Original Article

Modulation of gene expression by traditional Asian antidiabetic nutraceuticals: A review of potential effects

Katrin Roosita PhD[1], Karina Rahmadia Ekawidyani MD, PhD[1], Rosyanne Kushargina PhD[2], Fathimah MPH[3,4], Mohamad Rafi PhD[5], Uus Saepuloh PhD[6]

[1]*Department of Community Nutrition, Faculty of Human Ecology, IPB University, Bogor, Indonesia*
[2]*Nutrition Study Program, Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta, Jakarta, Indonesia*
[3]*Doctoral Study Program in Nutrition Sciences, Department of Community Nutrition, Faculty of Human Ecology, IPB University, Bogor, Indonesia*
[4]*Nutritional Science Study Program, Faculty of Health Sciences, Universitas Darussalam Gontor, Ponorogo, East Java, Indonesia*
[5]*Department of Chemistry, Faculty of Mathematics and Natural Science, IPB University, Bogor, Indonesia*
[6]*Primate Research Center IPB University, Bogor, Indonesia*

Background and Objectives: Type 2 diabetes mellitus (T2DM) has emerged as a significant global public health concern. Multiple studies have shown that traditional nutraceuticals are potential to treat T2DM and its complications. This review will explore traditional nutraceuticals with antidiabetic properties with a focus on traditional Asian nutraceuticals and their antioxidant effects on gene expression associated to T2DM. **Methods and Study Design:** Literature searching was conducted in Pubmed, Scopus, and Science Direct using the keywords "nutraceutical", "antidiabetic", "insulin resistance", "Diabetes Mellitus", "herbal medicine", "mechanism", "pathway", "traditional food", "functional food", "antioxidant", "clinical", "preclinical", "animal studies", and "Asian" combined with Boolean operators "OR". **Results:** Nutraceuticals sourced from traditional Indonesian herbal beverages, including Galohgor, Bir Pletok, and Wedang Uwuh, have shown potential efficacy in reducing hyperglycemia, oxidative stress, and obesity in T2DM. Furthermore, multiple Asian plants and their bioactive compounds, such as curcumin, kaempferol, cinnamon, saponin, quercetin, myricetin, anthocyanin, terpenoid, alkaloid, and gallic acid, have been shown to beneficially influence glucose homeostasis, insulin sensitivity, and problems associated with diabetes. Moreover, bioactive compounds of these traditional nutraceuticals have been proven in modulating gene expression associated with β-cell function, insulin signaling pathway, and antioxidant activity, which may offer a new therapeutic target. **Conclusions:** This review highlights the increasing scientific evidence on the role of traditional nutraceuticals for the prevention and management of diabetes mellitus, presenting promising alternatives to standard pharmacological therapy. Nonetheless, double-blind randomized clinical trials are required to validate these antidiabetic effects.

Key Words: antioxidants, Asian traditional nutraceutical, gene expression, oxidative stress, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus has become a major global public health issue, with its prevalence quadrupling over the past three decades.[1] The global prevalence of diabetes among individuals aged 20–79 was estimated at 10.5%, affecting approximately 536.6 million people. This figure is projected to rise to 12.2% (783.2 million) by 2045. Diabetes rates were comparable between men and women, with the highest prevalence observed in the 75–79 age group. The prevalence in urban areas (12.1%) was higher than in rural areas (8.3%), and diabetes was more common in high-income countries (11.1%) compared to low-income nations (5.5%). The most significant relative increase in diabetes prevalence between 2021 and 2045 is projected in middle-income countries (21.1%), surpassing that of high-income (12.2%) and low-income (11.9%) nations.[2,3]

Diabetes mellitus is a burdensome disease due to its long-term complications and potential to cause disability. It is also the ninth primary cause of death.[1] In 2021, an estimated 6.7 million deaths worldwide were attributed to diabetes among individuals aged 20–79 years.[4] Furthermore, global direct healthcare expenditure on diabetes for individuals aged 20–79 was estimated at USD 966 billion in 2021 and is projected to rise to USD 1,054 billion by

Corresponding Author: Prof. Katrin Roosita and Dr Karina Rahmadia Ekawidyani, Department of Community Nutrition, Faculty of Human Ecology, IPB University, Jl. Lingkar Akademik, Kampus IPB Darmaga, Bogor 16680, Indonesia
Tel: +622518625066
Email: kroosita2@apps.ipb.ac.id; karinare@apps.ipb.ac.id
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2045.[2] The long-term complication of diabetes mellitus involved micro- and macrovascular complications, including cardiovascular complications, kidney failure, and cerebral complications.[5]

Current treatment for type 2 diabetes mellitus (T2DM) involves pharmacological therapy and lifestyle modification. Antidiabetic drugs are classified into several groups, including insulin sensitizers (including biguanides, thiazolidinediones), insulin secretagogues (including sulfonylureas, meglitinides), alpha-glucosidase inhibitors, as well as newer therapies such as incretin-based agents and sodium-glucose co-transporter 2 (SGLT2) inhibitors.[6]

Due to the potential adverse effects of long-term medication use, natural therapeutic approaches, such as nutraceuticals, have gained increasing attention as complementary or alternative treatments for diabetes.[6,7] Nutraceuticals are products containing food extracts or bioactive components that have demonstrated significant health advantages for customers in recent years.[8] According to Mali et al. (2022), nutraceutical is a food or a part of food that has a long historical background in the treatment of various diseases. Nutraceuticals play a significant role in maintaining normal physiological functions and overall human health. They encompass a wide range of products, including dietary supplements, herbal products, genetically engineered "designer" foods, and isolated nutrients. One category of nutraceuticals, known as traditional nutraceuticals, is derived directly from natural sources and includes nutrients, herbs, and phytochemicals.[9] These are habitually used within specific groups, communities, or cultures.

The efficacy of traditional nutraceuticals and functional food in the treatment of T2DM and its complications has been demonstrated in multiple previous studies.[7,10,11] In addition, Blahova et al.[6] and Venkatakrishnan et al.[7] concluded that combining conventional hypoglycemic drugs with lifestyle modifications and functional foods or traditional nutraceuticals can significantly improve glucose control and reduce diabetes-related complications.

Asia possesses diverse ancient medicinal system originating from herbs and functional foods, including traditional Chinese medicine, Ayurvedic practices from India, and Jamu from Indonesia. In the past decade, there has been a surge in research on traditional nutraceuticals components and functional foods exhibiting antidiabetic properties.[11–13] These herbal remedies and functional foods contain bioactive compounds, including flavonoid and non-flavonoid polyphenols, which have been shown to lower blood sugar levels.[6] These bioactive compounds exhibit multiple antidiabetic mechanisms, including antioxidant activity and the regulation of various processes: enhancement of glucose reabsorption, glucagon-like peptide-1 homeostasis, beta cell function, and insulin resistance.[14]

Several comprehensive reviews have examined traditional nutraceuticals and functional foods with antidiabetic properties, highlighting the molecular pathways involved in the prevention and management of diabetes.[6,7,14] Nonetheless, these studies exclusively address the antidiabetic properties of individual plants or food. This review aims to explore traditional nutraceuticals with antidiabetic properties derived from various plants and foods, with a particular emphasis on Asian traditional medicine. This review will focus on their mechanisms for improving hyperglycemia, highlighting their antioxidant effects on gene expression involved in the pathophysiology of T2DM.

METHODS

Literature searching was conducted in Pubmed, Scopus, and Science Direct using the keywords "nutraceutical", "antidiabetic", "insulin resistance", "Diabetes Mellitus", "herbal medicine", "mechanism", "pathway", "traditional food", "functional food", "antioxidant", "clinical", "preclinical", "animal studies", and "Asian" combined with Boolean operators "OR". Articles from 1973–2024 were included in this review. The inclusion criteria for articles in this review are in vitro studies, animal studies, and clinical trials that investigated the effect of nutraceuticals, herbal, and traditional medicine from Asian countries as antidiabetic and its mechanistic pathway. The exclusion criteria are systematic reviews and meta-analyses articles. We also discovered some relevant literature by manually searching the references to the included articles and using Google Scholar. Ethics approval is not required for this type of study.

RESULTS

Development of type 2 diabetes mellitus

T2DM is a metabolic disorder primarily characterized by hyperglycemia. However, it also disrupts lipid and protein metabolism due to reduced insulin secretion, insulin resistance, or both.[15] T2DM is a complex condition influenced by hereditary and environmental factors. Risk factors for developing diabetes mellitus include advanced age, non-white ancestry, family history of diabetes, genetic factors, overweight or obesity, polycystic ovarian syndrome, history of atherosclerotic heart disease, unhealthy eating habits (such as red meat, sugary drinks, low intake of whole grains and fiber), smoking, sedentary lifestyle, history of macrosomia or gestational diabetes, skin hyperpigmentation (acanthosis nigricans), short or excessively long sleep duration, shift work, and economic and psychosocial factors.[15]

Unhealthy foods are an important risk factor for T2DM. Several pathways could be influenced by the consumption of particular foods and nutrients. Refined grains and sugar sweetened beverages contain simple carbohydrates that directly induce postprandial plasma glucose and insulin secretion. Simple carbohydrates are rapidly absorbed, thus rapidly increase postprandial plasma glucose. Prolonged intake of high simple carbohydrate could increase insulin resistance.[16,17]

Insulin resistance

Insulin resistance is characterized by a reduced biological response to insulin in target tissues, primarily the liver, muscle, and adipose tissue. This impairment disrupts glucose metabolism, prompting a compensatory increase in insulin secretion by pancreatic β-cells, resulting in hyperinsulinemia.[18] In obesity, insulin resistance in the adipose tissue increases lipolysis and free fatty acids (FFA) level in plasma. The rise of plasma FFA stimulates gluconeogenesis, worsens insulin resistance in muscle and the liver, and plays a role in β-cell failure, impairing insulin

secretion. These abnormalities caused by increased plasma FFA are called lipotoxicity.[17,18]

In obese T2DM patients, increased levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and Tumor Necrosis Factor alpha (TNF-α), and increased numbers of macrophages and other inflammatory cells are observed in adipose tissue, liver, and serum. Inflammation appears mainly in adipose tissue and the liver. Infiltration of macrophages in adipose tissue promotes lipolysis and an increase level of IL-6 can trigger hepatic gluconeogenesis and generate hepatic insulin resistance.[15]

Initially, insulin resistance occurs but can be compensated by elevated insulin production. As the condition advances, the pancreatic beta cells lose their capacity to sustain elevated insulin production, resulting in reduced glucose tolerance and manifest diabetes. Factors contributing to beta-cell failure comprise glucotoxicity, lipotoxicity, inflammation, and abnormalities in genetics.

