	Leaves	Flavonoids	703.78 ± 16.34	Reduces blood sugar	45
2	*Pinus roxburghii Sarg*	Pinaceae	Leaves	Phenolic acids	99	Hypoglycemia	46
3	*Terminalia sericea*	Combretaceae	Stem Bark	β-sitosterol, and stigmasterol	92	Lowers blood glucose	47,48
4	*Tournefortia hartwegiana*	Boraginaceae	Leaves	Triterpenoids	3.16 mg/mL	Antidiabetic	49
5	*Albizia antunesiana*	Fabaceae	Leaves	Triterpenoids (α-and β-amyrin)	4.35 ± 0.56	Improves glucose tolerance	50
6	*Tagetes spp*	Asteraceae	Flower Patels	Phenolic, flavonoid, and carotenoid	3.12 and 7.40 mg/mL	Hypoglycemia	51
7	*Morinda citrifolia*	Rubiaceae	Fruit	Noni	206.26 µg/mL	Reduces blood sugar	52
8	*Andrographis paniculata*	Acanthaceae	Leaf	Andrographolide	-	Antidiabetic	53
9	*Ficus racemosa*	Moraceae	Bark	5-methoxypsoralen	56.3 µg/mL	Decreases glucose absorption	54
10	*Momordica charantia*	Cucurbitaceae	Fruit	Charantin	0.7–7 µg/mL	Improves insulin sensitivity	55
11	*Aegle marmelos*	Rutaceae	Leaf	Aegeline	47.08 g/mL	Lowers blood glucose	56
12	*Pterocarpus marsupium*	Fabaceae	Heartwood	Pterosupin	18.3 µg/mL	Antidiabetic	57
13	*Syzygium cumini*	Myrtaceae	Seed	Jamboline	8.6 ± 3.0 µg/mL	Hypoglycemic effect	58
14	*Salacia reticulata*	Celastraceae	Root	Salacinol	4.9 (µM)	Reduces blood glucose levels	59
15	*Gymnema sylvestre*	Apocynaceae	Leaf	Gymnemic acids	145 µg/mL	Lowers sugar levels	60
16	*Trigonella foenum-graecum*	Fabaceae	Seed	Trigonelline	233 ± 0.12 (µM)	Improves glucose tolerance	61
17	*Coccinia indica*	Cucurbitaceae	Leaf	Beta-carotene	-	Reduces blood glucose	62,63
18	*Azadirachta indica*	Meliaceae	Leaf	Azadirachtin	13.81±0.06 µg/mL	Decreases glucose levels	64
19	*Ocimum sanctum*	Lamiaceae	Leaf	Eugenol	1.91 µg/mL	Lowers blood sugar	65

20	*Costus igneus*	Costaceae	Leaf	Diosgenin	26.41 µM	Lowers blood glucose	66
21	*Allium sativum*	Amaryllidaceae	Bulb	Allicin	4.15 µg	Reduces glucose levels	67
22	*Tinospora cordifolia*	Menispermaceae	Stem	Cyanidin 3-O-sambubiosyl 5-O-glucoside	-	Hypoglycemic	68
23	*Zingiber officinale*	Zingiberaceae	Rhizome	Gingerol	81.78 ± 7.79 µM	Lowers blood sugar	69
24	*Cinnamomum verum*	Lauraceae	Bark	Cinnamaldehyde	16.9 µg/mL	Decreases blood sugar	70,71
25	*Piper nigrum*	Piperaceae	Fruit	Piperine	105 mg/mL)	Reduces glucose levels	72
26	*Curcuma longa*	Zingiberaceae	Rhizome	Curcumin	13.33 µM	Lowers blood glucose	73
27	*Nigella sativa*	Ranunculaceae	Seed	Thymoquinone	50 µM	Decreases blood sugar	74
28	*Ocimum basilicum*	Lamiaceae	Leaf	Linalool	160 ± 10 µg/mL	Reduces glucose levels	75
29	*Petroselinum crispum*	Apiaceae	Leaf	Apigenin	10.73 ± 3.21 µM	Hypoglycemic	76,77
30	*Rheum emodi*	Polygonaceae	Root	Emodin	30 µg/mL	Antidiabetic	78
31	*Murraya koenigii*	Rutaceae	Leaf	Carbazole alkaloids	-	Reduces glucose levels	79
32	*Swertia chirata*	Gentianaceae	Whole plant	Amarogentin	64.08±6.26	Lowers blood sugar	80
33	*Withania somnifera*	Solanaceae	Root	Withafer, (20R, 22R-14a, 20a)-dihydroxy1-oxowitha-2,5,16,24 tetraenolide in A	98.60 µg/mL	Reduces glucose levels	81
34	*Bauhinia variegata*	Fabaceae	Leaf	Kaempferol	63.0 and 98.3 µM	Hypoglycemic effect	82
35	*Terminalia chebula*	Combretaceae	Fruit	Chebulinic acid	5.6 mg/mL	Lowers blood sugar	83
36	*Phyllanthus emblica*	Phyllanthaceae	Fruit	Emblicanin	51.3±16.5 ug/mL	Decreases glucose levels	84

