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A REVIEW OF THE ANTIDIABETIC POTENTIAL OF NATURALLY OCCURRING FLAVONOIDS

SARKAR D

Faculty of Pharmaceutical Science, Assam down town University, Sankar Madhav Path, Gandhinagar, Panikhaiti, Guwahati, Assam- 781026, India

***Corresponding Author: Dr. Dhrubajyoti Sarkar; E Mail: dhrub.s@gmail.com**

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder that affects millions of people worldwide. Traditional treatments for diabetes, such as insulin therapy and oral hypoglycemic agents, have various limitations and side effects. Natural flavonoids, which are widely found in plants and have demonstrated antioxidant, anti-inflammatory, and hypoglycemic properties, are promising candidates for the treatment of diabetes. This review article focuses on the natural flavonoids commonly used for the treatment of diabetes mellitus. It covers the chemical structures, sources, and mechanisms of action of these flavonoids, as well as their potential therapeutic benefits. The article highlights the antidiabetic effects of flavonoids on insulin secretion, glucose uptake, and insulin signalling pathways. Several studies have shown that natural flavonoids can effectively lower blood glucose levels, improve insulin sensitivity, and prevent diabetic complications. The article also discusses the safety profile of these compounds, including their potential toxicity and interactions with other medications. Overall, the review suggests that natural flavonoids hold great potential as alternative or adjunctive therapies for the treatment of diabetes mellitus. However, further research is needed to better understand the optimal doses, formulations, and modes of administration of these compounds, as well as their long-term safety and efficacy.

Keywords: Flavonoids; Diabetes Mellitus; Hypoglycemic; Insulin Sensitivity; Natural Compounds

INTRODUCTION

A major issue impacting the entire world, diabetes mellitus (DM) has shown a sharp rise in incidence over time. In low- to middle-income nations, in particular, the incidence of DM has been rising. World Health Organization (WHO) global research claims that from 108 million in 1980 to 422 million in 2014, the number of persons with DM has nearly tripled. Around 1.5 million of the 2.2 million fatalities in 2012 that were directly or indirectly related to hyperglycaemia were also caused by diabetes **[1]**. A significant increase in death rates is being caused by DM, which over time has also been linked to serious organ failure. DM is now among the non-communicable ailments that are responsible for this rise **[2]**. The three primary kinds of diabetes, type 1, type 2, and gestational diabetes, respectively target children, adults, and pregnant women **[3]**.

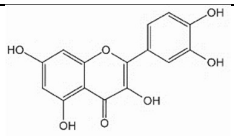
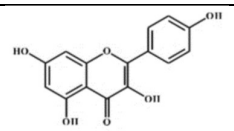
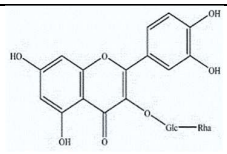
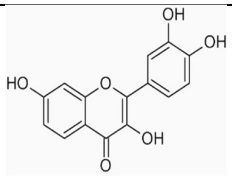
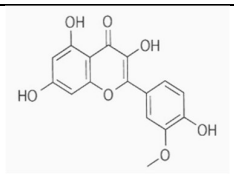
Natural substances have beneficial effects in treating a wide range of diseases and lowering the chances of developing a new disorder. They are safe to use in everyday diets **[4]**. The bioactive substances extracted from plants have demonstrated beneficial benefits in both *in vivo and in vitro* investigations, leading to hypocholesterolaemia, hypotension, hypoglycaemia, and antioxidant properties. Hence, this review article attempts to summarise various relevant research that has demonstrated the antidiabetic potential of several natural flavonoids and their molecular mechanism in treating and preventing diabetes.