The core defects in T2DM are insulin resistance in the muscle and liver, along with reduced insulin secretion by the pancreatic β-cells.[15] Insulin resistance in muscle results in reduced glucose uptake, whereas in the liver increased hepatic glucose production (gluconeogenesis).[5]

β-cell dysfunction

In normal condition, insulin secretion by β-cell is governed tightly by coupling between glucose metabolites from the tricarboxylic acid (TCA) cycle and nucleotides. Glucose enters the β-cell via glucose transporter 2 (Glut2) by exploiting a concentration gradient.[19] During glycolysis, glucose undergoes phosphorylation that creates pyruvate, which is then transported into the mitochondria, resulting in Adenosine Triphosphate (ATP) generation. This process also produces reactive oxygen species (ROS) as by-products. Increased ATP elevates the ATP/Adenosine Diphosphate (ADP) ratio causing the cellular KATP-channels to close, subsequently depolarizes cell membrane and opens the Ca^{2+} channels.[20] The increase of Ca^{2+} levels in the cytosol triggers insulin exocytosis.[21]

During hyperglycemic states, pyruvate excess enters the TCA cycle elevates nicotinamide adenine dinucleotide/flavin adenine dinucleotide (NADH/FADH2) entry into the mitochondrial electron transport chain, hence augmenting ROS formation.[22] In hyperlipidemia, increased FFA levels result in the oxidation of both FFA and acetyl coenzyme A (CoA) within the TCA cycle. This enhances donation of NADH/FADH2 to the electron transport chain, leading to excessive ROS generation and oxidative stress.[23] Elevated amounts of ROS can induce mitochondrial injury by triggering the mitochondrial permeability transition pore to open and subsequent depolarization. Consequently, endogenous antioxidants escape from mitochondria, resulting in mitochondrial depletion and death.[24] Mitochondrial injury diminishes the ATP/ADP ratio, obstructing membrane depolarization and the activation of Ca^{2+} channels. This results in hindered and inadequate insulin secretion.[25]

The involvement of other systems or organs in hyperglycemia

According to De Fronzo et al.,[15] there were eight organs known as the 'ominous octet' involved in the pathogenesis of hyperglycemia in T2DM. They are pancreas β-cells and α-cells, muscle, liver, adipose tissue, gastrointestinal (stomach, intestine, and colon), kidney, and brain. In addition, three pathophysiological abnormalities contributing to muscle insulin resistance, i.e., activation of inflammatory pathways and immune system, as well as impaired insulin-mediated vasodilation, also have a role in hyperglycemia, making the 'decadent decuplet' (Figure 1).

Normally, incretin effects performed by glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) increase insulin secretion when glucose is administered orally compared to intravenously. Meanwhile, GLP-1 deficiency and GIP resistance is found in T2DM, which reduce incretin effects in the gastrointestinal tract, consequently, increase hyperglycemia.[5]

Accelerated gastric emptying is more common in early diabetes with few complications. Gastric emptying is a major factor that influences postprandial blood glucose and vice versa. Accelerated gastric emptying will increase the rate of nutrient delivery to small intestine which will increase the glucose absorption in the intestine and stimulates the release of GLP-1 and GIP. Increased glucose absorption will increase the level of postprandial blood glucose. Both the acute hyperglycemia and GLP-1 will slow gastric emptying. Meanwhile, GLP-1 and GIP will stimulate the secretion of insulin from pancreas, that will lower the blood glucose. However, in the chronic and complicated diabetes, gastroparesis (delayed gastric emptying) is more common.[26] In addition, dysbiosis of the gut microbiota also contributes to the development of T2DM through production of abnormal metabolites, including short chain fatty acids, lipopolysaccharides, trimethylamine, and metabolites of aromatic amino acids.[27]

The function of pancreas α-cells is to produce glucagon. During the fasting state, its level in plasma will increase. This increase, together with augmented hepatic sensitivity to glucagon, will enhance hepatic glucose production.[5,15]

Kidney also has a role in T2DM pathogenesis. The maintenance of hyperglycemia is in part due to increased renal glucose reabsorption by the sodium/glucose co-transporter 2 (SGLT2) and the increased threshold for glucose spillage in the urine.[15] The kidney filters 163 g of glucose in a day, of which 90% are reabsorbed by SGLT2 in the convoluted proximal tubule. The rest 10% will be reabsorbed by SGLT1 in the ascending and descending tubules; thus, no glucose will be found in urine. In T2DM patients, SGLT2 gene expression is increased.[5]

The brain is involved in controlling the appetite that can contribute to weight gain and loss. Unfortunately, insulin resistance also happens in the brain impairing the appetite-suppressive effects of insulin. In addition, leptin resistance, GLP1, amylin, and peptide YY, together with low brain dopamine and increased brain serotonin levels, contribute to weight gain. All of this exacerbates the underlying resistance.[15]

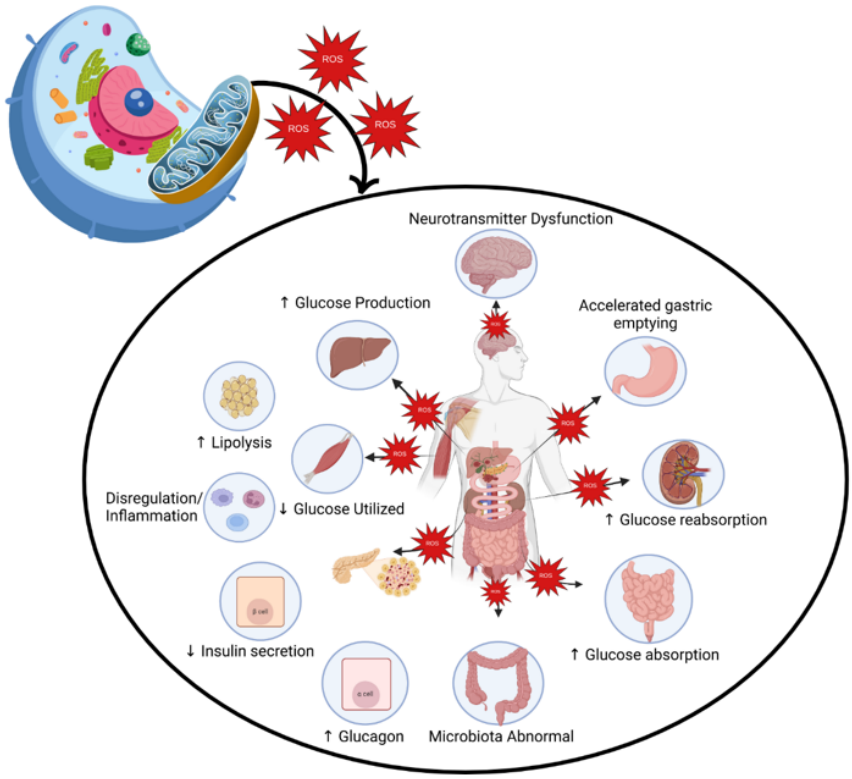

Figure 1. Organs involved in the pathogenesis of hyperglycemia in type 2 diabetes mellitus (T2DM). The pathogenesis of hyperglycemia in TD2M begins with oxidative stress in cells caused by increased Reactive Oxygen Species (ROS). Eleven organs and cells were involved in the pathogenesis of hyperglycemia in TD2M, including neurotransmitter dysfunction in the brain, dysfunction in pancreas β-cells and α-cells, accelerated gastric emptying, increased glucose reabsorption in the kidney, glucose absorption in the intestine and abnormal microbiota in the colon, lipolysis in adiposity, and glucose production in the liver. Pathogenesis also involves insulin resistance, decreased glucose utilization in muscle cells and dysregulation of Antibody Cell. (This figure was generated using BioRender.com)

Vascular insulin resistance reduces microvascular recruitment, in which only one of three capillaries are open at rest.[15] In normal conditions, vasodilation results from insulin metabolic signaling via increased endothelial cell nitric oxide (NO) production, thus increasing bioavailable NO. Conversely, insulin resistance promotes vasoconstriction and vascular proliferation by activating the mitogen-activated protein kinase (MAPK) cascade. This cascade coordinates vasoconstriction induced by insulin resistance and growth-promoting effects.[28]

The modulation of gene expression involved in the gluconeogenesis pathway plays a pivotal role in the regulation of glucose homeostasis within the body. The mechanism of gluconeogenesis involving the phosphoenolpyruvate carboxy kinase (PEPCK) and glucose-6-phosphatase (G6Pase) genes is crucial in the regulation of glucose production in the liver. PEPCK is a key enzyme in the gluconeogenesis pathway that catalyzes the conversion of oxaloacetate to phosphoenolpyruvate (PEP). PEPCK gene expression is regulated by various transcription factors influenced by hormones, such as glucagon and cortisol, which increase PEPCK expression in the fasting state to increase glucose production. G6Pase is an enzyme that catalyzes the hydrolysis of glucose-6-phosphate (G6P) to glucose, which is the final step in gluconeogenesis. G6Pase gene expression is also regulated by hormones and metabolic conditions. When glucose levels are low, hormones such as glucagon will increase the expression of G6Pase to favor the release of glucose into the circulation. The expression of these two genes (PEPCK and G6Pase) is regulated by hormonal signals that reflect the nutritional status of the body. In the fasting state, hormones such as glucagon and cortisol will increase the expression of these genes, while insulin will decrease their expression to reduce glucose production. Although the liver is the main source of glucose production, studies show that when gluconeogenesis in the liver is impaired, extra-hepatic tissues such as the kidneys and intestines can compensate by increasing their gluconeogenic enzyme activity.[29]

Role of oxidative stress in T2DM development and complications

ROS are primary contributors to oxidative stress, and their generation is an inevitable result of metabolic processes. The main source of ROS production is the leakage of electrons from the mitochondrial respiration process, which then converts to molecular oxygen, leading to the synthesis of superoxide anion (O_2^-).[30] The activation of the NADPH oxidase enzyme could also generate O_2^-.[31] Elevated auto-oxidation and nonenzymatic glycosylation are additional potential pathways that may initiate the generation of free radicals and radical-induced lipid peroxidation. The elevated generation of ROS disrupts the equilibrium between oxidant and antioxidant levels, leading to a pro-oxidative condition.[32]

Oxidative stress is also involved in the pathogenesis and development of T2DM. Genetic predispositions and other environmental factors including overnutrition, high energy intake, high fat and carbohydrate consumption,

and physical inactivity may contribute to obesity and metabolic syndrome. This condition increases oxidative stress due to high levels of ROS. Oxidative stress together with increase in FFA and cytokines produced by adipose tissue will induce insulin resistance.[33]

Hyperglycemia induces ROS overproduction through the activation of the polyol pathway, augmented production of advanced glycation end products (AGEs), stimulation of the diacylglycerol-protein kinase C (DAG-PKC) pathway, and excessive activation of the hexosamine pathway. These mechanisms interact to facilitate mitochondrial failure, inflammation, and disruption of insulin signaling, leading to insulin resistance and pancreatic β-cell malfunction, which are characteristic of T2DM.[32,34] Pancreatic beta cells generate elevated levels of ROS and have decreased synthesis of antioxidative enzymes. Consequently, these cells possess a diminished endogenous antioxidant capability, rendering them particularly vulnerable to oxidative stress.[35] They only have approximately 50% of the superoxide dismutase (SOD) and 5% of the hydrogen peroxide-scavenging enzymes, i.e. glutathione peroxidase (GPx) and catalase (CAT), relative to the quantities present in the liver.[35–37]

