Food & Medicine Homology

ISSN 3006-6867 (print); 3006-4252 (online)
https://doi.org/10.26599/FMH.2025.9420068

Review Article

A review and a bibliometric analysis of tropical herbs and their bioactive compounds for modulating gut microbiota function and glucose regulation in type 2 diabetes

Maziah Mohd Ghazaly[1], Gaik Ee Lee[2] (✉), Nyuk Ling Ma[1, 2], Petr Heděnec[2], Maulidiani[1], Nur Roshima Hassan[1], Muhammad Faiz Zulkifli[1], Arifullah Mohammed[3, 4], Mohd Sabri Mohd Ghazali[1]

[1] *Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, Kuala Nerus 21030, Malaysia*
[2] *Institute of Tropical Biodiversity and Sustainable Development, Universiti Malaysia Terengganu, Kuala Nerus 21030, Malaysia*
[3] *Department of Agriculture Science, Faculty of Agro-Based Industry, Universiti Malaysia Kelantan, Jeli 17600, Malaysia*
[4] *KL College of Agriculture, Koneru Lakshmaiah University, Vaddeswaram Campus, Guntur, Andhra Pradesh, India - 522 302*

Received: 9 June 2024 / **Revised:** 30 June 2024 / **Accepted:** 1 July 2024

Abstract: Diabetes mellitus (DM) remains a pressing global health concern, with escalating incidence and mortality rates. Excessive sugar causes pancreatic β cell dysfunction and reduces insulin production, resulting in significant healthcare and economic burdens. In response, using natural herbal remedies for DM treatment is rising. This review focuses on type 2 diabetes mellitus (T2DM) and examines herbal alternatives for lowering blood glucose levels. Research indicates that extracts and bioactive compounds from tropical herbs, such as bitter melon (*Momordica charantia*), curry tree (*Murraya koenigii*), garlic (*Allium sativum*), ginger (*Zingiber officinale*) and noni (*Morinda citrifolia*) exhibit anti-diabetic and anti-hyperglycaemic properties. Their alkaloids act on insulin-related pathways, effectively regulating insulin secretion, blocking glucose absorption, and maintaining glucose homeostasis. This article provides a descriptive explanation of how phytochemical compounds found in tropical herbs work to regulate glucose levels within human cells. This paper proposes that the metabolic pathways by which these bioactive compounds in tropical herbs function are significant as a foundation for treating T2DM. Additionally, the paper integrates a bibliometric analysis, offering comprehensive research into the trends of published papers. This analysis aids in understanding the connections among researchers, organizations, and countries. It uncovers emerging trends, assesses the impact of key research findings, and tracks the progression of specific topics.

Keywords: herbal remedies; traditional knowledge; diabetes; bibliometric

Citation: Ghazaly M. M., Lee G. E., Ma N. L., et al. A review and a bibliometric analysis of tropical herbs and their bioactive compounds for modulating gut microbiota function and glucose regulation in type 2 diabetes. *Food & Medicine Homology*, 2025, 2: 9420068. https://doi.org/10.26599/FMH.2025.9420068

1 Introduction

Diabetes mellitus (DM) is a chronic hyperglycaemic disorder with a persistent health threat and potentially fatal outcomes[1]. The global prevalence of diabetes is on the rise, a trend attributed partly to the effects of urbanization[2]. For example, higher consumption of high-caloric, high-sugar foods and sedentary lifestyles in urban areas contribute to this trend. The substantial increase in type 2 diabetes mellitus (T2DM), affecting millions worldwide, is primarily linked to factors such as obesity. Patients with type T2DM have a 15% increased risk of all-cause mortality, which is twice as high in young people and in those who are younger than 55 years of age and have a concentration of glycated haemoglobin (HbA1c) of 6.9% (55 mmol/mol) or less, it is twice as high compared with people without diabetes[3]. The organs associated with T2DM development include the pancreas (β cells and α cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue[4].

Current research revealed the prevalence of T2DM in patients with relatives already affected by DM. For instance, the study by Poznyak *et al.*[5] reported a heightened risk of T2DM development among individuals with first-degree relatives affected by the disease. Interestingly, T2DM prevalence and incidence exhibit geographic variations, with over 80% of patients residing in low-to-middle-income countries posing challenges in finding effective treatments. This is probably due to limited resources and healthcare access, along with a preference for cheap processed foods, which worsens the issue. This phenomenon contributes to underestimating the disease burden, as approximately one out of three people with diabetes remain misdiagnosed[6]. Insulin resistance holds significant importance, as it is associated with the biological response after insulin stimulation, particularly in adipose tissue, muscle, and liver. Consequently, β-cell insulin production escalates due to increased glucose consumption[7].

Address correspondence to Gaik Ee Lee, gaik.ee@umt.edu.my

Nevertheless, research indicates promising therapeutic avenues for managing T2DM through maintenance and preventive measures. Weight control and adopting a healthy diet emerge as pivotal strategies for balancing sugar levels in individuals with T2DM[8]. Although numerous oral hypoglycaemic medications are available, they often have significant complications, for example, hypoglycemia, where blood sugar levels drop too low[9].

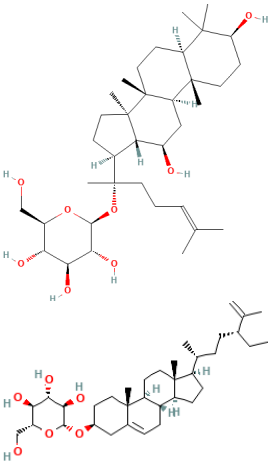
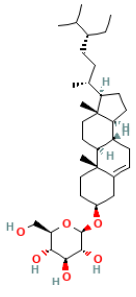
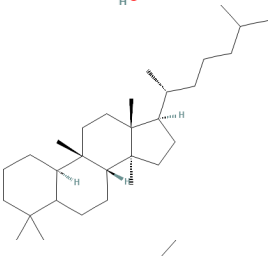
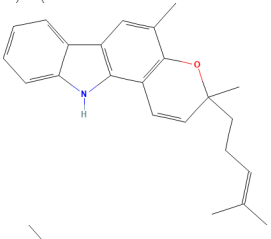
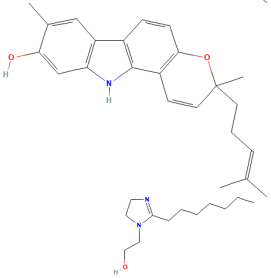
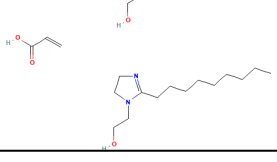
As an alternative, herbal plants have been used for generations in traditional medicine to treat various diseases, including diabetes. In developing and low-income countries in tropical area, local communities rely on traditional knowledge passed down through generations. Moreover, empirical evidence suggests these herbs can help regulate blood sugar levels and improve insulin sensitivity. Many have found relief from diabetes symptoms by incorporating natural herbs into their diets. These natural herbs are often readily available in tropical climates and affordable compared to pharmaceutical medications. Most of these natural herbs offer additional health benefits beyond their anti-diabetic properties. Furthermore, herbal medicine is gaining preference due to its reduced side effects[10]. Thus, communities around the globe appreciate these herbs for their comprehensive positive effects on human health. Natural herbs generally contain phytochemicals or active compounds. These compounds are essential in plant development and pharmacological applications[11]. Selective herbs such as bitter melon (*Momordica charantia*) exhibit hypoglycaemic properties and contain phytochemicals with the potential to prevent and manage diabetes[12, 13]. Phytochemicals such as flavonoids, alkaloids, terpenes, saponins, phenols, and tannins have been identified for their ability to lower blood glucose levels in patients with T2DM[14]. Additionally, some bioactive compounds identified in various tropical herbs that regulate T2DM include ginsenoside compound K, charantin, cucurbitane, mahanimbine, isomahanine, caproic and caprylic acids, coumarins, allicin, ajoene, gingerol, and zingerone (Table 1).