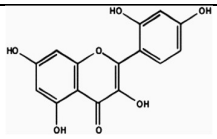
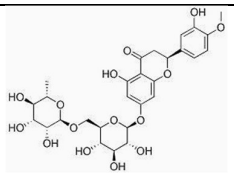
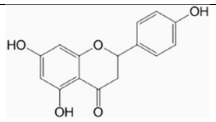
Plant Flavonoids and diabetes

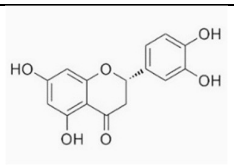
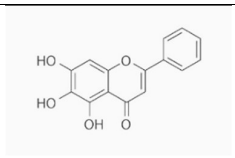
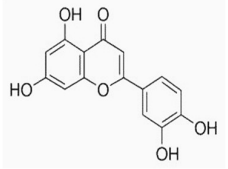
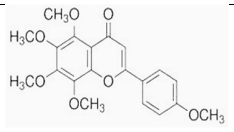
Plant-derived flavonoids have demonstrated antidiabetic efficacy throughout time through several pathways, both in vitro and in vivo. Quercetin, kaempferol, rutin, naringenin, fisetin, and morin are examples of common flavonoids with hypoglycemic effects. Flavonoid-rich plants including *Tetracera indica, Gynura procumbens*, and *Fagopyrum tataricum* have also been documented to have strong hypoglycemic effects **[5]**. Flavonoids with the capacity to bind metals and remove free radicals. It is scientifically conceivable that consuming flavonoids or foods high in flavonoids may lower the chance of developing diabetes given the relationship between inflammation and diabetes and flavonoids' capacity to defend the body against free radicals and other pro-oxidative chemicals **[6, 7]**. This tendency has given rise to new ideas including nutraceuticals, nutritional treatment, phytonutrients, and phytotherapy. Functional foods and phytomedicines can prevent particular DM by altering immunological function and regulating blood glucose levels, glucose uptake, insulin production, and glucose uptake. Several strategies have been developed in recent

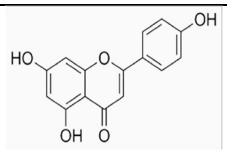
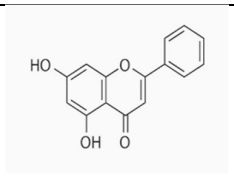
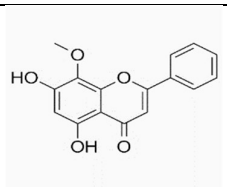
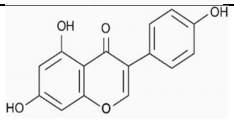
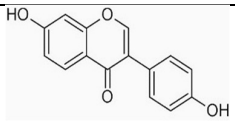
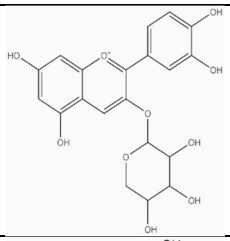
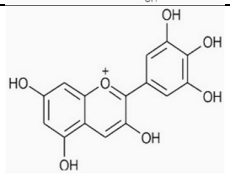
years to use flavonoids in vitro and in vivo models by adding a few unique techniques to enhance their antidiabetic efficacy **[8, 9]**. A few flavonoids are listed below which has been reported to have antidiabetic potentials.

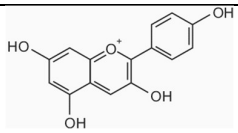
Table 1: A few flavonoids with antidiabetic potential

