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Potential Role of Flavonoids as Anti-diabetic Agents-A Comprehensive Review

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Abstract

Diabetes mellitus is a widespread and debilitating metabolic disorder marked by sustained elevated blood glucose levels, which can culminate in a range of severe complications if unmanaged. Flavonoids, polyphenolic chemicals originating from plants, have attracted a great deal of attention in the field of diabetes research because of their antidiabetic properties. These naturally occurring substances, which are 15 carbons in structure, are widely distributed in fruits, vegetables, and other plant-based diets, have been shown to offer a number of positive benefits, including the capacity to regulate many facets of insulin and glucose homeostasis. These compounds are classified into six major subclasses based on their structural differences. Numerous in vivo and in vitro studies have looked at the antidiabetic potential of flavonoids. Flavonoids have been found to modulate enzymes such as ά-glucosidase and ά-amylase, which are the key enzymes for the reduction of blood glucose levels. Emerging evidence suggests that flavonoids may exert their antidiabetic effects through their ability to modulate various cell signaling pathways involved in glucose metabolism, insulin sensitivity, and inflammation. It has been demonstrated that flavonoids contain anti-inflammatory and antioxidant qualities. These qualities are vital for reducing inflammation and oxidative stress, which are crucial factors to the onset of diabetes. This review aims providing comprehensive elucidation of the cellular and molecular mechanisms underlying the antidiabetic effects of flavonoids, considering their potential impact on various metabolic pathways involved in diabetes.

Keywords: *Diabetes Mellitus, Flavonoids, Glycemic Control, Health and well-being, Novel methods, Signaling Pathways*

Introduction

Insulin resistance or inadequate insulin synthesis is the etiology of diabetes mellitus, an endocrine condition. This condition is caused by the body's reduced ability to make or effectively use the hormone insulin, which is crucial for maintaining appropriate blood sugar management. Diabetes mellitus is a widespread metabolic disease characterized by chronic hyperglycemia [1]. Diabetes is categorized into two types: type 1 (T1DM) and type 2 (T2DM). The depletion of β cells causes diabetes type 1 (T1DM). The cause of type 2 diabetes mellitus is increased insulin

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resistance [2]. The International Diabetes Federation states that 537 million persons aged 20 to 79 have diabetes. Additionally, it projects that by 2030 there will be 630 million people on the planet who will have diabetes [3]. For many years, the management and treatment of diabetes in modern medicine have relied on a range of pharmacological interventions, including insulin therapy, oral hypoglycemic medications, and other pharmaceuticals. Although these drugs have been shown to help control blood sugar levels, they are often linked to several side effects. Consequently, the use of natural remedies, namely phytochemicals derived from medicinal plants, as an additional or alternative form of therapy for managing diabetes is becoming popular [4].

Flavonoids

Flavonoids are one class of phytoconstituents that has drawn a lot of interest in the treatment of diabetes. Flavonoids are a broad class of secondary metabolites derived from plants that contain more than 10,000 polyphenolic compounds. A broad class of compounds called flavonoids is present in fruits, vegetables, nuts, seeds, spices, tea, chocolate, grape seeds, apples, and herbs. Their anti-inflammatory, anti-diabetic, and antioxidant qualities have all been demonstrated. that have attracted a lot of interest in the field of diabetes research because of their intriguing therapeutic potential. Numerous studies conducted in vitro and using animal models have demonstrated the diverse antidiabetic characteristics of flavonoids, such as their hypoglycemic effects and capacity to stop or slow the development of diabetic complications [5–6]. Studies examining the relationship between structure and activity have shown that flavonoids with particular substitutions, such as hydroxy substitutions at positions C5 and C7 and a double bond between C2 and C3, have significant antidiabetic activity [7].

