Current Drug Discovery Technologies, 2026, *23*, e15701638333208

REVIEW ARTICLE

Therapeutic Potential of Flavonoids in Diabetes Mellitus Management: Molecular Insights and the Future Directions for Drug Design

Ritika Chauhan[1], Srinivasa Rao Sirasanagandla[2], Vishnu Priya Veeraraghavan[3], Selvaraj Jayaraman[3,*] and Shobana Chandrasekar[1,*]

[1]*Department of Biochemistry, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India;* [2]*Department of Human and Clinical Anatomy, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat 123, Oman;* [3]*Centre of Molecular Medicine and Diagnostics (COMManD), Department of Biochemistry, Saveetha Dental College & Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, 600077, India*

ARTICLE HISTORY

Received: July 19, 2024
Revised: January 30, 2025
Accepted: February 12, 2025

DOI:
10.2174/0115701638333208250522050837

Abstract: Diabetes mellitus (DM) is a prevalent metabolic disorder with a rapidly rising global incidence, presenting a significant burden to healthcare systems worldwide. Flavonoids, a class of naturally occurring polyphenolic compounds, are well-documented for their diverse pharmacological activities, particularly their anti-diabetic and anti-inflammatory effects. These secondary metabolites are commonly found in fruits, vegetables, and fungi and are classified into six main subclasses: flavanols, flavones, flavanones, isoflavones, anthocyanidins, and chalcones. The interplay between hyperglycemia, inflammation, and vascular complications in diabetes is now well recognized. Flavonoids with anti-diabetic properties may help mitigate inflammation by reducing hyperglycemia through various mechanisms. This review explores the antidiabetic potential and molecular mechanisms of citrus flavonoids, drawing on updated evidence from *in vitro* and *in vivo* studies. Flavonoids are shown to regulate biomarkers of glycemic control, lipid metabolism, renal function, hepatic enzymes, and antioxidant defenses. They also modulate signaling pathways implicated in glucose uptake and insulin sensitivity, which are central to the development of diabetes and its complications. Furthermore, this review synthesizes current knowledge on the antidiabetic effects of dietary flavonoids, emphasizing their molecular mechanisms in modulating key pathways such as glucose transporters, hepatic enzymes, tyrosine kinase inhibitors, AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and nuclear factor kappa B (NF-κβ). Further research is essential to deepen our understanding of flavonoids' therapeutic mechanisms in managing diabetes.

Keywords: Diabetes mellitus, hyperglycaemia, flavonoids, inflammation, biomarkers, metabolic disorder.

1. INTRODUCTION

Diabetes mellitus (DM) is a significant global health concern, contributing to substantial economic and societal burdens [1]. Approximately 463 million persons between the ages of 20 and 79 have diabetes, with the majority of them pervading in developing and underdeveloped countries, according to the International Diabetic Federation's (IDF) concluding report. By 2045, this number is expected to rise to 700 million [2]. According to a report by the World Health Organization (WHO), the death rate is projected to double between 2005 and 2030, making it one of the leading causes of death by 2030 [3]. It is broadly classified into acute and chronic forms, with acute diabetes involving short-term com plications like diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, and chronic diabetes leading to long-term conditions such as cardiovascular disease and neuropathy [1].

Fig. (**1**) interpretation of the normal glycemic effects of various bioactive phytochemicals, in comparison to acute and chronic diabetes-also known as prolonged hyperglycemia-which results from the dysregulation of protein, lipid, and carbohydrate metabolism and is considered a hallmark of diabetes mellitus. Type 1 Diabetes Mellitus (T1DM) is an autoimmune disorder where the body's immune system attacks and destroys pancreatic β-cells, leading to insulin deficiency and hyperglycemia. It typically presents during childhood or early adulthood, and lifelong insulin therapy is required for its management. Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance (IR) in tissues such as skeletal muscle, liver, and adipose tissue, with the pancreas initially compensating by producing more insulin. However, over

*Address correspondence to these authors at the Centre of Molecular Medicine and Diagnostics (COMManD), Department of Biochemistry, Saveetha Dental College & Hospitals, Saveetha Institute of Medical & Technical Sciences, Saveetha University, Chennai-600 077, India;
E-mail: selvarajj.sdc@saveetha.com (S.J.)
Department of Biochemistry, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India;
E-mail: shobana.sls@velsuniv.ac.in (S.C.)

1875-6220/26 $65.00+.00

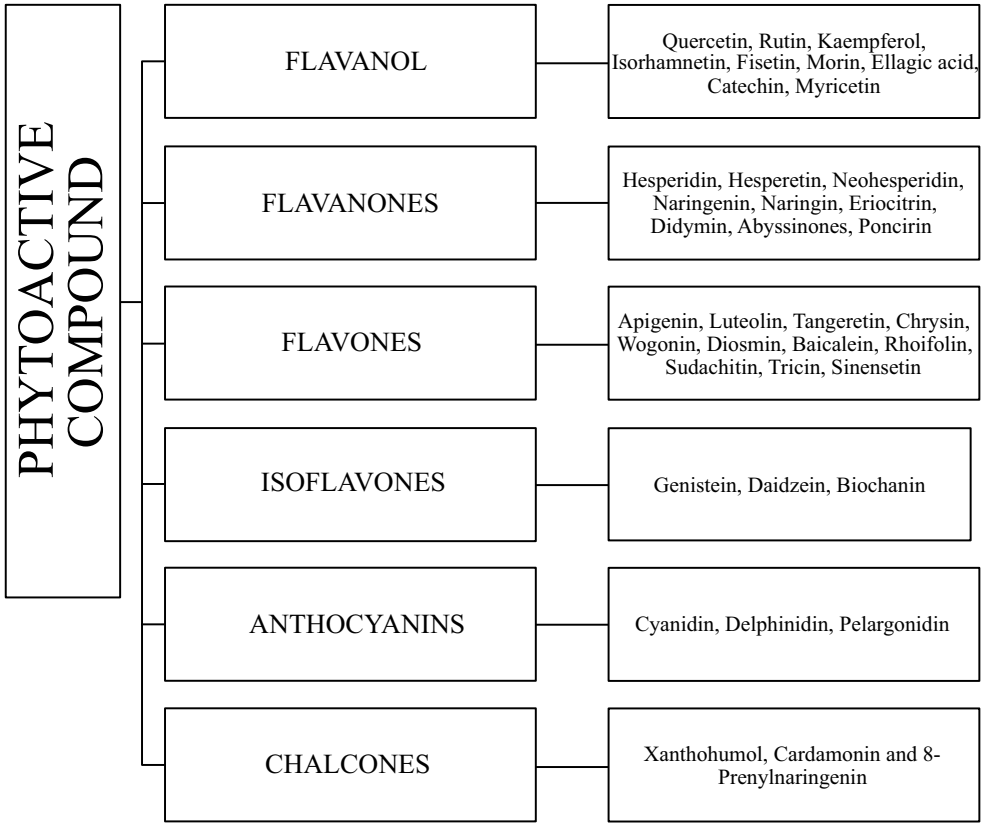


Fig. (1). Various bioactive phytochemicals and their corresponding bioactive compounds from different medicinal plants with normoglycemic effects. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

time, β-cell function declines, leading to persistent hyperglycemia. T2DM is most commonly observed in adults, especially those with obesity and a sedentary lifestyle. If left untreated, it can result in damage to vital organs, including the heart, kidneys, and eyes. Type 3 Diabetes is a term sometimes used to describe Alzheimer's disease due to its association with IR in the brain. It is thought that impaired insulin signaling may contribute to the cognitive decline seen in Alzheimer's disease. All ages are affected by the three main types of diabetes: type 1, type 2, and type 3 gestational diabetes [4]. Moreover, T2DM remains the most prevalent and is closely linked to lifestyle changes and various environmental factors. This metabolic imbalance results in excessive glucose accumulation in the bloodstream as the body's cells become less responsive to insulin. Over time, these factors also impair pancreatic β-cell function, exacerbating the condition. Additionally, genetic predisposition combined with these modifiable risk factors further accelerates the progression of T2DM. Addressing these lifestyle factors through diet, exercise, and stress management can play a crucial role in preventing or managing T2DM. Symptoms include polyuria (frequent urination), polyphagia (increased hunger), polydipsia (increased thirst), weight loss, and sleepiness [3, 4].To control diabetes, various medications are available in the markets, including Metformin, which activates AMP-activated protein kinase (AMPK) by inhibiting complex I of the mitochondrial electron transport chain (ETC). This inhibition impairs ATP synthesis, thereby increasing the AMP/ATP and ADP/ATP ratios, ultimately enhancing insulin sensitivity. Sulphonylureas stimulate the release of insulin from pancreatic beta cells. Thiazolidinediones (TZDs) activate peroxisome proliferator-activated receptor-gamma (PPAR-γ), modulating genes involved in glucose and lipid metabolism. Biguanides reduce hepatic glucose production, and insulin administration, commonly used T1DM, lowers blood glucose levels while promoting lipogenesis and protein synthesis [5, 6]. Despite the availability of several effective oral hypoglycaemic medications, 5-10% of cases experience subsequent failure. This secondary failure can be attributed to factors such as declining βeta-cell activity, medication non-adherence, weight gain, physical inactivity, dietary changes, MDR, or underlying illnesses. The adverse effects of synthetic medications can sometimes be alleviated through the use of herbal therapies.

Historically, numerous medicinal plants have been utilized to manage diabetes. Due to their availability, affordability, and minimal side effects, plant-derived bioactive compounds have become essential components of modern therapeutics, particularly in rural areas [5-8], with flavonoids being among the most prominent. Countless flavonoids originating from citrus fruits have been declared to diminish oxidative stress, improve glucose tolerance and insulin sensitivity, modulate lipid metabolism and adipocyte differentiation, suppress inflammation and apoptosis, and improve endothelial dysfunction, which indicates their potential anti-diabetic effect [8]. Flavonoids, a diverse group of polyphenolic compounds, offer a wide range of health benefits due to their varied structures and mechanisms of action [8].

Flavonols like quercetin and rutin provide cardiovascular and cerebrovascular protection, antioxidative, antidiabetic, and anti-inflammatory effects, with rutin also offering vasoprotective and neuroprotective benefits [8]. Kaempferol and isorhamnetin exhibit anti-aging, anti-inflammatory, and antioxidative properties, with isorhamnetin additionally promoting organ protection and obesity prevention. Fisetin is recognized for its anti-oxidant, anti-inflammatory, and anti-tumor effects, as well as its protective role in myocardial and kidney injuries [8]. Among flavanones, hesperidin and naringin deliver anti-oxidant, anti-inflammatory, and cardioprotective effects, with naringin also reducing adiposity and osteoporosis risk, while naringenin is noted for its lipid-lowering and insulin-like activities [8].

Flavanonols, such as silymarin, support insulin sensitivity, cardiovascular health, and neuroprotection while regulating blood pressure and lipid profiles. Anthocyanins, like anthocyanin, are known for their anti-oxidative, cardiovascular, neuroprotective, and anti-obesity effects. Flavones, including baicalin, apigenin, and luteolin, protect cardiovascular, hepatic, and renal systems while offering anti-inflammatory, anti-oxidative, and anti-cancer benefits. Scutellarin and myricetin contribute additional anti-obesity and antiviral effects, respectively. Isoflavones such as puerarin and biochanin A lower blood glucose levels, improve IR and provide cardioprotective and antioxidative benefits [8]. Finally, flavan-3-ol compounds, like (−)-epigallocatechin-3-gallate (EGCG), deliver anti-oxidative, anti-obesity, and anti-insulin resistance effects, highlighting the therapeutic and preventive potential of flavonoids in diverse health domains [8]. Nearly 40 citrus flavonoids, including quercetin, rutin, kaempferol, isorhamnetin, fisetin, morin, ellagic acid, myricetin, hesperidin, hesperetin, neohesperidin, naringenin, naringin, eriocitrin, didymin, abyssinones, poncirin, apigenin, luteolin, tangeretin, chrysin, wogonin, diosmin, baicalein, rhoifolin, sudachitin, tricin, genistein, daidzein, biochanin, cyanidin, delphinidin, pelargonidin, xanthohumol, cardamonin, and 8-prenylnaringenin, have shown significant potential in managing T2DM (Fig. **1**). Flavonoids, including lutein, scutellarin, biochanin A, naringenin, rutin, puerarin, quercetin, kaempferol, silymarin, epigallocatechin gallate (EGCG), and fisetin, are renowned for their therapeutic potential in diabetes-induced complications such as diabetic cardiomyopathy (DCM) and diabetic nephropathy (DN) [8]. These compounds, depicted around central illustrations of the heart and kidneys affected by DCM and DN, respectively, highlight their cardioprotective and renoprotective effects. By leveraging mechanisms such as antioxidation, anti-inflammatory activity, and the regulation of lipid and glucose metabolism, these flavonoids contribute to improved heart health and protection of renal function. Specifically, in DCM, flavonoids help mitigate cardiac damage and preserve cardiac function, while in DN, compounds like kaempferol, luteolin, naringenin, rutin, baicalin, myricetin, anthocyanin, puerarin, fisetin, hesperetin, and EGCG are particularly effective in preventing the progression of kidney damage. Together, these flavonoids provide significant therapeutic benefits for managing diabetes-related complications and promoting overall cardiovascular and renal health. Current treatments for type 2 diabetes, such as pharmaceutical drugs, often show side effects and limited efficacy, creating a need for alternative and safer therapeutic options. Flavonoids are emerging as promising candidates due to their ability to target IR, a hallmark of type 2 diabetes [8]. To further understand the mechanisms underlying various animal models, researchers investigate the interplay between genetic and environmental factors. This review focuses on the role of flavonoid compounds in developing novel antidiabetic agents specifically aimed at managing type 2 diabetes, providing a foundation for safer and more effective treatments.

1.1. Glucose Regulation and Insulin Resistance (IR)

Glucose regulation is crucial for maintaining blood sugar levels, primarily through the actions of the hormone insulin and glucagon, which help to control blood sugar levels after carbohydrate-rich meals. Pancreatic α-amylase plays a key role by hydrolyzing starch and glycogen into oligosaccharides and disaccharides. These are then further broken down into monosaccharides by the enzyme α-glucosidase on the intestinal brush border, facilitating glucose absorption and contributing to postprandial hyperglycemia [9]. Targeting α-amylase and α-glucosidase inhibitors has become a primary strategy for managing hyperglycemia. While synthetic inhibitors like acarbose and miglitol can cause side effects, flavonoids have shown promise as natural enzyme inhibitors and antioxidants, offering protection to cells while helping regulate blood sugar levels [10, 11]. Also, the prime hormone insulin, produced by the pancreatic β-cells, is secreted in response to elevated glucose levels. It promotes glucose uptake by activating glucose transporter type 4 (GLUT4) translocation, stimulates protein synthesis, and encourages glucose storage [11, 12]. On the other hand, glucagon, released by α-cells when glucose levels are low, triggers hepatic glucose production and lipolysis in adipose tissue [12-14]. Glucose transport across cell membranes is facilitated by GLUT proteins, which are encoded by the solute carrier family 2 (SLC2) genes. Among these, GLUT2 is particularly important for pancreatic glucose sensing and insulin secretion [13, 14]. Moreover, IR, which is characterized by diminished glucose uptake due to impaired signalling, can be triggered by tumor necrosis factor-alpha (TNF-α) and free fatty acids (FFAs). These molecules inhibit insulin receptor substrate 1 (IRS-1) and prevent GLUT4 translocation [15]. Other proteins, including protein tyrosine phosphatase 1B (PTP1B), phosphatase and tensin homolog (PTEN), and suppressor of cytokine signaling 1/3 (SOCS-1/3), further suppress insulin signaling, while lipid accumulation in the liver and muscle exacerbates the condition [16, 17]. As a compensatory response, pancreatic β-cells increase insulin secretion, leading to β-cell hypertrophy and expansion of the islets [18].

1.2. Insulin Receptor Signaling and Mechanisms of IR in Type 2 Diabetes

Tyrosine kinase (TK), an insulin receptor, mediates insulin's intracellular actions by auto-phosphorylating tyrosine residues when insulin binds to its extracellular domain, causing a conformational shift. Phosphotyrosine binding proteins such as growth factor receptor-bound protein 2 (GRB2),

insulin receptor substrate (IRS), GRB10, and Src homology and collagen (SHC) are activated as a result of TK activation [19]. For instance, GRB10 phosphorylation and stabilization by mammalian target of rapamycin complex 1 (mTORC1) provide feedback inhibition to the insulin receptor (INSR), triggered by insulin signaling. Other substrates, like SH2B2 adapter protein 2 (SH2B2/APS), initiate the metabolic insulin response [20]. Insulin signaling involves proximal processes, including the phosphorylation of IRS, phosphatidylinositol 3-kinase (PI3K), AKT isoforms, and INSR. These processes start at the plasma membrane in insulin-target tissues. Three pathways result from phosphorylation: the PI3K-dependent pathway, which mediates glucose, lipid, and protein metabolism; the mitogen-activated protein (MAP) kinase pathway, regulating cell proliferation; and the pathway affecting glucose and lipid metabolism through IRS phosphorylation by TK. Phosphatidylinositol 3,4,5-trisphosphate (PIP3) recruits AKT, activating phosphoinositide-dependent protein kinase 1 (PDK1) and mTORC2, which mediate insulin's effects on glucose uptake and nutrient reserving [21].

In insulin-sensitive organs, insulin regulates metabolic adaptation between fasting and postprandial states, promoting anabolic activities and nutrient storage. Insulin suppresses fatty acid oxidation, glycogenolysis, gluconeogenesis, apoptosis, and autophagy, while promoting glucose uptake and storage in muscle, fat, and liver [22]. However, IR T2DM attenuates this transition, resulting in impaired insulin action. GLUT1 and GLUT4, responsible for glucose transport, are less effective in diabetic individuals, reducing glucose uptake and increasing IR. Diabetes also impacts liver enzyme activity and insulin signaling, slowing lipid metabolism and contributing to hyperglycemia and IR [23, 24]. Glycated proteins from hyperglycemia reduce PI3K, protein kinase B (PKB), and glycogen synthase kinase-3 (GSK-3) activity, worsening IR. Glucosamine increases IRS1 glycosylation, reducing insulin response [25, 26]. Additionally, IR decreases insulin's capacity to promote glycogen synthesis, as observed in T2DM patients with reduced TK activity in the liver and muscle [27]. Severe IR can cause ectopic fat buildup in peripheral tissues like skeletal muscle and liver. Leptin therapy or weight loss can reverse hepatic IR in T2DM and non-alcoholic fatty liver disease patients. Ectopic lipid accumulation mediates IR *via* lipid metabolites, such as diacylglycerol, which inhibit TK activity and deactivate IRS2, PI3K, and AKT2 [28, 29]. Increased c-Jun N-terminal kinase (JNK) activity, observed in obese rats and humans, contributes to IR, as JNK1 knockout mice exhibit improved insulin sensitivity [30]. Immune cells and cytokines contribute to IR in the liver, especially with prolonged lipid exposure [31]. Adiponectin receptors 1 and 2 activate AMPK and PPAR-α signaling, suppressing gluconeogenesis and enhancing glucose absorption, while their deletion contributes to IR [32].

1.3. Inflammatory Response and IR

In both humans and animals with insulin resistance (IR), it is important to note that leptin levels increase while adiponectin levels decrease. Leptin directly affects insulin action by binding to its receptor (LepRb) and activating the JAK/STAT3 signaling pathway [33]. Leptin reduces the synthesis of glucose in the liver, enhances insulin sensitivity, and restricts the secretion of insulin. Insulin then promotes the synthesis of leptin in adipose tissue. Interestingly, monocytes and macrophages emit pro-inflammatory substances such as IL-6, TNF-α, and IL-12 when leptin levels linked to IR are high. The onset of IR in those with dyslipidemia or obesity. A mechanism that causes IR in the liver and pancreatic β-cells is ER stress, which is exacerbated in obesity [34].

1.4. Search Methodology and Selection Standards

A comprehensive literature search was conducted using the keywords "flavonoids", "phytochemicals", "flavonoids and anti-diabetics", "phytochemicals diabetes mellitus", and "flavonoids OR flavonoid subclasses AND diabetes" across ScienceDirect, Scopus, and PubMed databases to identify relevant studies published in the past 10 years. The inclusion criteria were original research articles, reviews, and meta-analyses that specifically investigated the role of flavonoids and phytochemicals in diabetes mellitus. Studies unrelated to diabetes, those lacking experimental evidence, or articles without sufficient data were excluded. From the identified records, 189 papers meeting the criteria were selected and thoroughly examined. Data extraction focused on study design, intervention details, molecular mechanisms, and key outcomes to ensure a comprehensive and transparent synthesis of the literature.

1.5. Flavanoids in Diabetes Management

The tropical and subtropical regions of Oceania (Queensland and Australia) and Asia (from North China to India) are home to diverse citrus species with high sexual compatibility, allowing spontaneous crossover and improved hybrids through human intervention [35]. The global citrus industry produces 100 million tonnes of fruit annually, with 60% consumed locally, 10% exported, and 30% utilized commercially, including oranges, lemons, limes, pomelos, grapefruit, mandarins, and hybrids. Recently, interest in unusual varieties like blood oranges, kumquats, yuzu, and kaffir lime has grown. The first flavonoid, hesperidin, was discovered in the citrus genus in the late 19th century, followed by the identification of 44 naturally occurring citrus flavonoids [36].