Current research investigates plant-derived compounds to understand their biological and medicinal properties in regulating glucose levels and managing diabetes. Some studies have highlighted the therapeutic potential of natural products in addressing insulin resistance and disruptions of insulin signals, for example, in Saadeldeen *et al.* [15]. Moreover, bioactive compounds derived from natural herbs have shown promise in enhancing pancreatic beta cell function and insulin release[16]. Despite the severe impact of the T2DM problem globally, a comprehensive review of the mechanisms of these biologically active compounds and their capabilities in treating pancreatic beta cells remains scarce. This review explores the therapeutic potential of specific tropical herbs: bitter melon (*M. charantia*), curry tree (*Murraya koenigii*), garlic (*Allium sativum*), ginger (*Zingiber officinale*) and noni (*Morinda citrifolia*). It focuses on understanding the mechanisms of bioactive constituents, offering an alternative approach for treating individuals with T2DM and contributing to pharmaceutical research in this field. It also includes a bibliometric analysis to understand trends in published research, aiding in tracking emerging topics and connections among researchers, organizations, and countries.

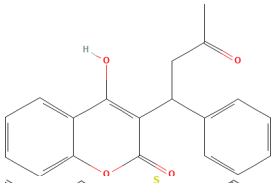
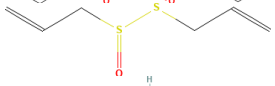
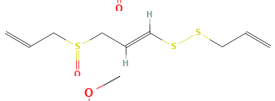
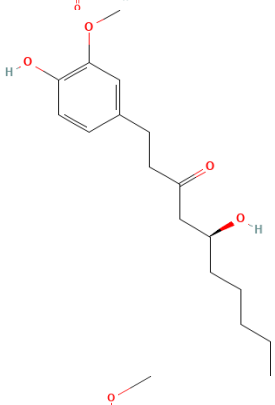
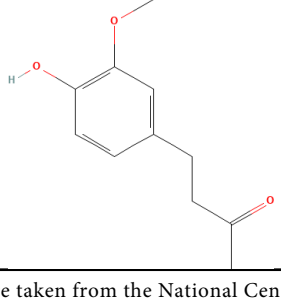
2 Endocrinology background and gut microbiota

Recent progress in endocrinology research showed significant potential for treating diabetes through advanced therapeutic strategies to restore normal glucose metabolism. The research focused on incretin-based therapies revealed that the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4

Table 1 Some of the bioactive compounds identified in various tropical herbs regulate T2DM

Compound	Chemical structure*
Ginsenoside compound K	
Charantin	
Cucurbitane	
Mahanimbine	
Isomahanine	
Caproic and caprylic acids	

(Continued)

Compound	Chemical structure*
Coumarins	
Allicin	
Ajoene	
Gingerol	
Zingerone	

Note: *Chemical structures were taken from the National Center for Biotechnology Information. Retrieved June 24, 2024, from https://pubchem.ncbi.nlm.nih.gov/compound.

(DPP-4) inhibitors have the potential to enhance insulin secretion and reduce glucagon release, improving blood sugar levels[17]. Therefore, endocrine secretion has great potential as a targeted medication for T2DM treatment. Incretins are gut-derived peptide hormones that are rapidly secreted after eating. The two main incretins in humans are glucose-dependent insulinotropic polypeptide and GLP-1[18]. They stimulate pancreatic β-cells, postprandially, to secrete insulin. The secretion of incretins has been implicated in changes to the gastrointestinal microbiome, immune dysregulation, and inflammation, emerging as important pathophysiological factors[19].

The human gastrointestinal tract represents one of the largest interfaces (250–400 m^2) between the host, environmental factors and antigens in the human body[20]. The gastrointestinal tract is colonized by many commensal microorganisms, such as bacteria, viruses, protozoa, and fungi. The gut microbiome lives in unique equilibrium with the host, from which they get energy through substrates provided by food[20]. In contrast, the gut microbiome can benefit host organisms by excreting specific metabolites, which helps maintain homeostasis[20]. Diet, lifestyle, medications, and toxic exposure significantly shape the diversity and composition of the gut microbiome, which may explain different responses to similar pathogenic stimuli, diet or medications[21]. For example, a study by Larsen *et al.*[22] reported a ratio of Bacteroidetes to Firmicutes and the Bacteroides-Prevotella group to *Clostridium coccoides-Eubacterium rectale* group were closely related to blood glucose concentration. Furthermore, a study by Larsen *et al.*[22] revealed that members of Betaproteobacteria were highly enriched in T2DM patients. Therefore, the gut microbiome is fundamental for physiological and metabolic processes, whereas recent evidence suggests that alterations in its composition, termed dysbiosis, could be implicated in the pathogenesis of metabolic disorders, cardiovascular diseases, intestinal bowel diseases, colorectal cancer and diabetes[22,23].

A study by Iatcu *et al.*[21] reported differences in gut microbiota composition observed in preclinical animal models as well as patients with T2DM and complications such as diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, cerebrovascular disease, coronary heart disease and peripheral artery disease compared to healthy controls. In addition, the same study revealed that the severity of gut microbiota dysbiosis was associated with disease severity and restoration with probiotic administration in animal models and human patients has been associated with improvement of symptoms and disease progression[23].

Some bacteria in the gastrointestinal tract produce butyrate, which can enhance insulin sensitivity and regulate glucose metabolism by increasing the secretion of GLP-1, an incretin hormone that stimulates insulin secretion and inhibits glucagon release. In a study by Cui *et al.*[24] associations among butyrate-producing taxa and insulin sensitivity, insulin secretion, disposition index, insulin clearance, and prevalence of dysglycemia (prediabetes plus diabetes, 46% of the cohort), adjusting for age, sex, body mass index (BMI), and race. In summary, butyrate improves insulin sensitivity and glucose metabolism, reduces inflammation, and promotes gut health, all contributing to better insulin regulation and metabolic health.

Modulating the gut microbiota via probiotics, prebiotics, synbiotics and fecal microbial transplantation (FMT) is a promising tool for treating T2DM[25]. Probiotics, which are live beneficial bacteria, can improve insulin sensitivity and reduce inflammation, a key contributor to insulin resistance[26]. Prebiotics, non-digestible fibers that feed beneficial gut bacteria, have been shown to enhance the production of short-chain fatty acids like butyrate, which play a role in glucose regulation and improving metabolic health[25]. Synbiotics, combining probiotics and prebiotics, offer synergistic effects, promoting a more favorable gut microbiota composition and improving glycemic control. FMT, the transfer of fecal matter from a healthy donor to the gastrointestinal tract of a diabetic patient, has shown potential in restoring a healthy gut microbiota balance, improving insulin sensitivity, and reducing systemic inflammation.

Traditional herbal medicine has great potential to treat diabetes via its effect on the gut microbiome. Various herbal medicines can increase the abundance of beneficial bacteria such as *Akkermansia* or *Blautia* and reduce the abundance of harmful bacteria such as *Escherichia-Shigella*[27]. In addition, microbes in the gastrointestinal tract can metabolize herbal compounds and thereby increase their bioavailability and bioactivity. For example, a study by Yang *et al.*[28] reported that berberine, an alkaloid from *Berberis kansuensis* showed a hypoglycemic effect via short-chain fatty acids producing bacteria and bacteria related to bile acid metabolism. In addition, berberine alters host lipid and cholesterol levels in patients with hyperlipidemia by regulating gut bacteria associated with lipid synthesis. Similarly, the water extract of Caulis Spatholobi, derived from the dried stems of *Spatholobus suberectus*, effectively maintained blood glucose homeostasis and

corrected microbiota dysbiosis in a diet-induced obesity mouse model. This was achieved mainly by increasing the abundance of bacterial genera associated with anti-obesity and anti-diabetic effects, including *Parabacteroides, Bacteroidetes*, *Anaerotruncus*, and *Bifidobacterium*[29]. These and many other examples illustrate the potential of herbal medicines to treat T2DM via the effect of specific herbal alkaloids on the gut microbiome, highlighting the importance of understanding gut-health interactions in developing effective diabetes therapies.

3 Bioactive compound regulating glucagon signalling

Bioactive compounds such as alkaloids from *Dendrobium officinale* have great potential in regulating glucagon signalling, which is an essential aspect of glucose metabolism and T2DM treatment. The study by Liu *et al.*[30] reported that the *D. officinale* polysaccharide (DOP) ameliorates glucose metabolism by influencing glucagon-mediated signalling pathways and altering liver glycogen structure. DOP administration resulted in improved liver glycogen storage and reduced hepatic glucose output, highlighting its potential as a therapeutic agent in managing diabetes through the modulation of glucagon signalling pathways[30].