Mechanism of Flavonoid

Flavonols

One type of flavonoid that has potent anti-diabetic effects is flavonol; it inhibits the enzymes that break down carbohydrates and lowers the absorption of glucose [8]. By inhibiting enzymes such as α-glucosidase and aldose reductase. Flavonoids, particularly flavonols, have the ability to lower hyperglycemia [9]. These findings highlight the potential of flavonols as natural compounds with promising antidiabetic properties, making them valuable candidates for further research and drug development.

Quercetin

Quercetin is a flavonoid that has potent anti-diabetic effects through many molecular mechanisms. It alleviates insulin sensitivity and pancreatic histological changes in mice with type 2 diabetes (T2DM) by targeting the miR-92b-3p/EGR1 axis [10]. Quercetin promotes pancreatic β-cell activity, which leads to insulin production, reduces inflammatory markers, and raises oral glucose tolerance [11].

Kaempferol

A naturally occurring flavonol, kaempferol, has antidiabetic effects through a variety of molecular mechanisms. By inhibiting apoptosis, decreasing caspase-3 activity, and increasing antiapoptotic proteins, including Akt and Bcl-2, it enhances pancreatic β-cell survival and function [12]. Moreover, pancreatic and duodenal homeobox-1 (PDX-1) expression, synthesis, and secretion of insulin are stimulated by kaempferol [13]. This highlights the role of kaempferol in the pancreatic β-cell survival factor that fights diabetes.

Galangin

By altering several molecular pathways, the flavonoid galangin, which exhibits a broad variety of biological actions, may have therapeutic value as an antidiabetic agent. Through its regulation of key proteins including AKT, AMPK, G6 Pase, and Pepck, galangin may have an impact on inflammation, glucose production, and resistance to insulin [14].

Flavones

A subclass of flavonoids called flavones has a number of different mechanisms by which they work to prevent diabetes. Research has demonstrated that specific structural characteristics of flavones, such as the addition of acetate groups at positions C-5 and C-7 of the flavone skeleton and the methoxy group at position C-8, contribute significantly to their antidiabetic properties by enhancing the processes involved in the absorption of glucose [6]. It has been demonstrated that flavones have antioxidant qualities, lower insulin resistance, increase the proliferation of pancreatic β-cells, and lower α-amylase. These effects are crucial in regulating type 2 diabetes and its aftereffects [15]. These findings highlight the multifaceted mechanisms through which flavones exhibit their antidiabetic effects, emphasizing their potential as natural compounds for diabetes prevention and treatment. Some examples of flavones are apigenin, luteolin, chrysin, and baicalein.

Apigenin

Numerous biochemical routes allow apigenin, a flavonoid with numerous biological activities, to exert its antidiabetic effects. Research has indicated that apigenin can prevent diabetic nephropathy by regulating the miR-423-5p-USF2 axis, which in turn reduces renal cell fibrosis, inflammation, and the epithelial-mesenchymal transition [16]. It has been demonstrated that apigenin and its derivatives enhance cells' uptake of glucose and suppress the activity of α-glucosidase, indicating their potential as anti-diabetic medications [17]. These results demonstrate the several molecular mechanisms by which apigenin carries out its anti-diabetic actions, indicating that it may be used as a potential candidate for the creation of novel diabetes treatment methods.

Baicalein

A bioactive flavonoid called baicalein has been connected through several different molecular routes to potential antidiabetic effects. It inhibits pancreatic elastase in a non-competitive manner inhibits acetyl cholinesterase (AChE) in a monophasic kinetic mechanism [18], and decreases the formation of toxic aggregates that contribute to the pathogenicity of type II diabetes [19]. These findings suggest that baicalein's broad range of actions on several molecular targets supports its potential as a medication for diabetes.

Flavanones

Flavonones found in citrus fruits, such as naringenin and hesperidin. Research has shown that flavanones contain properties that make insulin more sensitive, which may help with the control of diabetes [20]. Due to their many benefits, flavonones are a great option for further study and incorporation into diabetes management strategies.