Oxidative stress is a major factor of glucose toxicity in DM as it leads to decreased levels of two insulin gene transcription factors, Pancreatic and Duodenal Homeobox 1 (PDX-1) and MafA. PDX-1 and MafA normally bind to the insulin promoter and stimulate insulin gene transcription. Decreased levels of these two proteins lead to decreased insulin promoter activity, insulin gene expression and insulin secretion.[38] Clinical observations of the relationship between glucose toxicity and oxidative stress are associated with decreased levels of two insulin promoter transcription factors namely, PDX-1 and Regulatory Insulin Promoter Element (RIPE)-3b1 activator / Musculoaponeurotic fibrosarcoma oncogene homolog A (MafA).[39] Hyperglycemic risk in mice is increased due to disruption of PDX-1, MafA binding to Deoxyribonucleic Acid (DNA), decreased insulin messenger Ribonucleic Acid (mRNA), decreased glucose-induced insulin secretion in islets of Langerhans in the pancreas.[40]

Among various transcription factors, PDX-1 plays an important role in pancreatic development and pancreatic beta cell differentiation and serves as a transcriptional activator of the insulin gene. Neurogenin-3 (Ngn3) and NeuroD are also important transcription factors for pancreatic endocrine cell differentiation. MafA expression is at a late stage of pancreatic beta cell differentiation and functions as a potential insulin gene activator of transcription.[41] Pancreatic transcription factors have the potential to induce various beta cell-related genes including insulin.[41]

MafA is β-cell specific and also functions as an insulin gene activator. Expression of pancreatic transcription factors in non-beta cells of the pancreas, liver, intestine, and bone marrow cells induces gene expression of various beta cells including insulin. Baumel-Alterzon S. et al[42] reported that nuclear factor erythroid 2-related factor (Nrf2) controls redox balance and affects PDX-1 levels, where pharmacological activation of the Nrf2 pathway can alleviate diabetes by maintaining PDX-1 levels.

Oxidative stress also contributes to the development of T2DM complications. Increased ROS could immediately impair DNA, proteins, and lipids, modifying their function as well as their structure, leading to cellular malfunction and impairment of normal biological functions. Oxidative damage also stimulates inflammation which contributes to the onset of microvascular problems such as diabetes nephropathy, retinopathy, and neuropathy, and it also causes macrovascular complications such as cardiovascular disease.[34,43]

Given the significant impact of oxidative stress in the development and complications of T2DM, efforts for limiting oxidative stress in diabetes should include antioxidant therapy, in addition to lifestyle changes and efficient hyperglycemic management. Yet, more study is required to completely figure out the fundamental mechanisms of oxidative stress in diabetes. Additionally, studies to assess the effectiveness of antioxidant therapies, including natural antioxidants derived from traditional nutraceuticals, in managing diabetes and preventing its complications are also essential. By focusing on oxidative stress, it is expected to reduce diabetes problems and enhance the health of patients.[43]

Traditional nutraceuticals from Asia with potential antidiabetic effects

Traditional nutraceuticals from Indonesia

Traditional nutraceuticals from Indonesia have gained attention for their potential health effects, especially those passed down through generations, such as galohgor, *bir pletok*, *wedang uwuh*, and loloh Bali. These herbal concoctions, rich in natural bioactive compounds, are deeply rooted in Indonesian culture and have been used for centuries to promote health and wellness. The diverse blend of spices, herbs, and medicinal plants in these traditional drinks contributes to their ability to help regulate blood glucose levels, improve insulin sensitivity, and combat oxidative stress. This makes them promising alternatives or complementary options for managing diabetes in a natural way.

Galohgor

Galohgor is one of the Indonesian traditional herbal medicines (Jamu) originating from the Sundanese ethnicity of West Java. The composition of Galohgor found in Sukajadi Village, Tamansari District, Bogor Regency, consists of 56 types of medicinal plants in the form of leaves, nuts, herbs, and spices. Based on literature studies, kaempferol was identified in 75% of the plant species used in the formulation of Galohgor, contributing to 95.4% of the total weight of the 56 plants analyzed. Notably, several of these plants have demonstrated potential antidiabetic properties, including *Psidium guajava*,[44] *Zingiber aromaticum Veleton*,[45] *Kaempferia galanga L.*,[46] *Melastoma malabathricum*,[47] *Sonchus arvensis L.*,[48] *Myristica fragrans*,[49] *Zingiber officinale*,[50] *Persea americana*,[51] *Piper betle*,[52] *Pluchea indica*, *Zea mays L.*,[53] *Phaseolus radiatus L.*,[53] and *Amomum cardamomum L.*[45] (Table 1). Galohgor is consumed by the Sundanese people in powder form as a snack. Galohgor has a content of fat, protein, carbohydrates, zinc, magnesium, vitamin C, carotenoids (β-carotene), vitamin E, and phenolic compounds. Based on pre-clinical and clinical studies,

Table 1. Types and nutraceutical content of Asian plants with potential to improve diabetes mellitus outcome

Plant name	Phytochemicals	Potential effect on DM
Ficus religiosa (*Bodhi* in Indonesia and Malaysia, *Peepal* in India, *puti shu* in China, *Pho* in Thailand)	Tanin, saponin, Polyphenol compounds, flavonoid, dan sterol Leucocyanidin 3-O-β-D-galactosyl cello bioside, leucopelargonidin-3-O-alpha-L rhamnoside[130,131]	-Antidiabetic[96] -Antihyperglicemic[97] -↓ blood glucose levels -increased insulin levels -modulates antioxidant enzymes to counteract oxidative stress
Eugenia jambolana (*Jamblang* and *Duwet* in Indonesia, *Jambulana* in Malaysia, *Jamun* in India, *Hei pu tao* in China, *Wa* in Thailand)	Seeds: alkaloid, jambosine and the glycoside jambolin, Fruits: Glucose, fructose, raffinose, malic acid, anthocyianin[132] Leaves: Acylated flavonol glycosides, quercetin, myricetin, and tanin[133]	-antioxidant defense -hypoglycemic -↓ glucose -↑ insulin secretion inhibition of insulin degradation[98] -↓ blood cholesterol, triglycerides, and free fatty acids[134] -↓ 3-HMG Co-A reductase enzyme activity[135] -↓ blood pressure
Momordica charantia (*Pare* or *Paria in Indonesia, Peria or Peria Katak* in Malaysia, *Karela* in India, *Kugua* in China, *Mara* in Thailand)	Seeds: Vicine, charantin, and triterpenoids along with several antioxidants, saponin[99]	-hipoglycemic[133] -antidiabetic and hypoglycemic[136] -reduction in waist circumference, improvement in diabetes, and symptoms of metabolic syndrome[100] -repair β-cells stimulate insulin levels[137] -↑ insulin sensitivity/signaling[138] -inhibits glucose uptake[139] -inhibits β-glucosidase activity[140] -inhibition of β-amylase and β-glucosidase -stimulates insulin secretion[141]
Ocimum sanctum L *(Ruku-ruku/kemangi hutan/ holy Basil* in Indonesia, *Selasih Hutan* or *Selasih India* in Malaysia, *Tulsi* in India, *Luole* in China, *Kaphrao* in Thailand),	Leaves: Eugenol, flavonoids, saponins, tannins, triterpenoids, rosmarinic acid, apigenin, isothymusin, isothymonin, cirsimaritin, orientin, vicenin, and anthocyanin [142] Seeds: fatty acid and sitosterol	-↓ blood glucose[143] -↑ insulin secretion[144] -↓ glucose serum[145] -↑ antioxidant[146] -↓ glucose serum, cholesterol, triglyserid, dan LDL[147]
Pterocarpus marsupium *(Vijaysar* in India)	Terpenoids and phenolic compounds: β-sitosterol, lupeol, aurone glycosides, epicatechin and iso-flavonoid[92]	-Antidiabetic activity[148] -hypoglycemic and β cell regeneration[149] -improves HbA1C[150] -regulates glucose production through modulating AKT and AMPK in HepG2 cells[151]
Trigonella foenum-graecum *(Kelabat* in Indonesia, *Halba* in Malaysia, *Methi* in India, *Hu' lu' ba'* in China, *Luk Sanai* in Thailand)	Saponins, 4-hydroxyisoleucine, trigonelline, alkaloid, and steroid[92]	-↓ glucose and lipid[152] -↑ insulin sensitivity and glucose uptake in peripheral tissues[153]

3-HMG Co-A: 3-Hydroxy-3-Methylglutaryl-Coenzyme A, LDL: Low-Density Lipoprotein, HbA1C: Hemoglobin A1c, AKT : serine/threonine kinase, AMPK: AMP-activated protein kinase, HepG2: Human Hepatocellular Carcinoma cell line 2, GLUT-4 : Glucose Trasporter 4, 3T3-L1: mouse embryo fibroblasts, MDA: Malondialdehyde, AR: Androgen Receptor, TNF-α: Tumor Necrosis Factor-alpha, IL-6: Interleukin 6, SOD: Superoxide Dismutase, PTP1B: Protein Tyrosine Phosphatase 1B, HOMAIR: Homeostasis Model Assessment of Insulin Resistance, ROS: Reactive Oxygen Species.

Table 1. Types and nutraceutical content of Asian plants with potential to improve diabetes mellitus outcome (cont.)