In another study, Tian *et al.*[31] explored the effects of the ginsenoside metabolite compound K on GLP-1 secretion in NCI-H716 cells. The research demonstrated that compound K stimulates GLP-1 secretion via the RhoA/ROCKs/YAP signalling pathway and cytoskeleton formation. By enhancing GLP-1 secretion, compound K helps in promoting insulin secretion and improving glycemic control. A study by Tian *et al.*[31] underscores the large therapeutic potential of ginsenoside metabolites in diabetes management through their regulatory effects on glucagon signalling and GLP-1 secretion.

Additionally, a study by Onyango[32] reviewed various mechanisms involved in the regulation and dysregulation of glucagon secretion. Complex interactions between oxidative stress and glucagon secretion indicated oxidative damage, which disrupted normal glucagon signalling and contributed to hyperglycemia in diabetes. Recent progress in bioinformatics and transcriptomics revealed the inhibitory effects of Huanglian-Renshen-Decoction on hepatic glucose production via the PI3K/Akt/FoxO1 signalling pathway in type 2 diabetes mice[33]. This herbal decoction modulates glucagon signalling, thereby reducing hepatic glucose output and improving overall glucose homeostasis. These findings collectively highlight the diverse ways bioactive compounds can modulate glucagon signalling to manage diabetes[34].

4 Bioactive compounds in tropical herbs improve blood glucose levels

4.1 Bitter melon (*M. charantia* L.)

M. charantia, commonly known as bitter melon, is a member of the Cucurbitaceae family. The fruit consistently retains its distinctive bitter and astringent taste, even when sourced from other parts of the plant. *M. charantia* is extensively cultivated in Southeast Asian countries, including Malaysia, India, Brazil, and various parts of South America. This species is prominent within subtropical and tropical climates, which are the characteristics of the mentioned countries[35]. This plant has held a significant place as traditional medicine in ancient cultures for thousands of years. Its applications encompass the treatment of T2DM, hypertension, cancer, acquired immunodeficiency syndrome (AIDS), and viral and bacterial infections[36]. Scientific research has shed light on the potential of *M. charantia* in the treatment of T2DM, owing to its hypoglycaemic properties and rich composition of phytochemical constituents. Historically, various parts of plants, such as fruits, leaves, seeds, and roots, have served as sources of bioactive compounds, including flavonoids, alkaloids, and charantin. Particularly noteworthy among the bioactive compounds that hold significance in anti-diabetic and anti-hyperglycemic actions are polysaccharides, terpenoids, and saponins[37,38]. Research by Peter *et al.*[39] highlights the capacity of *M. charantia* to stimulate the regeneration of beta cells, a phenomenon observed in both *in vitro* and *in vivo* experiments. In a study involving diabetic rats induced by streptozotocin (STZ), it was observed that *M. charantia* polysaccharide (MCPIIa) and the polysaccharide chromium (III) complex (MCPIIaC) played a role in safeguarding pancreatic cells and enhancing plasma insulin levels. The dietary administration of powdered extract of *M. charantia* fruit led to improved insulin production, potentially due to its stabilizing effects on β cells, as observed in conjunction with the consumption of *M. charantia*[37].

The mechanism by which terpenoids function as α-glucosidase inhibitors, orchestrating glucose regulation, is elucidated in Fig. 1. By inhibiting enzymes such as α-amylase and α-glucosidase, they reduce carbohydrate digestion, slow down glucose absorption, and ultimately lead to decreased blood glucose levels[40]. The inhibition of these enzymes serves as a mechanism to reduce blood glucose levels in both animals and humans by preventing the breakdown of carbohydrates in the small intestine. Among the enzymes responsible for carbohydrate metabolism, α-glucosidase stands out due to its pivotal role in carbohydrate hydrolysis, making it a promising target for controlling carbohydrate digestion[41].

4.2 Curry tree (*M. koenigii* (L.) Spreng.)

M. koenigii, widely recognized as curry leaf in the general population, is a culinary ingredient renowned for its aromatic properties and diverse applications as a natural remedy. This traditional ingredient, originating in India, offers various healing properties, including potential benefits for antidiabetics, antioxidants, anti-inflammatory properties, and antibacterial properties[42]. The leaves of *M. koenigii* harbor a collection of bioactive compounds, particularly phenolic compounds, terpenoids, alkaloids, and flavonoids[43]. A research study by Jadhav and Dhudum[44] explored curry leaf powder as a treatment for individuals with T2DM, demonstrating significant reductions in blood glucose levels without adverse effects. Similarly, Al-Ani and Al-Azzawi[45] conducted an experiment employing curry leaf powder on diabetic adult rats. Their findings highlighted the anti-hyperglycaemic potential of *M. koenigii* aqueous extract in STZ-induced diabetic rats, yielding significant reductions in blood glucose levels toward normal ranges. The study offers substantial evidence supporting the ability of *M. koenigii* extract to lower blood sugar levels while protecting the renal and endocrine functions in diabetic rats induced by STZ[45].

Figure 2 illustrates that the insulin receptor (IR) signalling is believed to encounter inhibition from protein-tyrosine phosphatase 1B (PTP1B) within insulin pathways. This inhibition stems from PTP1B's ability to bind with the activated IR or insulin receptor substrates (IRSs), inducing subsequent dephosphorylation. Cellular overexpression of PTP1B manifests in reduced IR and/or IRS-1 phosphorylation levels upon insulin

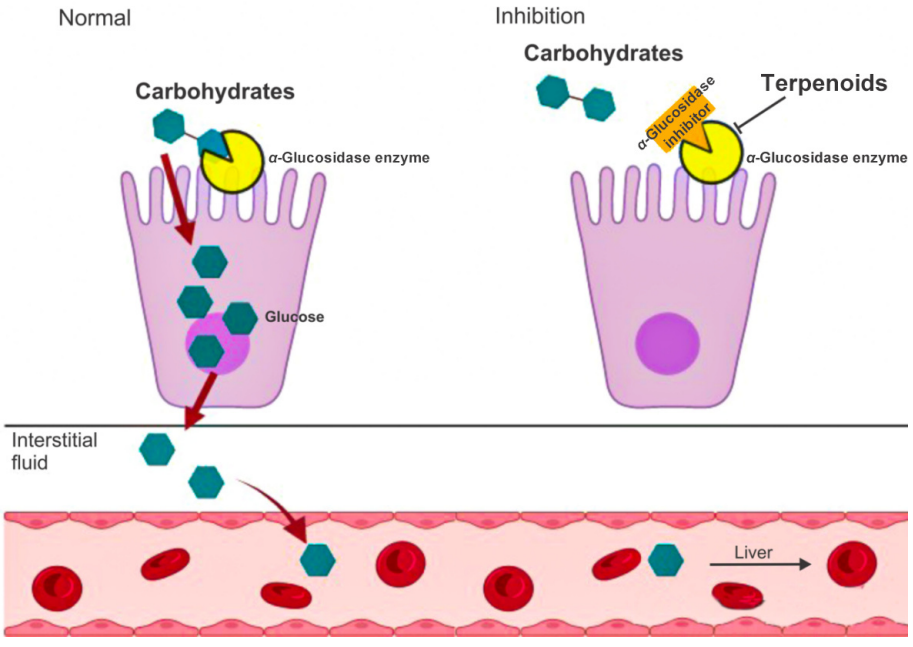


Figure 1 Contribution of α-glucosidase inhibitors to regulating glucose production. In the normal process, carbohydrates interact with α-glucosidase, undergoing hydrolysis to form glucose, which is transported via the bloodstream to the liver. The inhibition phase illustrates how terpenoids inhibit α-glucosidase, resulting in the non-hydrolysis of carbohydrates. The figure was created using BioRender.com based on data from Hossain *et al.* (2020).