comorbidity associated with T2DM, by its effects on lipid metabolism. Quercetin is a potential supplementary medication for managing T2DM due to its diverse biochemical activities.[89]

Berberine

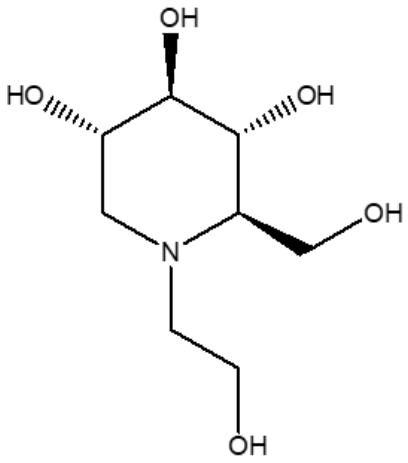
Many plants contain the alkaloid berberine, which is effective in treating T2DM. The activation of AMP-Activated Protein Kinase (AMPK) promotes glucose absorption by tissues and improves insulin sensitivity. In addition to improving glycemic management, berberine also suppresses hepatic gluconeogenesis and modifies gut microbiota. Its anti-inflammatory and antioxidant qualities further bolster its therapeutic effect in T2DM.[90,48]

Curcumin

Turmeric's terpenoid curcumin has several advantages for treating T2DM. Modifying insulin signalling pathways lowers insulin resistance and inhibits the chronic inflammation linked to diabetes. Additionally, curcumin has antioxidant qualities that guard against oxidative damage to pancreatic β-cells. Furthermore, it helps with diabetes-related problems by improving cholesterol levels and lowering BGL.[91,48]

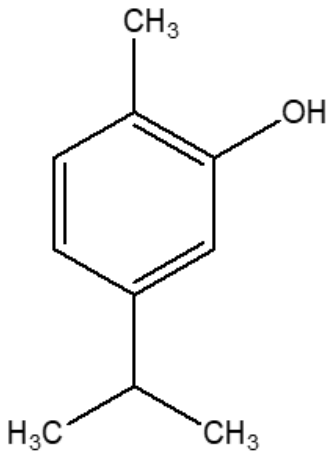
Epigallocatechin gallate

Green tea's flavonoid Epigallocatechin Gallate (EGCG), which has anti-inflammatory and antioxidant properties, is essential for managing T2DM. By activating AMPK, EGCG increases glucose absorption and insulin sensitivity. Moreover, it suppresses



Miglitol

Figure 3: Chemical structure of miglitol.