Flavonoids have a 15-carbon skeleton comprising two aromatic rings (A and B) linked by a three-carbon oxygenated heterocyclic C ring and are classified into six subtypes: flavonols, flavanones, flavones, isoflavones, anthocyanins, and catechins, based on their structure and functional groups [37]. Bioflavonoids, discovered by Albert Szent Györgyi in 1938, are polyphenols responsible for the vibrant colors of flowers, fruits, and leaves, offering health benefits for metabolic disorders, including diabetes, cancer, obesity, and cardiovascular diseases [38]. Acting as antioxidants, flavonoids mitigate oxidative stress by scavenging reactive oxygen species (ROS) and preventing cellular damage [39]. Their anti-diabetic properties involve regulating glucose uptake, insulin signaling, lipid metabolism, and reducing hyperglycemia by influencing glucose metabolism in liver cells [40, 41]. Bioactive components such as hydroxyl groups and α and β ketones contribute to these effects [42]. Flavonoids also enhance glucose uptake by modulating the expression and translocation of glucose transporters like GLUT4 in insulin-sensitive tissues, promoting glucose homeostasis and reducing IR [43].

Since flavonoids have been extensively studied for diabetes treatment, various experimental models, including rodents and non-rodents such as pigs, rabbits, rhesus monkeys, and zebrafish, have been employed to understand IR and evaluate potential therapies. These models include chemically induced diabetes models (*e.g.*, streptozotocin or alloxan), autoimmune models, transgenic models, virus-induced models, T2D models, monogenic and polygenic obesity models, high-fat diet models, and advanced approaches like CRISPR-Cas9, microbiome-modified models, humanized mice, and specialized mouse strains [44, 45]. Considering the significance of these models in diabetes research, this review highlights 40 flavonoids and summarizes their characteristics as studied for diabetes management through *in vitro* and *in vivo* approaches.

2. FLAVONOLS

2.1. Quercetin

The most common flavonoid found in human diets is quercetin dihydrate, also known as 3,5,7,3',4'-Pentahydroxyflavone. Flowers, apples, tomatoes, tomato seeds, berries, fennel, tea leaves, almonds, onions, broccoli, pepper, lovage, and shallots make up nearly all of their constituents. Based on *in vitro* research it prevents the enlargement of high-glucose-induced cells by inhibiting the synthesis of vascular endothelial growth factor [46]. In *in vitro* conditions, it decreases intestinal α-glucosidase, pancreatic α-amylase and the rate of glucose absorption in the gastrointestinal tract by reducing α-glucosidase activity. It lowers triglycerides, total cholesterol and VLDL-C (very low-density lipoprotein-cholesterol) in rats with hyperlipidemic conditions. It increases the synthesis of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, HDL-C (high-density lipoprotein) cholesterol and adiponectin in the body. Quercetin administration at a dose of 25 mg/kg/day improved the synthesis of anti-oxidants [47]. The rise in the levels of transforming growth factor β-1 (TGF-β1) and connective tissue growth factor (CTGF) was decreased, and this helped diabetic nephropathic rat's renal function better. In diabetic mice, by decreasing the CYP2E1(Cytochrome P450 2E1) liver enzyme, it is possible to stop diabetic liver oxidative damage [48]. Also, quercetin with/without resveratrol decreased blood glycosylated haemoglobin (HbA1c) and C-peptide levels; that is, insulin secretion decreases in diabetic rats, which decreases the harm to pancreatic β-cell. In STZ (streptozotocin)/alloxan-induced diabetic mice, it also promoted insulin secretion and repaired pancreatic islets. In order to prevent non-alcoholic fatty liver disease (NAFLD), it can restore damaged metabolite and microbiota in the gut as well as decrease the levels of liver enzymes like ALT (Alanine transaminase), AST (Aspartate transaminase), oxidative stress, and inflammation [49]. Pro-inflammatory cytokines that quercetin has been proven to reduce production include interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-4 (IL-4) IL-4 and Tumor necrosis factor alpha (TNF-α) [50].

2.2. Rutin

The glycosidic flavonoid known as rutin (quercetin 3-rutinoside, C27H30O16) is frequently found in dietary sources. Oranges, grapefruits, lemons, and limes are the primary citrus fruits that contain rutin. It is a flavonoid found in many plants and shows a wide range of biological activities, including anti-inflammatory, antioxidant, neuroprotective, nephroprotective, and hepatoprotective effects. Diabetic mice with type 1 diabetes mellitus (T1DM) exhibited decreased body weight, HDL-C levels, and fasting insulin, along with increased fasting serum glucose, total cholesterol (TC), triglycerides (TG), and LDL-C levels. Elevated levels of pro-inflammatory cytokines, such as TNF-α and IL-6, were also observed. Similar metabolic alterations were reported in other mouse models. Fasting serum insulin was elevated in T2DM mice, in contrast to T1DM models. Treatment addressed both T1DM and T2DM mice, alleviating common disorders associated with lipid and glucose metabolism [51]. Stellaria media tea, which contains rutin, prevented diabetes-induced STAT3 phosphorylation in cardiac tissue—an effect that may help mitigate diabetes-related cardiac complications without altering fasting blood glucose levels or glucose tolerance. Rutin was administered at a dosage of 100–200 mg per kilogram of body weight daily for four weeks [52]. Additionally, the ethanol extract of the mushroom *Coprinus comatus* demonstrated antidiabetic and antioxidant activities in streptozotocin-induced diabetic rats [53].

2.3. Kaempferol

Significant amounts of the non-toxic flavonoid 3,4,5,7-tetrahydroxyflavone are found in various foodstuffs, including grapes, apples, onions, tomatoes, beans, kale, broccoli, potatoes, tea, and spinach. Kaempferol holds anti-inflammatory, antibacterial, antioxidant, neuroprotective, and anticancer properties. In a study employing the insulin secretagogue glibenclamide (GBN) as the control substance, it was discovered that kaempferol increased plasma insulin levels and decreased blood glucose levels in streptozotocin (STZ) - induced diabetic rats. In a C57BL/6 mice model of DN, kaempferol increased levels of insulin, glucagon-like peptide-1 (GLP-1), cAMP (Cyclic adenosine monophosphate) and glutathione (GSH). By increasing glucokinase (GCK) levels and glycogen, kaempferol lowers blood glucose levels [54, 55]. It decreases AMPK (AMP-activated protein kinase) activity because IR raises insulin sensitivity. The pharmacological goal of AMPK activation in the treatment of diabetes is significant. AMPK activators include metformin and TZDs, Kaempferol also shows similar activity. It promotes the phosphorylation of ACC (Acetyl-CoA carboxylase) and AMPK in the liver, adipose tissues and muscles. An appealing pharmaceutical target for the treatment of diabetes, obesity, and metabolic syndrome is α-glucosidase, which hydrolyzes glucoside bonds to glucose. By blocking the ASK1/MAPK signalling cascade, controlling oxidative stress, enhancing cardiac function, and decreasing apoptosis, kaempferol prevents myocardial hypertrophy [56]. It has been demonstrated that kaempferol causes an increase in Nrf2 levels and enhances cardiac function. Also, in normal β-cells, oxidative stress brought on by brief hyperglycemia is controlled in part by antioxidant response element (ARE) driven gene transcription [57].

2.4. Isorhamnetin

Oenanthe javanica (Chinese celery, Japanese parsley, blume, minari in Korean), *Hippophae rhamnoides* (also

known as sea buckthorn), and *Ginkgo biloba* (often known as ginkgo) are examples of medicinal plants that contain an O-methylated bioactive component. Metformin and isorhamnetin may share a similar mechanism of action for treating hyperglycemia. Isorhamnetin enhances sensitivity to insulin by reducing the activity of mTOR, based on a new study. Isorhamnetin was administered orally by gastric gavage at doses ranging from 10 to 40 mg/kg for three weeks [58]. In our type 2 diabetes (T2D) model, it significantly reduced total cholesterol, low-density lipoprotein (LDL), triglycerides (TGs), and the risk of cardiovascular disease. Additionally, in the high-fat diet/streptozotocin (HFD/STZ)-induced type 1 diabetic rat model, isorhamnetin lowered plasma malondialdehyde (MDA) levels, indicating reduced oxidative stress. It raises GSH (Glutathione) levels by boosting the activity of antioxidant enzymes, superoxide dismutase (SOD), and catalase (CAT), demonstrating an antioxidant effect [59]. Isorhamnetin's activation of AMPK may decrease oxidative stress and inflammation, simultaneously decreasing the production of proteins and fatty acids. It can increase glucose absorption through the AMPK-GLUT4 pathway by increasing the expression of both GLUT4 and p-AMPK in skeletal muscle [60]. Further, in diabetic mice, this compound decreased the HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) measurement. These benefits might be attributed to an increase in p-AMPK levels, which increase GLUT4 translocation to the cell surface, promoting glucose absorption in skeletal muscles and enhancing responsiveness to insulin [61]. Lower levels of inflammatory mediators such as ICAM-1(intercellular adhesion molecules), TNF-α and IL-6 were seen because they blocked the NF-kB signalling pathway [62].

2.5. Fisetin

Numerous fruits and vegetables, including cucumbers, onions, apples, grapes, persimmons and strawberries, contain a significant quantity of 3,7,3',4'-tetrahydroxyflavone. Fisetin has neurotrophic, anti-inflammatory, and anti-diabetic properties. It inhibits the cell migration ability of high glucose-induced human retinal microvascular endothelial cells (HRMECs) [63]. Angiogenesis is mostly caused by excessive blood sugar and diabetic retinopathy (DR) is prevented by downregulating VEGF/ERK/FAK/Src) pathway signalling [64]. A powerful inhibitor of the cyclin-dependent kinase that triggers the G1/S transition is CDKN1B, also known as p27. Fisetin raised the levels of CDKN1B mRNA expression in high glucose-cultured podocytes. In the podocytes of STZ-induced diabetic rats and *db/db* mice, the Nod-like receptor protein 3 (NLRP3) inflammasome was found to be activated. It decreased the amounts of NLRP3, cleaved caspase-1, and IL-1 protein. It lessened high glucose-induced podocyte damage and STZ-induced DN in mice *via* restoring CDKN1B /P70S6K-mediated autophagy and decreasing NLRP3 inflammasome. Fisetin is a naturally occurring CDKN1B agonist that may have kidney protective effects in both HG(high glucose)-induced podocyte injury and type 1 diabetic animal models. Over eight weeks, mice were given oral fisetin (5, 10, or 20 mg/kg) every two days [65].

2.6. Morin

Traditional medicinal plants, including *Chlorophora tinctoria* L., *Prunus dulcis*, and fruits like figs and guava, are the main sources of the natural flavonoid morin. Morin reduced the oxidative stress brought on by midbrain carotid artery constriction in rats by decreasing MDA levels and increasing the activity of antioxidant enzymes GPx, SOD and GSH. Oral administration of morin (30 mg/kg b.wt.) continued for seven days [66]. In human lens epithelial (HLE-B3) cells, morin triggered ERK-Nrf2 signalling cascades, which elevated HO-1(Heme oxygenase) expression and had a cytoprotective effect against oxidative stress [67]. Tert-butyl hydroperoxide (tBHP) increased ROS production in primary rat hepatocytes exposed to it. It enhanced the expression of peptides of Nrf2, along with its downstream genes HO-1 and NQO1[NAD(P)H dehydrogenase quinone 1] [68]. Morin also strengthened intracellular antioxidants catalase and SOD), and it activated the Nrf2/ARE signalling pathway to protect pancreatic cells from DNA damage caused by oxidative stress, according to an *in vitro* study [69]. It reduced the expression of the genes for inducible nitric oxide synthase (iNOS), 5-lipoxygenase (5-LOX), and cyclooxygenase-2 (COX)-2. Also, it activated both the MAPK pathways (ERK and p38) and prevented the phosphorylation of the NF-κB proteins IκB-α and P65 [70]. The IL-6, IL-1β and TNF-α production of pro-inflammatory cytokines were inhibited by morin pre-treatment. Through NF-κB (IκB-α, p65) signalling and the NLRP3, pro-caspase-1, and ASC inflammasome pathway, it also reduced inflammation [71]. Similar to this, morin reduced the phosphorylation of JNK, ERK, p65, IκB-α, and p38 in the primary bovine mammary epithelial cells to attenuate the LPS (Lipopolysaccharide) inflammation through NF-κB & MAPK signalling pathway [72]. The morin therapy enhanced MnSOD GPx, GR and GSH while lowering the amount of ROS. The morin dramatically regulated the effects of hyperglycemia, which included an increase in the expression of the anti-apoptotic gene B-cell lymphoma 2 (Bcl-2) and a decrease in the expression of the pro-apoptotic gene Bcl-2 associated X protein (Bax) [73]. The brains of diabetic mouse models treated with Morin exhibited a reduction in inflammation-related markers (TNF-α, IL-1β, and IL-6) [74]. In contrast, oral supplementation of Morin to diabetic rats improved the level of neurotrophic and insulin growth factors (NGF, IGF-1, and BDNF) [75].

2.7. Ellagic Acid

Ellagic acid (EA) is a flavonoid that exists in large quantities in a wide range of fruits, including strawberries, pomegranate, guava, walnuts, almonds, and green tea of hydrolyzable tannins known as ellagitannins. Ellagitannins are transformed into EA in the colon, which is then transformed into urolithin, one of the most absorbable metabolites [76]. It functions as an antioxidant, anti-apoptotic, antibacterial, antiviral, anti-inflammatory, anti-malarial, anti-diabetic, anti-anxiety, and anticarcinogenic chemical [77]. EA stopped liver damage in rats with diabetes produced by the HFD in multiple animal models. Additionally, through inhibiting

SREBP1a and activating PPARα, EA reduced hyperlipidemia and guarded against steatosis of the liver in HFD, transgenic and obese rats with T2DM. Furthermore, by activating AMPK and concurrently suppressing the enzyme HMG-CoAR (β-hydroxy β-methylglutaryl-CoA reductase), EA inhibited cholesterol (CHOL) production in both rats fed cholesterol *in vivo* and *in vitro* studies [78]. EA releases insulin and has hypolipidemic, hypoglycaemic, and hypolipidemic effects that are AMPK-dependent. EA inhibits the histological levels of hepatic lipid accumulation in an AMPK-dependent way. EA inhibits NF-κB, p65 and activates Nrf2 to reduce oxidative stress and inflammation in an AMPK-dependent way. Both the control and T1DM-induced rats' livers exhibit increased AMPK phosphorylation in response to EA. EA inhibits SREBP1/2 and activates the PPAR-α /CPT1 in an AMPK-dependent way to inhibit hepatic lipogenesis. EA (50 mg/kg) administered orally daily for 12 weeks [77] might enhance GLUT4 expression in the skeletal muscle of diabetic rats to modulate blood glucose levels [79].

2.8. Catechin

Broad beans, grapes and tea are rich sources of catechins, a kind of natural flavonoid polyphenol. It can stimulate LKB1 to activate AMPK, inhibit IRS-1 phosphorylation, and improve insulin sensitivity. It stimulates AMPK and INSR in adipose tissue. Intriguingly, it functions as an insulin-mimetic substance, encourages the relocation of GLUT4 to the cell membrane *via* the PI3K/AKT signalling pathway, and improves cellular glucose absorption. It can boost GLUT4 translocation through the AMPK signalling pathway and PI3K/AKT signalling pathway, both of which need a mediator [80]. In STZ-induced rats with diabetes, it can return GS, G6P, GK and G-6-Pase, to their equilibrium levels when isolated from cassia seeds. It was given at varying doses (5, 10, and 20 mg/kg b.w) for eight weeks [81]. By blocking the gene expression of JNK1/2, PTP1B (Protein tyrosine phosphatase 1B) and IKK (Inhibitory kappa B kinase)/NF-κB (Nuclear factor κ-B), as well as IR in mice, it prevents HFD (high-fat diet)-induced obesity and diminishes oxidative stress [82]. The IRS-1/PI3K/FoxO1 pathway may be the linking factor between mitochondrial dysfunction and IR [83]. By boosting UCP-3 (uncoupling protein 3) expression, preserving ATP generation, enhancing mitochondrial membrane potential, boosting cell activity and insulin secretion, and lowering β-cell apoptosis, it can help stabilise mitochondrial function [84]. It enhances Bcl-2 expression to protect cells against interferon-gamma (IFN-γ), Interleukin (IL)-1β and TNF-α induced apoptosis *via* the mitochondrial pathway and restores GSIS (glucose-stimulated insulin secretion) [85]. It can reduce cytokine-induced β-cell death by inhibiting NF-κB activation, which downregulates iNOS(Nitric oxide synthases). It regulates NLPR3-related inflammatory signal molecules and NF-κB activation to ameliorate insulin sensitivity and β-cell damage caused by chemokines and cytokines [86].

2.9. Myricetin

There are several natural sources of myricetin Hexahydroxyflavone (3,5,7,3',4',5'- cannabiscetin), including fruits, berries, tea, medicinal herbs, and red wine. Myricetin has a greater daily consumption (1.0 mg/day) than other natural flavonols. Additionally, myricetin has been demonstrated to guard renal and pancreatic cells from oxidative damage in diabetes patients [87]. Due to its high neuroprotective and antioxidant properties, myricetin may be able to treat DPN. Diabetes-related deterioration in sensation, nerve conduction speeds, and nerve blood flow were markedly improved by myricetin. Myricetin also greatly increased Na^+, K^+-ATPase activity and antioxidant activities in the nerves of diabetic rats, and it considerably decreased the production of advanced glycation end-products (AGEs) and reactive oxygen species (ROS). Further studies showed that in diabetic rats, myricetin considerably increased the levels of hydrogen sulphide (H_2S) and increased the protein expression of the enzymes. Additionally, myricetin can decrease peripheral glucose levels in people with diabetes. Collectively, the results of our current investigation suggested that myricetin might improve poor motor and sensory abilities in diabetes patients. Intraperitoneal injections of myricetin at several doses (0.5 mg/kg/day, 1.0 mg/kg/day, and 2.0 mg/kg/day) were administered for two weeks [88]. When T2DM mice were treated with myricetin, their FBG and blood lipid levels drastically decreased, but their SOD levels rose. In T2DM mice, myricetin reduced polyuria, weight loss, polydipsia, and polyphagia. The intestinal flora of mice was disturbed by T2DM, but it was restored by myricetin treatment [89].

3. FLAVANONES

3.1. Hesperidin

Hesperidin is a flavanone glycoside that is found in large quantities in citrus fruits like oranges and lemons. It is said to have significant pharmacological advantages, such as anti-inflammatory and antioxidant properties. In Sprague-Dawley rats, diabetic neuropathy was produced by giving them an HFD for 12 weeks. Hesperidin treatment increased SIRT1-reduced IR and protected against oxidative stress damage by inhibiting NOX4 in HFD rats and Palmatine encountered glial C6 cells, thus improving mechanical and thermal sensitivity in rats with HFD-induced diabetic neuropathy. Oxidative stress and inflammation were reduced, and the number of antioxidant enzymes was increased. Hesperidin was given orally at a dose of 100 mg/kg [90]. Through its antioxidant action in SH-SY5Y neuronal cells, it significantly reduced high glucose-induced ROS generation. Hesperidin efficiently shielded SHSY5Y neuronal cells from oxidative damage, ER stress, and death by scavenging ROS. Additionally, hesperidin restored the MAPK signalling-decreased cell viability by preventing the oxidative stress-induced activation of ERK and JNK. According to our research, hesperidin is a potential biomolecule for the treatment of diabetic neuropathy [91]. CEBP/α and PPAR mRNA and protein expression in 3T3-L1 (derived from the original 3T3 Swiss albino cell line) cells were all reduced [92].

As a significant citrus flavonoid and the aglycone derivative of hesperidin, hesperetin ((S)-2,3-dihydro-5,7-dihydroxy-2-(hydroxy-4-methoxyphenyl)-4-benzopyran) is an aromatic substance mostly present in bitter oranges and lemons. Due to the rutinoside moiety connected to the flavonoid, it has a greater bioavailability than hesperidin. In diabetic

rats, it generated considerable decreases in glucose levels but significant increases in insulin and glucagon levels. In contrast, its treatment significantly decreased the blood levels of the enzymes AST, ALT, ALP, α-amylase, and lipase. Giving this to diabetic rats caused considerable reductions in the amount of TC, TG, and LDL, as well as a substantial increase in HDL levels. Significant improvements in the pancreatic SOD, CAT, and GPX enzyme activity under treatment with it revealed improvement in the antioxidative state. Thiobarbituric acid reactive substances (TBARS) and AGE, two indicators of pancreatic oxidative stress, decreased because of the treatment, demonstrating their antioxidant properties. Hexokinase and glucokinase activity both increased significantly after its therapy. Its delivery to diabetic groups led to noticeably lower levels of gluconeogenic enzymes in the pancreas. TNF-α and IL-6 levels in the pancreas were markedly lowered. It improved pancreatic shape and restored normal blood vessel function in tissue sections taken from diabetic rats [93]. In addition to up-regulating the detoxicating enzyme glyoxalase 1 and inhibiting the AGEs/RAGE axis and inflammation, it improved the structural alterations and renal functioning of diabetic rats. It also up-regulated γ-glutamyl cysteine synthetase, a well-known Nrf2/ARE signalling target gene, significantly increasing Nrf2. It could decrease the degenerative progression of (DN) by Glo-1increase, which was brought through the activation of the Nrf2/ARE pathway. Oral gavage of hesperetin (50 and 150 mg/kg) was administered once daily for six weeks [94].