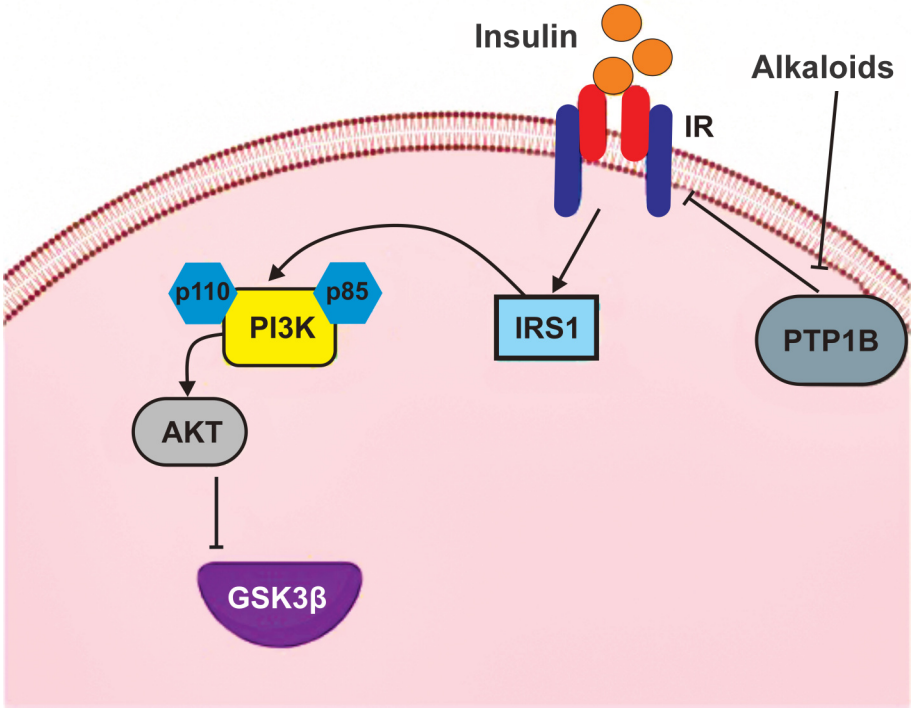


Figure 2 Inhibition of GSK3β and PTP1B in lowering blood glucose. The figure was created using BioRender.com based on data from Zhang *et al.* (2020).

stimulation. Furthermore, literature analysis indicates the susceptibility of PTP1B to inhibition by various substances[46]. Conversely, when insulin binds to receptor substrate 1 (IRS1), it initiates phosphorylation, activating phosphatidylinositol-3-kinase (PI3K). This activation increases glycogen production by upregulating synthase kinase 3β (GSK3β). Once the p110 and p85 subunits of PI3K are activated, phosphorylated AKT (pAKT) emerges, thus affecting GSK3β inhibition[47].

4.3 Noni (*M. citrifolia* L.)

Locally known as 'mengkudu' in Malaysia, is a member of the Rubiaceae family[48, 49]. Due to its potential as a functional food with health benefits, this plant has garnered substantial research attention. The plant is widespread in tropical climates, encompassing countries like Malaysia, Indonesia, Thailand, India, Fiji Islands, Tahiti, Brazil, and the United States, particularly Hawaii[50]. In traditional medicine, *M. citrifolia* addresses diabetes, infectious diseases, inflammations, cancer, psychiatric issues, and high blood pressure[51]. The plant contains various phytochemical compounds such as flavonoids, phenolics, alkaloids, triterpenoids, and saponins, each contributing to its hypoglycaemic effects[52, 53]. In an 8-week clinical trial conducted by Algenstaedt *et al.*[54],

patients with T2DM were given *M. citrifolia* fruit juice at a daily dose of 2 mL/kg of body weight. The study revealed significant reductions in blood glucose and haemoglobin A1c (HbA1c) levels. Additionally, C-peptide data indicated enhanced insulin secretion[54]. In another study by Dafriani *et al.*[55] participants with diabetes were divided into intervention and control groups. Over 10 days, the intervention group consumed *M. citrifolia* extract. The results demonstrated a significant reduction in blood sugar levels among the intervention group, in contrast to higher blood glucose levels observed in the control group[55].

The mechanism through which flavonoids exhibit anti-diabetic effects is illustrated in Fig. 3. In essence, insulin binds to the IR on the plasma membrane, initiating signalling pathways that regulate cell development and metabolism[56]. Flavanols play a role in modulating carbohydrate function within the stomach, thereby maintaining glucose homeostasis. Increased flavanol-enriched catechins have been associated with heightened insulin release in response to glucose stimulation. Additionally, myricetin treatment in diabetic contexts has been shown to enhance the phosphorylation of AKT and IRS1 while also prompting the expression of glucose transporter type 4 (GLUT4)[57]. GLUT4, a pivotal insulin-responsive molecule, is critical in glucose absorption. The malfunctioning translocation of GLUT4 from intracellular vesicles to the plasma membrane is linked to reduced glucose absorption, insulin resistance, and T2DM. Addressing GLUT4-related anomalies offers a targeted therapeutic avenue for T2DM, given its essential role in maintaining overall glucose homeostasis[58]. Adipose tissue and fat cells are activated by insulin signalling molecules to facilitate the intracellular-to-cell membrane translocation of GLUT4, thereby enhancing glucose absorption and intake[59].

4.4 Garlic (*A. sativum* L.)

A. sativum, commonly called garlic, is a bulb-flowering plant within the Amaryllidaceae family[60]. This versatile plant thrives in temperate and tropical climates globally[61]. Over time, garlic has been widely valued in traditional Chinese medicine for its numerous health benefits. Garlic is rich in various bioactive compounds derived from its extract, contributing to its medicinal properties encompassing anti-diabetic, antioxidant, antimicrobial, anti-mutagenic, anticancer, and anti-inflammatory attributes[62,63]. Garlic has been linked to maintaining stable blood glucose levels and has the potential to aid in reducing overall blood sugar concentrations within the body[64]. Moreover, it is frequently used as a culinary condiment to impart a flavorful dimension to dishes[61]. The edible portion of garlic primarily resides in its fresh bulbs[65]. Garlic contains a variety of bioactive compounds, each with distinct functions. These include sulphur compounds like ajoene and allicin, flavonoids, and polyphenols. Allicin, the primary chemically active component of garlic, has been shown to stimulate insulin secretion, enhance liver metabolism, and regulate lipid peroxidation[66]. Among the potential benefits of garlic, allicin plays a central role by promoting insulin secretion, optimizing liver metabolism, and modulating lipid peroxidation[64]. The intricate interplay continues with DPP-4, an enzyme hastening the degradation of glucagon-like peptides GLP-1 and GLP-2.

The presence of phytochemicals in garlic extract intervenes by inhibiting DPP-4, a mechanism illustrated in Fig. 4, thereby impeding the breakdown of GLP-1 and GLP-2. This action contributes to enhanced insulin production, reduced postprandial glucagon, and improved beta-cell activity, leading to delayed gastric emptying in the pancreatic islets[67]. Sulphur compounds in plant extracts are also vital, especially concerning insulin resistance and hyperglycaemia mitigation, often through various formulations[68]. A study that investigated the use of ethanol garlic extract on diabetic rabbits and rats induced with STZ and alloxan revealed its potent anti-diabetic effects, particularly its ability to enhance insulin secretion from the parietal cells of the pancreas[69]. Additionally, garlic and onion peel extracts are potential novel pharmacological agents for T2DM treatment. In a study involving male Wistar rats, the administration of ethanol extracts from garlic and onion peel reduced blood glucose levels in diabetic rats. However, no significant difference was observed in insulin-induced diabetic rats[70].

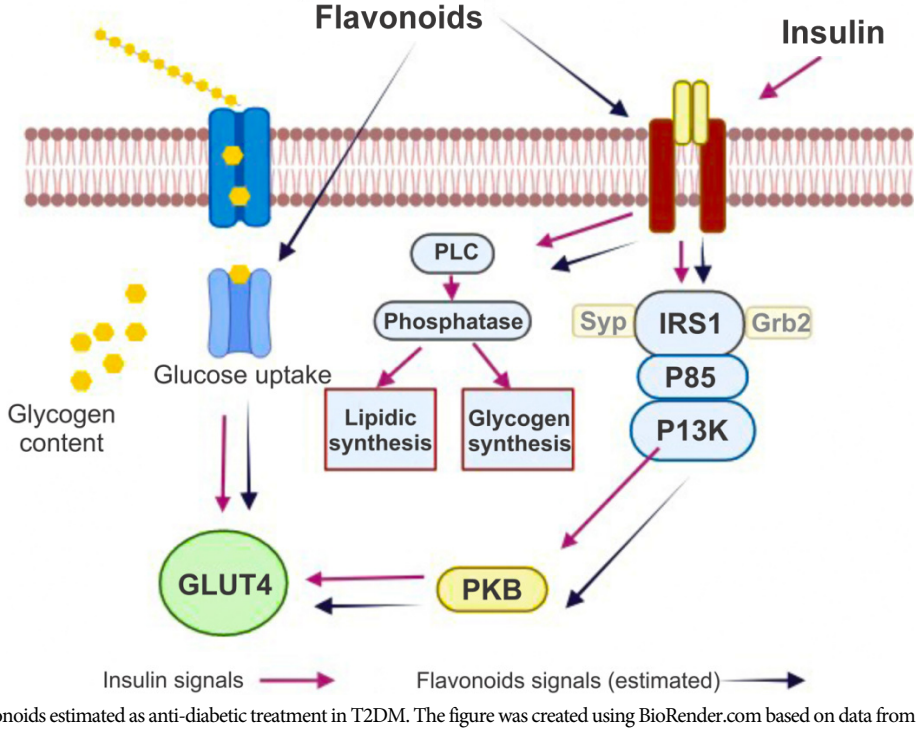


Figure 3 Flow of flavonoids estimated as anti-diabetic treatment in T2DM. The figure was created using BioRender.com based on data from Hussain *et al.* (2020).