Carvacrol

Figure 4: Chemical structure of carvacrol.

the enzymes that break down carbohydrates, lessening blood glucose increases after meals. Moreover, how EGCG affects lipid metabolism helps treat dyslipidemia, a disease commonly seen in people with diabetes.[92]

Ginsenosides

Ginseng's key ingredients, ginsenosides, have demonstrated encouraging results in treating T2DM. Various signalling mechanisms increase insulin sensitivity and secretion. Furthermore, ginsenosides' anti-inflammatory and antioxidant effects protect against diabetes-related oxidative stress and inflammation. Moreover, they improve glycemic control in T2DM patients by regulating glucose metabolism and lowering hepatic glucose generation.[93]

Resveratrol

Resveratrol is a natural polyphenolic compound predominantly found in grapes, red wine, and certain berries. It has emerged as a promising phytoconstituent for the management of T2DM due to its antioxidant, anti-inflammatory, and insulin-sensitizing properties. Resveratrol activates SIRT1 and AMPK pathways, both of which enhance insulin sensitivity and glucose uptake in peripheral tissues. It also plays a key role in reducing oxidative stress and inhibiting pro-inflammatory cytokines, thereby protecting pancreatic β-cells from damage.[94] Furthermore, resveratrol suppresses hepatic gluconeogenesis and improves lipid metabolism, helping to mitigate diabetic dyslipidemia. Its multifaceted mechanisms make resveratrol a valuable candidate for adjunct therapy in T2DM management.[95]

Apigenin

Apigenin is a naturally occurring flavonoid found abundantly in parsley, chamomile, celery, and other plant-based foods. It has shown significant potential in the management of T2DM due to its antioxidant, anti-inflammatory, and anti-hyperglycemic properties. Apigenin enhances insulin sensitivity by modulating key insulin signaling pathways and reduces BGL by promoting glucose uptake in skeletal muscles.[96] It also inhibits hepatic gluconeogenesis and helps protect pancreatic β-cells from oxidative damage. Additionally, apigenin improves lipid profiles and reduces the risk of diabetic complications by modulating inflammatory cytokines and oxidative stress markers. Its multi-targeted mechanisms make it a promising compound in phytochemical-based antidiabetic therapies.[97]

THERAPEUTIC POTENTIAL AND CLINICAL IMPLICATIONS

AGIs derived from phytoconstituents have several therapeutic advantages in the treatment of T2DM. These natural chemicals are a better alternative than manufactured medications for many people since they often have fewer adverse effects. Because they impede alpha-glucosidase enzymes, they slow down the digestion and absorption of carbs, which is essential for glycemic management and helps lower postprandial BGL.[98] In addition to their primary function, these phytoconstituents have antioxidant and anti-inflammatory qualities, which improve health in other ways. Research has indicated that berberine is effective in mitigating inflammation and oxidative stress, in addition to improving insulin sensitivity and blood glucose levels. Numerous fruits and vegetables contain quercetin, which has antioxidant properties that will enhance general metabolic health and inhibit alpha-glucosidase.[99] Turmeric's main ingredient, curcumin, has anti-inflammatory qualities that help it modify insulin signalling and provide protection against problems connected to diabetes. Likewise, ginsenosides from ginseng and EGCG from green tea

have demonstrated encouraging effects in lowering oxidative stress and enhancing insulin sensitivity.[100] Lowering the risk of diabetes-related complications, managing BGL and adding these natural AGIs to T2DM therapy regimens may improve patient outcomes. More clinical research and trials are required to understand their mechanisms of action and optimize their usage completely. By including these phytoconstituents in traditional diabetes care strategies, there is a significant chance that the quality of life for those with T2DM may be improved.[101]

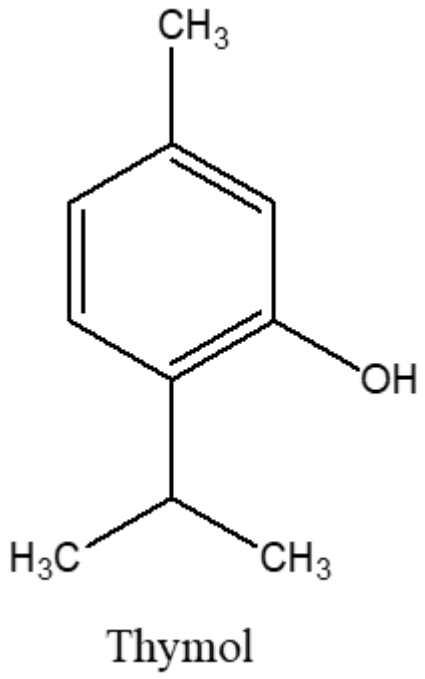


Figure 5: Chemical structure of thymol.