Plant name	Phytochemicals	Potential effect on DM
Gymnema sylvestre (*Gurmart* in Indonesia, *Pokok Mas Cotek Gurmar* in Malaysia, *Gurmar* in India, *Jian ming cao* in China, *Khwao Khurea* in Thailand)	Triterpenoid saponins, gymnemic acids, and gymnema saponins	-Regeneration of β cells in the pancreas reduce blood sugar levels[154]
Allium sativum (*Bawang Putih* in Indonesia and Malaysia, *Lahsun* in India, *Da suan* in China, *Krathiam* in Thailand)	allicin, allixin, ajoene, and other organosulfur compounds.	-↓ fasting blood sugar level[155] -↑ insulin secretion from β cells -↑ endogenous antioxidant defense[156]
Tisanes (*Wedang* in Indonesia, *Teh herbal* in Malaysia, *Kadha* in India, *Huacao cha* in China, *Nam Chea* in Thailand)	alkaloids, carotenoids, coumarins, flavonoids, phenolic acids, polyacetylenes, saponins, terpenoids[93]	-↑ insulin secretion[93]
Rhus chinensis Mill (*Kakkarsingi* in India, *Yan fu mu* in China)	Leaves, stem and branches: Phenolics (protocatechuic acid, p-coumaric acid, gallic acid, catechin, quercetin, methyl gallate), antioxidants (hydroxydammarenone, semialactone, moronic acid, betulonic acid) Fruit: Antioxidants, phenolics (gallic acid, tannic acid), flavonoids Gall: Hydrolysable tannins (gallotannins), phenolic acid (gallic acid), antioxidant	-↓ Postprandial glucose levels[95]
Murraya koenigii l. (meethi nimba) (*Daun Kari* in Indonesia and Malaysia, *Kadi Patta* in India, *Yue ju* in China, *Bai karip* in Thailand)	α-pinene, sabinene, dan β-caryophyllene	-↓ hyperglycemia -↑ insulin sensitivity[94]
Andrographis paniculata (Burm.f.) Nees/ Fa thalai chon[157] (*Sambiloto* in Indonesia, *Hempedu bumi* in Malaysia, *Kalmegh* in India, *Chuan xin lian* in China, *Fah Talai Jone* in Thailand)	Aerial parts *:* Glycosides, terpenoid, alkaloid, flavonoid, saponin, tannins	-↓ HbA1c
Pluchea indica (L.) Less/ Khluu[64] (*Beluntas* in Indonesia and Malaysia, *rasna* in India, *Po bu mu* in China, *Phak Krathin Ban* in Thailand)	Leaves : chlorogenic acid (CGA), 3,4-O-dicaffeoylquinic acid (3,4 diCQA), 3,5-O-dicaffeoylquinic acid (3,5 diCQA), quercetin, kaempferol, myricetin, monoterpenes, and sesquiterpenoids	-↓ Blood glucose levels
Apium graveolens L. /Khuen chaai[65] (Celery) (*Seledri* in Indonesia, *Seleri* in Malaysia, *Ajmod* in India, *Qincai* in China, *Khuen Chai* in Thailand)	flavonoids, alkaloids, terpenoids, and phenolic acids	-↓ Blood glucose levels
Aloe vera (L.) Burm.f./Wan Hang Chora Khe Nees[67–69,158] (*Lidah buaya* in Indonesia and Malaysia, *Ghritkumari* in India, *Lu hui* in China, *Wan Hang Chora Khe Nees* in Thailand)	Aloe-emodin, Aloetic-acid, Anthranol, Barbaloin, Mannan, 8-C-glusoly-(2′-O-cinnamoly), −7-O-methlyaloediol A, Alkaline phosphatese, amylase, bradykinase, carboxypeptidase, catalase, cyclooxidase, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate, carboxylase	-↓ weight -↓ fat mass -↓ insulin response -↓ Blood glucose levels

3-HMG Co-A: 3-Hydroxy-3-Methylglutaryl-Coenzyme A, LDL: Low-Density Lipoprotein, HbA1C: Hemoglobin A1c, AKT : serine/threonine kinase, AMPK: AMP-activated protein kinase, HepG2: Human Hepatocellular Carcinoma cell line 2, GLUT-4 : Glucose Trasporter 4, 3T3-L1: mouse embryo fibroblasts, MDA: Malondialdehyde, AR: Androgen Receptor, TNF-α: Tumor Necrosis Factor-alpha, IL-6: Interleukin 6, SOD: Superoxide Dismutase, PTP1B: Protein Tyrosine Phosphatase 1B, HOMAIR: Homeostasis Model Assessment of Insulin Resistance, ROS: Reactive Oxygen Species.

Table 1. Types and nutraceutical content of Asian plants with potential to improve diabetes mellitus outcome (cont.)

Plant name	Phytochemicals	Potential effect on DM
Ipomoea aquatica Forssk./ Pak bung[70]	euphornin, lucidenic acid, and myricitin glycosides,	-↓ Blood glucose levels
Lagerstroemia speciosa (L.) Pers./ Inthanin nam[71] *(Kangkung* in Indonesia and Malaysia, *Kalmi Saag* in India, *Kong xin cai* in China, *pak bung* in Thailand)	flavonoids, saponins, tannins, steroids, and triterpenoids	-↓ Blood glucose levels
Terminalia bellirica (Gaertn.) Roxb. /Samo phi phek[75] *(Balirik* in Indonesia, *Bahera* in Malaysia and India, *He zi* in China, *Samo Phi Phe* in Thailand)	Fruit: gallic acid, galloyl glucose, chebulagic acid, ellagic acid, β-sitosterol, ethylgallate, sugar, bellericanin, lignans, and flavan.	-↓ Blood glucose levels -↓ Lipids levels -↑ Antioxidants
Terminalia chebula Retz./ Samo thai[75] *(Kayu kuning / haritaki in Indonesia, Ketepeng and Buah Keras in Malaysia, Haritaki in India, He zi in China, Samo Thailand)*	chebulanin, chebulagic acid, and chebulinic acid	-↓ Blood glucose levels -↓ Lipids levels -↑ Antioxidants
Morinda citrifolia L. /Yo Baan[79] (noni) *(Mengkudu* in Indonesia and Malaysia, *Indian Mulberry/noni* in India, *Ba ji Tian* in China, *Yo Ban* in Thailand)	amino acids, anthraquinones, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols, terpenoid Bark, leaf: α-ketoglutaric and malic acids	-↓ Blood glucose levels
Zea mays L./Khao Phot[78] *(Jagung* in Indonesia and Malaysia, *Makai* in India, *Yumi* in China, *Khao Phot* in Thailand)	volatile oils, steroids, saponins, polysaccharides, alkaloids, flavonoids, organic acids and other phenolic compounds	-↓ Blood glucose levels -↓ oxidative damage in the brain of diabetic mice[65]
Eclipta prostrata (L.) / Ka meng [80] *(Urang-aring* in Indonesia and Malaysia, *Bhringraj* in India, *Mo Han Lian* in China, *Ka meng* in Thailand)	Whole plant: wedelolactone, eclalba saponins, ursolic acid, oleanolic acid, luteolin, and apigenin	-↓ Blood glucose levels -↓ Postprandial glucose levels
Phyllanthus amarus / Ma kham pom[81,82] *(Meniran* in Indonesia and Malaysia, *Bhui Amla* in India, *Yi ke yin chen* in China, *Ma kham pom* in Thailand)	Alkaloids: securinine, epibubbialine, isobubbialine	-↓ Blood glucose levels -↓ Postprandial glucose levels
Curcuma longa L. /Khamin[83] *(Kunyit* in Indonesia and Malaysia, *Haldi* in India, *Jiang Huang* in China, *Khamin* in Thailand)	Rhizomes: Curcumin, curcumol, and bisdemethoxycurcumin	-↓ Blood glucose levels -↓ Postprandial glucose levels -↓ Arterial stiffness, -↓ Endothelial dysfunction -↑ β-cells function
Gymnema inodorum (Lour.) Decne./Chiang Daa[72] *(Chiang Daa* in Thailand)	Leaves: phenolic acids, flavonoids, triterpenoid compounds, and pregnane glycosides	-↓ Postprandial glucose levels

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Table 1. Types and nutraceutical content of Asian plants with potential to improve diabetes mellitus outcome (cont.)

Plant name	Phytochemicals	Potential effect on DM
Aegle marmelos (L.) / Ma tuum[73] *(Maja* in Indonesia, *Pokok Maja* in Malaysia, *Bael* in India, *Mu Ju* in China, *Matum* in Thailand)	marmenol, marmin, marmelosin, marmelide, psoralen, alloimperatorin, rutaretin, scopoletin, aegelin, marmelin, fagarine, anhydromarmelin, limonene, â-phellandrene, betulinic acid, marmesin, imperatorin, marmelosin, luvangentin and auroptene	-↓ Postprandial glucose levels
Glycine max (L.) Merr[159]*/black soybean (Kedelai* in Indonesia, *kacang soya* in Malaysia, *Soya Bean* in India, *Dadou* in China, *Tua Luang* in Thailand)	Leaf: isoflavones and anthocyanins	-↓ Postprandial glucose levels
Salacia chinensis L./ Kam paeng jed chan[160] *(Srigading/akar kuning* in Indonesia, *Akar kuning/seruntun* in Malaysia, *Ponkoranti* in India, *Hei Mian Shen* in China, *Ching-cha-cha* in Thailand)	Steam: salacinol, kotalanol, ponkoranol, and salaprinol and their corresponding de-0-sulfonated compounds. In addition, triterpenes, sesquiterpenes, lignans, xanthones, flavanols, flavonoids	-↓ Postprandial glucose levels -Hypoglycemic effect
Artocarpus heterophyllus Lam. / Khanun[66] (Jackfruit) *(Nangka* in Indonesia and Malaysia, *Kethal* in India, *Boluomi* in China, *Khanun* in Thailand)	Leaves: flavonoid	-↑ insulin response
Phyllanthus emblica L./ Ma Kham Pom[77] *(Malaka/Ciremai India* in Indonesia, *Melaka/Pokok malaka* in Malaysia, *Amla* in India, *Yougan* in China, *Ma-Kham-Pom* in Thailand)	Fruits: phenolic compounds (such as tannins, phenolic acids, and flavonoids), alkaloids, phytosterols, terpenoids, organic acids, amino acids, and vitamins	-↓ oxidative stress[77]
Guava leaf / Psidium guajava Linn (Jambu biji/Jambu klutuk in Indonesia, *Jambu batu* in Malaysia, *Amrud* in India, *Fan shiliu* in China, *Farang* in Thailand)	Potassium, phosporus, nitrogen, ascorbic acid, ficose, rhamnose, arabinose, galactose, glucose, mannose, xylose, phenol, sulfat, carbohydtrat, proteins, vitamin, minerals, α-Pinene Benzaldehyde, p-cymene 0.52% Limonene, 1,8-Cineole, β-cis-Ocimene, γ-Terpinene, α-Terpineol, β-Caryophyllene, α-Humulene, Quercetin, avicularin, apigenin, guaijaverin, kaempferol, hyperin, myricetin, Gallic acid, catechin, epicatechin, chlorogenic acid, epigallocatechin gallate, caffeic acid, Proanthocyanidins (PAs)[161]	-↑ the function of β-cells of pancreatic islets and hepatocyte morphology[108] -↓ activity of the blood glucose homeostasis enzyme dipeptidyl-peptidase IV[162] -inhibited intracellular lipid aggregation by impeding glucose uptake through GLUT-4 in vitro and revealed no distinct toxicity for 3T3-L1 adipose cells[163] -reduction in total cholesterol, triglycerides, glycated serum protein, creatinine, fasting blood glucose, and malonaldehyde content, and increased total superoxide dismutase and total antioxidant capacity enzyme activity in vivo[164] -inhibitors of α-amylase and α-glucosidase enzyme can decline postprandial glucose absorption[165]
Kaempferia galangal L (Kencur in Indonesia, *Cekur* in Malaysia, *Chandramula* in India, *Shajiang* in China, *Proh Horm* in Thailand)	Terpenoids (kaempulchraol I, E, L, kaemgalangol A) phenolics (p-methoxybenzoicacid, p-hydroxybenzoic acid, vanillic acid, ferulic acid), and flavonoids (kaempferol, luteolin, kaempferide)[166]	-↓ blood lipid levels, along with reducing MDA, AR, TNF-α, and IL-6 levels and increasing SOD levels, ↓ blood glucose, insulin resistance, reducing the AR pathway as well as anti-oxidation and anti-inflammation[167]

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Table 1. Types and nutraceutical content of Asian plants with potential to improve diabetes mellitus outcome (cont.)