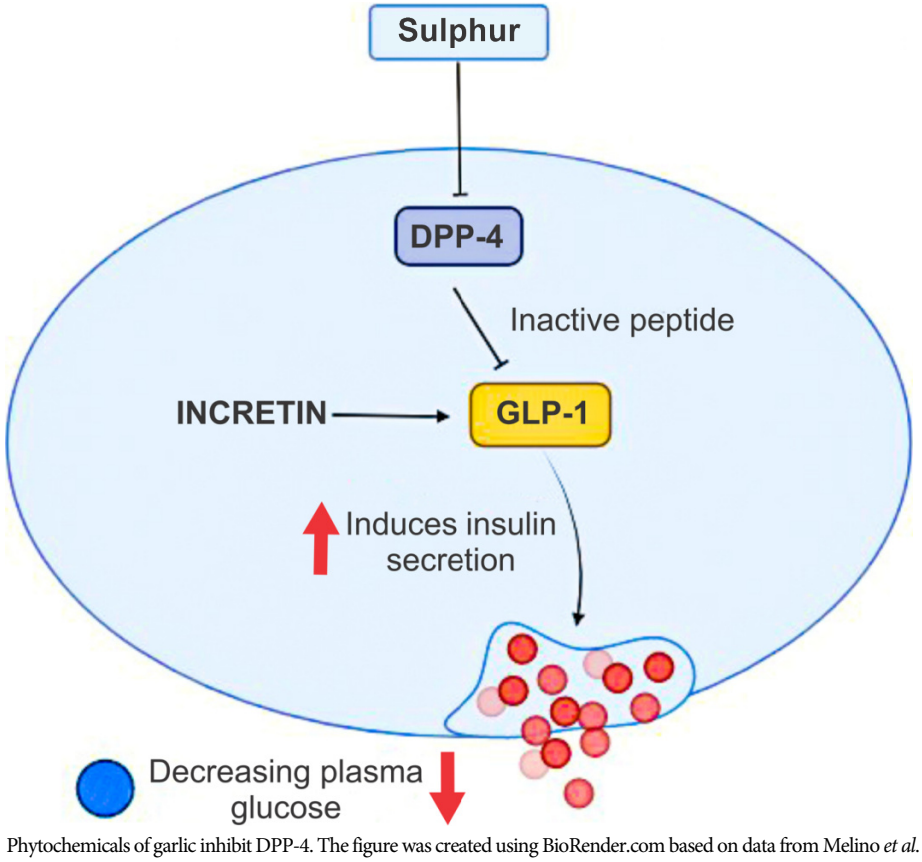


Figure 4 Phytochemicals of garlic inhibit DPP-4. The figure was created using BioRender.com based on data from Melino *et al.* (2019).

4.5 Ginger (*Z. officinale* Roscoe)

Z. officinale, a member of the Zingiberaceae family, is renowned as a culinary spice and herbal remedy[71]. This versatile root is ubiquitously found across various countries, including India, Indonesia, Thailand, Malaysia, China, and Nepal[72,73]. The benefits of ginger include anti-inflammatory, anti-diabetic, anticancer, antioxidative, antifungal, cholinesterase inhibition, and supportive roles in conditions such as hypertension, indigestion, nausea, and asthma[74-76]. The herb also has diverse chemical constituents, comprising gingerol, shogaols, zingiberene, and zingerone, along with essential vitamins and minerals[77].

The polyphenol molecules undergo degradation and modification by the saliva's hydrolysing enzyme, such as the lactase-phlorizin hydrolase (LPH), and subsequently being modified by the intestinal microbiota and get absorbed into the intestine[78]. This mechanism effectively leads to the molecule's degradation. Furthermore, it experiences processing by intestinal enzymes and absorption facilitated by microbiota. Applying a phenolic extract significantly reduces glucose levels by impeding carbohydrate digestion and absorption. Phenolic compounds present in the extract obstruct glucose and sodium (Na^+) access to this site due to their binding with sodium/glucose cotransporter 1 (SGLT), as illustrated in Fig. 5. In a prior study conducted by Otunola and Afolayan[79], an investigation was undertaken using STZ-induced diabetic and normal rats to examine the impact of ginger extract on the blood sugar levels of these rats. The study revealed that raw and cooked ginger extracts lowered blood glucose levels in diabetic rats, demonstrating a comparable effect to glibenclamide[79]. Additionally, ginger juice has demonstrated the ability to decrease blood sugar levels while increasing insulin levels[53]. In a study by Srinivasan[80], an ethanol extract of ginger was employed to evaluate its hypoglycaemic effects on normal rabbits. The study outcomes indicated effective hypoglycaemia, making it a practical means of lowering blood sugar levels. Furthermore, the oral administration of ginger ethanolic extract at a dosage of 800 mg/kg significantly lowered fasting blood glucose levels in STZ-diabetic rats within one hour, with the most pronounced effect occurring after 4 h[80]. Moreover, ginger has exhibited potential in safeguarding the nervous system, liver, and kidneys in patients with T2DM[75].

4.6 Other tropical herbs

A review article by Nur Akmal *et al.*[81] has highlighted the presence of similar phytochemical compounds in Malaysian herbs such as *Andrographis paniculata*, *Clinacanthus nutans*, *Ficus deltoidea*, *Leucaena leucocephala*, and *Melastoma malabathricum*. These herbs offer various beneficial effects on the human body, particularly in managing diabetes. For instance, they have demonstrated the ability to regulate glucose levels by enhancing glucose uptake, stimulating insulin secretion, and upregulating GLUT4 expression (Fig. 6). Additionally, these herbs promise to improve insulin resistance by increasing insulin secretion while preserving the structural integrity of pancreatic cells under high glucose conditions. Furthermore, they have been found to modulate lipid levels and synthesis effectively. These herbs exhibit anti-inflammatory properties and diverse antioxidants, all contributing to their potential to manage glycemic indices in the human body[81].

In a study conducted by Agarwal *et al.*[82], it was observed that administering increasing doses of the aerial part of *A. paniculata*, ranging from 600 mg to 1.8 g daily for 12 weeks, to 20 patients with T2DM did not result in significant side effects. Instead, it led to a notable reduction in HBA1c and fasting insulin levels. This effect is likely attributed to the herb's capacity to peripherally