Name of Plant flavonoids	Structure	Sources of plant	Mechanism of action
Quercetin		***Acanthopanax senticosus*, *Ginkgo biloba*, *Psidium guajava*, *Momordica charantia*, *Polygonum perfoliatum*, *Phyllanthus Emblica*, *Allium cepa L*, *Allium fistulosum*, *Piper nigrum*, *Solanum lycopersicum*, *Acacia Arabica*, *Asparagus officinalis*, *Lactuca sativa* etc.**	**It Suppresses glucose transporter activity [5], Promotes glucose absorption in skeletal muscle cells by activating the AMPK signalling pathway[10], Lowers the synthesis of hepatic glucose and decreases glucosidase activity [11].**
Kaempferol		***Ginkgo biloba, Tilia spp. Sophora japonica, Malus domestica, Vitis vinifera, Camellia sinensis* etc.**	**α-glucosidase inhibitory action [12] , Defend against -cell toxicity brought on by hyperglycaemia[11] , Enhances AMPK and GLUT4 expression [13].**
Rutin		***Ruta graveolens, Morus alba Amaranthus viridis, Fagopyrum esculentum, Forsythia suspense, Hydrangea macrophylla* etc.**	**The research found that continuous rutin treatment reduced plasma glucose, increased insulin levels, and restored the levels of glycogen and glycolytic enzymes in streptozotocin-induced diabetic rats [14]. Rutin-treated diabetic rats showed decreased fasting plasma glucose, glycosylated haemoglobin, and C-peptide and increased glucose absorption in the soleus muscle [15, 16].**
Fisetin		***Fragaria virginiana , Fragaria chiloensis , Diospyros virginiana , Malus pumila , Allium cepa , Vitis vinifera , Actinidia deliciosa , Prunus persica , Cucumis sativus* etc.**	**Fisetin treated diabetic rats showed a decrease in the activity of glucose-dependent glucose-6-phosphate dehydrogenase. Restrict the entry of pyruvate into mitochondria to prevent the generation of gluconeogenesis, Reduce glycogen metabolism to avoid hyperglycaemia and lower blood sugar level, Hb1Ac, IL-1β, and NF-κB p65 unit [17, 18].**
Isorhamnetin		***Capsicum annuum, Petroselinum crispum , Anethum graveolens , Oenanthe javanica, Hippophae rhamnoides, Lactuca sativa, Brassica rapa, Ginkgo biloba L* etc.**	**In the streptozotocin/high-fat diet-induced Type-2-DM rat models, the study demonstrated that isorhamnetin, when administered in three distinct dosages (10, 20, and 40 mg/kg for three weeks) had an anti-diabetic effect via controlling the insulin route at the microscopic, molecular, and protein levels [19]. Improves insulin secretion, Increases Glucose transporter 2 (GLUT 2) [20].**

Morin		***Morus alba L, Maclura pomifera, Malus pumila, Allium cepa, Prunus dulcis, Chlorophora tinctoria, Castanea sativa, Artocarpus heterophyllus Psidium guajava, prunus dulcis, Chlorophora tinctoria* etc.**	**Control of β-cell function and carbohydrate metabolic enzyme activity [21],** **Reduce diabetic encephalopathy by reducing inflammation, oxidative stress, and neurotrophic support Reduces hepatic NF-κB activation[22].** **Increases hexokinase and G6PD enzymatic activities[23].**
Hesperidin		***Citrus aurantium, Citrus sinensis, Citrus unshiu, Citrus mitis, Ficus erecta var, Citrus reticulate, Citrus limon, Vitis vinifera* etc.**	**The essential hepatic enzymes involved in glycolysis and gluconeogenesis are glucose-6 phosphatase and phosphoenolpyruvate carboxykinase. These were both inhibited by hesperidin while glucokinase activity was increased [24].** **Hesperidin increases insulin sensitivity by triggering the insulin receptor pathway[25].**
Naringenin		***Citrus paradise, Citrus aurantium, Prunus cerasus, Solanum lycopersicum, Origanum vulgare, Citrus bergamia, Theobroma cacao, Mentha aquatic, Aglaomorpha quercifolia, Phaseolus vulgaris* etc.**	**Naringenin (75 µM, 2 h) administration led to an increase in glucose absorption in L6 muscle cells. Moreover, naringenin drastically elevated the phosphorylation and activity of the 5′ AMP-activated protein kinase (AMPK), and AMPK inactivation through short interfering RNA eliminated the naringenin-stimulated glucose absorption [26].** **Suppression of α-glucosidase activity, which postponed the absorption of carbohydrates, lowering post-meal blood sugar levels [27]. improves hyperglycemia by upregulating GLUT4 and controlling the expression of hepatic enzymes involved in gluconeogenesis and glycolysis. [28] [29]. Inhibition of intestinal sodium-glucose co-transporter's ability to transport glucose [30]. Much research employing animal models produced by streptozotocin (STZ) looked into the effects of naringenin. In STZ and nicotinamide-induced diabetic Wistar rats, naringenin therapy (50 mg/kg b.w./day) for five days lowered blood glucose, total cholesterol, and triglyceride levels[31]. Naringenin (1% and 2% of food) treatment during 10 weeks in Streptozotocin diabetic mice lowered sugar levels and urea levels dramatically while increasing serum insulin levels[32]. The diabetic phenotype was attenuated by naringin therapy, which dramatically decreased serum glucose levels and raised serum insulin levels[33].**