CHALLENGE AND LIMITATIONS

The variation in these natural chemicals' potency and bioavailability poses a serious difficulty. The consistency and effectiveness of the active ingredients might be affected by variables, including the source of the plant, the extraction process, and the preparation methods used.[102] This heterogeneity makes standardization challenging since it might result in uneven clinical results. The absence of extensive clinical trials and long-term investigations is another drawback. Most research on phytoconstituent-based AGIs has been done *in vitro* or in animal models; few human studies have verified their safety and effectiveness.[103] It is difficult to set firm treatment recommendations and doses for these natural inhibitors without strong clinical data. Patients, particularly those taking many drugs, are at risk for drug-herb interactions. When used with other antidiabetic medications or therapies, phytoconstituent-based AGIs might have unanticipated side effects that need close monitoring and guidance from medical professionals.[104] There are significant regional differences in the regulatory landscape for natural goods. Concerns regarding patient safety and quality control are raised by the possibility that, in some regions, phytoconstituents are not subject to the same stringent testing and approval procedures as synthetic medications.[105]

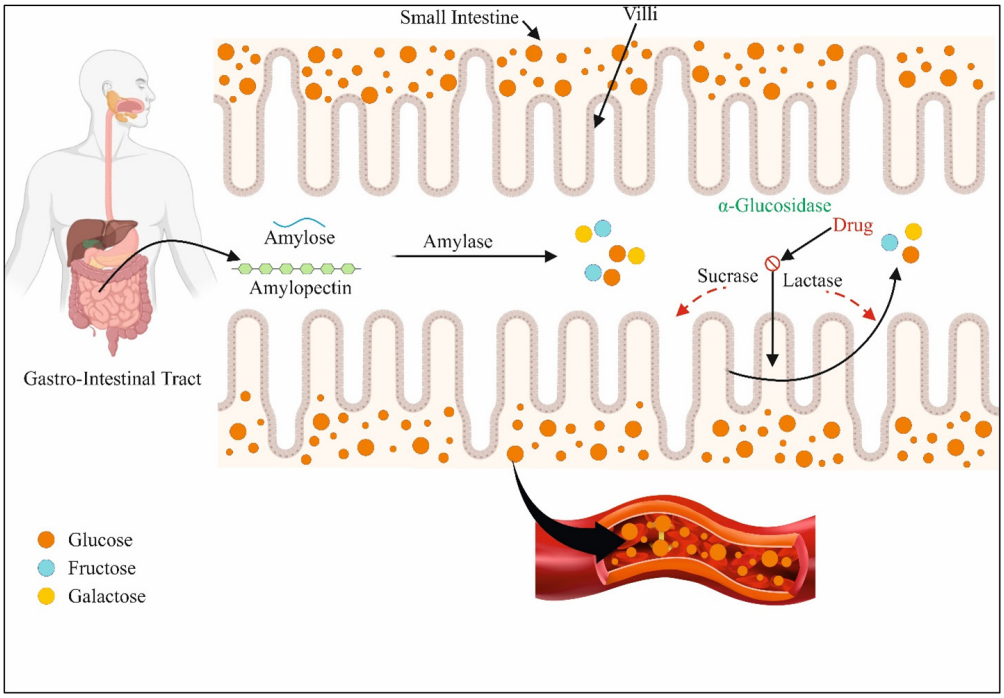


Figure 6: Mechanism of action of phytoconstituents on alpha-glucosidase enzyme: Illustration of carbohydrate digestion and inhibition by AGIs. Starch is broken down by amylase into sugars, which are further digested by sucrase and lactase. AGIs block α-glucosidase, reducing glucose absorption and postprandial blood sugar levels.