Plant name	Phytochemicals	Potential effect on DM
Cinnamomum verum (*Kayu manis* in Indonesia and Malaysia, *Dalchini* in India, *ZhenGui* in China, *Ob Chuey* in Thailand)	cinnamic acid , *E*)-cinnamaldehyde , cinnamaldehyde dimethyl aceta , Ascorbic acid, Fumaric acid, Caffeic acid, Luteolin-7-rutinoside, Luteolin 7-glycoside, Rutin, Apigenin 7-glycoside, Quercitrin, Quercetin, kaempferol, Naringenin, Luteolin, Apigenin, Hispidulin, Chrysin[168,169]	- Modulating insulin secretion and insulin receptor signaling, enhancing GLUT4 expression, and exhibiting anti-α-glucosidase and anti-α-amylase activities
Zingiber aromaticum Veleton (*Lempuyang* in Indonesia, *Lempoyang* in Malaysia, *Fangxiang Jiang* in China, *Plai Farang* in Thailand)	humulatrien-5-ol-8-one, kaempferol-3,4'-di-O-methyl ether, and (S)-6-gingerol.[45]	-Inhibits the activity of the enzyme protein tyrosine phosphatase 1B (PTP1B)[45]
Melastoma malabathricum (*Senduduk* in Indonesia and Malaysia, *Malabar Malastome* in India, *Ye mudan* in China, *Koi / Ngaa Khao* in Thailand)	quercetin, quercitrin, rutin, kaempferol, kaempferol-3-O-(2″,6″-di-O-p-trans-coumaroyl)-β-D-glucoside, naringin, malabathrins A, B, C, and D, nobotanins B, D, G, and H, casuarictin, strictinin, pterocarinin C, pedunculagin, epicatechin, epicatechin gallate, and patriscabatrin.[170]	-↓ Blood glucose levels[47]
Soncus arvensis L. (*Tempuyung* in Indonesia, *Tempuyung/Daun dewa liar* in Malaysia, *ku cai* in China, *Phak Kat Khwai* in Thailand)	Terpenoid, flavonoid (catechin, mirecetin, kaempferol, quercetin), phenolic, alkaloids.[171]	-↓ blood glucose levels and cell regeneration in the tubular[48]
Myristica fragrans (*Pala* in Indonesia and Malaysia, *Jaiphal* in India, *Rou Dou Kou* in China, *Chan Thet* in Thailand)	ellagic acid (35.42 mg/g), rutin (91.07 mg/g), quercitrin (35.83 mg/g), quercetin (41.16 mg/g), and kaempferol (36.81 mg/g)[172]	-↓ fasting blood glucose and HbA1C[173]
Zingiber officinale (*Jahe* in Indonesia, *Halia* in Malaysia, *Adrak* in India, *Sheng Jiang* in China, *Khing* in Thailand)	ginger, such as gingerol, shogaols, paradols, and zingerone, phenolic compounds (rutin, kaempferol, 6-gingerol, zingerone, naringenin, and quercetin).[174]	-↓ fasting blood glucose, HbA1C, HOMAIR[50]
Persea americana (*Alpukat* in Indonesia, *Avocado* in Malaysia, *Makhanphal* in India, *Niu You Guo* in China, *Abo-Ka-Do* in Thailand)	Kaempferol 3-O-β-d-fucopyranoside, juglanin and astragaline, afzelin and quercitrin, catechin and epicatechin[175]	-↓ fasting blood glucose and regeneration of islets of Langerha[51]
Piper betle (*Sirih* in Indonesia, *Sireh* in Malaysia, *Paan* in India, *Luo Ye* in China, *Phlu* in Thailand)	alkaloids, terpenoids/steroids, flavonoids, polyphenols, tannins, and saponins[176]	-↓ Blood glucose levels[52]
Pluchea indica (*Beluntas* in Indonesia and Malaysia, *Rasan* in India, *Ci Hao* in China, *Khlu* in Thailand)	kaempferol 3-[2‴,3‴,5‴-triacetyl]-alpha-L-arabinofuranosyl-(1->6)-glucoside, myricetin 3-glucoside-7-galactoside, quercetin 3-(3″-sulfatoglucoside), and kaempferol 7,4′-dimethyl ether 3-O-sulfate[177]	-↓ Blood glucose levels[53]
Phaseolus radiatus L (*Kacang Hijau* in Indonesia and Malaysia, *Moong Dal* in India, *Lu Dou* in China, *Tua Kiew* in Thailand)	flavonol (quercetin and kaempferol) aglycones while few others contain either of the two aglycone.[178]	-↓ROS formation, inhibits alpha glucosidase and alpha amylase activity[179]

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Table 2. Modulation of gene expression in diabetic conditions by traditional nutraceuticals compound

Nutraceutical compound and target genes	Actions	References
Curcumin		
SOD, GSH	Upregulate SOD expression in the liver Significantly increased reduced glutathione (GSH) levels in diabetic rats, highlighting its ability to enhance antioxidant defenses. Activate the Nrf2 pathway, which protects β-cells from oxidative damage.	Xia et al. 2020[103] Belhan et al. 2020[101] Serafini et al. 2020[105] Shahcheraghi et al. 2021[106]
Kaempferol (flavonoid)		
SOD1, SOD2. GSH-Px	Upregulates the expression of SOD1 and SOD2 genes Increasing glutathione peroxidase (GSH-Px) activity, enhancing intracellular GSH levels, and promoting the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates the expression of antioxidant genes.	Kluska et al. 2022[123] Al-Abbasi and Kazmi, 2022[122] Alshehri et al. 2021[124]
IRS-1, PI3K, PIP2, PIP3, AKT, GLUT4	Enhances insulin signaling in diabetic conditions by modulating IRS-1 gene expression, upregulates IRS-1 in skeletal muscle, activating the insulin receptor pathway. This leads to PI3K activation, PIP3 production, and subsequent activation of AKT, which phosphorylates downstream targets, including GLUT4. The process facilitates GLUT4 translocation to the plasma membrane, improving glucose uptake into muscle cells and enhancing cellular glucose utilization.	Jayachandran et al, 2020[120] Moore at al. 2023[102]
SIRT1	Modulates the SIRT1 pathway	Chong et al., 2024[111]
Cinnamon		
PI3K, AKT, PPARy	Regulating the expression of genes related to the insulin signaling pathway (PI3K and AKT), and enhancing the expression of PPARγ genes, which can reduce insulin resistance.	Cortez-Navarrete et al. 2023[104]
Saponin		
SOD1	Activate SOD1 gene expression.	Kim et al. 1996[125] Cui et al. 2021[126]
TCF7F2, β-catenin	Increasing activities of SOD, GSH-Px and CAT in the 200 μg/mL alfalfa saponin protecting β cell survival and regeneration by mechanisms involving the activation of Wingless-related integration site (Wnt3a)/β-catenin/ transcription factor 7-like 2 (TCF7L2) signaling	Cui et al. 2020[127]
Quercetin (flavonoids)		
SOD1, CAT, GPX1	Quercetin normalized the expression mRNA levels of CAT, SOD1, GPX1 to near the normal level. Moreover, quercetin treatment normalized TAC levels.	Bagheri et al. 2021[180]
Sirt3	Protected islet β-cells from oxidation-induced apoptosis via Sirt3 in T2DM	Wang et al. 2021[181]

glutathione (GSH), glutathione peroxidase (GSH-Px), nuclear factor erythroid 2-related factor 2 (Nrf2), insulin receptor substrate (IRS), phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), Akt substrate of 160 kDa (AS160), glucose transporter 4 (GLUT4), phosphatidylinositol-3,4-bisphosphate (PIP2), phosphatidylinositol-3,4,5-trisphosphate (PIP3), sirtuin 1 (SIRT1), superoxide dismutase (SOD), peroxisome proliferator-activated receptor gamma (PPARγ), Wingless-related integration site (Wnt3a)/β-catenin/ transcription factor 7-like 2 (TCF7L2), catalase (CAT), protein kinase B (PKB), glucose transporter−2 (GLUT−2), high glucose (HG), endoplasmic reticulum (ER), cyclin-dependent kinase 5 (CDK5), pancreatic duodenal homeobox 1 (PDX1), sarcoendoplasmic reticulum calcium ATPase 2b (SERCA2b), nitric oxide (NO), nuclear factor kappa-light-chain-enhancer of activated B (NF-κB), tumor necrosis factor alpha (TNF-α), interleukin (IL), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1), transforming growth factor beta (TGF-β), AMP-activated protein kinase (AMPK), phosphorylated transducer of regulated CREB 2 (p-TORC2), uncoupling protein 2 (UCP2), insulinoma cell line (INS-1E).

Table 2. Modulation of gene expression in diabetic conditions by traditional nutraceuticals compound (cont.)