3.2. Neohesperidin

Numerous citrus fruits contain Hesperetin-7-neohesperidoside, also known as neohesperidin, a weakly polar glycoside of flavanone with a harsh flavour. Neohesperidin (NHP), a dihydrochalcone that is mostly found in bitter oranges, has special qualities that make it valuable to the food business and nutraceutical companies. These qualities include hiding unfavourable flavours and increasing fruity and citrus flavours. In mice given an HFD, therapy lowered serum and liver ALT and AST levels, indicating better liver function and also reduced their hepatic steatosis. Its treatment reduced TC, TG, and serum non-esterified fatty acid (NEFA) blood levels. Hepatic TC and TG levels, as well as liver weight, decreased after taking it. It also reduced the observed hepatic fat accumulation in HFD mice by almost 50%. In HFD-fed rats, its administration notably decreased fasting blood glucose (FBG) and HOMA-IR levels, thus increasing fasting serum insulin. It significantly reduced peripheral IR and glucose intolerance in HFD mice, according to the outcomes of oral glucose tolerance tests (OGTT) and insulin tolerance tests (ITT). Chronic, excessive fat build-up in the liver can result in oxidative stress and inflammatory response. Neohesperidin was delivered at a dose of 50 mg/kg daily for 12 weeks [95]. When compared to the HFD group, the NHP-treated group had fewer myeloperoxidase (MPO) positive neutrophils. The NHP therapy also decreased the mRNA expression of inflammatory factors like Il-6, Il-1β, and TNF-α. Oxidative stress markers, such as MDA and ROS, were considerably decreased by NHP therapy in the liver. Additionally, its administration elevated the mRNA expression of the antioxidant genes CAT, SOD1, GPX1 and UCP2. It also raised ROS scavenger (GSH) levels and intracellular antioxidant enzymes (SOD, CAT) in the liver of HFD-induced animals. Increased lipid production and decreased fatty acid oxidation are favourable conditions for hepatic steatosis [96].

3.3. Naringenin

The primary flavanone in citrus fruits known as naringenin (4,5,7-trihydroxy-flavanone) has drawn growing amounts of scientific attention due to its bioavailability and pharmacological properties, which include antioxidant, anti-inflammatory, anti-atherosclerotic, anti-cancer, antiviral, and hepatoprotective activities. Mice exposed to STZ had impaired glucose homeostasis and islet dysfunction, in which naringenin improves TBARS, a marker of oxidative stress, and were considerably lower in the serum by naringenin. Apoptotic proteins, such as cleaved caspase-3, -9, and -8, were considerably more expressed in the pancreas of STZ-vehicle animals. However, its treatment suppresses pancreatic β-cell apoptosis induced by STZ. Animals driven by STZ exhibited increased levels of TNF-α and IL-1β protein expression as well as the phosphorylation of p65, JNK, and ERK, which are crucial mediators of cytokine-induced apoptosis in β-cells [97]. NF-kB and MAPK activations brought on by cytokine-induced macrophage infiltration into the pancreas are avoided by its treatment; thus, it prevents STZ-induced β-cell death. Besides the pancreas, in the liver and skeletal muscles, the STZ administration enhanced p65 phosphorylation while significantly decreasing AKT and PI3K expression levels, which showed anomalies in insulin signalling, although naringenin restored this. Fibroblast growth factor 21 (FGF21), a crucial regulator of glucose metabolism, had its protein production decreased by STZ, although naringenin in the pancreas increased it. The trial involved gavage once a day with varying dosages of NG 25, 50, and 75 mg/kg [98]. In mice forced to develop type 1 diabetes by streptozotocin (STZ), NG decreased cardiac fibrosis and cardiomyocyte death. By preventing reactive oxygen species and pro-inflammatory cytokines, NG(Naringenin) successfully reduced cell death in H9C2 myocardial cells exposed to high glucose levels. In tests on animals and cells, it inhibits NF-kB and activates Nrf2 [99]. Key markers involved in the endoplasmic reticulum stress response include phosphorylated eukaryotic translation initiation factor 2 (p-eIF2), phosphorylated protein kinase RNA-like endoplasmic reticulum kinase (p-PERK), spliced X-box binding protein 1 (XBP1s), activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP) were among the ER stress marker proteins whose expression was downregulated by naringenin supplementation during hyperglycaemic renal damage *in vitro* and *in vivo*. ATF4 and CHOP nuclear translocation in diabetic kidneys and hyperglycaemic renal cells was inhibited [100]. Naringenin significantly reduced intracellular oxidative stress and human retinal endothelial cell (HREC) apoptosis brought on by high glucose, which may be related to naringenin-mediated guanosine triphosphate cyclohydrolase-1 (GTPCH1)/endothelial nitric oxide synthase (eNOS) upregulation [101].

3.4. Naringin

Chinese herbal remedies such as *Citrus aurantium* L. (C.A.), *Drynaria fortunei* (Kunze) J. Sm. (D.F.) and *Citrus medica* L. (CM) contain naringin (NR), a flavanone glycoside made from the flavanone naringenin and the disaccharide neohesperidose. It is also prevalent in citrus fruits and gives citrus juices a bitter flavour. Allodynia and hyperalgesia are features of STZ-induced diabetic neuropathy as a result of increased sensory response and lowered tolerance to painful stimuli [102]. Animals with long-term diabetes have sensitised neurons as a result of damage to motor and sensory fibres, which reduces the time it takes for the paw to stop moving. Naringin was supplemented at doses of 40 and 80 mg/kg for four weeks [103]. According to findings, hyperglycaemia causes haemoglobin to become glycated; that is, an increased level of advanced glycosylated end-products (AGEs), called HbA1c, has been associated with impaired neuronal function or slowed wound healing. Treatment with naringin to DN mice selectively decreased blood glucose and HbA1c levels. When rats are fed a diet rich in fat and cholesterol, naringin lowers hypercholesteremia, plasma LDL, and triglycerides, under-expressing gluconeogenesis enzymes and inhibiting HMG-CoA reductase, without changing HDL cholesterol levels by overexpressing AMPK [104]. Naringin shows its antioxidant potential by decreasing oxidative stress in diabetic rats, increasing SOD, GSH, and catalase activity, and simultaneously reducing ROS and lipid peroxidation [105]. MDA levels in DN rats were higher. The increased lipid peroxidation indicates an increase in oxidative stress, which was alleviated by medication therapy. Naringin's effectiveness in reducing inflammation is shown by the decrease in TNF-α and IL-6 production [106]. Rats with persistent hyperglycemia exhibit severe brain damage in multiple brain regions. The results of the present investigation imply that DM may benefit both in avoiding and treating brain damage. One of the main reasons for pancreatic cell death is the connection between cell death/apoptosis and oxidative stress [107].

3.5. Eriocitrin

Citrus fruits are rich in flavanones, particularly eriocitrin, having significant antioxidant, anticancer, and anti-allergic characteristics. Eriocitrin, in contrast to hesperidin and naringin, is more effective in reducing oxidative stress in chronic disorders brought on by excessive oxidative stress [108]. Rats were given the unprocessed lemon juice formulations, which significantly affected diabetes and liver damage. In STZ-induced diabetic rats, eriocitrin (0.2%) exposure decreased oxidative stress and a reduction in the levels of thiobarbituric acid was observed in their blood serum, kidney and liver tissues. The benefits of eriocitrin include lowering blood sugar levels, glycemic index and inflammation throughout the body and increasing GLP-1 [109]. In rats receiving an HFD or a high-cholesterol diet (HCD), Eriocitrin (0.35%) lowers the levels of triglycerides, total cholesterol, VLDL and LDL and phospholipids in the blood of rats, but there is no change in the levels of HDL. When compared to untreated animals, there is no appreciable increase in the excretion of bile acids from the faeces, nor was there any indication that the mRNA levels for LDL receptors in liver cells had increased [110]. Eriocitrin improved dyslipidemia and decreased lipid levels in hepatocytes. Numerous transcriptional factors connected to mitochondrial biogenesis, including cytochrome c oxidase subunit 4, NRF1 and MTF, were shown to have higher mRNA levels by DNA microarray analysis. Eriocitrin has increased overall mtDNA content as well as mitochondrial size. As an outcome, ATP production in zebrafish and HepG2 cells was increased. It stimulates the transcription of mRNAs involved in mitochondrial biogenesis. Eriocitrin was administered orally at a dose of 32 mg/kg/day for 28 days [111]. Through its antioxidant activity, eriocitrin inhibits increases in lipid peroxidation and the glutathione disulfide/glutathione (GSSG/GSH) ratio. It also suppresses the expression of MuRF-1 (an E3 ubiquitin ligase involved in protein ubiquitylation) and atrogin-1 [112]. In RAW264.7 cells and a mouse model, the flavonoid eriocitrin and the polyphenol resveratrol have demonstrated strong anti-inflammatory effects against ear edema. These effects target inflammatory responses mediated by lipopolysaccharide (LPS), including the expression of IL-1β, nitric oxide (NO), TNF-α, and NF-κB. Additionally, the combination of these two drugs has a potent inhibitory effect on the (MAPK), AKT, and STAT3 signalling cascades [113].

3.6. Didymin

Didymin is an oral bioactive citrus flavonoid-O-glycoside found in various citrus fruits, including oranges, lemons, grapefruits, and mandarins. It has a strong anticancer ability while possessing a strong antioxidant potential [114]. This flavanone functions to prevent high-glucose-induced death of human umbilical vein endothelial cells by modulating oxidative stress pathways that generate reactive oxygen species (ROS) and activate Erk1/2. It upregulates the anti-apoptotic protein Bcl-2 and downregulates caspase-3. Additionally, it inhibits monocyte adhesion to endothelial cells, restores nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) levels, and reduces the expression of several inflammatory cytokines, including IL-1β, IL-2, IL-6, TNF-α, and IFN-γ. Collectively, these effects contribute to alleviating high glucose-induced endothelial dysfunction [113]. Studies conducted *in vitro* revealed that didymin inhibited α-glucosidase, AGE formation, HRAR (human recombinant aldose reductase) and RLAR (rat lens aldose reductase) and improved insulin sensitivity. It decreased the expression of PTP1B (protein tyrosine phosphatase) and increased the phosphorylation of GSK3 β, Akt, IRS-1, and PI3K. These modifications restricted glucose production in the liver in insulin-intolerant HepG2 cells [115].

3.7. Abyssinones

Prenylated flavonoid (2S)-Abyssinone II is derived from the Chinese medicinal plant Broussonetia papyrifera and Erythrina abyssinica [116]. It is evaluated as a breast cancer chemopreventive and had 20-fold greater activity against human aromatase than the basic molecule. Inhibition of protein tyrosine phosphatase-1B (PTP1B) has been proposed as a therapeutic strategy for obesity and type 2 diabetes. Three novel isoprenylated flavonoids were isolated, including abyssinone, which inhibited PTP1B activity using bioassay-guided fractionation of an EtOAc-soluble extract of Erythrina mildbraedii's root bark utilising an *in vitro* PTP1B inhibitory test [117].

3.8. Poncirin

Poncirin is a naturally occurring flavanone glycoside that is prevalent in many citrus fruits. Its antidiabetic mechanism hasn't yet been studied, though. The capacity of concern to decrease the production of protein tyrosine phosphatase 1B (PTP1B), α-glucosidase, human recombinant aldose reductase (HRAR), rat lens aldose reductase (RLAR), and advanced glycation end products (AGE) was done. PTP1B expression was downregulated, and glucose absorption was enhanced in C2C12 skeletal muscle cells. By triggering the IRS-1/PI3K/Akt/GSK-3 signalling pathway, poncirin raised the amount of GLUT-4 expression. The development of fluorescent AGE, nonfluorescent CML (carboxymethyl-lysine), fructosamine, and β-cross amyloid structures in glucose-fructose-induced BSA (bovine serum albumin) glycation was also significantly suppressed by poncirin. It also significantly inhibited protein oxidation by decreasing protein carbonyl and a dose-dependent uptake of protein thiol. It has the potential for the treatment of diabetes and its associated problems. Poncirin (0.5–50 μM) during four distinct research weeks [118].

4. FLAVONES

4.1. Apigenin

The family Apiaceae genus Apium is named after the compound apigenin (4′,5,7-trihydroxyflavone). It may be found in large quantities in a variety of fruits and vegetables, including celery, parsley, oranges, and garlic, as well as in several herbs, including chamomile and snow lotus. It reduces oxidative stress, aberrant glycolipid metabolism, and IR. IR is lessened by apigenin's inhibition of tyrosine nitration of the insulin receptor kinase domain. Tyrosine nitration of intracellular β subunits of the insulin receptor) may result in reduced tyrosine phosphorylation, impairing insulin signal transmission in HFD mice [119]. MiRNAs (micro RNA), which are linked to IR and glucose balance, are regulated by apigenin. The apigenin-mediated suppression of the phosphorylation of transactivating response RNA-binding proteins (TRBP) is confirmed by *in vitro* research using Huh7 cells and *in vivo* investigations using miR103 transgenic mice [120]. In KK-Ay mice's L6 cells and insulin target organs, apigenin derived from Sophora davidii increases GLUT4 expression and activates AMPK phosphorylation [121]. Apigenin's inhibition of α-amylase contributes to the alleviation of T2DM symptoms. Additionally, oxidative stress plays a critical role in β-cell dysfunction, impaired glucose tolerance, and IR. In RINm5F pancreatic cells and diabetic rats, apigenin pre-treatment increases the expression of antioxidant enzymes such as (SOD), (CAT), and (GSH-Px). API was given for seven weeks at intraperitoneal dosages of 10, 20, and 40 mg/kg [122]. Human blood plasma proteins were *in vitro* treated with apigenin to lower the amounts of AGEs and decrease oxidative stress [123]. The Nrf2-binding site is occupied by apigenin, which facilitates Nrf2's nuclear translocation and enhances its anti-oxidant activity by preventing Keap1(Kelch-like ECH-associated protein 1), an inhibitor of Nrf2 from binding to Nrf2 [124]. Apigenin substantially impairs the ability of mitogen-activated protein kinase activation (MAPK) to suppress NF-κB-TNFα-axis-mediated inflammation and apoptosis (increased Bcl-2 expression and reduced Bax and caspase-3) in diabetic rats [125].

4.2. Luteolin

Luteolin (LUT), a flavone belonging to the flavone group of flavonoids, is a 3',4',5,7-tetrahydroxy flavone. Luteolin is abundant in apple peels, cabbage, celery, artichokes, peppers, onion, and carrots. In plants, it is mostly found in its glycosylated form. In diabetic rats, three weeks of LUT supplementation dramatically reduced hyperglycaemia, HbA1c, hyperlipidaemia, and inflammation, thus increasing the activity of antioxidant enzymes. Male rats with alloxan-induced diabetes were given oral extracts of *M. cymbalaria*'s skin and seeds (250 and 500 mg/kg) for 28 days [126]. Oral treatment of LUT dramatically slowed the weight loss, bringing the rats back to a weight that was close to normal [127]. In diabetic animals, LUT can decrease IR. Histological analysis revealed cellular shrinkage, necrosis, and damaged cell populations in diabetic groups; however, these abnormalities were notably reversed following luteolin (LUT) administration, supporting its therapeutic potential [128]. Lessened dyslipidaemia, inhibition of lipid production, and further improvement of diabetes may be brought on by the decreased lipid action observed in its therapy [129]. Through the prevention of DM-related protein breakdown, LUT can lessen renal impairment in diabetic complications. In diabetic groups, there was evidence of decreased SOD, CAT, and GSH activity; however, following its therapy, there was evidence of a decrease in TNF-α and IL-6 levels. The current study shows a good antidiabetic impact and is extremely comparable to the standard glibenclamide [130].

4.3. Tangeretin

Tangeretin (TAG) is a pentamethoxyflavone. The rinds of citrus fruits like mandarin oranges are rich in tangeretin. In rats with STZ-induced diabetes, tangeretin oral treatment boosts G6PD activity. An increase in hepatic glycogen content by tangeretin oral administration in the diabetic rats' liver after STZ induction indicates that it can alter the activity of the enzyme glycogen synthase to reduce blood sugar levels. When LDH is elevated, it interferes with pancreatic cells' normal ability to secrete insulin and decreases glucose-stimulated insulin production in diabetic experimental mice and was brought back to normal after oral tangeretin treatment. Diabetic rats were supplemented with Tangeretin was supplemented (100 mg/kg body weight) orally for 30 days [131]. In mouse musculature and C2C12 myotubes, tangeretin boosted AMPK pathway activity, which led to a decrease in obesity-induced glucose intolerance and an increase in glucose absorption [132]. It mediates insulin signalling pathways that include AKT1/2, PKA (protein kinase A) and PI3K (phosphatidyl inositol three kinases), in target tissues. It boosted the 3T3-F442A mouse adipocytes' ability to absorb glucose. By activating crucial downstream pathways in the insulin signalling system, such as the levels of p-GSK3b(Ser9) (Glycogen synthase kinase-3), p-AKT (Thr-473) and blocking the MAPK-ERK1/2 pathway, tangeretin (50 mg/kg) significantly

increased glucose homeostasis and hepatic insulin sensitivity is a potential insulin action enhancer [133]. It alleviates IR because it stimulates the production of an insulin-sensitizing factor adiponectin, while simultaneously inhibiting IR factor that is by the release of MCP-1(monocyte chemoattractant protein 1) in 3T3-L1 adipocytes [134]. In human RPE (retinal pigment epithelium) cells, the production of cytokines like IL-6, IL-1, TGF-1 and VEGF, which are elevated to excessive levels under high glucose environments, was significantly reduced by tangeretin [135]. Treatment with different doses of tangeretin significantly decreased ROS levels, proteinuria and urea, eventually improving structures and tasks associated with the kidneys. It lessens inflammatory cell infiltration and inflammatory mediators by altering TNF-α/NF-κB signalling. For 30 days, diabetic rats were administered oral tangeretin (100 mg/kg b.wt/day) to prevent alterations in their heart weight and body weight. Lactate dehydrogenase (LDH), creatine phosphokinase (CPK), Aspartate aminotransferase (AST), and other cardiac marker enzymes, as well as inflammatory cytokines like TNF-α and IL-6 in the plasma and cardiac tissues, were decreased as a result of this treatment. It boosts the ATPases that are membrane-bound in action by lowering oxidative stress inside the cells, cardiac indicators and proinflammatory cytokine levels in the blood, as well as by improving the lipid levels in the rats' hearts after diabetes brought on by STZ [136]. Treatment with tangeretin decreased TAG (triglycerides) synthesis, DAG (diacylglycerol) acyltransferase activity, apoB (apolipoprotein B) secretion and activation of the PPAR (peroxisome proliferator-activated receptor) in Hep G2 cells (a cell line for hepatocellular carcinoma) [137]. Consistently expressing human SGLT1 (Sodium/glucose cotransporter 1) in the Chinese Hamster Ovary cells (CHO cell line), an epithelial-like cell line. Tangeretin inhibits SGLT1, which can delay apoptosis and delay the formation of diabetic cardiomyopathy [138].

4.4. Chrysin

Honey, fruits, bee pollen, propolis, bee pollen, and medicinal plants, including *Passiflora caerulea* L. and *Tilia tomentosa,* all contain large amounts of 5,7-diacetyl chrysin. Diacetylchrysin was administered orally to *db/db* animals to reduce the activation of vascular endothelial growth factor (VEGF) and VEGF receptor 2, which leads to the diabetes-related progression of illness retinal neovascularization [139]. The research supported chrysin's beneficial effects on obesity, IR, kidney damage, renal function, lipid buildup, inflammation, and oxidative stress, all of which are strongly associated with the beginning or advancement of diabetic nephropathy (DN). It enhances DN by controlling AMPK-mediated lipid metabolism [140]. By reducing hyperglycemia, exhibiting anti-oxidant, anti-apoptotic impact and actions that reduce inflammation, triggering the NGF (nerve growth factor)/p-AKT/GSK-3β pathway, CHY(Chrysin)-NanoVesicles ameliorates STZ-induced DPN (diabetic peripheral nephropathy) behavioural and histological abnormalities [140]. In STZ-induced rats, it causes a decrease in glucose, TC, LDL-C, MDA, and TG. While increase in SOD, CAT, HDL-C, total protein, and GST [141]. Chrysin at a dose of 20, 40,80mg/kg/day was administered [142]. Chrysin reduced the expression of protein collagen-IV in tissue from the kidneys and improved renal disease [12]. In rats with diabetes, it lowered the oxidation of lipids and blood sugar levels, and raised insulin concentration [140].

4.5. Wogonin

Wogonin (5, 7-dihydroxy-8-methoxy flavone) is a major flavonoid extracted from the root of *Scutellaria baicalensis* Gerogi (*Scutellariae radix*). Wogonin enhances the expression of PPARα and adiponectin through AMPK activation, thereby exerting beneficial effects on glucose and lipid metabolism. It does not produce adverse effects such as weight gain or fatty liver; therefore, it shows promise as a potential treatment for type 2 diabetes [143]. In the tubulointerstitium of diabetic mice, wogonin reduced urine albumin and histological damage. It controls inflammation and autophagy in the PI3K/Akt/NF-κB signalling pathway-mediated reduction of tubulointerstitial fibrosis and renal tubular cell damage therefore, effective treatment for DN's tubular epithelial damage since it specifically targets PI3K. For 16 weeks, wogonin (10, 20, and 40 mg/kg) was administered intragastrically [144]. In streptozotocin (STZ)-induced diabetic mice, oral administration of Wogonin (10, 20, and 40 mg/kg) for 12 weeks resulted in increased activity of antioxidant enzymes such as SOD1/2 and catalase (CAT), along with elevated levels of other antioxidative defenses. This treatment led to a reduction in reactive oxygen species (ROS), malondialdehyde (MDA) production, and pro-inflammatory cytokines including TNF-α, PAI-1 (plasminogen activator inhibitor-1), IL-1β, and IL-6. Furthermore, Wogonin inhibited NF-κB signaling. Collectively, these effects contributed to the attenuation of hyperglycemia-induced cardiomyocyte damage by mitigating oxidative stress and inflammation [145]. By blocking the NF-κB and TGF-β1/Smad3(Mothers against decapentaplegic homolog 1) signalling pathways, wogonin may reduce kidney fibrosis and inflammation in diabetic nephropathy [146].