Eriodictyol		***Eridictyon californicum, Millettia duchesnei De Wild, Eupatorium arnottianum, Millettia duchesnei, Piptadeniastrum africanum, Rosa canina* etc.**	**Eriodictyol is a dietary supplement that reduces lipogenesis-related attributes in mice and improves insulin resistance by enhancing glucose metabolism, suppressing hepatic gluconeogenesis, and modifying the production and release of the incretin hormones gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)[34]**
Baicalein		***Scutellaria lateriflora L, Scutellaria baicalensis , Oroxylum indicum , Scutellaria galericulata , Scutellaria rivularia Wall,* etc.**	**In type 2 diabetic mice, baicalein at dosages of 0.25 and 0.5 g/kg/d for five weeks increased glucose intolerance, blood insulin sensitivity, and hyperglycemia. Also, it was shown that baicalein (5 mM) greatly increased glucose-stimulated insulin production and considerably increased vitality in human islet culture cells and insulin-secreting pancreatic INS382/13 cells (GSIS)[35].**
Luteolin		***Daucus carota*, *Allium cepa*, *Apium graveolens, Capsicum annuum, Brassica oleracea, Malus domestica*, *Salvia rosmarinus, Mentha piperita* , *Ginkgo biloba* etc.**	**Luteolin can scavenge reactive oxygen species (ROS) and shield the components of other antioxidant systems from ROS by blocking the enzymes that produce them[36]. The pancreas is protected and insulin secretion is boosted by luteolin's antioxidant properties and hypoglycemic potential. Diabetes-induced animal models have been used to demonstrate the suppression of lipid peroxidation and the control of free radical production[37]. According to reports, luteolin affects the Akt2 kinase to increase insulin sensitivity. Since Akt2 stops the insulin receptor from losing its phosphorylation, the insulin signalling mechanism isn't diminished. The translocation of the glucose transporter GLUT4 to the cell's surface mediates the impact of Akt2, which is also in charge of controlling glucose absorption[38,39].**
Tangeretin		***Poncircus trifoliate l*, *Citrus paradise, Citrus aurantium, Citrus reticulata*, *Malus domestica* etc.**	**In HFD-induced obese mice, the injection of tangeretin (200 mg/kg) decreased blood sugar, total cholesterol, and body weight, and controlled adipocytokines such as leptin, IL-6, and adiponectin[40]. Tangeretin (100 mg/kg) treatment for 30 days significantly improved glycolytic enzymes, insulin levels, and haemoglobin levels while lowering glucose plasma levels and Hb1Ac[41].**