Nutraceutical compound and target genes	Actions	References
Myricetin (flavonoid)		
PKB, IRS1, IRS2, GLUT2, GLUT4	Normalized the insulin signaling molecule expression like PKB (protein kinase B), IRS−1 (insulin receptor−1), IRS−2 (insulin receptor−2), GLUT−2 (glucose transporter−2) and GLUT−4 (glucose transporter−4)	Kandasamy et al. 2014[182]
CDK5, PDX1, SERCA2b	Protects β-cells from high glucose (HG)-induced apoptosis by mitigating endoplasmic reticulum (ER) stress, potentially via cyclin-dependent kinase 5 (CDK5) inhibition, leading to the upregulation of pancreatic duodenal homeobox 1 (PDX1) and sarcoendoplasmic reticulum calcium ATPase 2b (SERCA2b).	Karunakaran et al. 2019[183]
Anthocyanin		
	increases nitric oxide (NO) bioactivity and upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), which induces the production of endogenous antioxidants and limits oxidative stress, proposed to downregulate nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) and lead to reduced expression and production of cytokines involved (tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1)) and further reduces the inflammatory response. NF-κB downregulates transforming growth factor beta (TGF-β) expression	Sapian et al. 2022[112]
Terpenoid		
IRS-1, Akt, GLUT4	Up-regulated the expression of the insulin receptor, insulin receptor substrate 1, glycogen synthase kinase 3β, Akt serine/ threonine kinase, and the transcript levels of GLUT4 and AMP-activated protein kinase.	Singh et al. 2022[121]
Alkaloids		
p-AMPK, p-TORC2, SOD1, UCP2	Up-regulated protein expression of liver kinase, AMPK, p-AMPK and p-TORC2. Down-regulated protein expression of gluconeogenic Enzymes Inhibited high glucose-elevated nitrotyrosine level, reduced SOD-1 and UCP2 expression and AMPK phosphorylation in INS-1E cells	Dange et al. 2016[113] Dong et al. 2016[184] Jiang et al. 2015[128]
Gallic acid		
PPARy, GLUT4, Akt	Concurrent activation of PPAR-γ and C/EBP promotes GLUT4 translocation in adipose cells; improves insulin sensitivity through regulation of Akt and AMPK signaling pathways; regulation of TNF-α and adipocytokine expression; and improves β-cell function by inhibiting caspase-9-related to cell apoptosis.	Xu et al. 2021[114]

glutathione (GSH), glutathione peroxidase (GSH-Px), nuclear factor erythroid 2-related factor 2 (Nrf2), insulin receptor substrate (IRS), phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), Akt substrate of 160 kDa (AS160), glucose transporter 4 (GLUT4), phosphatidylinositol-3,4-bisphosphate (PIP2), phosphatidylinositol-3,4,5-trisphosphate (PIP3), sirtuin 1 (SIRT1), superoxide dismutase (SOD), peroxisome proliferator-activated receptor gamma (PPARγ), Wingless-related integration site (Wnt3a)/β-catenin/ transcription factor 7-like 2 (TCF7L2), catalase (CAT), protein kinase B (PKB), glucose transporter−2 (GLUT−2), high glucose (HG), endoplasmic reticulum (ER), cyclin-dependent kinase 5 (CDK5), pancreatic duodenal homeobox 1 (PDX1), sarcoendoplasmic reticulum calcium ATPase 2b (SERCA2b), nitric oxide (NO), nuclear factor kappa-light-chain-enhancer of activated B (NF-κB), tumor necrosis factor alpha (TNF-α), interleukin (IL), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1), transforming growth factor beta (TGF-β), AMP-activated protein kinase (AMPK), phosphorylated transducer of regulated CREB 2 (p-TORC2), uncoupling protein 2 (UCP2), insulinoma cell line (INS-1E).

Galohgor as an antidiabetic has been proven to reduce hyperglycemia, oxidative stress, adipose tissue, and body weight in T2DM.[54,55]

Bir pletok

The traditional Indonesian herbal drink known as Bir Pletok, originating from the Betawi tribe, is renowned for its therapeutic properties. Historically used for its warming and health-promoting properties, Bir Pletok is made from a blend of spices including ginger (*Zingiber officinale*), lemongrass (*Cymbopogon citratus*), pandan leaves (*Pandanus amaryllifolius*) and cinnamon (*Cinnamomum verum*). Gingerols, flavonoids and polyphenols are among the bioactive compounds in *Bir Pletok*, known for their ability to regulate glucose metabolism and provide antioxidant protection. Due to its abundance of bioactive chemicals with antidiabetic properties, there has recently been increased interest in its potential use as a nutraceutical for the management of diabetes. With its blend of conventional herbal components, *Bir Pletok* may have encouraging antidiabetic benefits. Numerous studies have confirmed the ability of *Bir Pletok*'s main constituents to control blood sugar levels, improve insulin sensitivity and reduce inflammation.[56]

Wedang uwuh

Indonesia's traditional herbal drink from Yogyakarta, *Wedang Uwuh*, is well known for its abundance of natural spices and herbs and for its health advantages. Literally translating to "herbal trash drink," "*Wedang Uwuh*" refers to the vibrant concoction of ingredients that include nutmeg (*Myristica fragrans*), ginger (*Zingiber officinale*), cinnamon (*Cinnamomum verum*), cloves (*Syzygium aromaticum*), Sappan wood (*Caesalpinia sappan*), and lemongrass (*Cymbopogon citratus*). For centuries, people have drunk this beverage because of its warming properties and potential health benefits. *Wedang Uwuh* has garnered interest lately due to its potential as a conventional nutraceutical, especially in the treatment of long-term conditions like diabetes. Consequently, there is a growing interest in supplementary approaches to diabetes management, such as *Wedang Uwuh*, which are natural remedies. Bioactive substances like polyphenols, flavonoids, and essential oils found in the herbs and spices of *Wedang Uwuh* have been demonstrated to boost insulin sensitivity, lessen oxidative stress, and improve glucose metabolism.[57]

Loloh Bali

The herbal liquids known as *Loloh* are made and drunk only in Bali, Indonesia, and are used to treat and prevent a variety of illnesses. There are 51 plant species in all, from 32 families, that have been identified in the different Loloh preparations. Loloh is made from a variety of plants and plant components that are used to treat various ailments. The most common ways to prepare these plants are as decoctions, juices, or just as ingredients. *Alstonia scholaris (L.) R. Br.*, *Blumea balsamifera (L.) DC.*, *Cinnamomum burmanni Nees ex Bl.*, and *Piper betle L.* are the plants that are most frequently mentioned (>30 informants). The pharmacological effects of these well-researched plants, such as their antibacterial, anticancer, and antidiabetic properties, have been reported.[58]

Traditional Chinese Medicine

For thousands of years, traditional Chinese medicine (TCM) has been used to treat a wide range of illnesses, including metabolic diseases like diabetes. Traditional nutraceuticals, which are natural products made from medicinal plants and herbs, have drawn a lot of attention due to their potential therapeutic benefits among their various therapies. In addition to offering vital nutrients, these nutraceuticals also include bioactive substances that have positive effects on health, especially when it comes to managing chronic conditions like diabetes. The utilization of medicinal characteristics of herbs that have been demonstrated to control blood glucose levels, enhance insulin sensitivity, and lowering oxidative stress is how traditional Chinese nutraceuticals provide an alternative method. Preclinical and clinical research has shown encouraging antidiabetic effects for some TCM-based nutraceuticals. Herbs such as *Momordica charantia, Berberis aristata*, and *Panax ginseng* contain compounds that have been demonstrated to control glucose metabolism, boost pancreatic function, and reduce inflammation. Research on the discovery and characterization of these bioactive components from conventional nutraceuticals is still ongoing, intending to create safer and more efficient diabetes treatment therapies.[59]

Traditional nutraceuticals from Malaysia

Malaysia, a country renowned for its varied natural vegetation and rich cultural legacy, has long used traditional treatments for a range of illnesses, including diabetes. Traditional nutraceuticals, products derived from natural sources such as herbs and plants that provide both nutritional and therapeutic benefits, have gained popularity due to the nation’s rich diversity of medicinal plants. These age-old cures, which are frequently handed down through the generations, have drawn interest because of their possible application in the treatment of diabetes, an increasingly widespread health issue. Bioactive compounds found in traditional Malaysian nutraceuticals *Gynura procumbens* (Sabung Nyawa), and *Curcuma longa* (Turmeric) have been shown to potentially improve insulin sensitivity, lower blood sugar levels, and reducing the complications associated with diabetes. These therapeutic plants are currently being researched for their unique antidiabetic properties. Historically, they have been utilized to treat a wide range of illnesses.[60,61]

Traditional Thai medicine

Herbal medicine in Thailand has become popular in recent years through the Thai Traditional Medicine (TTM) revitalization program.[62] The Thai government has made various efforts to accelerate research on plants in Thailand that have nutraceutical content for various diseases, including diabetes mellitus. This is based on the habits of local rural communities in Thailand who use many herbal plants for diabetes mellitus. The nutraceutical contents of these herbal plants have been proven to exhibit a positive impact on the management of diabetes mellitus.[76] Research conducted from the *in vitro* stage to clinical trials

on healthy subjects and patients with diabetes mellitus conditions has been proven to reduce glycated hemoglobin A1c (HbA1C), blood glucose levels, postprandial glucose levels, body weight, fat mass, insulin, lipids levels, oxidative stress, arterial stiffness, and endothelial dysfunction. Besides, TTM also improves insulin response, antioxidants, and β-cells function. Various TTMs are used ranging from aerial parts,[63] leaves,[64–74] fruits,[75–77] styles,[78] bark, leaf,[79] whole plant,[80–82] stems,[98] and rhizomes.[83–85]

Different parts of the same plant often have similar phytochemical profiles, thus exhibiting identical pharmacological properties.[86] Current research continues to expand on the use of nutraceuticals in TTM for drug therapy,[63] but the use in the form of food therapy also remains an option. For example, Thai papaya cultivar leaves is a vegetable commonly consumed by Thai people. Research has shown that three types of Thai papaya cultivar leaves have antidiabetic activity.[87] Clinical trials on various commonly consumed food plants can increase consumption alternatives for the community to maintain health and management of non-communicable diseases including diabetes mellitus.

Various studies have proven that TTM can have a positive impact on DM conditions, including decreasing HbA1c, reducing blood glucose levels, increasing insulin response, and reducing oxidative damage in the brains of diabetic mice. These plants include *Andrographis paniculata (Burm.f.) Nees*, *Pluchea indica (L.) Less*, *Apium graveolens L.*, *Aloe vera (L.) Burm.f.*, *Ipomoea aquatica Forssk.*, *Lagerstroemia speciosa (L.) Pers.* (bungur leaf), *Terminalia bellirica (Gaertn.) Roxb.*, *Terminalia chebula Retz.*, *Momordica charantia L.*, *Zea mays L.*, *Morinda citrifolia L.*, *Eclipta prostrata (L.)*, *Phyllanthus amarus*, *Curcuma longa L.*, *Gymnema inodorum (Lour.) Decne.*, *Aegle marmelos (L.)*, *Glycine max (L.) Merr*, *Salacia chinensis L.*, *Artocarpus heterophyllus Lam.*, and *Phyllanthus emblica L.*, *Salacia chinensis L.* (Table 1).

India herbal plants

The prevalence of diabetes mellitus in India is reported to be high,[88] which is attributed to excess fat, low muscle mass and genetic factors of racial predisposition that increase the risk of T2DM in India.[89] Treatment of T2DM using herbs is growing in developing countries including India. World Health Organization (WHO) data states that 90% of people in developing countries use plants as traditional medicine for health.[90] India has 2500 species of herbal plants out of 21,000 plants worldwide registered by WHO.[91] The nutraceutical contents in various plants were studied and showed a positive impact on diabetes mellitus conditions, such as *Ficus religiosa*, *Pterocarpus marsupium*, *Gymnema sylvestre*, *Allium sativum*, *Eugenia jambolana*, *Momordica charantia*, and *Trigonella foenum-graecum* (Table 1).[92]

Various plants in India contain polyphenols, flavonoids, fatty acids, and fiber.[92–95] Ficus religiosa, which can be used for its flowers and stem bark, is known to have antidiabetic[96] and antihyperglycemic[97] effects which can reduce blood glucose levels and modulate antioxidant enzymes to fight oxidative stress. Consumption of Eugenia jambolana can affect antioxidant defenses, decrease glucose, increase insulin secretion, inhibit insulin degradation, and have hypoglycemic effects.[98] The parts of this plant that are commonly utilized are seeds, skin, fruit, and leaves. Momordica charantia is known to contain vicine, charantin, and triterpenoids along with several antioxidants, saponins[99] that have a positive impact on diabetic conditions.[100] Research at the clinical stage can continue to be developed to prove the potential of various nutraceuticals in Indian plants. Isolation, purification, and characterization of bioactive compounds contained therein can be used as a basis for the development of functional food products that are potential for the prevention and management of diabetes.