4.6. Diosmin

Scrophularia nodosa L. was the source of the first discovery of a naturally occurring flavonoid glycoside in 1925. The flavanone glycoside hesperidin derived from several plant sources may be dehydrogenated to isolate it. Glycemic control improved by taking diosmin orally for 45 days in male albino Wistar breed rats who were administered streptozotocin-nicotinamide (STZ-NA) to induce diabetes. Oral Diosmin (100 mg/kg b.w.) supplementation reduced glycosylated haemoglobin while increasing haemoglobin and plasma insulin. Additionally, reduces liver gluconeogenesis enzymes and enhances hexokinase. The body weight increased as well. In type-2 diabetes, glycoprotein profiles are corrected by diosmin. Glycoproteins accumulate when glucose is used by insulin-independent mechanisms in diabetics. Plasma glycoprotein levels substantially rose in diabetic rats induced with STZ-NA. Fucose, hexosamine and hexose levels were considerably higher, while sialic acid concentrations were noticeably lower in the liver and kidneys of diabetic rats. For 45 days, oral doses of diosmin are given at 25, 50, and 100 mg/kg b.w. [147]. The adverse effects of hyperglycemia-induced oxidative stress encompass the accumulation of polyols and advanced glycation end products, as well as diminished (Na^+/K^+)-ATPase activity and endothelial function.

The oxidative stress-induced death of neurons is known as apoptosis. High-fat diet and streptozotocin were used to cause type-2 diabetes in male Sprague-Dawley rats to examine its impact on diabetic neuropathy. Early diabetic neuropathy was prevented in rats after four weeks of supplementation with diosmin (50 and 100 mg/kg, p.o.). By restoring the NO, SOD and GSH activity that had been altered, it decreased oxidative stress [148, 149]. In Wistar mice given alloxan to cause diabetes, diosmin therapy significantly restored NF-κB to normal levels. Its therapy decreased glial cell activation and decreased cytokine production, including IL-1 and IL-33/St2 [150].

4.7. Baicalein

Scutellaria baicalensis, a perennial herb in Labiatae, uses its roots as medicine and mainly contains flavonoids, volatile oil, trace elements, *etc*. Baicalein has been demonstrated to be able to neutralise free radicals [151], activate protein kinase C and, inhibit α-glucosidase activity [151], protect β cells [152], among other things, contributing to the lowering of blood sugar and fat levels as well as the suppression of inflammatory responses. Baicalein can prevent apoptosis and decrease ROS generation [153]. Guo Yangyan discovered that baicalein may simultaneously block the Kv channel in pancreatic islets β cells, lessen intracellular calcium levels and inflammatory damage to INS-1(mammalian rat cell line) cells, and ultimately boost insulin production [154]. Baicalin, which is anticipated to be employed as a novel anti-hyperglycemia medication, can activate the insulin receptor substrate, AMPK, PI3K/Akt, and MAPK/ERK signal cascades [155]. The suppression of TNF-α signalling and augmentation of insulin signalling by baicalin may contribute to its potential to ameliorate IR [156]. Baicalin can lessen IR in the liver by inhibiting the production of p-p38 MAPK, PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) and p-CREB (cAMP response element-binding protein) in the p38-MAPK/PGC-1 pathway. Baicalin is administered once daily, intraperitoneally, for 21 days at a dose of 50 mg/kg of (i.p.) [157]. Baicalein improves IR by inhibiting free fatty acids, TNF-α, and inflammatory factors (IL-1β, IL-6, *etc.*) [158]. The progression of renal fibrosis is slowed concurrently with the inhibition of the p38MAPK inflammatory signal transduction system and its downstream signal molecule NF-κB [159].

4.8. Rhoifolin

A flavone glycoside called rhoifolin may be extracted from *Rhus succedanea* and *Citrus grandis* (L.) *Osbeck (red wendun)* leaves. This species's leaves and its essential oil are used as a culinary flavouring, and the dried leaves may be brewed with water as a drink [160]. Used as a herbal treatment to encourage blood flow and eliminate blood stasis in disordered body conditions [161]. Red wendun is a traditional Chinese anti-diabetic drug because of these factors. It increases adiponectin production, tyrosine phosphorylation of the insulin receptor β, and GLUT4 translocation; they are advantageous for diabetes complications. In mice exposed to whole-body radiation, it protects against radiation-induced reductions in blood platelets and cardiac biochemical abnormalities. It has several biological effects, such as anti-inflammatory [162], hepatoprotective [163], antioxidant, and anticancer potential [164].

4.9. Sudachitin

Sudachitin is a polymethoxylated flavone that was first discovered in the peel of the Citrus sudachi horticultural fruit. Its chemical name is 5,7,4′-trihydroxy-6,8,3′-trimethoxyflavone. Sudachitin has often been found in citrus fruits, including bitter oranges and mandarin oranges. C57BL/6J mice and diabetic db/db mice fed a regular diet were used in a high-fat diet (HFD) experiment to study obesity. The effects of sudachitin on energy metabolism, as well as lipid and glucose regulation, showed a reduction in body weight in HFD-fed mice, even without dietary modifications. Sudachitin administered at a dose of 5 mg/kg orally every day for 12 weeks. Supplementation reduced hyperinsulinemia and hyperglycemia, increased plasma adiponectin levels, decreased visceral fat accumulation, improved insulin sensitivity and glucose tolerance, and normalized plasma leptin levels. Sudachitin regulates metabolism-related genes by upregulating uncoupling proteins 1 and 3 (UCP1 and UCP3) and glucose transporter 4 (GLUT4) in the liver and white adipose tissue. According to *in vitro* studies, it influences mitochondrial biogenesis by activating key signaling pathways in myocytes and upregulating genes such as mitochondrial transcription factor A (mtTFA), nuclear respiratory factor 1 (NRF1), and nuclear respiratory factor 2 (NRF2). This leads to an increase in both the quantity and functionality of mitochondria. Additionally, it positively regulates SIRT1 and PGC-1α expression in skeletal muscle, contributing to the management of obesity, diabetes, and related metabolic disorders [165].

4.10. Tricin

Whole cereal grains such as oats, barley, rice, and wheat are dietary sources of Tricin (3',5'-dimethoxyflavone). Tricin is also found in grass-derived foods like sugarcane juice and barley leaf powders. Additionally, small amounts of tricin are preserved in bran components, including the aleurone, embryo, pericarp, and testa. Due to the presence of genes required for tricin biosynthesis, this compound is commonly found in the vegetative tissues of grasses but is absent from the cereal endosperm [166]. To investigate the role of Sestrin2 in diabetic retinopathy (DR) and evaluate the effects of tricin, Western blot and immunofluorescence assays were conducted to assess the expression of heme oxygenase-1 (HO-1), platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31), Sestrin2, nuclear factor erythroid 2–related factor 2 (Nrf2), and vascular endothelial growth factor receptor 2 (VEGFR2) in retinal tissues and ARPE-19 cells. In the retinal tissue and ARPE-19 cells of the model group, Sestrin2 expression was downregulated, along with decreased levels of Nrf2 and HO-1. Conversely, levels of malondialdehyde (MDA), reactive oxygen species (ROS), CD31 (cluster of differentiation 31), and VEGFR2 were elevated. Tricin was administered orally at doses of 75, 100, and 150 mg/kg once daily for one month [167].

4.11. Sinensetin

Orthosiphon stamineus contains sinensetin, also known as 3',4',5,6,7-pentametoksiflavon, and is colourless. Nearly 40% of diabetic patients develop diabetic nephropathy (DN), which can lead to renal failure due to impaired autophagy and increased oxidative stress. Sinensetin (SIN) exhibits strong antioxidant properties and positively affects high-glucose (HG)-treated MPC5 cells, a podocyte cell line, by enhancing cell survival and autophagy. For *in vivo* studies, DN mouse models were established using a 60% high-fat diet combined with streptozotocin (40 mg/kg). SIN was administered intraperitoneally at doses of 10, 20, and 40 mg/kg daily for eight weeks. SIN protected MPC5 cells from HG-induced damage by promoting autophagy and improved renal function in DN mice, suggesting its potential for therapeutic development [168].

5. ISOFLAVONES

5.1. Genistein

The Asian population consumes a lot of genistein, a polyphenolic isoflavone molecule that is prevalent in soy or soy-based goods. It exhibits potential antioxidant and anti-diabetic properties, decreases β-cell apoptosis, promotes β-cell proliferation, normalises the gut flora and prevents the generation of hepatic glucose. Studies on both humans and animals have noted this isoflavone's positive benefits on metabolic syndrome, diabetes, cardiovascular disease, osteoporosis, and cancer [169]. By lowering inflammatory infiltration, thickening the glomerular basement membrane, and preventing the growth of the mesangial matrix and podocyte autophagy in DN rats, genistein can lessen the histological damage to the kidneys. A multifunctional protein called Mfn2 (mitofusin 2) maintains the integrity of mitochondrial DNA and encourages mitochondrial fusion and transport. It has a significant function in the biogenesis and metabolism of diabetes. In diabetic nephropathy (DN) patients, a decline in Mfn2 protein levels has been associated with increased mitochondrial fission, as observed in a rat model of global cerebral ischemia [170]. Genistein, administered intravenously at a dose of 1 mg/kg five minutes prior to injury, was found to mitigate hippocampal damage by activating antioxidant pathways. It reduced mitochondrial reactive oxygen species (ROS) levels and enhanced cytochrome c release, which subsequently activated caspases. Additionally, genistein improved mitochondrial membrane potential and upregulated Mfn2 protein expression in rats [171]. Furthermore, genistein treatment led to the upregulation of NOX4 (NADPH oxidase 4), MAPK, p65, and p53, suggesting an inhibitory effect on the NF-κB/MAPK/p53 signaling pathway. This modulation contributed to a reduction in oxidative stress and inflammatory responses. In another study, genistein was administered for six weeks at daily doses of 30 and 50 mg/kg, further supporting its protective role [172].

5.2. Daidzein

Leguminous crops, particularly soybeans, possess the organically produced substance daidzein, 7-hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one. It increases glucose absorption in muscle cells and adipocytes by raising the GLUT4 to Na^+/K^+ ATPase ratio of L6 myotubes in the plasma membrane region and prevents the rise in blood glucose levels [173]. Oral administration of genistein to diabetic mice significantly reduced blood glucose levels and improved oral glucose tolerance. It markedly decreased hyperglycemia without affecting fasting blood sugar levels and had minimal influence on insulin secretion, thereby lowering the risk of hypoglycemia. It lowers triglycerides, LDL cholesterol, and total cholesterol while very slightly increasing HDL cholesterol levels [174]. DAI's (Daidzein) antioxidant action is a result of its ability to bind copper ions. The LDL particles tend to assemble and fuse when the Cu^{2+} stimulates lipoprotein oxidation in the blood. The antioxidant activity of Cu^{2+} chelation prevents the oxidative modification of LDL [175]. Interleukin-6, tumour necrosis factor and Interleukin-1β expression were all reduced by 100 M Daidzein. It also reduced lipopolysaccharide-induced reactive oxygen species production and increased superoxide dismutase activity through the upregulation of NFE2L2 expression and the downregulation of Kelch-like ECH-associated protein 1 [174].

5.3. Biochanin

An O-methylated isoflavone renowned for its lipid-lowering, anti-diabetic, anti-inflammatory and anti-cancer properties is 5,7-Dihydroxy-4,6-methoxyisoflavone, also known as biochanin A. It is present in a variety of plants, including *Lupinus termis*, *Trifolium pratense*, *Cicer arietinum*, and many other legume species. It has demonstrated an anti-diabetic action by turning on insulin signalling, increasing insulin sensitivity, lowering visfatin levels in type 1 diabetic animals' serum and protecting them from neuropathic pain. SIRT1 is activated by biochanin A in pancreatic tissue and other tissues [175]. Biochanin A was administered at doses of 10, 20, and 40 mg/kg for 28 days [176]. The glycolytic enzymes are improved, and the level of glucokinase activity is increased using glucose as fuel; thus, blood glucose levels drop [177, 178]. A considerable decrease in blood TC, LDL, TG and VLDL cholesterol, as well as a significant rise in HDL cholesterol, were seen after 42 days of BCA (Biochanin) therapy. It includes lowering SREBP-1gene expression, hence lowering fatty acid production in the liver [179]. The renal antioxidant capacity was reversed after BCA therapy, as seen by higher levels of GST, SOD and GSH in the kidneys of diabetic rats [179]. In kidneys with diabetes and HG-induced NRK-52E cells, BCA treatment increased Bcl-2 levels while reducing Bax and cleaving caspase-3 expression. Following BCA injection, NF-κB (p65) phosphorylation, IL-1β and TNF-α were significantly reduced, which reduced renal inflammation and damage to the kidneys. In this *in vitro* study, NRK-52E cells were cultured under high glucose (HG) conditions. Treatment with BCA reduced apoptotic cell death, suppressed NLRP3 inflammasome activation, and improved mitochondrial membrane potential [179].

6. ANTHOCYANINS

6.1. Cyanidin

Cyanidin-3-O-glucoside, a water-soluble anthocyanin, is one of the most widely distributed flavonoids in the plant kingdom. It is commonly found in a variety of fruits and veg-

etables, including wild blackberries, chokeberries, blueberries, strawberries, apples, oranges, red cabbage, asparagus, carrots, and cauliflower. This compound exhibits antihyperglycemic properties by inhibiting key digestive enzymes such as α-glucosidase, intestinal β-fructosidase, and pancreatic α-amylase. Through these mechanisms, it delays the absorption of disaccharides and helps regulate postprandial hyperglycemia [180]. It enhanced the viability of pancreatic β-cells, reduced mitochondrial reactive oxygen species (ROS) production, and prevented β-cell apoptosis. Additionally, it increased the levels of insulin-like growth factor II gene transcript and insulin protein in the rat insulinoma cell line (INS-1) because it controlled the expression of the pancreatic duodenal homeobox 1 gene. Following its treatment, lower blood glucose levels were seen in an animal model of diabetes [181]. It elevates BCL2, an anti-apoptotic protein, while pro-apoptotic proteins like BAX and apoptotic indicators like cleaved caspase-3 are considerably reduced. A bayberry fruit extract that is high in cyanidin-3-glucoside (C3G) (CRBFE) was administered twice a day, at a dose of 150 μg of C3G/10 g of body weight [182]. Extra blood sugar prevents AMPK from being phosphorylated and active, which disrupts its downstream signalling and worsens diabetes diseases by causing glycolysis and lipolysis. The quantity of free fatty acids (FFAs) and glycerol is decreased, and AMPK activity is increased when cultured 3T3-L1 adipocytes are exposed to hyperglycemia in the presence of cyanidin-3-O-glucoside [183]. It controls biological processes, including lipoprotein metabolism, energy homeostasis, and glucose metabolism, by increasing the gene expression of PPARs in human omental adipocytes [184]. According to a study conducted on diabetic mice given 0.2% of cyanidin-3-O-glucoside for 5 weeks, retinol-binding protein 4 expression decreased, attenuating hyperglycemia and improved insulin sensitivity. Additionally, it reduced the inflammatory adipocytokines TNF-α, IL-6 and monocyte chemotactic protein-1 and upregulated the glucose transporter 4 in the white adipose tissue [185].

6.2. Delphinidin

Maqui berries (*Aristotelia chilensis*), contain delphinidin anthocyanins that are particularly rich in glucoside and sambubioside derivatives. In rat duodenum, it has been shown to suppress SGLT1 activity, and in a healthy human, ingestion of 200 mg delphinol decreased postprandial blood glucose and increased insulin [186]. To study the dosage-associated (60, 120, and 180 mg) reduction of glucose absorption using just glucose for the OGTT test in a naturally delphinidin-rich maqui berry extract (Delphinol) to examine prediabetic patients. One of the primary anthocyanins in maqui berries, delphinidin 3-sambubioside 5-glucoside, has insulin-like actions in liver and muscle cells and, therefore, has anti-diabetic benefits [186]. It affects glucose metabolism by enhancing insulin sensitivity in target tissues, inhibiting intestinal glucose transporters and having an incretin-mediated effect on insulin secretion. As a result, delphinol has the potential to lower both blood glucose and insulin levels [186]. Delphinidin 100 mg/kg treatment in diabetic mice led to a decrease in albumin production rate and HbA1c glycation. At 8 weeks, diabetic mice were given 100 mg/kg liposomes filled with delphinidin chloride every day [187]. Delphinidin's anti-diabetic benefits result from its capacity to activate free fatty acid receptor 1 (FFAR1) or G-protein coupled receptor 40 (also known as GPCR40) activity in mouse jejunal tissue and human intestinal cell lines [187].

6.3. Pelargonidin

Berries, including blueberries, cranberries, and raspberries, are rich sources of pelargonidin, a flavonoid. Pelargonidin therapy lowers levels of oxidative stress and hyperglycemia [188]. On high-glucose/high-fat induced hepatocytes and *db/db* diabetic mice, the hyperglycemia-lowering impact of this bioactive compound produced from wild raspberries was examined; it increased glucose absorption. It promoted autophagy, while autophagy inhibitors prevented its hypoglycemic effects. It was discovered that there is a relation between Pelargonidin-induced autophagy and the Transcriptional Factor EB (master gene for lysosomal biogenesis), which performs a crucial role in controlling fundamental cellular processes, including lysosomal biogenesis and autophagy. An *in vivo* investigation revealed that its therapy improved glucose tolerance, insulin sensitivity, and autophagy activation. It improved the integrity of the intestinal barrier and modulated the composition of the gut microbiota, evidenced by an increased Bacteroidetes/Firmicutes ratio and a higher abundance of Prevotella. Therefore, it reduces hyperglycemia by triggering autophagy and altering gut flora, which is a nutritional treatment for T2D. Rats treated with pelletargonidin were given a single intraperitoneal injection of the flavonoid (3 mg/kg body weight) [189-192].

7. CHALCONES

7.1. Xanthohumol

Xanthohumol (XN), Prenylated chalconoid, also known as 3′-[3,3-dimethylallyl], -2′,4′,4-trihydroxy-6′-methoxychalcone is produced in the glandular trichomes of hop cones and is produced by *Humulus lupulus*' female inflorescences or hops. It has anticarcinogenic, anti-inflammatory, and antioxidant characteristics, and is found in citrus trees of the family Rutaceae. Both Keap1 cysteine alteration and XN-induced AMPK activation led to Nrf2 activation, which in turn boosted Nrf2 nuclear translocation, improved antioxidant protein production, and reduced oxidative stress, leading to rapid wound healing in STZ-induced diabetic rats [193]. Additionally, in DN mice, XN supplementation at a dose of 25 mg/kg, significantly reduced serum creatinine, blood urea nitrogen, urea protein, and the kidney weight/body weight ratio. Also, it declines in reactive oxygen species generation and the rise in superoxide dismutase and catalase activity in DN mice. This in DN mice showed a reduction in the mRNA levels of the Nrf2, Hmox1(heme oxygenase 1 gene), and Nqol [(NAD(P)H dehydrogenase quinone 1)] genes [194]. Through the Nrf2 signalling pathway, it protects the kidney by lowering oxidative stress. Also, a few data suggest that it inhibits diacylglycerol acyltransferase [195]. In male Sprague–Dawley rats, XN administered at 50 mg/kg/day for 4 weeks inhibited the phosphorylation of nuclear factor kappa-B (NF-κB) and protein kinase B (Akt), which are overactivated in the hippocampus of diabetic rats. This treatment resulted in lowered blood glucose levels and increased body weight, indicating that XN may be a potential therapeutic agent for diabetic encephalopathy [196].

7.2. Cardamonin

The chalcone cardamonin (2',4'-dihydroxy-6′-methoxychalcone) is one of the main elements of *Alpinia katsumadai* Hayata (Zingiberaceae), *C.operculatus*, *M.serrata*, *S. samarangense* and *S. campanulatum etc*. have hepatoprotective, cytoprotective, anti-inflammatory, antifungal, antibacterial, antituberculosis, antiviral, antispasmodic, antidiarrhoeal, antiapoptotic, antitumor, antimicrobial and antioxidant effect as well as low systemic toxicity [197]. The hypoglycemic and antioxidant properties of myotube cell lines were also demonstrated [198]. Type 2 diabetes is associated with a significant increase in hyperglycemia, gonadotropins, and insulin resistance, along with decreased serum insulin and testosterone levels. These alterations are linked to impaired activity of key androgenic enzymes in the testes and disruption of cellular redox balance. Administration of CARD at a dosage of 80 mg/kg for four weeks normalized all measured parameters, with improvements supported by epididymal sperm analysis. Notably, CARD inhibited cells exhibiting elevated autophagy markers and caspase-3 immunoreactivity, while upregulating the expression of glucose transporter-8 (GLUT-8) in the testes. CARD activity promoted the degradation of testicular Kelch-like ECH-associated protein-1 (Keap-1) in a p62-dependent manner, thereby preventing damage through the activation of Nrf2. This mechanism provides protection against testicular injury caused by diabetic stress. Oral gavage of CARD at 80 mg/kg for four weeks was shown to protect pancreatic β-cells from glucotoxicity-induced impairment of insulin production, contributing to its anti-diabetic and antihyperglycemic effects [199, 200]. Additionally, CARD enhanced glucose uptake and influenced adipocyte differentiation in 3T3-L1 cells [200]. Furthermore, it has been increasingly utilized as an effective oral glucosidase inhibitor [201, 202].