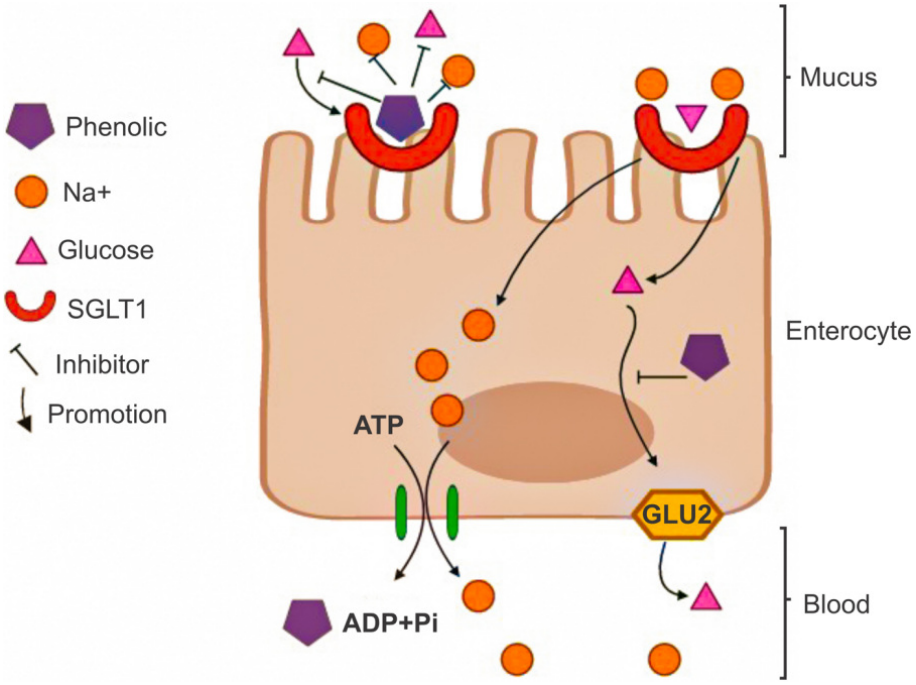


Figure 5 Polyphenols intake and glucose uptake inhibition processes. The figure was created using BioRender.com based on data from Zhao *et al.* (2020).

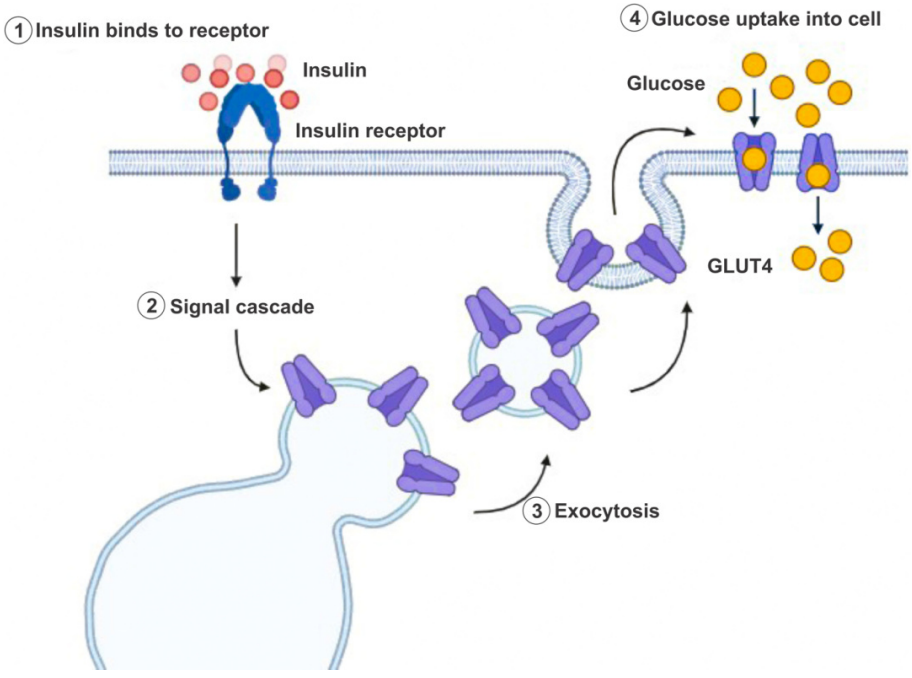


Figure 6 Regulation of glucose uptake by translocating glucose transporter 4 (GLUT4) through insulin signalling. The figure was created using BioRender.com based on data from Nur Akmal *et al.* (2021).

enhance glucose metabolism through its interaction with insulin rather than directly stimulating insulin release from pancreatic islet cells. Nevertheless, other potential mechanisms, known as extra-pancreatic effects, might be at play. These mechanisms might affect glucose regulation differently, potentially influencing the liver through enzymatic and non-enzymatic pathways or impacting the gastrointestinal tract, especially concerning carbohydrate absorption[82]. Other studies have reported similar results, demonstrating that *A. paniculata* can reduce blood triglyceride and (low density lipoprotein) LDL cholesterol levels[83]. However, the specific mechanisms remain unclear.

Moreover, another research study has highlighted the advantageous qualities of the phytochemical content and application of various herbs in the management of diabetes, including *Aloe vera, A. paniculata, Centella asiatica, Curcuma longa, Gynura procumbens,* and *Orthosiphon stamineus*, in the management of diabetes. The study revealed that certain antidiabetic medications derived from these plants demonstrated hypoglycemic effects that were more effective than commonly used oral diabetic medications in clinical practice[84]. Additionally, certain herbs, including *Anacardium occidentale, A. paniculata, Averrhoa bilimbi, Cosmos caudatus, G. procumbens, Hibiscus rosa-sinensis, Phyllanthus niruri, Piper sarmentosum* and *O. stamineus,* have demonstrated the capacity to regulate and manage

hyperglycaemic conditions, as documented by Mahendran *et al.*[85]. In both animal and human studies, these herbs achieve this by improving insulin sensitivity and modulating lipid profiles, particularly cholesterol and triglyceride levels. They effectively reduce blood glucose levels and regulate α-glucosidase, an enzyme responsible for glucose absorption in the intestines. Some of these herbs may also inhibit haemoglobin glycation and promote glycogen storage in the liver. Nevertheless, to establish the potential of these plants as effective alternative treatments for diabetes, further research is necessary at both molecular and clinical levels, encompassing pharmacological and toxicological investigations[85].

It is important to note that while these tropical herbs show promise in managing T2DM, they are not a replacement for prescribed medication. People with diabetes should always consult with healthcare professionals to develop a comprehensive treatment plan, which may include dietary changes, exercise, and, in some cases, medication. Using these tropical herbs as complementary treatments should be done under medical supervision to ensure they are safe and effective for everyone.

5 The global challenge of T2DM: a metabolomics perspective

The rapid proliferation of DM, a chronic metabolic disorder, has significantly contributed to the increasing global morbidity and mortality rates[86, 87]. These alarming trends align with the perspectives of global institutions such as the United Nations (UN) and the World Health Organization (WHO), which attribute the escalating health crises to the unhealthy management of modern lifestyles[88]. Predictions of this global health crisis indicate a staggering 693 million people living with diabetes by 2045[89]. This increasing prevalence of diabetes raises concern about its associated complications, which have detrimental effects on various organs, including nerves, eyes, hearts, kidneys, and blood vessels[90].

Hyperglycaemia, a hallmark of diabetes, disrupts metabolic processes, leading to impaired insulin conductivity, resistance to insulin activity, and reduced insulin response to secretion[89, 91]. Metabolomics, which aims at the comprehensive study of metabolites in biological systems (e.g., humans, plants, animals, and microorganisms)[92], can become one of the alternatives to address global challenges in managing DM. Metabolomics may aid in identifying specific biomarkers associated with diabetes[93]. The approach also enables early diagnosis and risk prediction that can lead to timely intervention and better management of the disease. As a result, comprehensive study-based metabolomics allows for a better understanding of the disease mechanisms via pathways[93]. Furthermore, metabolomics is useful for monitoring disease progression and metabolic alteration in response to treatments of herbal medicine or drugs[93]. It may highlight the potential therapeutic targets and aid in developing more effective drugs. Thus, this approach allows for the adjustment of therapeutic strategies to achieve better decisions in managing diabetes. On top of that, metabolomics can facilitate international research collaborations by pooling data and resources to tackle the global burden of diabetes more effectively. Integrating metabolomics with other-omics, e.g., genomics, transcriptomics, and proteomics, would greatly benefit researchers and healthcare providers by improving the prevention, diagnosis, and management of DM.

Over the past two decades, the global prevalence of T2DM has doubled, presenting a significant threat to human health and placing substantial economic burdens on nations. This is due to escalating medical costs and reduced workforce productivity. In cases of T2DM, when pancreatic beta cell function declines, oral medications are utilized to improve insulin sensitivity. However, this caused blood glucose regulation to continue to be compromised[94]. Metabolomics can play a pivotal role by identifying biomarkers that predict medication response, thus optimizing treatment plans and improving outcomes[95]. Unlike in T1DM, where daily insulin injections are essential due to pancreatic cell damage, T2DM patients typically turn to injections when oral medications are ineffective[96, 97]. The complex nature of this disorder, coupled with its association with cardiovascular risk factors, accentuates its propensity for secondary complications[98].