Nutraceutical compounds in traditional plants from Asia and their potential effect on diabetes mellitus are shown in Table 1. Some results from studies on the antidiabetic effects of Asian traditional nutraceutical metabolites include: 1) *Curcuma longa*[65] contains curcumin, curcumol, and bisdemethoxycurcumin, which help lower blood glucose and postprandial glucose levels while improving β-cell function; 2) *Zea mays*[61] is rich in volatile oils, steroids, saponins, polysaccharides, alkaloids, flavonoids, organic acids, and phenolic compounds, has been shown to reduce blood glucose levels; 3) Glycine max[101] contains isoflavones and anthocyanins, which are effective in lowering postprandial glucose levels; 4) Andrographis contains terpenoid glycosides, alkaloids, flavonoids, saponins, and tannins, which help reduce HbA1c levels; 4) Allium[102,103] contains allicin, allixin, ajoene, and other organosulfur compounds that reduce fasting blood sugar levels, enhance insulin secretion by β-cells, and boost antioxidant defenses of the body; 5) Phyllanthus[60] family contains phenolic compounds (e.g., tannins, phenolic acids, flavonoids), alkaloids, phytosterols, terpenoids, organic acids, amino acids, and vitamins, which reduce oxidative stress.

Other beneficial effects of traditional nutraceuticals in diabetes include reducing lipid levels and enhancing antioxidant activity, as seen in plants from the Terminalia family.[57] Additionally, some plants improve insulin sensitivity and stimulate glucose uptake in peripheral tissues,[104] such as *Trigonella foenum-graecum*, which contains saponins, 4-hydroxyisoleucine, trigonelline, alkaloids, and steroids.[66] These studies demonstrate that traditional nutraceutical metabolites from Asia hold promise as alternative non-pharmacological therapies for managing diabetes.

Modulation of gene expression by traditional nutraceuticals

There is significant potential for nutraceuticals to modulate gene expression in the treatment of diabetes. However, this review will focus on three main mechanisms of gene expression modulation based on the primary pathophysiology of T2DM, i.e., impaired insulin secretion from beta cells (β-cell dysfunction), disrupted insulin signaling mechanisms, and abnormalities induced by oxidative stress exacerbating the diabetic condition.

Genes involved in β-cell dysfunction

Traditional nutraceuticals, derived from natural plants, herbs, and bioactive compounds, have emerged as promising agents in modulating gene expressions involved in β-cell dysfunction (Table 2). Compounds such as curcumin, resveratrol, kaempferol, and quercetin have shown the ability to regulate pathways linked to oxidative stress, inflammation, and apoptosis. For instance, curcumin has been reported to upregulate the Nrf2 pathway, which protect β-cells from oxidative damage.[105,106] Similarly, resveratrol upregulate the sirtuin 1 (SIRT1) pathway, promoting β-cell survival and improving insulin secretion under stress conditions.[107,108] Resveratrol's inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) operates to downregulate the pancreatic β-cell apoptotic pathway resulting in improved β-cell survival.[109]

In pancreatic β-cells, kaempferol has been found to enhance glucose-stimulated insulin secretion (GSIS) by activating the mitochondrial calcium uniporter (MCU) and increasing mitochondrial calcium uptake.[110] This effect was validated in both insulinoma cell line (INS-1E) cells and human islets, suggesting that kaempferol can improve β-cell function under stress conditions. Interestingly, while kaempferol upregulate the SIRT1 pathway, other studies have identified alternative mechanisms for improving β-cell function and survival.[111]

Anthocyanins, a subclass of flavonoids with potent antioxidant and anti-inflammatory properties, have been shown to upregulate NO bioactivity and Nrf2. This activation strengthens endogenous antioxidant defense mechanisms and mitigates oxidative stress, which is a key contributor to pancreatic β-cell dysfunction in diabetes. The increased Nrf2 activity leads to enhanced production of endogenous antioxidants, providing protection against oxidative damage. Concurrently, anthocyanins are proposed to downregulate NF-κB, a key regulator of inflammation. This suppression results in the downregulation of pro-inflammatory cytokines, TNF-α, IL-1β, IL-6, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion protein 1 (VCAM-1), ultimately reducing chronic low-grade inflammation—a hallmark of insulin resistance and diabetes progression. Additionally, since NF-κB negatively regulates transforming growth factor-beta (TGF-β), its inhibition by anthocyanins indirectly upregulates TGF-β expression, contributing to improved cellular homeostasis and immune regulation. Through these mechanisms, anthocyanins play a crucial role in preserving pancreatic β-cell function, enhancing insulin sensitivity, and mitigating diabetes-related complications by reducing oxidative stress and inflammation.[112]

Alkaloids, a diverse group of naturally occurring bioactive compounds, have been shown to modulate key signaling pathways involved in glucose metabolism and oxidative stress regulation. These compounds upregulate the expression of liver kinase B1 (LKB1), AMPK, phosphorylated AMPK (p-AMPK), and phosphorylated transducer of regulated cyclic adenosine monophosphate responsive element-binding protein-2/CREB 2 (p-TORC2), which play critical roles in maintaining cellular energy balance and metabolic homeostasis.[113] Gallic acid, a polyphenolic compound with strong antioxidant and anti-inflammatory properties, has been found to enhance insulin sensitivity and β-cell function through multiple molecular mechanisms. It regulates the expression of TNF-α and adipocytokines, reducing inflammation associated with insulin resistance. Gallic acid also exerts a β-cell protective effect by inhibiting caspase-9-mediated apoptosis, which is essential for maintaining pancreatic function and preventing β-cell loss in diabetes.[114]

The therapeutic potential of these nutraceuticals lies in their ability to target multiple signaling pathways that influence β-cell health. By modulating genes involved in stress response, apoptosis, and insulin biosynthesis, traditional nutraceuticals offer a complementary approach to conventional diabetes treatments. Future research should focus on clinical studies to validate their efficacy and investigate the optimal doses and formulations for protecting and restoring β-cell function in diabetes.[115,116]

Genes involved in the insulin signaling pathway

Insulin gene expression is influenced by nutraceuticals including flavonoids (Table 2). Flavonoids are now considered as indispensable components in various nutraceutical, pharmaceutical, medicinal and cosmetic applications. This is due to their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties and their capacity to modulate enzyme function.[117]

Nutraceutical plants have shown significant potential in modulating gene expression in insulin signaling pathways, providing an alternative approach to diabetes management. Some of the herbs that have been extensively studied include turmeric (*Curcuma longa*), cinnamon (*Cinnamomum verum*), bitter melon (*Momordica charantia*), and guava leaf.[118]

Turmeric, with its main active compound curcumin, has been shown to improve insulin sensitivity by modulating the expression of genes involved in glucose and lipid metabolism.[119] Studies show that cinnamon extract can upregulate the expression of genes related to insulin signaling pathways, including phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT), which play an important role in glucose uptake by cells. In addition, cinnamon has also been shown to reduce insulin resistance by upregulating the expression of the Peroxisome Proliferator-Activated Receptor Gamma (PPAR)-γ gene, which is involved in lipid metabolism and insulin sensitivity.[104]

Guava leaf extract (GLE), which contains the bioactive compound kaempferol, has the potential to improve insulin signaling under diabetic conditions by modulating insulin receptor substrate 1 (IRS-1) gene expression. In diabetic rats, GLE enhances glucose uptake in cells by upregulating IRS-1 gene expression in skeletal muscle, thereby activating insulin receptors. Activated IRS-1 stimulates the enzyme PI3K, which subsequently converts phosphatidylinositol 4,5-bisphosphate (PIP2) in the cell membrane into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 acts as a signaling molecule that binds to and activates AKT, also known as PKB. Activated AKT phosphorylates several downstream targets, including proteins that regulate vesicles containing glucose transporter-4 (GLUT4). Phosphorylation by AKT induces upregulation of gene expression of GLUT4 (Solute carrier

family 2, member 4 (SLC2A4)), causing the vesicles containing GLUT4 to translocate to the plasma cell membrane. GLUT4 is a glucose transporter found in intracellular vesicles, and once translocated to the cell membrane, it facilitates glucose entry into the cell muscle.[102,120] Figure 2 shows modulation of IRS and GLUT4 genes by bioactive compounds of traditional nutraceuticals, i.e. kaempferol, myricetin and terpenoids.

Terpenoids, a diverse class of naturally occurring compounds derived from isoprene units, are widely found in medicinal plants. These bioactive compounds have been shown to upregulate the expression of key proteins involved in insulin signaling and glucose metabolism, including the insulin receptor (IR) and IRS-1, which play crucial roles in enhancing insulin sensitivity. Additionally, terpenoids upregulate the expression of glycogen synthase kinase 3β (GSK-3β) and Akt serine/threonine kinase (Akt), both of which regulate glycogen synthesis and glucose uptake. Furthermore, terpenoids promote the transcription of GLUT4 and AMPK, facilitating glucose uptake into cells and improving energy homeostasis. Through these molecular mechanisms, terpenoids contribute to enhanced insulin sensitivity, improved glucose utilization, and potential therapeutic benefits in metabolic disorders such as diabetes.[121] Additionally, alkaloids have been reported to downregulate the expression of key gluconeogenic enzymes, thereby reducing hepatic glucose production.[113]

Gallic acid concurrently activates PPAR-γ and CCAAT/enhancer-binding protein (C/EBP), which facilitate GLUT4 translocation in adipose cells, thereby promoting glucose uptake. Additionally, gallic acid improves insulin sensitivity by modulating the Akt and AMPK signaling pathways, which are crucial for glucose homeostasis.[114]

Modulation of antioxidant gene expression

SOD is a key antioxidant enzyme that catalyzes the conversion of superoxide radicals into hydrogen peroxide and oxygen, thereby reducing oxidative damage. Traditional nutraceuticals, such as turmeric (Curcuma longa), which contains curcumin—a natural polyphenol—have demonstrated significant effects on upregulated SOD gene expression (Table 2). For example, in a study investigating the effects of curcumin on high-fat diet and streptozotocin-induced hyperglycemia and hyperlipidemia in rats, curcumin treatment was found to upregulate SOD expression in the liver.[103] Furthermore, curcumin significantly increased reduced glutathione (GSH) levels in diabetic rats, highlighting its ability to enhance antioxidant defenses.[101]

Other traditional nutraceuticals, GLE which contain kaempferol as a primary secondary metabolite, have also shown promise in modulating antioxidant gene expression. In studies related to diabetes, kaempferol demonstrated the ability to increase the activity of glutathione peroxidase (GSH-Px) *in vivo*, indicating its potential to enhance the antioxidant defense system.[122] Additionally, research has shown that kaempferol at a concentration of 50 µg/mL modestly upregulates the expression of superoxide dismutase 1 (SOD1) and SOD2 genes.[123]

As a flavonoid, kaempferol exerts its antioxidant effects by enhancing cellular GSH levels, which is achieved by increasing the nuclear translocation of Nrf2, a key regulator of antioxidant response genes.[124] Collectively, these findings indicate that nutraceuticals such as curcumin and kaempferol hold significant potential in mitigating oxidative stress and improving antioxidant defenses through the modulation of key genes, including those encoding SOD and GSH-related enzymes.