Hesperidin

Natural flavanone hesperidin has the potential to prevent diabetes through a variety of molecular mechanisms. It reduces the generation of advanced glycation end products and fructosamine concentrations by inhibiting α-amylase activity [21]. Hesperidin treatment for diabetic rats has been shown to enhance spleen function by reducing oxidative stress and inflammation, modifying Bcl-2 family proteins, and preventing splenic cell death [22].

Naringenin

Citrus fruits contain a flavonoid called naringenin, which has anti-diabetic effects through a variety of molecular mechanisms.

Research indicates that naringenin enhances insulin-independent glucose uptake in high glucose-treated cells via phosphorylating AMP-activated protein kinase (AMPK) [23]. Naringenin's antidiabetic properties are further enhanced by its inhibition of alpha-glucosidase activity and activation of PPARγ receptors [24]. These investigations demonstrate the several a molecular mechanism by which naringenin prevents diabetes.

Flavanols

Flavanols, a kind of polyphenol found in abundance in fruits and vegetables, have the potential to prevent diabetes by influencing many metabolic pathways and immune responses [25]. It is also known as flavan-3-ols. Research has demonstrated the significant contributions flavonols, like epicatechin and catechin gallate (CGA), make to the management of diabetes. These flavanols suppress hepatic gluconeogenesis, enhance insulin sensitivity, control calcium channels involved in insulin secretion, and increase glucose uptake and insulin secretion [26].

Epigallocatechin Gallate

Through a variety of chemical mechanisms, catechin gallate, in particular epigallocatechin gallate (EGCG), has anti-diabetic properties. By interacting with important residues like Phe23 and Ile26, hIAPP is associated with type II diabetes [27]. Moreover, by scavenging free radicals, changing lysine residues, and dislodging protein aggregates in muscle cells, which are linked to diabetes, EGCG can stop the synthesis of advanced glycation end products (AGEs) [28]. These findings collectively highlight the diverse molecular mechanisms through which catechin gallate exerts its antidiabetic effects.

Catechins

Catechins, which are prevalent in tea and many plant-based diets, have intriguing anti-diabetic characteristics that target several systems. According to research, catechins can help with diabetes by improving insulin resistance, reducing oxidative stress, regulating mitochondrial function, alleviating endoplasmic reticulum stress, producing anti-inflammatory effects, lowering blood sugar levels, and regulating intestinal function [29]. Furthermore, catechin's suppression of dipeptidyl peptidase-4 (DPP-4) in Withania somnifera roots contributes to its antidiabetic activity via interactions with key enzymes involved in insulin release and GLP-1 production [30]. These findings highlight catechins as viable natural chemicals for treating diabetes through many molecular pathways.

Isoflavones

Numerous studies have demonstrated the significant antidiabetic action of isoflavones. It has been demonstrated that they affect adipocyte development, regulate glucose metabolism, decrease hyperglycemia, boost insulin sensitivity, and activate gene expression through peroxisome proliferator-activated receptors [31]. It has been demonstrated that isoflavones such as biochanin A, genistein, daidzein, glycitein, and formononetin alter how carbohydrates are metabolized, reduce insulin resistance, and control hyperglycemia, indicating that they may be employed as safe antidiabetic drugs [32].

Bis-pyrano prenyl

Numerous studies have demonstrated the potential antidiabetic benefits of isoflavone bis-pyranoprenyl. Research indicates that the anti-hyperglycemic characteristics of bis-pyranoprenyl isoflavone, which is isolated from Polygala molluginifolia, include improved glucose tolerance, increased liver glycogen, inhibition of maltase activity, promotion of GLP-1 and insulin secretion, and inhibition of DPP-4 [33]. These results demonstrate the potent antidiabetic properties of bis-pyranoprenyl isoflavones, which makes them a good candidate for more research and development in the treatment of diabetes.