Patients with DM often display distinct physical and mental attributes, including depression stemming from anxiety about the implications of the disease[99]. Hyperglycaemia-induced energy deficiency leads to persistent hunger and thirst[100]. Conditions such as retinopathy, characterized by retinal capillary permeability, contribute to distorted vision, while Acanthosis nigricans, characterized by skin discolouration, further underscores the diverse impacts of DM[101]. Central to diabetes management are β-cells located in the pancreas, responsible for the production and secretion of insulin hormone[102]. The distribution of glucose to cells relies on insulin's role in lowering blood glucose levels[103]. The development of DM is influenced by genetic predisposition, environmental factors such as obesity, and physical activity[104, 105]. The prevalence of T2DM following GDM emphasizes the need for obstetric intervention and stresses the importance of lifestyle modifications[106]. Metabolomics offers a powerful tool to identify metabolic signatures of gestational diabetes, which can lead to more effective prevention strategies and better postpartum care. The escalating prevalence of T2DM calls for global attention and concerted efforts toward prevention, management, and healthcare interventions. Integrating metabolomics into diabetes research and clinical practice holds the potential to transform our understanding and management of this complex disease, ultimately mitigating its far-reaching impacts.

6 Bibliometric analysis

A bibliometric analysis was conducted to understand the global progress, research trends, and utilization of tropical herbs for managing T2DM. Through the use of the available online database, the data source and search strategy were carried out, which yielded 9,577 publications from January 1976 to December 2022 with particular search terms (Fig. 7). A bibliometric map was constructed focusing on the co-occurrence of the author's keywords (Aks) using the 9,577 records in the Web of Science (WoS) database through the VOSviewer software (version 1.6.17).

6.1 Trend in research interest and number of publications

Figure 8 shows the evolution of publication numbers concerning bioactive compounds, hypoglycemia, and DM research. The number of publications has steadily increased over the years, particularly spiking in certain periods like 1991 and 2002, with 43 and 134 published articles, respectively. This upward trend continued until 2022, when 1022 documents were published this year alone. Between 1976 and 1990, there were very few publications (only about 2.3 per year) on hypoglycemia and DM. However, starting from 1991, there was a noticeable increase in

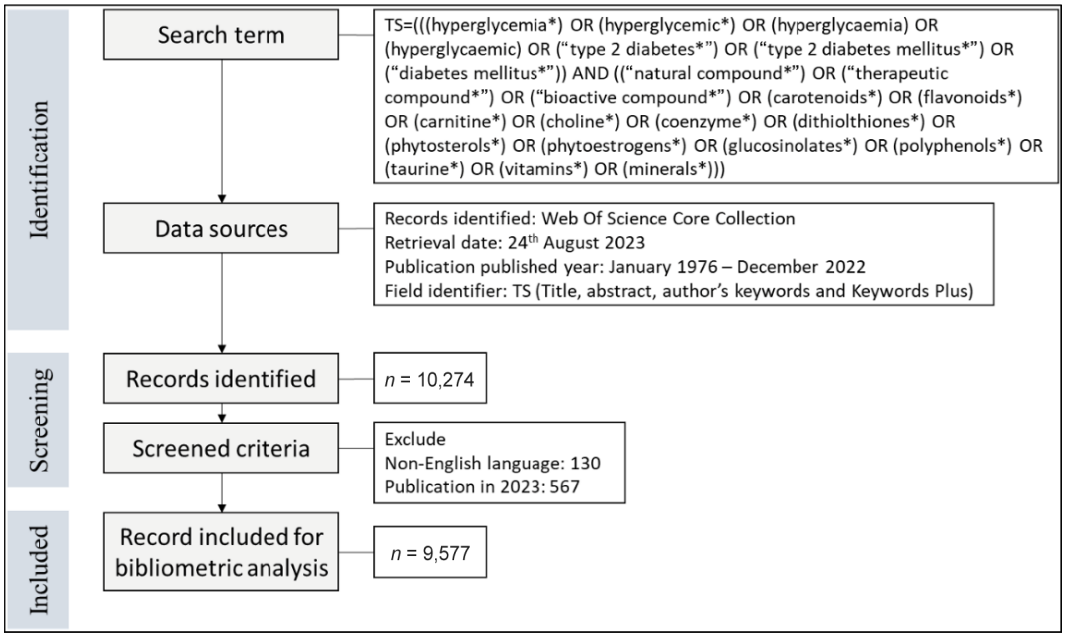


Figure 7 Methodological framework outlines the chosen search terms, data sources, and criteria for including records in the analysis.

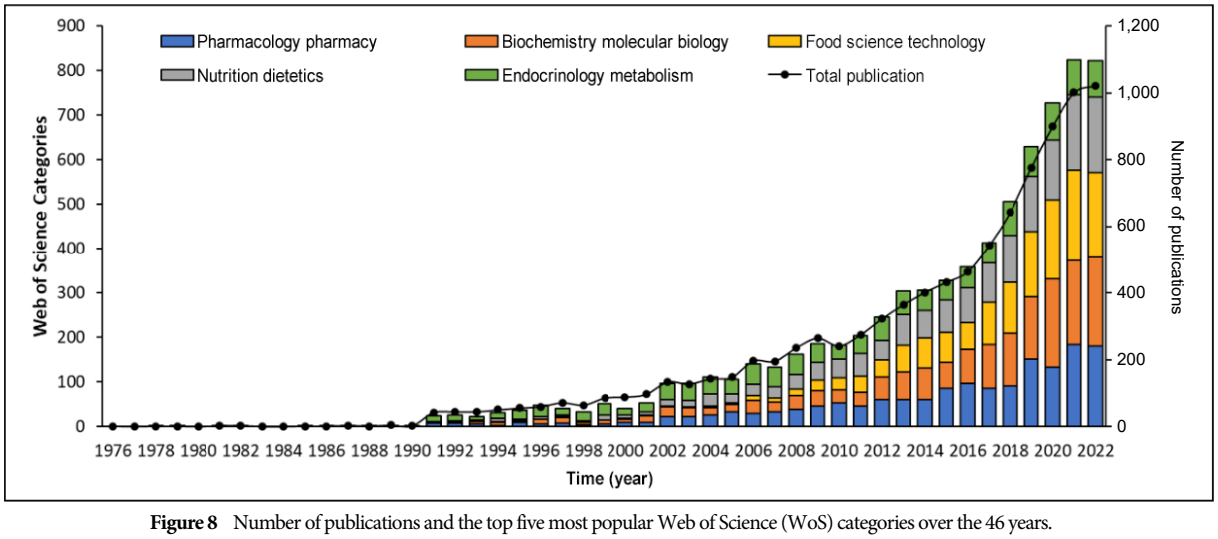


Figure 8 Number of publications and the top five most popular Web of Science (WoS) categories over the 46 years.

research output. The most cited paper in 1991 likely played a crucial role in sparking more interest in these topics. Since then, from 1991 to 2022, the number of publications has consistently risen, indicating a growing focus on understanding this topic. This ongoing increase suggests a growing awareness of the importance of these health issues and a continued effort to learn more about them. The top five most popular WoS categories are pharmacology pharmacy, biochemistry and molecular biology, food science and technology, nutrition dietetics, and endocrinology metabolism.

6.2 Top 10 publications with the highest citation

Table 2 shows the top 10 cited papers concerning isomaltulose from the last 46 years. As tabulated, all articles were published between 2002 and 2011, demonstrating that the older articles are more frequently cited due to the length of time that they have been indexed. The most cited paper, which garnered 2,131 citations, entitled "*Diabetes, oxidative stress, and antioxidants: a review*", authored by Maritim *et al.* and published in the Journal of Biochemical and Molecular Toxicology in 2003, provides a comprehensive review in exploring the intricate relationship between diabetes, oxidative stress, and the crucial role played by antioxidants. The list was followed by Ozcan *et al.*'s paper with 1946 citations entitled "*Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes*", published in Science. This study uses chemical chaperones to mitigate endoplasmic reticulum (ER) stress, offering insights into potential therapeutic interventions to restore glucose homeostasis in a mouse model of type 2 diabetes. While in 2007, Scuteri *et al.* published a significant paper with 1291 citations in PLoS Genetics, "*Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits*". This study employs a genome-wide association scan to identify genetic variants in the Fat mass and obesity-associated (*FTO*) gene linked to traits related to obesity, contributing valuable insights into the genetic factors influencing obesity.