7.3. 8-prenylnaringenin

It is found in the Citrus genus of plants in the Rutaceae family. Prenylflavonoid 8-prenylnaringenin, or xanthohumol metabolite, is only present in small amounts in citrus fruits, such as oranges, lemons, grapefruits, and tangerines. A subclass of flavonoids known as prenylflavonoids is made up of secondary metabolites that are produced from 2-phenylchromen-4-one and have a prenyl group connected to the flavone nucleus. The expression of Galectin-3 (Gal3), a protein overexpressed during the diabetic state, was shown to be normalised in an animal model of type 2 diabetes mellitus (C57Bl/6 mice) induced by a high-fat diet (HFD). Additionally, 8-prenylnaringenin was found to be strongly associated with oxidative stress in the liver and kidneys of diabetic mice. It also increases the synthesis of nitric oxide (NO) and decreases the generation of inflammation, glycation end products (AGEs), and 3-nitrotyrosine, which are hallmarks of cell damage [201]. Tissue stiffness, elevated blood pressure, heart failure, and endothelial dysfunction have all been linked to elevated levels of AGEs in response to diabetic inflammation (Table **1**). Thus, this polyphenol could have therapeutic value in the fight against diabetes mellitus. The expression of Galectin-3 (Gal3), a protein over-expressed during the diabetic state, was shown to be normalised in an animal model of type 2 diabetes mellitus (C57Bl/6 mice) induced by a high-fat diet (HFD). Additionally, 8-prenylnaringenin was found to be strongly associated with oxidative stress in the liver and kidneys of diabetic mice [202, 203].

Table 1. The description of the main characteristics of 40 flavonoids for the management of diabetes mellitus using *in vitro* and *in vivo* studies.

Phytocompound Type	Compound Name	Mode of Action in Diabetes	Doses, Duration, Methodology and Experimental Model	References
Flavanol	Quercetin	Prevents enlargement of high-glucose-induced cells by inhibiting VEGF synthesis. Decreases intestinal α-glucosidase, pancreatic α-amylase, and glucose absorption. Reduces triglycerides, total cholesterol, LDL, and VLDL. Suppresses TGF-β1 and CTGF, improving diabetic nephropathy. Increases insulin secretion and repairs pancreatic islets. Restores damaged metabolite and microbiota in NAFLD. Reduces pro-inflammatory cytokine production.	For 30 days, quercetin at a dose of 25 mg/kg/day was administered intraperitoneally. *In vitro*, Rat, Mice	[46-50]
	Rutin	Shows anti-inflammatory, antioxidant, and neuroprotective effects. Improves lipid and glucose metabolism disorders in diabetic mice. Prevents STAT3 phosphorylation in the heart. Exhibits antidiabetic and antioxidant activities in streptozotocin-induced diabetic rats	For four weeks, take 100–200 mg of rutin per kilogram of body weight every day *in vitro*. Rat, Mice	[51-53]
	Kaempferol	Encourages insulin secretion Increases insulin, GLP-1, cAMP, Ca2+, GSH levels. Lowers blood glucose levels by increasing GCK and glycogen. Activates AMPK, blocks glycogenic enzymes and lowers glucose synthesis. Improves glucose absorption in skeletal muscle cells. Decreases inflammatory mediators, oxidative stress, and apoptosis.	For forty-five days, kaempferol (100 mg/kg BW) was taken orally. In Rat, Mice	[54-57]

(Table 1) Contd…

Phytocompound Type	Compound Name	Mode of Action in Diabetes	Doses, Duration, Methodology and Experimental Model	References
-	Isorhamnetin	Enhances insulin sensitivity by reducing mTOR activity. Decreases total cholesterol, LDL, and TGs. Activates AMPK, decreases oxidative stress and inflammation. Increases glucose absorption through the AMPK-GLUT4 pathway.	For three weeks, isorhamnetin was given orally by gastric gavage at varying levels (10 mg/kg to 40 mg/kg). *In vitro*, Rat, Mice	[58-62]
	Fisetin	Exhibits neurotrophic, anti-inflammatory, and anti-diabetic properties. Inhibits HRMECs migration and prevents diabetic retinopathy. Restores CDKN1B/P70S6K-mediated autophagy, reduces NLRP3 inflammasome. Shows kidney protective effects and improves insulin and neurotrophic factor levels	Over the course of eight weeks, mice were given oral fisetin (5, 10, or 20 mg/kg) every two days. *In vitro*, Mice, Rat	[63-66]
	Morin	Reduces oxidative stress, activates ERK-Nrf2 signalling cascades Activates antioxidant enzymes and protects against DNA damage. Inhibits inflammatory pathways, reduces pro-inflammatory cytokines. Shows neuroprotective and kidney-protective actions.	Oral administration of morin (30 mg/kg b.wt.) for seven days a week. *In vitro*, Rat, Mouse, Male Adult Sprague-Dawley rats	[66-74]
	Ellagic Acid(EA)	Exhibits antioxidant, anti-apoptotic and anti-inflammatory properties. Protects against liver damage, reduces hyperlipidemia and steatosis. Activates AMPK, inhibits SREBP1/2, activates PPARα. Enhances insulin release, hypoglycemic and hypolipidemic effects.	EA (50mg/kg) was administered orally daily for 12 weeks to rats	[75-79]
	Catechin	Stimulates LKB1 to activate AMPK and improves insulin sensitivity. Acts as an insulin-mimetic substance and promotes GLUT4 translocation. Prevents HFD-induced obesity and reduces oxidative stress and inflammation. Regulates insulin signal transduction and inhibits IR.	For six weeks, it was given at varying doses (5, 10, and 20 mg/kg b.w). Rat, Human, Mouse	[80-86]
-	Myricetin	Guard renal and pancreatic cells from oxidative damage in diabetes patients. Exhibits significant neuroprotective and antioxidant properties. Increased Na+, K+-Atpase activity. Decreased the production of advanced glycation end-products (ages) and reactive oxygen species (ROS). Decrease peripheral glucose levels in people with diabetes. Their FBG and blood lipid levels drastically decreased, but their SOD levels rose. In T2DM mice, myricetin reduced polyuria, weight loss, polydipsia, and polyphagia.	For two weeks, intraperitoneal injections of myricetin at several doses (0.5 mg/kg/day, 1.0 mg/kg/day, and 2.0 mg/kg/day) were administered. Rat, Human, Mouse	[87-89]

(Table 1) Contd…

Phytocompound Type	Compound Name	Mode of Action in Diabetes	Doses, Duration, Methodology and Experimental Model	References
Flavanones	Hesperidin	Increased SIRT1-Reduced IR. Protected against oxidative stress damage Improved mechanical and thermal sensitivity. Reduced oxidative stress and inflammation. Increased antioxidant enzymes. Increased SIRT1 expression-Reduced NOX4 expression.	For one month, 100 mg/kg of hesperidin was orally administered to diabetic rats (Sprague-Dawley)	[90-92]
	Hesperetin	Decreased glucose levels. Increased insulin and glucagon levels. Improved pancreatic enzyme activity. Reduced oxidative stress indicators - Improved lipid levels. Increased antioxidant gene expression. Suppressed inflammation - Improved renal function.	Oral gavage of hesperetin (50 and 150 mg/kg) once daily for six weeks. Diabetic rats	[93, 94]
	Neohesperidin	Improved liver function. Reduced hepatic steatosis. Decreased blood glucose, insulin, and HOMA-IR levels. Improved IR. Reduced inflammation and oxidative stress. Regulated lipid metabolism.	Neohesperidin was delivered intragastrially at a dose of 50 mg/kg daily for 12 weeks. High-fat diet mice	[95, 96]
	Naringenin	Improved glucose homeostasis. Reduced oxidative stress markers. Suppressed apoptosis in pancreatic β-cells. Improved insulin signalling. Reduced cardiac fibrosis and cardiomyocyte death. Inhibited NF-kB and activated Nrf2.	The trial involved gavage once a day with varying dosages of NG 25, 50, and 75 mg/kg. Mice exposed to STZ (type 1 diabetes)	[97-101]
	Naringin	Decreased blood glucose and HbA1c levels. Improved lipid profile. Reduced oxidative stress and inflammation. Protected against brain damage.	40 and 80 mg/kg of naringin for four weeks STZ-induced diabetic neuropathy (DN) mice	[102-107]
	Eriocitrin	Lowered blood sugar levels. Decreased oxidative stress. Improved lipid profile. Increased GLP-1. Reduced inflammation. Anticancer activity.	Eriocitrin (32 mg/kg/day for 28 days) administered orally. Streptozotocin-induced diabetic rats	[108-113]
	Didymin	Anticancer ability. Antioxidant potential. Inhibited α-glucosidase, AGE formation, HRAR, and RLAR. Improved insulin sensitivity. Reduced inflammation.	Human umbilical vein endothelial cells, HepG2 cells	[114-116]
	Abyssinones	Inhibition of PTP1B activity	Not specified	[117]
	Poncirin	Downregulated PTP1B expression. Enhanced glucose absorption. Increased GLUT-4 expression. Suppressed glycation and protein oxidation.	Poncirin (0.5–50 μM) during four distinct research weeks. C2C12 skeletal muscle cells, BSA glycation model	[118]

(Table 1) Contd…

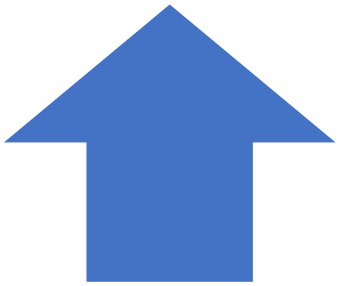
Phytocompound Type	Compound Name	Mode of Action in Diabetes	Doses, Duration, Methodology and Experimental Model	References
Flavone	Apigenin	Reduces oxidative stress, aberrant glycolipid metabolism, and IR Inhibits tyrosine nitration of insulin receptor kinase domain. Regulates miRNAs linked to IR Inhibits α-amylase. Enhances antioxidant enzyme expression. Modulates Nrf2 and MAPK pathways. Suppresses inflammation and apoptosis.	API for seven weeks at intraperitoneal dosages of 10, 20, and 40 mg/kg. HFD mice, KK-Ay mice, RINm5F pancreatic cells, diabetic rats, human blood plasma proteins, diabetic rats (multiple studies)	[119-125]
	Luteolin	Reduces hyperglycaemia, HbA1c, hyperlipidaemia, inflammation, and antioxidant enzyme activity. Improves IR Alleviates renal impairment. Shows anti-diabetic impact when compared to glibenclamide.	Male rats with alloxan-induced diabetes were given oral extracts of M. cymbalaria's skin and seeds (250 and 500 mg/kg) for a duration of 28 days. Diabetic rats (multiple studies)	[126-130]
Pentamethoxyflavone	Tangeretin	Boosts G6PD activity. Modulates AMPK pathway. Mediates insulin signaling. Reduces cytokine production. Improves kidney function. Decreases oxidative stress and inflammation.	Giving diabetic rats Tangeretin (100 mg/kg body weight) orally for 30 days STZ-induced diabetic rats, C2C12 myotubes, human RPE cells, and diabetic rats (multiple studies)	[131-138]
Flavone	Chrysin	Reduces retinal neovascularization. Controls AMPK-mediated lipid metabolism. Improves obesity, IR, kidney damage, lipid buildup, inflammation, and oxidative stress. Enhances renal disease.	Chrysin at a dose of 20, 40,80mg/kg/day was administered *db/db* animals, STZ-induced rats, and diabetic rats (multiple studies)	[12, 40. 139-142]
	Wogonin	Activates PPARα and adiponectin expression *via* AMPK. Reduces inflammation and autophagy. Inhibits NF-κB and TGF-β1/Smad3 signaling pathways.	For 16 weeks, wogonin (10, 20, and 40 mg/kg) was administered intragastrically. Diabetic mice, STZ diabetic mice (multiple studies)	[143-146]
Flavonoid Glycoside	Diosmin	Improves glycemic control. Reduces oxidative stress. Prevents diabetic neuropathy. Corrects glycoprotein profiles.	For 45 days, take oral doses of diosmin at 25, 50, and 100 mg/kg b.w. STZ-NA induced diabetic rats, diabetic rats, and alloxan-induced Wistar mice (multiple studies)	[147-150]
Flavone	Baicalein	Neutralizes free radicals. Activates insulin signaling cascades. Decreases inflammation. Slows renal fibrosis progression.	For 21 days in a row, administer 50 mg/kg of baicalin intraperitoneally (i.p.) once daily. *In vitro* studies, diabetic rats (multiple studies).	[153-159]
Flavone Glycoside	Rhoifolin	Increases adiponectin production. Enhances insulin sensitivity. Has anti-inflammatory, hepatoprotective, antioxidant, and anticancer potential.	Red wendun (Chinese anti-diabetic drug), *in vitro* studies.	[160-164]

(Table 1) Contd…

Phytocompound Type	Compound Name	Mode of Action in Diabetes	Doses, Duration, Methodology and Experimental Model	References
Polymethoxylated Flavone	Sudachitin	Decreases body weight, hyperinsulinemia, and hyperglycemia. Increases adiponectin levels. Improves insulin sensitivity and glucose tolerance. Upregulates UCP1 and UCP3.	5 mg/kg of sudachitin taken orally every day for 12 weeks. HFD mice, *in vitro* studies.	[165]
Flavone	Tricin	Studied for its role in diabetic retinopathy. It may impact Sestrin2 expression.	For four weeks, 75, 100, and 150 mg/kg of tricin was given orally once daily. Sprague-Dawley rats and a high glucose-induced retinal epithelial cell model.	[166, 167]
-	Sinensetin	Possesses excellent antioxidant capabilities. It shields MPC5 cells from harm due to HG by increasing cell autophagy activity and enhances the renal health of DN mice, so it can be used for therapeutic development.	Injections of SIN (10, 20, and 40 mg/kg) were administered intraperitoneally for eight weeks. Mouse and cell line studies.	[168]
Isoflavones	Genistein	Antioxidant properties. Anti-diabetic effects. Decreases β-cell apoptosis. Promotes β-cell proliferation. Normalizes gut flora. Prevents hepatic glucose generation.	Gavage genistein for six weeks at doses of 30 and 50 mg/kg/d. Humans, Animals	[169-172]
	Daidzein	Increases glucose absorption in muscle cells and adipocytes. Lowers blood glucose levels Decreases triglycerides, LDL cholesterol, and total cholesterol. Increases HDL cholesterol levels	Daidzein at 100 μM on hepatocyte damage Diabetic Mice.	[173, 174]
	Biochanin	Lipid-lowering, anti-diabetic, anti-inflammatory, and anti-cancer properties. Activates insulin signalling. Increases insulin sensitivity. Lowers visfatin levels. Protects against neuropathic pain.	28 days of treatment with 10, 20, and 40 mg/kg of biochanin A. Type 2 Diabetic Animals, Diabetic Rats, Cells.	[175-179]
Anthocyanins	Cyanidin	Inhibits α-glucosidase, intestinal β-fructosidase, and pancreatic α-amylase. Delays absorption of disaccharides. Increases β-cell viability. Reduces ROS generation. Regulates postprandial hyperglycemia.	Bayberry fruit extract that is high in cyanidin-3-glucoside (C3G) (CRBFE) Twice a day, 150 μg of C3G/10 g of body weight Animal Model of Diabetes	[180-185]
	Delphinidin	Suppresses SGLT1 activity in rat duodenum. Has insulin-like actions in liver and muscle cells. Enhances insulin sensitivity. Inhibits intestinal glucose transporters. Lowers blood glucose and insulin levels.	At 8 weeks, diabetic mice were given 100 mg/kg liposomes filled with delphinidin chloride every day. Human, Diabetic Mice.	[186, 187]
	Pelargonidin	Lowers oxidative stress and hyperglycemia. Improves glucose tolerance and insulin sensitivity. Triggers autophagy. Alters gut flora.	Rats treated with pelletargonidin were given a single intraperitoneal injection of the flavonoid (3 mg/kg bodyweight). Hepatocytes, *db/db* Diabetic Mice	[188-192]

(Table 1) Contd…

Phytocompound Type	Compound Name	Mode of Action in Diabetes	Doses, Duration, Methodology and Experimental Model	References
Chalcones	Xanthohumol	Anticarcinogenic, anti-inflammatory, and antioxidant characteristics. Activates Nrf2 pathway. Reduces oxidative stress. Improves wound healing. Lowers serum creatinine and blood urea nitrogen in DN mice.	Mice received a daily intraperitoneal injection of xanthohumol (25 mg/kg) for 20 weeks. STZ-induced Diabetic Rats, DN Mice, and Diabetic Rats [198].	[193-196]
	Cardamonin	Hypoglycemic and antioxidant properties. Improves myotube cell lines. Normalizes testosterone and gonadotropins levels in diabetic rats. Inhibits androgenic enzymes in testicles. Prevents testicular injury by diabetes stress.	Oral gavage of CARD for four weeks at a dosage of 80 mg/kg. Type 2 Diabetic Rats, Myotube Cell Lines	[197-201]
	8-Prenylnaringenin	Anti-diabetic effect. Decrease oxidative stress in the liver and kidneys. Decreases inflammation, nitric oxide (NO), and 3-nitrotyrosine. Increases Gal 3 protein abundance in skeletal muscle.	Type 2 Diabetic Mice C57B1/6 Model	[201-203]



FLAVONOID CURE DIABETES BY INCREASING-

AMPK, ARE AKT, Adiponectin, Anti-oxidant Enzymes, ATP Synthase, Anti-apoptotic Proteins, BDNF, BAX, BCL2, Beta Cell Proliferation, cAMP, CAT, CDKN1B, CPT1, CYT C OXIDASE, ERK, eNOS, Glycolysis, Gamma Glutamyl Cysteine Synthetase, GSGPx, GSH, GLP1, Glucose Absorption, GLUT, GSIS, GDNF, Glucagon, GLO1, Glucose Tolerance, HDL-C, HK, HO1, Hb, Hypoglycemia, Insulin Secretion, INSR, IRS1, Insulin Sensitivity, IGF, KEAP1, LKB1, Lipid Synthesis, MAPK, Mn SOD, MitoM.P., MTF, Mito. Size and biogenesis, Mfn2, Nrf2, NGF, NO, Na+K+ATPase, NRF1, NGF, NOX4, PPAR-gamma, PI3K, PKC, PGC1, PECAM1,Repaired pancreatic renal health, SOD, SIRT1, SESTRIN2, TFAM, Testosterone, UCP and wound healing.

FLAVONOIDS CURE DIABETES BY DECREASING-

Alpha-Glucosidase, ARE, AGE, Alpha –amylase, AST, ALT, ALP, ACC, ASK1, ASC, Apoptotic Protein, ATF4, Atrogen, Blood Glucose, Beta Cell Apoptosis, BAX, Blood Urea, Nitrogen, Cvd Risk, Caspase, COX2, CHOL, Cytokine, CTGF, C-peptide, CML, CBK, Cardiac Markers, CA+2, CYT-C, Cholesterol, DPP, DGAT1, Dislipidemia, ERK, Er Stress, FBG, FAK, FGF21, Fructosamine, Gluconeogenesis Enzyme, Glycemic Index, Gsk3-beta, Glial Cells, Galectin3, Glial Cells, HbA1c, HOMA-IR, HMG-CoR, HG, HRAR, Hyperglycemia, Hyperinsulenimia, Hyper Lipidemia, Inflammation, IKK-BETA, Insulin Resistance, iNOS, Interleukin, ICAM1, JNK, LDL, Lipase, LOX, LPS, Leptin, Lipid Peroxidation, MAPK, mTOR, MDA, MuRF1, miRNA, MCP1,mROS, NLRP3, NFKB, NQO1, NOX4, 3NT, Oxidative Stress, Polyurea, Polyphagia, Polydipsia, PGC1-alpha, pCREB,PKB, Collagen,ROS, RAGE, RLAR, STAT3, SRC, SREBP1, SGLT1, SMAD3, Creatinine, SOCS, TG, TC, TGF-1beta, TBARS, TNF-alpha, TRBP, Urine, Albumine, VEGF, VLDL, visceral fat and visfatin.

Fig. (2). Flavonoids cure diabetes by increasing and decreasing different metabolites. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

8. FUTURE DIRECTIONS TOWARDS DRUG DISCOVERY

The utilization of bioactive compounds derived from plant diet sources is an intriguing therapeutic approach, yet it necessitates a thorough understanding of their effects gleaned from diverse experimental models when applied to the treatment of different diabetes diseases. The 40 flavonoids from various plant sources that were examined in this review have a variety of effects and associated molecular pathways that can be used to treat and manage diabetes mellitus and its consequences. These citrus flavonoids, mostly through raising endogenous antioxidants like SOD, CAT, and GPx and lowering ROS concentrations, mitigated tissue damage caused by extended exposure to high glucose levels. Citrus flavonoids regulate important metabolic signalling markers by upregulating the expression of IRS-1, PI3K, GSK3β, PPARγ, and Akt. Citrus flavonoids are also implicated in modulating the expression of the NF-κB, IL1β, IL-2, IL-6, cytokines TNFα and INFη as well as activating and enhancing the production of GLUT4 and IR. Through increased glucose absorption in peripheral tissues, all of these activities lead to the attenuation of inflammatory mediators associated with the etiology and progression of diabetic vascular problems. Additionally, this

inhibits the growth of cells produced by excessive glucose. The existing understanding is that flavonoids may mitigate cellular oxidative stress and inflammatory markers such as IL-1β, IL-6, tumor necrosis factor TNF-α and IR to enhance the etiology of diabetes and its consequences.