Genistein

Through a number of molecular mechanisms, some isoflavones, including the naturally occurring isoflavone genistein, which is present in soybeans, have the ability to lower diabetes. By preventing hepatic glucose production, boosting β-cell proliferation, decreasing β-cell apoptosis, restoring hyperglycemia, and controlling the gut microbiota, genistein has been shown to improve glucose metabolism and insulin sensitivity [34]. The ability of genistein to stimulate the insulin signaling pathway is essential for reducing insulin resistance and preserving glucose homeostasis. This is notably true for boosting hepatic IRβ/PI3K/Akt signaling [35]. These results highlight genistein's potential as a natural therapeutic option for diabetics.

Anthocyanins

Numerous mechanisms enable anthocyanins to have anti-diabetic effects. By increasing insulin sensitivity, glucose, and lipid metabolism and acting as antioxidants and anti-inflammatory agents, anthocyanins may also aid in stopping the advancement of diabetes mellitus and maybe improve the results of islet transplantation [36]. These results highlight the potential of dietary anthocyanins as a treatment for diabetes and insulin resistance, two disorders that may be prevented and controlled.

Cyanidin-3-O-Glucoside

Anthocyanins, such as cyanidin-3-O-glucoside (C3G), are crucial for the body's ability to metabolize glucose and respond to insulin. Studies have demonstrated the benefits of anthocyanins in lowering insulin resistance, improving insulin sensitivity, and managing hyperglycemia [37]. Energy metabolism is regulated by PPARs, namely PPARα, which are activated by anthocyanins like C3G. As a result, cells experience increased fatty acid oxidation, ketogenesis, and glucose absorption [38]. These results highlight the potential of C3G as an insulin resistance and diabetes management and prevention treatment.

Delphinidin

A natural flavonoid compound called delphinidin has been demonstrated to protect pancreatic β cells and enhance insulin production, making it a potentially effective antidiabetic [39]. Pancreatic β cells experience less high-glucose-induced apoptosis when autophagy is activated by the AMPK signaling pathway. Inflammatory mediators and signaling pathways that contribute to diabetes-related inflammation, such as NF-κB and MEK1/2-ERK1/2, are inhibited by delphinidin [40].

Table 1. Antidiabetic Activity of Flavonoids

S. No.	Flavonoids	Example	Mechanism
1.	**Flavonol**	Quercetin, Kaempferol, Myricetin, Isorhamnetin, Fisetin, Galangin	By inhibiting enzymes such as α-glucosidase and aldose reductase [9]
2.	**Flavones**	Apigenin, Luteolin, Chrysin, Baicalein	Lower insulin resistance, increase the proliferation of pancreatic β-cells, and lower α-amylase [15]
3.	**Flavanones**	Hesperidin, Naringenin, Eriodictyol	Inhibiting α-amylase activity, Activation of

			PPARγ receptors [24]
4.	**Flavanols**	Catechin, Epicatechin, Epicatechin Gallate (ECG), Epigallocatechin Gallate (EGCG)	Suppress hepatic gluconeogenesis, enhance insulin sensitivity, control calcium channels involved in insulin secretion [26]
5.	**Anthocyanins**	Cyanidin, Delphinidin, Malvidin, Peonidin	Lowering insulin resistance, improving insulin sensitivity [40]
6.	**Isoflavones**	Genistein, Daidzein, Biochanin A, Bis-pyrano prenyl	Control hyperglycemia, reduce insulin resistance [32]

Conclusion

To summarize, flavonoids have emerged as chemicals of great interest in the search for effective antidiabetic drugs due to their prevalence in the human diet and their biological activity. The data gathered suggests that flavonoids may have a favorable effect on glucose metabolism and insulin sensitivity, providing a supplementary strategy in the treatment of type 2 diabetes. Their antioxidant, anti-inflammatory, and insulin-mimetic characteristics offer a multifaceted approach to managing diabetic pathogenesis. While in vitro and animal research has yielded encouraging findings, there is an urgent need for well-designed, large-scale clinical trials to determine the effectiveness, safety, and optimal dose of flavonoids in humans with diabetes.

Conflict of Interest

The authors hereby declare that there is no conflict of interest.

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