FUTURE PROSPECTIVE

AGIs based on phytoconstituents have bright futures in the treatment of T2DM. More research points to these agents as potentially safer and more natural substitutes for synthetic medications. The alpha-glucosidase enzyme, which is necessary for the absorption of carbohydrates, is strongly inhibited by phytoconstituents derived from plants.[106] The management of postprandial hyperglycemia, a significant issue among people with diabetes, is aided by inhibitors of the complicated metabolism of carbohydrates. To address several elements of diabetes development, future research may concentrate on developing new phytoconstituents that demonstrate diverse mechanisms, such as anti-inflammatory, antioxidant, and beta-cell protective characteristics and have alpha-glucosidase inhibitory actions.[107] Furthermore, these compounds can increase their bioavailability and effectiveness by developments in extraction, formulation, and delivery methods. Clinical studies must evaluate phytoconstituent-based AGIs' long-term safety and efficacy in diverse populations.[108] Moreover, the development of multi-target medications that include phytoconstituents or the combination of these natural inhibitors with conventional medicines may improve the management of diabetes.[109] Research on the genome and metabolome may provide light on customized treatment plans that maximize the utilization of phytoconstituents according to the unique characteristics of each patient. It is imperative that future treatment development focus on the integration of phytoconstituent-based AGIs into standard diabetes care since this presents a promising way to enhance glycemic control while lowering the adverse effects of synthetic medications.[110]

CONCLUSION

The growing interest in phytoconstituent-based AGIs offers promising therapeutic potential for managing T2DM. With many plant-based compounds demonstrating significant alpha-glucosidase inhibitory activity, these natural agents have emerged as potential alternatives to synthetic drugs for glycemic control. The capacity of phytoconstituents such as flavonoids, alkaloids, terpenoids, and saponins to reduce postprandial BGL, improve insulin sensitivity, and offer additional anti-inflammatory and antioxidant properties has been repeatedly demonstrated in the reviewed research. Challenges remain, particularly concerning the variability in potency, bioavailability, and standardization of these natural agents, which necessitates further research. Few clinical trials are available to prove the effectiveness and safety of these treatments in people; instead, most current studies are based on *in vitro* investigations or animal models. As research advances, future efforts should focus on refining extraction techniques, optimizing bioavailability, and conducting large-scale clinical trials to understand the long-term effects better and establish standardized therapeutic protocols. Phytoconstituent-based AGIs present a compelling avenue for developing new antidiabetic treatments, especially for patients seeking more natural and potentially safer alternatives. With continued investigation and innovation, these substances originating from plants may be essential for managing diabetes in the future.

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ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **AGIs:** Alpha-Glucosidase Inhibitors; **EGCG:** Epigallocatechin Gallate; **CGM:** Continuous Glucose Monitoring; **GLP-1:** Glucagon-Like Peptide-1; **IDF:** International Diabetes Federation; **TNF-α:** Tumour Necrosis Factor-Alpha; **BGL:** Blood Glucose Levels.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTION

T.A. conducted the primary literature review and drafted the initial manuscript. G.P.M. provided critical revisions, supervised the study, and ensured the accuracy of scientific content. Both authors reviewed and approved the final version of the manuscript.

SUMMARY

AGIs based on phytoconstituents have the encouraging potential for treating T2DM by improving insulin sensitivity and lowering postprandial blood glucose. Key compounds such as flavonoids, alkaloids, and terpenoids demonstrate strong inhibitory effects and provide antioxidant benefits. However, standardization, potency, and bioavailability challenges require further research, particularly in clinical trials. Future efforts should focus on refining extraction methods and optimizing therapeutic protocols. These natural agents may provide safer alternatives to synthetic antidiabetic drugs.

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