6.3 Leading countries and institutions

A ranking of document types, top 10 productive authors and top 10 productive affiliations in this research topic is presented in

Table 2 Top 10 publications with the highest citations related to bioactive compounds and hyperglycemia research

Ranks	Title	Source	TC	Year	Reference
1	Diabetes, oxidative stress, and antioxidants: a review	Journal of Biochemical and Molecular Toxicology	2131	2003	Maritim *et al.*
2	Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes	Science	1946	2006	Ozcan *et al.*
3	Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits	PLOS Genetics	1291	2007	Scuteri *et al.*
4	Newly identified loci that influence lipid concentrations and risk of coronary artery disease	Nature Genetics	1289	2008	Willer *et al.*
5	Flavonoid intake and risk of chronic diseases	American Journal of Clinical Nutrition	1259	2002	Knekt *et al.*
6	AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin-resistant mice	Cell Metabolism	1184	2011	Li *et al.*
7	Dysregulation of fatty acid metabolism in the aetiology of type 2 diabetes	Diabetes	1102	2002	McGarry
8	Antioxidants prevent health-promoting effects of physical exercise in humans	Proceeding of the National Academy of Science of the United States of America	1099	2009	Ristow *et al.*
9	AMP-activated protein kinase in metabolic control and insulin signalling	Circulation Research	1031	2007	Towler and Hardie
10	The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice	Journal of Clinical Investigation	1019	2003	Xu *et al.*

Table 3. It gives a closer look at the research and organizations that have been particularly active in publishing studies on bioactive compounds and hyperglycemia. The summary in Table 3 provides information on the leading contributors and affiliations across different document types in this field. In addition, Table 4 shows that the most significant published literature was from the USA, China, and India, accounting for 1,344, 1,122, and 577 publications, respectively. The total number of studies from the three countries accounted for more than half of the total reports, implying a high interest in research in bioactive compounds, hyperglycemia and DM.

6.4 Author's keywords

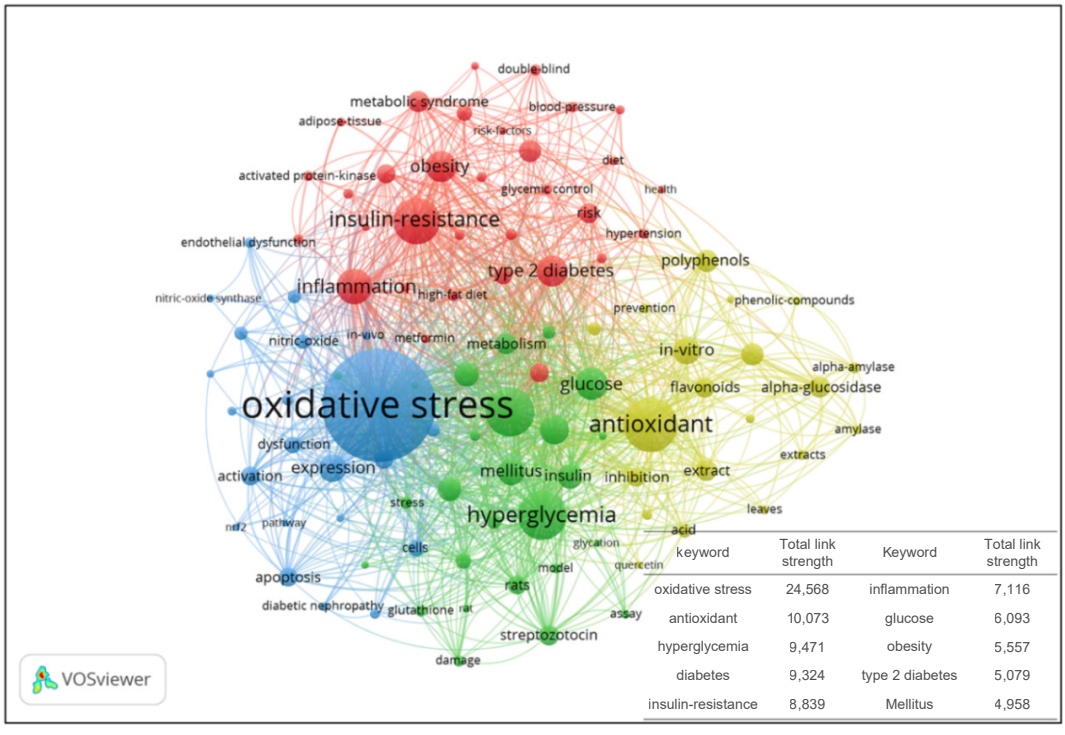
From 1976 to 2022, 34,717 author's keywords (Aks) were found in the analyzed papers. However, only the 100 most frequent Aks were used for this review. Figure 9 shows the Aks map, in which

Table 3 Information on document types, along with the most productive authors and institutions involved in the research

Ranks	Document types (Nu. of the document)	Top 10 productive authors				Top 10 productive affiliations		
		Names	TP	TC	H-index	Institutions	TP	TC
1	Article (7334)	Wang, Yu	47	2,779	22	Egyptian Knowledge Bank EKB	194	3510
2	Review Article (1994)	Chen, Liang	39	721	17	Harvard University	103	9649
3	Proceeding Paper (314)	Liu Y	38	1,235	15	University of California System	101	7280
4	Book Chapter (107)	Zhang Y	37	1,082	16	Institut National De La Sante Et De La Recherche Medicale Inserm	97	10757
5	Meeting Abstract (96)	Li Y	33	3,213	17	Udice French Research Universities	88	8450
6	Editorial Material (31)	Zengin G	29	1,140	15	Chinese Academy of Sciences	83	3716
7	Letter (23)	Islam MS	28	293	9	University of Texas System	78	7114
8	Note (11)	Liu J	26	1,074	14	Universidade De Sao Paulo	75	1456
9	News Item (2)	Li J	25	1,118	12	University of London	75	4886
10	Data Paper (1)	Li X	25	576	12	Ciber Centro De Investigacion Biomedica En Red	72	2949

Table 4 Top leading countries that have produced the most articles on bioactive compounds and hyperglycemia research

Ranks	Countries/Regions	Total publications (TP)	Total citations (TC)
1	USA	1,344	78,853
2	China	1,122	28,379
3	India	577	13,519
4	Japan	477	18,663
5	Italy	353	15,689
6	South Korea	348	10,198
7	England	294	15,785
8	Brazil	292	5,792
9	Spain	263	9,793
10	Canada	238	12,998



keyword	Total link strength	Keyword	Total link strength
oxidative stress	24,568	inflammation	7,116
antioxidant	10,073	glucose	6,093
hyperglycemia	9,471	obesity	5,557
diabetes	9,324	type 2 diabetes	5,079
insulin-resistance	8,839	Mellitus	4,958

Figure 9 .

the node size represents the number of times the keywords were used, and line thicknesses and colour indicate the cluster to which the item belongs.

7 Conclusion

In summary, these tropical herbs are critical in diabetes treatment because they provide natural alternatives to conventional medications. They play a vital role in regulating blood sugar levels, enhancing insulin sensitivity, and offering protection against the complications associated with diabetes. Their effectiveness and relatively low risk of side effects make them invaluable in diabetes management, whether used to complement existing treatments or as an integral part of a healthy diet and lifestyle. Furthermore, it is important to consult with a healthcare professional before incorporating these tropical herbs into a diabetes management plan to ensure they are used safely and effectively. Lastly, this review aims to enhance our understanding of how tropical herbs and their phytochemical components can be used to manage T2DM. Numerous global experiments and studies have delved into the effectiveness of specific tropical herbs in controlling T2DM by reducing blood glucose levels and stimulating insulin secretion from pancreatic cells. To assess the potential of these herbs, these studies have encompassed clinical investigations involving type 2 diabetes patients and animal models, including rodents and rabbits. Nevertheless, further analysis is necessary to fully comprehend their potential efficacy and mechanisms of action in managing diabetes.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

Acknowledgements

This research was financially supported by Universiti Malaysia Terengganu through the Research Intensified Grant Scheme (UMT/RIGS/2023/55437).

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