CONCLUSION

Citrus species are rich natural sources of flavonoids and hold significant potential as a foundation for future therapies aimed at managing and preventing diabetes and its associated complications.

To the best of our knowledge, this is the first review that outlines how the main citrus flavonoids affect the metabolic indices and essential physiological pathways associated with diabetes. This can facilitate the development of new treatments for diabetes and enhance our understanding of the biological profiles of the patients undergoing therapy. Moreover, further research should be conducted on less complicated and expensive ways to separate pure molecules so that thorough investigations into each possible antidiabetic flavonoid can be carried out. Instead of relying too heavily on artificial antidiabetic medications, flavonoids should be highlighted as safer, innovative antidiabetic medicines, as shown in Fig. (**2**). It is important to compile and disseminate accurate scientific data on citrus flavonoids as broadly as possible through publications and seminars. Conducting human clinical trials is the only definitive way to determine the effectiveness of citrus flavonoids in humans. Therefore, to elucidate the mechanisms of action across various pathways and to perform molecular gene expression studies involving T2DM-related genes, it is essential to conduct human clinical trials utilizing advanced molecular techniques based on the current knowledge of these compounds.

AUTHORS' CONTRIBUTIONS

R.C., S.J. and S.C. contributed to literature review and drafting the manuscript; S.R.S. contributed in data curation, critical revision of the scientific content, and formatting; V.P.V. contributed in providing methodological input and assisted in editing and refining the manuscript structure; S.J. supervised the project, contributed to the conceptual framework, and provided critical revisions and final approval of the manuscript; S.C. coordinated the manuscript development, ensured overall quality control, and contributed to final proofreading and editing; All authors read and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

DM	=	Diabetes Mellitus
IDF	=	International Diabetic Federation's
WHO	=	World Health Organization
T1DM	=	Type 1 Diabetes Mellitus
T2DM	=	Type 2 Diabetes Mellitus
IR	=	Insulin Resistance
TZDs	=	Thiazolidinediones
AMPK	=	AMP-activated Protein Kinase
ETC	=	Electron Transport Chain
PTP1B	=	Protein Tyrosine Phosphatase 1B
DCM	=	Diabetic Cardiomyopathy
EGCG	=	Epigallocatechin Gallate
TNF-α	=	Tumor Necrosis Factor-alpha
FFAs	=	Free Fatty Acids
IRS-1	=	Receptor Substrate 1
PTP1B	=	Protein Tyrosine Phosphatase 1B
DN	=	Diabetic Nephropathy
SLC2	=	Solute Carrier Family 2
GLUT4	=	Glucose Transporter Type 4
TK	=	Tyrosine Kinase
GRB2	=	Growth Factor Receptor-Bound Protein 2

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus - Present and future perspectives. Nat Rev Endocrinol 2012; 8(4): 228-36. http://dx.doi.org/10.1038/nrendo.2011.183 PMID: 22064493

[2] Saeedi P, Petersohn I, Salpea P. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract 2019; 157: 107843. http://dx.doi.org/10.1016/j.diabres.2019.107843

[3] Das H, Naik B, Behera HS. Classification of Diabetes Mellitus Disease (DMD): A Data Mining (DM) approach. In: Pattnaik P, Rautaray S, Das H, Nayak J, Eds. Progress in Computing, Analytics and Networking Advances in Intelligent Systems and Computing. Singapore: Springer 2018; pp. 539-49. http://dx.doi.org/10.1007/978-981-10-7871-2_52

[4] Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatr Diabetes 2009; 10(Suppl. 12): 3-12. http://dx.doi.org/10.1111/j.1399-5448.2009.00568.x PMID: 19754613

[5] Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World J Diabetes 2015; 6(6): 850-67. http://dx.doi.org/10.4239/wjd.v6.i6.850 PMID: 26131326

[6] Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: A nested case-control analysis. Diabetes Care 2008; 31(11): 2086-91. http://dx.doi.org/10.2337/dc08-1171 PMID: 18782901

[7] Salehi B, Ata A, V Anil Kumar N, *et al.* Antidiabetic potential of medicinal plants and their active components. Biomolecules 2019; 9(10): 551.

http://dx.doi.org/10.3390/biom9100551 PMID: 31575072
[8] Yi X, Dong M, Guo N, *et al.* Flavonoids improve type 2 diabetes mellitus and its complications: A review. Front Nutr 2023; 10: 1192131.
http://dx.doi.org/10.3389/fnut.2023.1192131 PMID: 37324738
[9] Zhang H, Ben Y, Han Y, Zhang Y, Li Y, Chen X. Phthalate exposure and risk of diabetes mellitus: Implications from a systematic review and meta-analysis. Environ Res 2022; 204(Pt B): 112109-22.
http://dx.doi.org/10.1016/j.envres.2021.112109 PMID: 34562484
[10] Sekhon-Loodu S, Rupasinghe HPV. Evaluation of antioxidant, antidiabetic and antiobesity potential of selected traditional medicinal plants. Front Nutr 2019; 6: 53.
http://dx.doi.org/10.3389/fnut.2019.00053 PMID: 31106207
[11] Kato-Schwartz CG, Corrêa RCG, de Souza Lima D, *et al.* Potential anti-diabetic properties of Merlot grape pomace extract: An *in vitro, in silico* and *in vivo* study of α-amylase and α-glucosidase inhibition. Food Res Int 2020; 137: 109462.
http://dx.doi.org/10.1016/j.foodres.2020.109462 PMID: 33233136
[12] Hanhineva K, Törrönen R, Bondia-Pons I, *et al.* Impact of dietary polyphenols on carbohydrate metabolism. Int J Mol Sci 2010; 11(4): 1365-402.
http://dx.doi.org/10.3390/ijms11041365 PMID: 20480025
[13] Mueckler M, Thorens B. The SLC2 (GLUT) family of membrane transporters. Mol Aspects Med 2013; 34(2-3): 121-38.
http://dx.doi.org/10.1016/j.mam.2012.07.001 PMID: 23506862
[14] Babu PVA, Liu D, Gilbert ER. Recent advances in understanding the anti-diabetic actions of dietary flavonoids. J Nutr Biochem 2013; 24(11): 1777-89.
http://dx.doi.org/10.1016/j.jnutbio.2013.06.003 PMID: 24029069
[15] Dresner A, Laurent D, Marcucci M, *et al.* Effects of free fatty acids on glucose transport and IRS-1–associated phosphatidylinositol 3-kinase activity. J Clin Invest 1999; 103(2): 253-9.
http://dx.doi.org/10.1172/JCI5001 PMID: 9916137
[16] Guillausseau PJ, Meas T, Virally M, Laloi-Michelin M, Médeau V, Kevorkian JP. Abnormalities in insulin secretion in type 2 diabetes mellitus. Diabetes Metab 2008; 34(Suppl. 2): S43-8.
http://dx.doi.org/10.1016/S1262-3636(08)73394-9 PMID: 18640585
[17] Kile BT, Schulman BA, Alexander WS, Nicola NA, Martin HME, Hilton DJ. The SOCS box: A tale of destruction and degradation. Trends Biochem Sci 2002; 27(5): 235-41.
http://dx.doi.org/10.1016/S0968-0004(02)02085-6 PMID: 12076535
[18] Samuel VT, Shulman GI. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. J Clin Invest 2016; 126(1): 12-22.
http://dx.doi.org/10.1172/JCI77812 PMID: 26727229
[19] Youngren JF. Regulation of insulin receptor function. Cell Mol Life Sci 2007; 64(7-8): 873-91.
http://dx.doi.org/10.1007/s00018-007-6359-9 PMID: 17347799
[20] Hsu PP, Kang SA, Rameseder J, *et al.* The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. Science 2011; 332(6035): 1317-22.
http://dx.doi.org/10.1126/science.1199498 PMID: 21659604
[21] Chang L, Chiang SH, Saltiel AR. Insulin signaling and the regulation of glucose transport. Mol Med 2004; 10(7-12): 65-71.
http://dx.doi.org/10.2119/2005-00029.Saltiel PMID: 16307172
[22] Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963; 281(7285): 785-9.
http://dx.doi.org/10.1016/S0140-6736(63)91500-9 PMID: 13990765
[23] Johnson AMF, Olefsky JM. The origins and drivers of insulin resistance. Cell 2013; 152(4): 673-84.
http://dx.doi.org/10.1016/j.cell.2013.01.041 PMID: 23415219
[24] Forlani G, Di Bonito P, Mannucci E, *et al.* Prevalence of elevated liver enzymes in Type 2 diabetes mellitus and its association with the metabolic syndrome. J Endocrinol Invest 2008; 31(2): 146-52.
http://dx.doi.org/10.1007/BF03345581 PMID: 18362506
[25] Krijnen PAJ, Simsek S, Niessen HWM. Apoptosis in diabetes. Apoptosis 2009; 14(12): 1387-8.
http://dx.doi.org/10.1007/s10495-009-0419-6 PMID: 19856207
[26] Batista TM, Haider N, Kahn CR. Correction to: Defining the underlying defect in insulin action in type 2 diabetes. Diabetologia 2022; 65(6): 1064.
http://dx.doi.org/10.1007/s00125-022-05684-8 PMID: 35320373
[27] Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol 2014; 6(1): a009191.
http://dx.doi.org/10.1101/cshperspect.a009191 PMID: 24384568
[28] Chen Y, Huang L, Qi X, Chen C. Insulin receptor trafficking: Consequences for insulin sensitivity and diabetes. Int J Mol Sci 2019; 20(20): 5007.
http://dx.doi.org/10.3390/ijms20205007 PMID: 31658625
[29] Petersen MC, Madiraju AK, Gassaway BM, *et al.* Insulin receptor Thr1160 phosphorylation mediates lipid-induced hepatic insulin resistance. J Clin Invest 2016; 126(11): 4361-71.
http://dx.doi.org/10.1172/JCI86013 PMID: 27760050
[30] Hirosumi J, Tuncman G, Chang L, *et al.* Author correction: A central role for JNK in obesity and insulin resistance. Nature 2023; 619(7968): E25.
http://dx.doi.org/10.1038/s41586-023-06285-0 PMID: 37328696
[31] Suganami T, Tanaka M, Ogawa Y. Adipose tissue inflammation and ectopic lipid accumulation. Endocr J 2012; 59(10): 849-57.
http://dx.doi.org/10.1507/endocrj.EJ12-0271 PMID: 22878669
[32] Yamauchi T, Nio Y, Maki T, *et al.* Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007; 13(3): 332-9.
http://dx.doi.org/10.1038/nm1557 PMID: 17268472
[33] Ceddia RB, Koistinen HA, Zierath JR, Sweeney G. Analysis of paradoxical observations on the association between leptin and insulin resistance. FASEB J 2002; 16(10): 1163-76.
http://dx.doi.org/10.1096/fj.02-0158rev PMID: 12153984
[34] Iikuni N, Kwan Lam Q, Lu L, Matarese G, Cava A. Leptin and inflammation. Curr Immunol Rev 2008; 4(2): 70-9.
http://dx.doi.org/10.2174/157339508784325046 PMID: 20198122
[35] Luro F, Gatto J, Costantino G, Pailly O. Analysis of genetic diversity in *Citrus*. Plant Genet Resour 2011; 9(2): 218-21.
http://dx.doi.org/10.1017/S1479262111000189
[36] Tripoli E, Guardia ML, Giammanco S, Majo DD, Giammanco M. *Citrus* flavonoids: Molecular structure, biological activity and nutritional properties: A review. Food Chem 2007; 104(2): 466-79.
http://dx.doi.org/10.1016/j.foodchem.2006.11.054
[37] Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr 2000; 130(Suppl 8): 2073S-85S.
http://dx.doi.org/10.1093/jn/130.8.2073S PMID: 10917926
[38] Middleton E, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer. Pharmacol Rev 2000; 52(4): 673-751.
http://dx.doi.org/10.1016/S0031-6997(24)01472-8 PMID: 11121513
[39] Kawser Hossain M, Abdal Dayem A, Han J, *et al.* Molecular mechanisms of the anti-obesity and anti-diabetic properties of flavonoids. Int J Mol Sci 2016; 17(4): 569.
http://dx.doi.org/10.3390/ijms17040569 PMID: 27092490
[40] Vinayagam R, Xu B. Antidiabetic properties of dietary flavonoids: A cellular mechanism review. Nutr Metab 2015; 12(1): 60.
http://dx.doi.org/10.1186/s12986-015-0057-7 PMID: 26705405
[41] Wedick NM, Pan A, Cassidy A, *et al.* Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. Am J Clin Nutr 2012; 95(4): 925-33.
http://dx.doi.org/10.3945/ajcn.111.028894 PMID: 22357723
[42] Barone E, Calabrese V, Mancuso C. Ferulic acid and its therapeutic potential as a hormetin for age-related diseases. Biogerontology 2009; 10(2): 97-108.
http://dx.doi.org/10.1007/s10522-008-9160-8 PMID: 18651237
[43] Gandhi GR, Vasconcelos ABS, Wu DT, *et al.* Citrus flavonoids as promising phytochemicals targeting diabetes and related complications: A systematic review of *in vitro* and *in vivo* studies. Nutrients 2020; 12(10): 2907.
http://dx.doi.org/10.3390/nu12102907 PMID: 32977511
[44] Tanveer A, Akram K, Farooq U, Hayat Z, Shafi A. Management of diabetic complications through fruit flavonoids as a natural remedy. Crit Rev Food Sci Nutr 2017; 57(7): 1411-22.

http://dx.doi.org/10.1080/10408398.2014.1000482 PMID: 26065867

[45] Athmuri DN, Shiekh PA. Experimental diabetic animal models to study diabetes and diabetic complications. MethodsX 2023; 11: 102474.
http://dx.doi.org/10.1016/j.mex.2023.102474 PMID: 38023309

[46] Oboh G, Ademosun A, Ayeni PO, Omojokun OS, Bello FO. Comparative effect of quercetin and rutin on α-amylase, α-glucosidase, and some pro-oxidant-induced lipid peroxidation in rat pancreas. Comp Clin Pathol 2015; 24(5): 1103-10.
http://dx.doi.org/10.1007/s00580-014-2040-5

[47] Adewole SO, Caxton-Martins EA, Ojewole JA. Protective effect of quercetin on the morphology of pancreatic beta-cells of streptozotocin-treated diabetic rats. Afr J Tradit Complement Altern Med 2006; 4(1): 64-74.
PMID: 20162074

[48] Bell W, Jennings A, Thompson AS, *et al.* A flavonoid-rich diet is associated with lower risk and improved imaging biomarkers of nonalcoholic fatty liver disease: A prospective cohort study. Am J Clin Nutr 2024; 120(6): 1325-34.
http://dx.doi.org/10.1016/j.ajcnut.2024.09.022 PMID: 39341459

[49] Yi H, Peng H, Wu X, *et al.* The therapeutic effects and mechanisms of quercetin on metabolic diseases: Pharmacological data and clinical evidence. Oxid Med Cell Longev 2021; 2021(1): 6678662.
http://dx.doi.org/10.1155/2021/6678662 PMID: 34257817

[50] Aghababaei F, Hadidi M. Recent Advances in Potential Health Benefits of Quercetin. Pharmaceuticals (Basel)202316(7):1020.
http://dx.doi.org/10.3390/ph16071020.

[51] Ghorbani A. Mechanisms of antidiabetic effects of flavonoid rutin. Biomed Pharmacother 2017; 96: 305-12.
http://dx.doi.org/10.1016/j.biopha.2017.10.001 PMID: 29017142

[52] Demján V, Sója A, Kiss T, *et al. Stellaria media* tea protects against diabetes-induced cardiac dysfunction in rats without affecting glucose tolerance. J Tradit Complement Med 2022; 12(3): 250-9.
http://dx.doi.org/10.1016/j.jtcme.2021.08.003 PMID: 35493309

[53] Ratnaningtyas NI, Hernayanti H, Ekowati N, Husen F. Ethanol extract of the mushroom *Coprinus comatus* exhibits antidiabetic and antioxidant activities in streptozotocin-induced diabetic rats. Pharm Biol 2022; 60(1): 1126-36.
http://dx.doi.org/10.1080/13880209.2022.2074054 PMID: 35675226

[54] Al-Numair KS, Chandramohan G, Veeramani C, Alsaif MA. Ameliorative effect of kaempferol, a flavonoid, on oxidative stress in streptozotocin-induced diabetic rats. Redox Rep 2015; 20(5): 198-209.
http://dx.doi.org/10.1179/1351000214Y.0000000117 PMID: 25494817

[55] Sharma D, Kumar Tekade R, Kalia K. Kaempferol in ameliorating diabetes-induced fibrosis and renal damage: An *in vitro* and *in vivo* study in diabetic nephropathy mice model. Phytomedicine 2020; 76: 153235.
http://dx.doi.org/10.1016/j.phymed.2020.153235 PMID: 32563017

[56] Feng H, Cao J, Zhang G, Wang Y. Kaempferol attenuates cardiac hypertrophy *via* regulation of ASK1/MAPK signalling pathway and oxidative stress. Planta Med 2017; 83(10): 837-45.
http://dx.doi.org/10.1055/s-0043-103415 PMID: 28219095

[57] Baumel-Alterzon S, Katz LS, Brill G, Garcia-Ocaña A, Scott DK. Nrf2: The master and captain of beta cell fate. Trends Endocrinol Metab 2021; 32(1): 7-19.
http://dx.doi.org/10.1016/j.tem.2020.11.002 PMID: 33243626

[58] Matboli M, Saad M, Hasanin AH, *et al.* New insight into the role of isorhamnetin as a regulator of insulin signaling pathway in type 2 diabetes mellitus rat model: Molecular and computational approach. Biomed Pharmacother 2021; 135: 111176.
http://dx.doi.org/10.1016/j.biopha.2020.111176 PMID: 33401224

[59] Wu L, Parhofer KG. Diabetic dyslipidemia. Metabolism 2014; 63(12): 1469-79.
http://dx.doi.org/10.1016/j.metabol.2014.08.010 PMID: 25242435

[60] Viollet B, Lantier L, Devin-Leclerc J, *et al.* Targeting the AMPK pathway for the treatment of Type 2 diabetes. Front Biosci 2009; Volume(14): 3380-400.
http://dx.doi.org/10.2741/3460 PMID: 19273282

[61] Angin Y, Beauloye C, Horman S, Bertrand L. Regulation of carbohydrate metabolism, lipid metabolism, and protein metabolism by AMPK. EXS 2016; 107: 23-43.
http://dx.doi.org/10.1007/978-3-319-43589-3_2 PMID: 27812975

[62] Hämäläinen M, Nieminen R, Vuorela P, Heinonen M, Moilanen E. Anti-inflammatory effects of flavonoids: Genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. Mediators Inflamm 2007; 2007: 45673.
http://dx.doi.org/10.1155/2007/45673 PMID: 18274639

[63] Lai M, Lan C, Zhong J, Wu L, Lin C. Fisetin prevents angiogenesis in diabetic retinopathy by downregulating VEGF. J Ophthalmol 2023; 2023: 7951928.
http://dx.doi.org/10.1155/2023/7951928 PMID: 36777991

[64] Long L, Li Y, Yu S, *et al.* Scutellarin prevents angiogenesis in diabetic retinopathy by downregulating VEGF/ERK/FAK/src pathway signaling. J Diabetes Res 2019; 2019(4875421): 1-17.
http://dx.doi.org/10.1155/2019/4875421 PMID: 31976335

[65] Dong W, Jia C, Li J. Fisetin attenuates diabetic nephropathy-induced podocyte injury by inhibiting NLRP3 inflammasome. Front Pharmacol 2022; 13: 783706.
http://dx.doi.org/10.3389/fphar.2022.783706 PMID: 35126159

[66] Chen Y, Li Y, Xu H, Li G, Ma Y, Pang YJ. Morin mitigates oxidative stress, apoptosis and inflammation in cerebral ischemic rats. Afr J Tradit Complement Altern Med 2017; 14(2): 348-55.
http://dx.doi.org/10.21010/ajtcam.v14i2.36 PMID: 28573251

[67] Park JY, Kang KA, Kim KC, Cha JW, Kim EH, Hyun JW. Morin induces heme oxygenase-1 *via* the ERK-Nrf2 signalling pathway. J Cancer Prev 2013; 18(3): 249-56.
http://dx.doi.org/10.15430/JCP.2013.18.3.249 PMID: 25337552

[68] Rizvi F, Mathur A, Krishna S, Siddiqi MI, Kakkar P. Suppression in PHLPP2 induction by morin promotes Nrf2-regulated cellular defenses against oxidative injury to primary rat hepatocytes. Redox Biol 2015; 6: 587-98.
http://dx.doi.org/10.1016/j.redox.2015.10.002 PMID: 26513344

[69] Vanitha P, Senthilkumar S, Dornadula S, Anandhakumar S, Rajaguru P, Ramkumar KM. Morin activates the Nrf2-ARE pathway and reduces oxidative stress-induced DNA damage in pancreatic beta cells. Eur J Pharmacol 2017; 801: 9-18.
http://dx.doi.org/10.1016/j.ejphar.2017.02.026 PMID: 28216051