Apigenin		***Petroselinum crispum, Spinacia oleracea, Citrus sinensis, Apium graveolens , Allium sativum , Daucus carota , Camellia sinensis*** **etc.**	**Apigenin increases insulin release from the pancreas and stimulates glucose metabolism and its transport in peripheral tissues. The capacity of apigenin to delay β-cell apoptosis and trigger insulin release[42]. In the skeletal muscles of diabetic rats, apigenin extract can interact with traditional cellular insulin metabolic signalling to increase the level of GLUT-4 protein and facilitate GLUT4 translocation [43].**
Chrysin		***Tilia tomentosa , Passiflora caerulea L. , Passiflora incarnata, Oroxylum indicum Apis mellifera (*****Honey bee*****)*****etc.**	**According to a recent study, chrysin therapy reduced renal pathology and reduced the expression of the proteins TGF-β, fibronectin, and collagen-IV in renal tissues[44]. Chrysin has anti-inflammatory actions in the kidney by selectively targeting the TNF- pathway, preventing the onset of diabetic neuropathy (DN) in HFD (High-fat diet)/STZ(Streptozotocin)-induced diabetic rats[45].**
Wogonin		***Scutellaria baicalensis , Scutellaria radix. ginkgo biloba , Mentha arvensis , Capsicum annuum , Matricaria chamomilla*** **etc.**	**By the activation of AMPK(activated protein kinase) and PPARα (Peroxisome-proliferator-activated-receptor) wogonin has various beneficial effects on insulin sensitivity, blood glucose, and lipid metabolism[46].**
Genistein		***Lupinus spp., Vicia faba, Glycine max, Pueraria lobata, Psoralea corylifolia*** **etc.**	**Employing the cAMP (Cyclic adenosine monophosphate) /PKA (protein kinase A) pathway, lower blood sugar levels, Reduce p-ERK(Phosphorylated Extracellular Signal-Regulated Kinase) and Intercellular Adhesion Molecule-1 (ICAM-1) levels and the tyrosine kinase enzyme's activity enhance the mass of -cells and glucose intolerance.**
Daidzein		***Lupinus spp., Vicia faba, Glycine max, Pueraria lobata, Psoralea corylifolia*** **etc.**	**Daidzein reduces the risk of developing diabetes by improving lipid and glucose metabolism[47]. Hamsters were given pure synthetic daidzein, which dramatically reduced blood glucose and plasma total cholesterol compared to the control group [48].**
Cyanidin		***Vitis vinifera , Syzygium cumini L , Prunus avium , Vaccinium macrocarpon , Prunus domestica , Brassica oleracea , Allium cepa*** **etc.**	**Cyanidin blocks the pancreatic and intestine -glucosidase [49].** **By inhibiting pancreatic apoptosis and stimulating insulin receptor phosphorylation, cyanidin restored degenerative alterations in -cells in STZ-induced diabetic rats. [50].**
Delphinidin		***Vaccinium Corymbosum, Ipomoea batatas, Brassica oleracea, Solanum lycopersicum, Solanum melongena*** **etc.**	**Delphinidin 100 mg/kg given to diabetic mice resulted in a reduction in HbA1c glycation and albumin production rates[51]. Delphinidin was found to improve insulin resistance in high-fat-fed rats, which in turn reduced**

			inflammation and regulated redox signalling pathways. The capacity of delphinidin to decrease glucose absorption in mouse jejunal tissue and human intestinal cell lines through free fatty acid receptor 1 is what causes it to have anti-diabetic effects (also named GPR40)[52].
Pelargonidin		***Vaccinium Corymbosum* , *Rubus idaeus* , *Fragaria ananassa* , *Vaccinium macrocarpon* etc.**	**Pelargonidin therapy lowers levels of oxidative stress and hyperglycemia[53]. Pelargonidin inhibits the synthesis of thiobarbituric acid reactive compounds (TBARS) and antioxidant defence enzymes in diabetic rats[54]. Pelargonidin and its aglycon, pelargonidin-3-galactoside, were shown to promote the release of insulin in an in vitro experiment [55].**