Myricetin, a flavonoid compound commonly found in Asia traditional nutraceutical, has been shown to protect pancreatic β-cells from apoptosis induced by high glucose (HG) conditions. This antioxidant protective effect is primarily mediated through the attenuation of endoplasmic reticulum (ER) stress, potentially via the inhibition of cyclin-dependent kinase 5 (CDK5). Consequently, this pathway enhances the regulation of PDX1, a critical

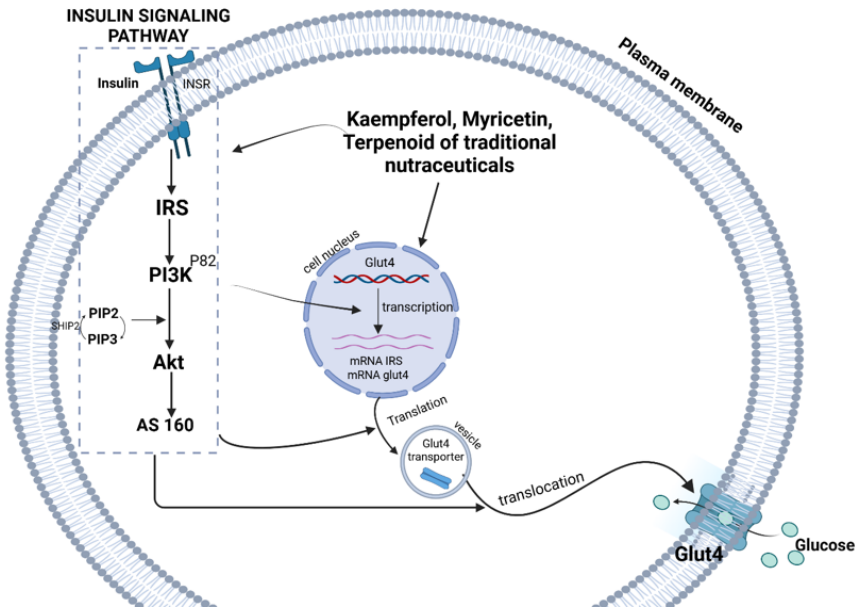

Figure 2. Modulation of IRS and GLUT4 genes by bioactive compounds of traditional nutraceuticals, i.e. kaempferol, myricetin and terpenoids. (This figure was generated using BioRender.com)

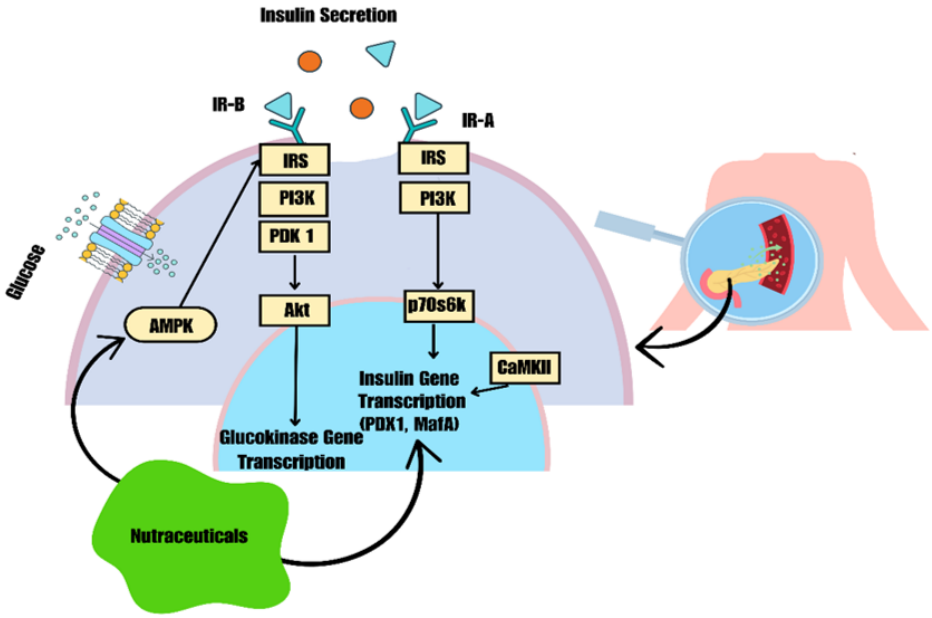

Figure 3. Nutraceuticals Modulation of PDX-1 and MafA Gene Expression Involved in Alleviating β-Cell Dysfunction. (This figure was generated using BioRender.com)

transcription factor for β-cell function and survival (Figure 3).

Saponins, a class of bioactive glycosides with strong antioxidant and cytoprotective properties, have been shown to upregulate SOD1 gene expression, thereby enhancing the endogenous antioxidant defense system.[125] Treatment with 200 μg/mL alfalfa-derived saponins significantly increases the enzymatic activities of SOD, GSH-Px, and CAT, which collectively mitigate oxidative stress and prevent cellular damage.[126] Furthermore, saponins play a critical role in preserving pancreatic β-cell viability and promoting β-cell regeneration through the activation of the Wingless-related integration site (Wnt3a)/β-catenin/transcription factor 7-like 2 (TCF7L2) signaling pathway. This pathway is essential for maintaining β-cell function, enhancing proliferation, and regulating insulin secretion.[127]

Alkaloids inhibit high glucose-induced nitro tyrosine accumulation, a marker of oxidative stress, while simultaneously downregulate SOD-1 and uncoupling protein 2 (UCP2) expression, which are linked to mitochondrial dysfunction. In INS-1E pancreatic β-cells, alkaloids prevent excessive AMPK phosphorylation, thereby protecting against cellular stress and dysfunction, highlighting their potential role in diabetes management.[128]

Conclusion

Various traditional nutraceuticals from Asia have potential antidiabetic effects. These nutraceuticals contain antioxidants and exert their effect on modulating gene expressions involved in β-cell dysfunction, insulin signaling pathway, and antioxidant activity. This review highlights the growing scientific interest in exploring traditional nutraceuticals for the prevention and management of diabetes mellitus, offering potential alternatives to conventional treatments. However, further clinical trials are needed to confirm these antidiabetic effects.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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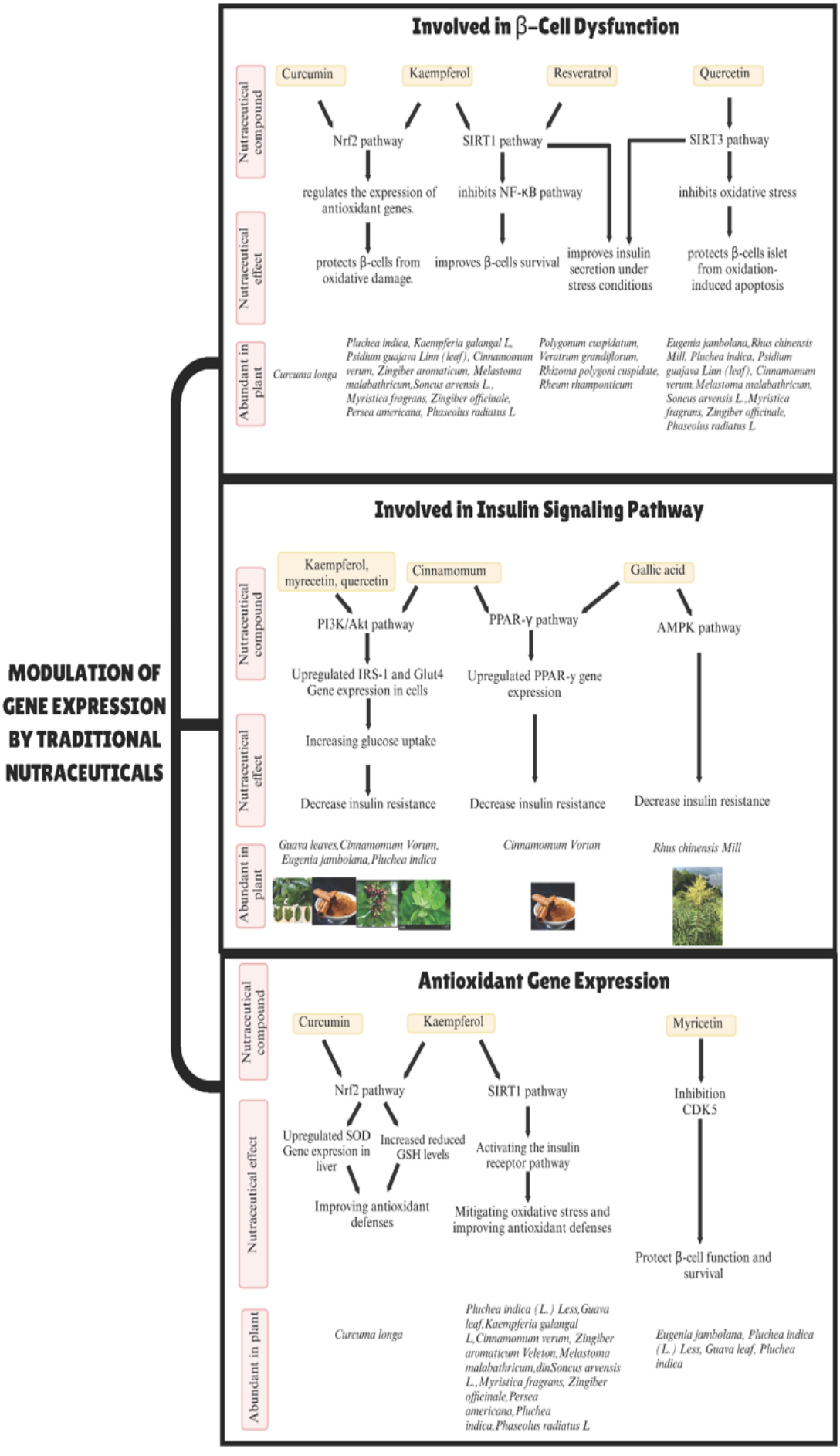

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