[70] Kim JM, Lee EK, Park G, *et al.* Morin modulates the oxidative stress-induced NF-κB pathway through its anti-oxidant activity. Free Radic Res 2010; 44(4): 454-61.
http://dx.doi.org/10.3109/10715761003610737 PMID: 20187708

[71] Yu S, Liu X, Yu D, Changyong E, Yang J. Morin protects LPS-induced mastitis *via* inhibiting NLRP3 inflammasome and NF-κB signalling pathways. Inflammation 2020; 43(4): 1293-303.
http://dx.doi.org/10.1007/s10753-020-01208-x PMID: 32140901

[72] Wang J, Guo C, Wei Z, *et al.* Morin suppresses inflammatory cytokine expression by downregulation of nuclear factor-κB and mitogen-activated protein kinase (MAPK) signaling pathways in lipopolysaccharide-stimulated primary bovine mammary epithelial cells. J Dairy Sci 2016; 99(4): 3016-22.
http://dx.doi.org/10.3168/jds.2015-10330 PMID: 26851851

[73] Kapoor R, Kakkar P. Protective role of morin, a flavonoid, against high glucose induced oxidative stress mediated apoptosis in primary rat hepatocytes. PLoS One 2012; 7(8): e41663.
http://dx.doi.org/10.1371/journal.pone.0041663 PMID: 22899998

[74] Ola MS, Aleisa AM, Al-Rejaie SS, *et al.* Flavonoid, morin inhibits oxidative stress, inflammation and enhances neurotrophic support in the brain of streptozotocin-induced diabetic rats. Neurol Sci 2014; 35(7): 1003-8.
http://dx.doi.org/10.1007/s10072-014-1628-5 PMID: 24413816

[75] Djedjibegovic J, Marjanovic A, Panieri E, Saso L. Ellagic acid-derived urolithins as modulators of oxidative stress. Oxid Med Cell Longev 2020; 2020: 1-15.
http://dx.doi.org/10.1155/2020/5194508 PMID: 32774676

[76] Okla M, Kang I, Kim DM, *et al.* Ellagic acid modulates lipid accumulation in primary human adipocytes and human hepatoma Huh7 cells *via* discrete mechanisms. J Nutr Biochem 2015; 26(1): 82-90.
http://dx.doi.org/10.1016/j.jnutbio.2014.09.010 PMID: 25458530

[77] Poulose N, Prasad CNV, Haridas PAN, Anilkumar G. Ellagic acid stimulates glucose transport in adipocytes and muscles through AMPK mediated pathway. J Diabetes Metab 2011; 2(5): 149. http://dx.doi.org/10.4172/2155-6156.1000149

[78] Kang I, Kim Y, Tomás-Barberán FA, Espín JC, Chung S. Urolithin A, C, and D, but not iso-urolithin A and urolithin B, attenuate triglyceride accumulation in human cultures of adipocytes and hepatocytes. Mol Nutr Food Res 2016; 60(5): 1129-38. http://dx.doi.org/10.1002/mnfr.201500796 PMID: 26872561

[79] Lee KH, Jeong ES, Jang G, *et al.* Unripe rubus coreanus miquel extract containing ellagic acid regulates AMPK, SREBP-2, HMGCR, and INSIG-1 signalling and cholesterol metabolism *in vitro* and *in vivo.* Nutrients 2020; 12(3): 610. http://dx.doi.org/10.3390/nu12030610 PMID: 32110925

[80] Mechchate H, Es-Safi I, Haddad H, *et al.* Combination of Catechin, Epicatechin, and Rutin: Optimization of a novel complete antidiabetic formulation using a mixture design approach. J Nutr Biochem. 2021; 88: 108520. http://dx.doi.org/10.1016/j.jnutbio.2020.108520."

[81] Daisy P, Balasubramanian K, Rajalakshmi M, Eliza J, Selvaraj J. Insulin mimetic impact of Catechin isolated from *Cassia fistula* on the glucose oxidation and molecular mechanisms of glucose uptake on Streptozotocin-induced diabetic Wistar rats. Phytomedicine 2010; 17(1): 28-36. http://dx.doi.org/10.1016/j.phymed.2009.10.018 PMID: 19931438

[82] Daveri E, Cremonini E, Mastaloudis A, *et al.* Cyanidin and delphinidin modulate inflammation and altered redox signaling improving insulin resistance in high fat-fed mice. Redox Biol 2018; 18: 16-24. http://dx.doi.org/10.1016/j.redox.2018.05.012 PMID: 29890336

[83] Cheng Z, Guo S, Copps K, *et al.* Foxo1 integrates insulin signaling with mitochondrial function in the liver. Nat Med 2009; 15(11): 1307-11. http://dx.doi.org/10.1038/nm.2049 PMID: 19838201

[84] Jia X, Luo Z, Gao Y, *et al.* EGCG Upregulates UCP_3 Levels to Protect MIN_6 Pancreatic Islet Cells from Interleukin-1β-Induced Apoptosis. Drug Des Devel Ther 2020; 14: 4251-61. http://dx.doi.org/10.2147/DDDT.S270345 PMID: 33116413

[85] Zhang Z, Ding Y, Dai X, Wang J, Li Y. Epigallocatechin-3-gallate protects pro-inflammatory cytokine induced injuries in insulin-producing cells through the mitochondrial pathway. Eur J Pharmacol 2011; 670(1): 311-6. http://dx.doi.org/10.1016/j.ejphar.2011.08.033 PMID: 21925162

[86] Song EK, Hur H, Han MK. Epigallocatechin gallate prevents autoimmune diabetes induced by multiple low doses of streptozotocin in mice. Arch Pharm Res 2003; 26(7): 559-63. http://dx.doi.org/10.1007/BF02976881 PMID: 12934649

[87] Ong KC, Khoo HE. Effects of myricetin on glycemia and glycogen metabolism in diabetic rats. Life Sci 2000; 67(14): 1695-705. http://dx.doi.org/10.1016/S0024-3205(00)00758-X PMID: 11021354

[88] Ma J, Liu J, Chen Y, Yu H, Xiang L. Myricetin improves impaired nerve functions in experimental diabetic rats. Front Endocrinol 2022; 13: 915603. http://dx.doi.org/10.3389/fendo.2022.915603 PMID: 35928887

[89] Zhao Z, Chen Y, Li X, *et al.* Myricetin relieves the symptoms of type 2 diabetes mice and regulates intestinal microflora. Biomed Pharmacother 2022; 153: 113530. http://dx.doi.org/10.1016/j.biopha.2022.113530 PMID: 36076610

[90] Syed AA, Reza MI, Yadav H, Gayen JR. Hesperidin inhibits NOX4 mediated oxidative stress and inflammation by upregulating SIRT1 in experimental diabetic neuropathy. Exp Gerontol 2023; 172: 112064. http://dx.doi.org/10.1016/j.exger.2022.112064 PMID: 36528304

[91] Lim C, Zhen AX, Ok S, *et al.* Hesperidin protects SH−SY5Y neuronal cells against high glucose−induced apoptosis *via* regulation of MAPK signaling. Antioxidants 2022; 11(9): 1707. http://dx.doi.org/10.3390/antiox11091707 PMID: 36139782

[92] Khalil HE, Abdelwahab MF, Emeka PM, *et al.* Ameliorative effect of *Ocimum forskolei* Benth on diabetic, apoptotic, and adipogenic biomarkers of diabetic rats and 3T3-L1 fibroblasts assisted by *in silico* approach. Molecules 2022; 27(9): 2800. http://dx.doi.org/10.3390/molecules27092800 PMID: 35566151

[93] Abdou HM, Hamaad FA, Ali EY, Ghoneum MH. Antidiabetic efficacy of *Trifolium alexandrinum* extracts hesperetin and quercetin in ameliorating carbohydrate metabolism and activating IR and AMPK signaling in the pancreatic tissues of diabetic rats. Biomed Pharmacother 2022; 149: 112838. http://dx.doi.org/10.1016/j.biopha.2022.112838 PMID: 35344738

[94] Chen YJ, Kong L, Tang ZZ, *et al.* Hesperetin ameliorates diabetic nephropathy in rats by activating Nrf2/ARE/glyoxalase 1 pathway. Biomed Pharmacother 2019; 111: 1166-75. http://dx.doi.org/10.1016/j.biopha.2019.01.030 PMID: 30841430

[95] Toney AM, Fan R, Xian Y, Chaidez V, Ramer-Tait AE, Chung S. Urolithin A, a gut metabolite, improves insulin sensitivity through augmentation of mitochondrial function and biogenesis. Obesity (Silver Spring) 2019; 27(4): 612-20. http://dx.doi.org/10.1002/oby.22404 PMID: 30768775

[96] Price NL, Gomes AP, Ling AJY, *et al.* SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. Cell Metab 2012; 15(5): 675-90. http://dx.doi.org/10.1016/j.cmet.2012.04.003 PMID: 22560220

[97] Park S, Sim KS, Hwangbo Y, Park SJ, Kim YJ, Kim JH. Naringenin and phytoestrogen 8-prenylnaringenin protect against islet dysfunction and inhibit apoptotic signaling in insulin-deficient diabetic mice. Molecules 2022; 27(13): 4227. http://dx.doi.org/10.3390/molecules27134227 PMID: 35807469

[98] He Y, Wang S, Sun H. Naringenin ameliorates myocardial injury in STZ-induced diabetic mice by reducing oxidative stress, inflammation and apoptosis *via* regulating the Nrf2 and NF-κB signaling pathways. Front Cardiovasc Med 2022; 9: 946766. http://dx.doi.org/10.3389/fcvm.2022.946766

[99] Khan MF, Mathur A, Pandey VK, Kakkar P. Naringenin alleviates hyperglycemia-induced renal toxicity by regulating activating transcription factor 4–C/EBP homologous protein mediated apoptosis. J Cell Commun Signal 2022; 16(2): 271-91. http://dx.doi.org/10.1007/s12079-021-00644-0 PMID: 34613591

[100] Xue B, Wang Y. Naringenin upregulates GTPCH1/eNOS to ameliorate high glucose-induced retinal endothelial cell injury. Exp Ther Med 2022; 23(6): 428. http://dx.doi.org/10.3892/etm.2022.11355 PMID: 35607381

[101] Gul H, Yildiz O, Dogrul A, Yesilyurt O, Isimer A. The interaction between IL-1β and morphine: Possible mechanism of the deficiency of morphine-induced analgesia in diabetic mice. Pain 2000; 89(1): 39-45. http://dx.doi.org/10.1016/S0304-3959(00)00343-2 PMID: 11113291

[102] Kandhare AD, Raygude KS, Ghosh P, Ghule AE, Bodhankar SL. Neuroprotective effect of naringin by modulation of endogenous biomarkers in streptozotocin induced painful diabetic neuropathy. Fitoterapia 2012; 83(4): 650-9. http://dx.doi.org/10.1016/j.fitote.2012.01.010 PMID: 22343014

[103] Baskaran G, Shukor MY, Salvamani S, Ahmad SA, Shaharuddin NA, Pattiram PD. HMG-CoA reductase inhibitory activity and phyto component investigation of *Basella alba* leaf extract as a treatment for hypercholesterolemia. Drug Des Devel Ther 2015; 9: 509-17. http://dx.doi.org/10.2147/DDDT.S75056 PMID: 25609924

[104] Mahmoud AM, Ashour MB, Abdel-Moneim A, Ahmed OM. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats. J Diabetes Complications 2012; 26(6): 483-90. http://dx.doi.org/10.1016/j.jdiacomp.2012.06.001 PMID: 22809898

[105] Bodhankar SL, Raygude K, Kandhare AD, Ghosh P. The ameliorative effect of fisetin, a bioflavonoid, on ethanol-induced and pylorus ligation-induced gastric ulcer in rats. Int J Green Pharm 2011; 5(3): 236-43. http://dx.doi.org/10.4103/0973-8258.91233

[106] Sakurai K, Katoh M, Someno K, Fujimoto Y. Apoptosis and mitochondrial damage in INS-1 cells treated with alloxan. Biol Pharm Bull 2001; 24(8): 876-82. http://dx.doi.org/10.1248/bpb.24.876 PMID: 11510477

[107] Minato K, Miyake Y, Fukumoto S, *et al.* Lemon flavonoid, eriocitrin, suppresses exercise-induced oxidative damage in rat liver. Life Sci 2003; 72(14): 1609-16.

http://dx.doi.org/10.1016/S0024-3205(02)02443-8 PMID: 12551749

[108] Cesar TB, Ramos FMM, Ribeiro CB. Nutraceutical Eriocitrin (Eriomin) reduces hyperglycemia by increasing glucagon-like peptide 1 and downregulates systemic inflammation: A crossover-randomized clinical trial. J Med Food 2022; 25(11): 1050-8. http://dx.doi.org/10.1089/jmf.2021.0181 PMID: 35796695

[109] Miyake Y, Suzuki E, Ohya S, *et al.* Lipid-lowering effect of eriocitrin, the main flavonoid in lemon fruit, in rats on a high-fat and high-cholesterol diet. J Food Sci 2006; 71(9): S633-7. http://dx.doi.org/10.1111/j.1750-3841.2006.00192.x

[110] Hiramitsu M, Shimada Y, Kuroyanagi J, *et al.* Eriocitrin ameliorates diet-induced hepatic steatosis with activation of mitochondrial biogenesis. Sci Rep 2014; 4(1): 3708. http://dx.doi.org/10.1038/srep03708 PMID: 24424211

[111] Takase T, Ikeuchi S, Inoue T, Mukai R. Eriocitrin contained in lemon peel ameliorates disuse muscle atrophy by suppressing the expression of atrogin-1 and MURF-1 in denervated mice. J Nat Prod 2021; 84(7): 2048-52. http://dx.doi.org/10.1021/acs.jnatprod.1c00271 PMID: 34189920

[112] Liu J, Huang H, Huang Z, *et al.* Eriocitrin in combination with resveratrol ameliorates LPS-induced inflammation in RAW264.7 cells and relieves TPA-induced mouse ear edema. J Funct Foods 2019; 56: 321-32. http://dx.doi.org/10.1016/j.jff.2019.03.008

[113] Hung JY, Hsu YL, Ko YC, *et al.* Didymin, a dietary flavonoid glycoside from citrus fruits, induces Fas-mediated apoptotic pathway in human non-small-cell lung cancer cells *in vitro* and *in vivo*. Lung Cancer 2010; 68(3): 366-74. http://dx.doi.org/10.1016/j.lungcan.2009.08.013 PMID: 19733932

[114] Ali MY, Zaib S, Rahman MM, *et al.* Didymin, a dietary citrus flavonoid exhibits anti-diabetic complications and promotes glucose uptake through the activation of PI3K/Akt signaling pathway in insulin-resistant HepG2 cells. Chem Biol Interact 2019; 305: 180-94. http://dx.doi.org/10.1016/j.cbi.2019.03.018 PMID: 30928401

[115] Gao F, Wang T, Xiao J, Huang G. Antibacterial activity study of 1,2,4-triazole derivatives. Eur J Med Chem 2019; 173: 274-81. http://dx.doi.org/10.1016/j.ejmech.2019.04.043 PMID: 31009913

[116] Na M, Jang J, Njamen D. Protein tyrosine phosphatase-1B inhibitory activity of isoprenylated flavonoids isolated from *Erythrina mildbraedii*. J Nat Prod 2006; 69(11): 1572-6. http://dx.doi.org/10.1021/np0601861

[117] Ali MY, Zaib S, Rahman MM. Poncirin, an orally active flavonoid exerts antidiabetic complications and improves glucose uptake activating PI3K/Akt signaling pathway in insulin resistant C_2C1_2 cells with anti-glycation capacities. Bioorg Chem 2020; 102: 104061. http://dx.doi.org/10.1016/j.bioorg.2020.104061

[118] Charbonneau A, Marette A. Inducible nitric oxide synthase induction underlies lipid-induced hepatic insulin resistance in mice: Potential role of tyrosine nitration of insulin signaling proteins. Diabetes 2010; 59(4): 861-71. http://dx.doi.org/10.2337/db09-1238 PMID: 20103705

[119] Xu Q, Li Y, Shang YF, Wang HL, Yao MX. miRNA-103: Molecular link between insulin resistance and nonalcoholic fatty liver disease. World J Gastroenterol 2015; 21(2): 511-6. http://dx.doi.org/10.3748/wjg.v21.i2.511 PMID: 25593466

[120] Huang Y, Hao J, Tian D, *et al.* Antidiabetic activity of a flavonoid-rich extract from *Sophora davidii* (Franch.) Skeels in KK-Ay mice *via* activation of AMP-activated protein kinase. Front Pharmacol 2018; 9: 760. http://dx.doi.org/10.3389/fphar.2018.00760 PMID: 30061831

[121] Mao XY, Yu J, Liu ZQ, Zhou HH. Apigenin attenuates diabetes-associated cognitive decline in rats *via* suppressing oxidative stress and nitric oxide synthase pathway. Int J Clin Exp Med 2015; 8(9): 15506-13. PMID: 26629041

[122] Liu L, Xie Y, Song Z, Shang S, Chen X. Influence of dietary flavonoids on the glycation of plasma proteins. Mol Biosyst 2012; 8(8): 2183-7. http://dx.doi.org/10.1039/c2mb25038a PMID: 22710272

[123] Abed DA, Lee S, Hu L. Discovery of disubstituted xylylene derivatives as small molecule direct inhibitors of Keap1-Nrf2 protein-protein interaction. Bioorg Med Chem 2020; 28(6): 115343. http://dx.doi.org/10.1016/j.bmc.2020.115343 PMID: 32046917

[124] Malik S, Suchal K, Khan SI, *et al.* Apigenin ameliorates streptozotocin-induced diabetic nephropathy in rats *via* MAPK-NF-κB-TNF-α and TGF-β1-MAPK-fibronectin pathways. Am J Physiol Renal Physiol 2017; 313(2): F414-22. http://dx.doi.org/10.1152/ajprenal.00393.2016 PMID: 28566504

[125] Maiti R, Das UK, Ghosh D. Attenuation of hyperglycemia and hyperlipidemia in streptozotocin-induced diabetic rats by aqueous extract of seed of *Tamarindus indica*. Biol Pharm Bull 2005; 28(7): 1172-6. http://dx.doi.org/10.1248/bpb.28.1172 PMID: 15997092

[126] Elangovan A, Subramanian A, Durairaj S, *et al.* Antidiabetic and hypolipidemic efficacy of skin and seed extracts of *Momordica cymbalaria* on alloxan induced diabetic model in rats. J Ethnopharmacol 2019; 241: 111989. http://dx.doi.org/10.1016/j.jep.2019.111989 PMID: 31150795

[127] Nouri Z, Hajialyani M, Izadi Z, Bahramsoltani R, Farzaei MH, Abdollahi M. Nanophytomedicines for the prevention of metabolic syndrome: A pharmacological and biopharmaceutical review. Front Bioeng Biotechnol 2020; 8: 425. http://dx.doi.org/10.3389/fbioe.2020.00425 PMID: 32478050

[128] Zang Y, Igarashi K, Li Y. Anti-diabetic effects of luteolin and luteolin-7-O-glucoside on KK-A(y) mice. Biosci Biotechnol Biochem 2016; 80(8): 1580-6. http://dx.doi.org/10.1080/09168451.2015.1116928 PMID: 27170065

[129] Donath MY, Böni-Schnetzler M, Ellingsgaard H, Halban PA, Ehses JA. Cytokine production by islets in health and diabetes: Cellular origin, regulation and function. Trends Endocrinol Metab 2010; 21(5): 261-7. http://dx.doi.org/10.1016/j.tem.2009.12.010 PMID: 20096598

[130] Sundaram R, Shanthi P, Sachdanandam P. Effect of tangeretin, a polymethoxylated flavone on glucose metabolism in streptozotocin-induced diabetic rats. Phytomedicine 2014; 21(6): 793-9. http://dx.doi.org/10.1016/j.phymed.2014.01.007 PMID: 24629597

[131] Kim MS, Hur HJ, Kwon DY, Hwang JT. Tangeretin stimulates glucose uptake *via* regulation of AMPK signaling pathways in C_2C1_2 myotubes and improves glucose tolerance in high-fat diet-induced obese mice. Mol Cell Endocrinol 2012; 358(1): 127-34. http://dx.doi.org/10.1016/j.mce.2012.03.013 PMID: 22476082

[132] Guo J, Chen J, Ren W, *et al.* Citrus flavone tangeretin is a potential insulin sensitizer targeting hepatocytes through suppressing MEK-ERK1/2 pathway. Biochem Biophys Res Commun 2020; 529(2): 277-82. http://dx.doi.org/10.1016/j.bbrc.2020.05.212 PMID: 32703423

[133] Miyata Y, Tanaka H, Shimada A, *et al.* Regulation of adipocytokine secretion and adipocyte hypertrophy by polymethoxyflavonoids, nobiletin and tangeretin. Life Sci 2011; 88(13-14): 613-8. http://dx.doi.org/10.1016/j.lfs.2011.01.024 PMID: 21295043

[134] Qin D, Jiang Y. Tangeretin inhibition of high-glucose-induced IL-1*β*, IL-6, TGF-*β*1, and VEGF expression in human RPE cells. J Diabetes Res 2020; 2020: 1-8. http://dx.doi.org/10.1155/2020/9490642 PMID: 33354576