Some common essential Flavonoids

Quercetin

One of the significant bioflavonoids found in more than 20 different plant species is quercetin which has been shown to have anti-inflammatory, anti-hypertensive, vasodilator, anti-obesity, anti-hypercholesterolemic, and anti-atherosclerotic properties. One of the main causes of illnesses including hypertension, vascular problems, and metabolic syndrome is free radicals. The term quercetin, which belongs to the family of compounds known as flavonols and cannot be made by the human body, is derived from the Latin word "Quercetum," which means oak forest. It is yellow-coloured and insoluble in cold water. However, it is fairly soluble in alcohol and lipids. One of the most prevalent dietary flavonoids, it is present in a wide variety of foods, including olive oil, many seeds, buckwheat, nuts, flowers, bark, broccoli, apples, onions, green tea, red grapes, red wine, dark cherries, and berries like blueberries and cranberries. It is primarily found in citrus fruits. The foods and beverages with the greatest levels of flavonols were fruits and vegetables such as apples, cherries, and berries as well as tea and red wine **[56]**.

Kaempferol

A polyphenol antioxidant called kaempferol may be found in fruits and vegetables. Dietary kaempferol has been shown in several trials to reduce the risk of chronic illnesses, including cancer. The antioxidant defence of the body against free radicals, which encourage the growth of cancer, may be strengthened by kaempferol. Kaempferol has been shown to modify a variety of essential components in cellular signal transduction pathways connected to apoptosis, angiogenesis, inflammation, and metastasis on a molecular level. Kaempferol

has been identified from plant sources including delphinium, witch hazel, grapefruit, and others. The melting point of kaempferol is 276-278 degrees centigrade. Kaempferol is a yellow crystalline solid and soluble in water, but it dissolves readily in hot ethanol and diethyl ether **[57]**.

Rutin

Rutin is a flavonol that is widely distributed in plants, including apples, buckwheat, tea, and passion flower. It is an essential part of food's nutrition. The plant Ruta graveolens, which also contains rutin, is where the word "rutin" originates. Rutin has a melting point of 176–178 °C and has a light yellow or yellow-green needle crystal or crystalline powder appearance. It has a somewhat unpleasant flavour and typically contains three crystals of water. Rutin is rarely soluble in cold water, chloroform, carbon disulfide, ether, benzene, and petroleum ether. It is soluble in methanol, pyridine, alkaline solution, and boiling water. Rutin is widely distributed in nature and almost entirely found in all members of the Rutaceae and Sectaceae plant families. Chemically, it is a glycoside made up of the disaccharide rutinose and the flavonol aglycone quercetin. It has shown a variety of pharmacological effects, including anti-inflammatory, anti-cancer, cytoprotective, vasoprotective, neuroprotective, and cardioprotective effects **[58]**.

Apigenin

Apigenin is one of the most well-known phenolic compounds, with a wide range of beneficial nutritional and organoleptic properties. Nevertheless, and this is more intriguing, it may also contribute to health benefits, which may make it a possibility to be included in nutraceutical formulations. The wide range of pharmacological effects of apigenin and its significance for human health make a thorough understanding of its mechanism of action essential for any future use in nutraceuticals. Much research conducted over the years has shown that apigenin has a wide range of intriguing pharmacological actions and the potential for use in nutraceuticals. For instance, its antioxidant effects are widely recognised, and it may also be used as a therapeutic agent to treat conditions including inflammation, autoimmune, neurological, and even a few different forms of cancer. Compared to other structurally similar flavonoids, it exhibits low inherent toxicity on normal vs malignant cells. One of the most prevalent flavonoids in plants, apigenin is nominally a member of the flavone sub-class. One of the most pervasive in the plant kingdom and one of the most well-researched phenolics is apigenin, one of the flavonoids. Apigenin is mostly found in plants such as parsley, celery, onions, oranges, and herbs including chamomile, thyme, oregano, and basil as well as plant-based drinks (tea, beer, and wine). The

primary sources of this chemical are Asteraceae plants, specifically those in the Artemisia, Achillea, Matricaria, and Tanacetum genera. A potential agent for the treatment of cancer is apigenin. Both a dietary supplement and an adjuvant chemotherapeutic drug for cancer treatment seem to be possible uses for apigenin. It is Pale Yellow Crystalline Solid. Apigenin is soluble in ethanol, DMSO and DMF and sparingly soluble in aqueous buffers **[59]**.

Luteolin

A typical flavonoid called luteolin may be found in a wide variety of plants, including fruits, vegetables, and therapeutic herbs. In Chinese traditional medicine, luteolin-rich plants have been used to cure a variety of illnesses, including cancer, inflammatory disorders, and hypertension. Luteolin operates biochemically as either an antioxidant or a pro-oxidant and has a variety of biological properties including anti-inflammation, anti-allergy, and anti-cancer. Celery, parsley, broccoli, onion leaves, carrots, peppers, cabbages, apple peels, and chrysanthemum flowers are just a few examples of fruits and vegetables that are high in luteolin. Luteolin is a golden crystalline powder when it is pure. Luteolin is a substance made of golden needles that contain a crystallised water molecule that forms from ethanol. It is soluble in alcohol and diethyl ether, soluble to a lesser extent in hot water, and insoluble in cold water. Its aqueous solution displays a pleasant yellow hue and can be diluted in 10% sodium hydroxide aqueous solution to produce a dark yellow colour. In usual circumstances, it is stable **[36]**.

Hesperidin

Citrus fruits contain significant amounts of hesperidin, a bioflavonoid. Its usage has been linked to several health advantages, including antioxidant, antibacterial, antimicrobial, anti-inflammatory, and anticarcinogenic qualities. Hesperidin is a member of the flavanone subclass of flavonoids. It is utilised as a radioprotector, a therapy for type 2 diabetes, cancer, cardiovascular disease, and neurological and psychiatric disorders, and has lately undergone significant testing for its health-promoting and pharmacological benefits. Hesperidin administrations can also improve many cutaneous functions in both healthy and diseased skin. It has white needle-like crystals that are pure and only mildly acidic. It serves as vitamin P's primary constituent as well. It is a crystalline powder that is light yellow in colour and has a melting point of 258–262 °C (softens about 252 °C). It dissolves readily in pyridine, sodium hydroxide solution, dimethyl formamide, methanol, and hot glacial acetic acid, and it dissolves only a little bit in ether, acetone, chloroform, and benzene. This product can dissolve in 50L of

water at a rate of 1g. It has no flavour or odour **[60]**.

DISCUSSION

The article "Natural Flavonoids Used for the Treatment of Diabetes Mellitus" presents a comprehensive review of the current knowledge on the potential therapeutic effects of flavonoids in managing diabetes mellitus. The study highlights the benefits of flavonoids, which include their antioxidant, anti-inflammatory, and hypoglycemic properties, and the various mechanisms by which they may help regulate blood glucose levels and improve insulin sensitivity **[61]**.

Several studies have shown that natural flavonoids can effectively lower blood glucose levels, improve insulin sensitivity, and prevent diabetic complications **[62]**. Quercetin, a common flavonoid, has been shown to increase insulin secretion and enhance insulin sensitivity, while also reducing oxidative stress and inflammation **[63]**. Other flavonoids such as naringenin, apigenin, and kaempferol have also been shown to have hypoglycemic effects by improving insulin sensitivity and glucose uptake **[64], [65]**.

Furthermore, natural flavonoids have been shown to have a positive effect on lipid metabolism, which is often dysregulated in patients with diabetes mellitus. Studies have demonstrated that flavonoids can reduce serum triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels while increasing high-density lipoprotein (HDL) cholesterol levels **[66]**.

Despite the promising benefits of natural flavonoids, the authors note that further research is needed to fully understand their mechanisms of action and potential side effects. Additionally, the use of flavonoids as a therapeutic option for diabetes should be approached with caution, as some compounds may interact with other medications and have potential toxicity.

CONCLUSION

Natural flavonoids have shown great potential as an alternative or adjunctive therapy for the treatment of diabetes mellitus. However, more research is needed to determine the optimal doses, formulations, and modes of administration of these compounds, as well as their long-term safety and efficacy.

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