[135] Sundaram R, Shanthi P, Sachdanandam P. Tangeretin, a polymethoxylated flavone, modulates lipid homeostasis and decreases oxidative stress by inhibiting NF-κB activation and proinflammatory cytokines in cardiac tissue of streptozotocin-induced diabetic rats. J Funct Foods 2015; 16: 315-33. http://dx.doi.org/10.1016/j.jff.2015.03.024

[136] Kurowska EM, Manthey JA, Casaschi A, Theriault AG. Modulation of hepG2 cell net apolipoprotein B secretion by the citrus polymethoxyflavone, tangeretin. Lipids 2004; 39(2): 143-51. http://dx.doi.org/10.1007/s11745-004-1212-8 PMID: 15134141

[137] Plodkowski RA, McGarvey ME, Huribal HM, *et al.* SGLT2 inhibitors for type 2 diabetes mellitus treatment. Fed Pract 2015; 32(Suppl. 11): 8S-15S. PMID: 30766102

[138] Kang YH, Park SH, Sim YE, *et al.* Highly water-soluble diacetyl chrysin ameliorates diabetes-associated renal fibrosis and retinal microvascular abnormality in db/db mice. Nutr Res Pract 2023; 17(3): 421-37. http://dx.doi.org/10.4162/nrp.2023.17.3.421 PMID: 37266111

[139] Zhou Y, Tao H, Xu N, *et al.* Chrysin improves diabetic nephropathy by regulating the AMPK-mediated lipid metabolism in HFD/STZ-induced DN mice. J Food Biochem 2022; 46(12): e14379. http://dx.doi.org/10.1111/jfbc.14379 PMID: 35976957

[140] El-Marasy SA, AbouSamra MM, El-Mosallamy AEMK, *et al.* Chrysin loaded nanovesicles ameliorated diabetic peripheral neuropathy. Role of NGF/AKT/GSK-3β pathway. Chem Biol Interact 2023; 375: 110402. http://dx.doi.org/10.1016/j.cbi.2023.110402 PMID: 36804429

[141] Adeghate E, Ponery AS, Sheen R. Streptozotocin-induced diabetes mellitus is associated with increased pancreatic tissue levels of noradrenaline and adrenaline in the rat. Pancreas 2001; 22(3): 311-6. http://dx.doi.org/10.1097/00006676-200104000-00014 PMID: 11291935

[142] Ahad A, Ganai AA, Mujeeb M, Siddiqui WA. Chrysin, an anti-inflammatory molecule, abrogates renal dysfunction in type 2 diabetic rats. Toxicol Appl Pharmacol 2014; 279(1): 1-7. http://dx.doi.org/10.1016/j.taap.2014.05.007 PMID: 24848621

[143] Lei L, Zhao J, Liu XQ, *et al.* Wogonin alleviates kidney tubular epithelial injury in diabetic nephropathy by inhibiting PI3K/Akt/NF-κB signaling pathways. Drug Des Devel Ther 2021; 15: 3131-50. http://dx.doi.org/10.2147/DDDT.S310882 PMID: 34295152

[144] Khan S, Zhang D, Zhang Y, Li M, Wang C. Wogonin attenuates diabetic cardiomyopathy through its anti-inflammatory and anti-oxidative properties. Mol Cell Endocrinol 2016; 428: 101-8. http://dx.doi.org/10.1016/j.mce.2016.03.025 PMID: 27013352

[145] Zheng Z, Zhu W, Lei L, Liu X, Wu Y. Wogonin ameliorates renal inflammation and fibrosis by inhibiting NF-κB and TGF-β1/Smad3 signaling pathways in diabetic nephropathy. Drug Des Devel Ther 2020; 14: 4135-48. http://dx.doi.org/10.2147/DDDT.S274256 PMID: 33116403

[146] Pari L, Srinivasan S. Antihyperglycemic effect of diosmin on hepatic key enzymes of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats. Biomed Pharmacother 2010; 64(7): 477-81. http://dx.doi.org/10.1016/j.biopha.2010.02.001 PMID: 20362409

[147] Eraslan G, Sarıca ZS, Bayram LÇ, Tekeli MY, Kanbur M, Karabacak M. The effects of diosmin on aflatoxin-induced liver and kidney damage. Environ Sci Pollut Res Int 2017; 24(36): 27931-41. http://dx.doi.org/10.1007/s11356-017-0232-7 PMID: 28988357

[148] Jain D, Bansal MK, Dalvi R, Upganlawar A, Somani R. Protective effect of diosmin against diabetic neuropathy in experimental rats. J Integr Med 2014; 12(1): 35-41. http://dx.doi.org/10.1016/S2095-4964(14)60001-7 PMID: 24461593

[149] Fattori V, Rasquel-Oliveira FS, Artero NA, *et al.* Diosmin treats lipopolysaccharide-induced inflammatory pain and peritonitis by blocking NF-κB activation in mice. J Nat Prod 2020; 83(4): 1018-26. http://dx.doi.org/10.1021/acs.jnatprod.9b00887 PMID: 32083866

[150] Kwak HJ, Yang D, Hwang Y, Jun HS, Cheon HG. Baicalein protects rat insulinoma INS-1 cells from palmitate-induced lipotoxicity by inducing HO-1. PLoS One 2017; 12(4): e0176432. http://dx.doi.org/10.1371/journal.pone.0176432 PMID: 28445528

[151] Yang JR, Luo JG, Kong LY. Determination of α-glucosidase inhibitors from ScutScutellaria baicalensis using liquid chromatography with quadrupole time of flight tandem mass spectrometry coupled with centrifugal ultrafiltration. Chin J Nat Med 2015; 13(3): 208-14. http://dx.doi.org/10.1016/S1875-5364(15)30006-6 PMID: 25835365

[152] Wei X-F, Lin SB, Xiong HP, Yu Y, Qiang Z, Jing X. Discussion on the effect of baicalin on pancreatic islet function in diabetic rats and its mechanism. J Integr Cardiovasc Cerebrovasc Dis Chin West Med 2019; 17(19): 2933-5.

[153] Guo Y-Y, Liu M-M, Yang X-H, *et al.* Study on the effect and mechanism of baicalin on insulin secretion in rats. Chin J Pharmacol 2018; 34(06): 820-4.

[154] Kuo YT, Lin CC, Kuo HT, *et al.* Identification of baicalin from Bofutsushosan and Daisaikoto as a potent inducer of glucose uptake and modulator of insulin signaling-associated pathways. Yao Wu Shi Pin Fen Xi 2019; 27(1): 240-8. http://dx.doi.org/10.1016/j.jfda.2018.07.002 PMID: 30648577

[155] Chen Z, Liu C, Wang F, Qin S. Research progress of active ingredients of Chinese medicine for the treatment of insulin resistance in type 2 diabetes mellitus. Hunan J Tradit Chin Med 2019; 35(12): 127-9.

[156] Fang P, Sun Y, Gu X, *et al.* Baicalin ameliorates hepatic insulin resistance and gluconeogenic activity through inhibition of p38 MAPK/PGC-1α pathway. Phytomedicine 2019; 64: 153074. http://dx.doi.org/10.1016/j.phymed.2019.153074 PMID: 31473580

[157] Lee JM, Kim SR, Yoo SJ, Hong OK, Son HS, Chang SA. The relationship between adipokines, metabolic parameters and insulin resistance in patients with metabolic syndrome and type 2 diabetes. J Int Med Res 2009; 37(6): 1803-12. http://dx.doi.org/10.1177/147323000903700616 PMID: 20146878

[158] He RM, Men L, Yi WY, Yi TG, Li Shun M, Yang Shu D. Effect of baicalin on the expression of p38MAPK in renal tissue of rats with diabetic nephropathy. Guangdong Med 2016; 37(20): 3006-9.

[159] Wang YC, Chuang YC, Hsu HW. The flavonoid, carotenoid and pectin content in peels of citrus cultivated in Taiwan. Food Chem 2008; 106(1): 277-84. http://dx.doi.org/10.1016/j.foodchem.2007.05.086

[160] Li SJ. Self-incompatibility in Matou Wendun (*Citurs grandis* (L.) Osb.). Hortic Sci 1980; 15: 298-300.

[161] Cheng L, Ren Y, Lin D, Peng S, Zhong B, Ma Z. The anti-inflammatory properties of *Citrus wilsonii tanaka* extract in LPS-induced RAW 264.7 and primary mouse bone marrow-derived dendritic cells. Molecules 2017; 22(7): 1213. http://dx.doi.org/10.3390/molecules22071213 PMID: 28753918

[162] Sultana B, Yaqoob S, Zafar Z, Bhatti HN. Escalation of liver malfunctioning: A step toward herbal awareness. J Ethnopharmacol 2018; 216: 104-19. http://dx.doi.org/10.1016/j.jep.2018.01.002 PMID: 29309862

[163] Koyuncu I. Evaluation of anticancer, antioxidant activity and phenolic compounds of *Artemisia absinthium* L. Extract. Cell Mol Biol 2018; 64(3): 25-34. http://dx.doi.org/10.14715/cmb/2018.64.3.5 PMID: 29506627

[164] Tsutsumi R, Yoshida T, Nii Y, *et al.* Sudachitin, a polymethoxylated flavone, improves glucose and lipid metabolism by increasing mitochondrial biogenesis in skeletal muscle. Nutr Metab 2014; 11(1): 32. http://dx.doi.org/10.1186/1743-7075-11-32 PMID: 25114710

[165] Lam PY, Lui ACW, Wang L, *et al.* Tricin biosynthesis and bioengineering. Front Plant Sci 2021; 12: 733198. http://dx.doi.org/10.3389/fpls.2021.733198 PMID: 34512707

[166] Yang X, Li D. Tricin attenuates diabetic retinopathy by inhibiting oxidative stress and angiogenesis through regulating Sestrin2/Nrf2 signaling. Hum Exp Toxicol 2023; 42: 09603271231171642. http://dx.doi.org/10.1177/09603271231171642 PMID: 37077025

[167] Kong Z, Lv W, Wang Y, *et al.* Sinensetin ameliorates high glucose-induced diabetic nephropathy *via* enhancing autophagy *in vitro* and *in vivo*. J Biochem Mol Toxicol 2023; 37(10): e23445. http://dx.doi.org/10.1002/jbt.23445 PMID: 37393522

[168] Liang HW, Qiu SF, Shen J, *et al.* Genistein attenuates oxidative stress and neuronal damage following transient global cerebral ischemia in rat hippocampus. Neurosci Lett 2008; 438(1): 116-20. http://dx.doi.org/10.1016/j.neulet.2008.04.058 PMID: 18467029

[169] Xu XW, Shi C, He ZQ, *et al.* Effects of phytoestrogen on mitochondrial structure and function of hippocampal CA1 region of ovariectomized rats. Cell Mol Neurobiol 2008; 28(6): 875-86. http://dx.doi.org/10.1007/s10571-008-9265-2 PMID: 18311520

[170] Kindy MS. Inhibition of tyrosine phosphorylation prevents delayed neuronal death following cerebral ischemia. J Cereb Blood Flow Metab 1993; 13(3): 372-7. http://dx.doi.org/10.1038/jcbfm.1993.50 PMID: 8386729

[171] Li Y, Ou S, Liu Q. Genistein improves mitochondrial function and inflammatory in rats with diabetic nephropathy *via* inhibiting MAPK/NF-κB pathway. Acta Cir Bras 2022; 37(6). http://dx.doi.org/10.1590/acb370601

[172] Das D, Sarkar S, Bordoloi J, Wann SB, Kalita J, Manna P. Daidzein, its effects on impaired glucose and lipid metabolism and vascular inflammation associated with type 2 diabetes. Biofactors 2018; 44(5): 407-17. http://dx.doi.org/10.1002/biof.1439 PMID: 30191623

[173] Toda S, Shirataki Y. Comparison of antioxidative and chelating effects of daidzein and daidzin on protein oxidative modification by copper *in vitro*. Biol Trace Elem Res 2001; 79(1): 83-9. http://dx.doi.org/10.1385/BTER:79:1:83 PMID: 11318239

[174] Yu Z, Yang L, Deng S, Liang M. Daidzein ameliorates LPS-induced hepatocyte injury by inhibiting inflammation and oxidative stress. Eur J Pharmacol 2020; 885: 173399. http://dx.doi.org/10.1016/j.ejphar.2020.173399 PMID: 32712091

[175] Oza MJ, Kulkarni YA. Biochanin A improves insulin sensitivity and controls hyperglycemia in type 2 diabetes. Biomed Pharmacother 2018; 107: 1119-27. http://dx.doi.org/10.1016/j.biopha.2018.08.073 PMID: 30257324

[176] Harini R, Ezhumalai M, Pugalendi KV. Antihyperglycemic effect of biochanin A, a soy isoflavone, on streptozotocin-diabetic rats. Eur J Pharmacol 2012; 676(1-3): 89-94. http://dx.doi.org/10.1016/j.ejphar.2011.11.051 PMID: 22178203

[177] Torres N, Torre-Villalvazo I, Tovar AR. Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders. J Nutr Biochem 2006; 17(6): 365-73. http://dx.doi.org/10.1016/j.jnutbio.2005.11.005 PMID: 16481155

[178] Wang F, Li R, Zhao L, Ma S, Qin G. Resveratrol ameliorates renal damage by inhibiting oxidative stress-mediated apoptosis of podocytes in diabetic nephropathy. Eur J Pharmacol 2020; 885: 173387. http://dx.doi.org/10.1016/j.ejphar.2020.173387 PMID: 32710953

[179] Ram C, Gairola S, Verm S. Biochanin A ameliorates nephropathy in high-fat diet/streptozotocin-induced diabetic rats: Effects on NF-kB/NLRP3 axis, pyroptosis, and fibrosis. Antioxidants 2023; 12(5): 1052. http://dx.doi.org/10.3390/antiox12051052

[180] Akkarachiyasit S, Charoenlertkul P, Yibchok-anun S, Adisakwattana S. Inhibitory activities of cyanidin and its glycosides and synergistic effect with acarbose against intestinal α-glucosidase and pancreatic α-amylase. Int J Mol Sci 2010; 11(9): 3387-96. http://dx.doi.org/10.3390/ijms11093387 PMID: 20957102

[181] Sun CD, Zhang B, Zhang JK, *et al.* Cyanidin-3-glucoside-rich extract from Chinese bayberry fruit protects pancreatic β cells and ameliorates hyperglycemia in streptozotocin-induced diabetic mice. J Med Food 2012; 15(3): 288-98. http://dx.doi.org/10.1089/jmf.2011.1806 PMID: 22181073

[182] Chen Y, Li X, Su L, *et al.* Cyanidin-3-O-glucoside ameliorates palmitic-acid-induced pancreatic beta cell dysfunction by modulating chop-mediated endoplasmic reticulum stress pathways. Nutrients 2022; 14(9): 1835. http://dx.doi.org/10.3390/nu14091835 PMID: 35565803

[183] Guo H, Guo J, Jiang X, Li Z, Ling W. Cyanidin-3-O-β-glucoside, a typical anthocyanin, exhibits antilipolytic effects in 3T3-L1 adipocytes during hyperglycemia: Involvement of FoxO1-mediated transcription of adipose triglyceride lipase. Food Chem Toxicol 2012; 50(9): 3040-7. http://dx.doi.org/10.1016/j.fct.2012.06.015 PMID: 22721980

[184] Scazzocchio B, Varì R, Filesi C, *et al.* Cyanidin-3-O-β-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPARγ activity in human omental adipocytes. Diabetes 2011; 60(9): 2234-44. http://dx.doi.org/10.2337/db10-1461 PMID: 21788573

[185] Sasaki R, Nishimura N, Hoshino H, *et al.* Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity due to downregulation of retinol binding protein 4 expression in diabetic mice. Biochem Pharmacol 2007; 74(11): 1619-27. http://dx.doi.org/10.1016/j.bcp.2007.08.008 PMID: 17869225

[186] Hidalgo J, Flores C, Hidalgo MA, *et al.* Delphinol® standardized maqui berry extract reduces postprandial blood glucose increase in individuals with impaired glucose regulation by novel mechanism of sodium glucose cotransporter inhibition. Panminerva Med 2014; 56(2Suppl 3): 1-7. PMID: 24861886

[187] Alvarado JL, Leschot A, Olivera-Nappa Á, *et al.* Delphinidin-rich maqui berry extract (Delphinol®) lowers fasting and postprandial glycemia and insulinemia in prediabetic individuals during oral glucose tolerance tests. BioMed Res Int 2016; 2016: 1-10. http://dx.doi.org/10.1155/2016/9070537 PMID: 28025651

[188] Pineda A, Arenas A, Balmaceda J, Zúñiga GE. Extracts of fruits and plants cultivated *in vitro* of *Aristotelia chilensis* (Mol.) Stuntz show inhibitory activity of aldose reductase and pancreatic alpha-amylase enzymes. Plants 2022; 11(20): 2772. http://dx.doi.org/10.3390/plants11202772 PMID: 36297800

[189] Gharib A, Faezizadeh Z, Godarzee M. Treatment of diabetes in the mouse model by delphinidin and cyanidin hydrochloride in free and liposomal forms. Planta Med 2013; 79(17): 1599-604. http://dx.doi.org/10.1055/s-0033-1350908 PMID: 24108435

[190] Hidalgo J, Teuber S, Morera F, *et al.* Delphinidin reduces glucose uptake in mice jejunal tissue and human intestinal cells lines through FFA1/GPR40. Int J Mol Sci 2017; 18(4): 750. http://dx.doi.org/10.3390/ijms18040750 PMID: 28379159

[191] Roy M, Sen S, Chakraborti AS. Action of pelargonidin on hyperglycemia and oxidative damage in diabetic rats: Implication for glycation-induced hemoglobin modification. Life Sci 2008; 82(21-22): 1102-10. http://dx.doi.org/10.1016/j.lfs.2008.03.011 PMID: 18440560

[192] Su H, Xie L, Xu Y, *et al.* Pelargonidin-3-*O*-glucoside derived from wild raspberry exerts antihyperglycemic effect by inducing autophagy and modulating gut microbiota. J Agric Food Chem 2020; 68(46): 13025-37. http://dx.doi.org/10.1021/acs.jafc.9b03338 PMID: 31322351

[193] Lu X, Liu M, Dong H, Miao J, Stagos D, Liu M. Dietary prenylated flavonoid xanthohumol alleviates oxidative damage and accelerates diabetic wound healing *via* Nrf2 activation. Food Chem Toxicol 2022; 160: 112813. http://dx.doi.org/10.1016/j.fct.2022.112813 PMID: 34999176

[194] Li F, Zhang J, Luo L, Hu J. Protective effects of xanthohumol against diabetic nephropathy in a mouse model. Kidney Blood Press Res 2023; 48(1): 92-101. http://dx.doi.org/10.1159/000528650 PMID: 36592619

[195] Goto K, Asai T, Hara S, *et al.* Enhanced antitumor activity of xanthohumol, a diacylglycerol acyltransferase inhibitor, under hypoxia. Cancer Lett 2005; 219(2): 215-22. http://dx.doi.org/10.1016/j.canlet.2004.07.034 PMID: 15723722

[196] Ma S, Zhang R, Li L, *et al.* Xanthohumol protect cognitive performance in diabetic model rats by inhibiting protein kinase B/nuclear factor kappa-B pathway. Neuroreport 2021; 32(8): 651-8. http://dx.doi.org/10.1097/WNR.0000000000001595 PMID: 33913932

[197] Tram LH, Giang PM, Son PT. Biologically active phenolic constituents from *Alpinia gagnepainii* K. Schum. (Zingiberaceae). Vietnam J Chem 2007; 45: 126-30.

[198] Yamamoto N, Kawabata K, Sawada K, *et al.* Cardamonin stimulates glucose uptake through translocation of glucose transporter-4 in L6 myotubes. Phytother Res 2011; 25(8): 1218-24. http://dx.doi.org/10.1002/ptr.3416 PMID: 21305634

[199] Samir SM, Elalfy M, Nashar EM. Cardamonin exerts a protective effect against autophagy and apoptosis in the testicles of diabetic male rats through the expression of Nrf2 *via* p62-mediated Keap-1 degradation. Korean J Physiol Pharmacol 2022; 25(4): 341-54. http://dx.doi.org/10.4196/kjpp.2021.25.4.341

[200] Hu YC, Hao DM, Zhou LX, *et al.* 2′,4′-Dihydroxy-6′-methoxy-3′,5′-dimethylchalcone protects the impaired insulin secretion induced by glucotoxicity in pancreatic β-cells. J Agric Food Chem 2014; 62(7): 1602-8. http://dx.doi.org/10.1021/jf405365d PMID: 24437980

[201] Rajput MS, Dahima R. Inhibition of glucosidase by dimethyl cardamonin: Kinetic analysis, synergism with α-acarbose and mechanistic approach. Asian J Pharm Pharmacol 2019; 5(5): 66-70. http://dx.doi.org/10.31024/ajpp.2019.5.s1.9

[202] Łój D, Janeczko T, Bartmańska A, Huszcza E, Tronina T. Biotransformation of xanthohumol by entomopathogenic filamentous fungi. Int J Mol Sci 2024; 25(19): 10433. http://dx.doi.org/10.3390/ijms251910433 PMID: 39408760

[203] Luís C, Costa R, Rodrigues I, *et al.* Xanthohumol and 8-prenylnaringenin reduce type 2 diabetes–associated oxidative stress by downregulating galectin-3. Porto Biomed J 2019; 4(1): e23. http://dx.doi.org/10.1016/j.pbj.0000000000000023 PMID: 31595252