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INVITED REVIEW

Exploring the Potential of Flavonoids as Efflorescing Antidiabetic: An Updated SAR and Mechanistic Based Approach

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ABSTRACT

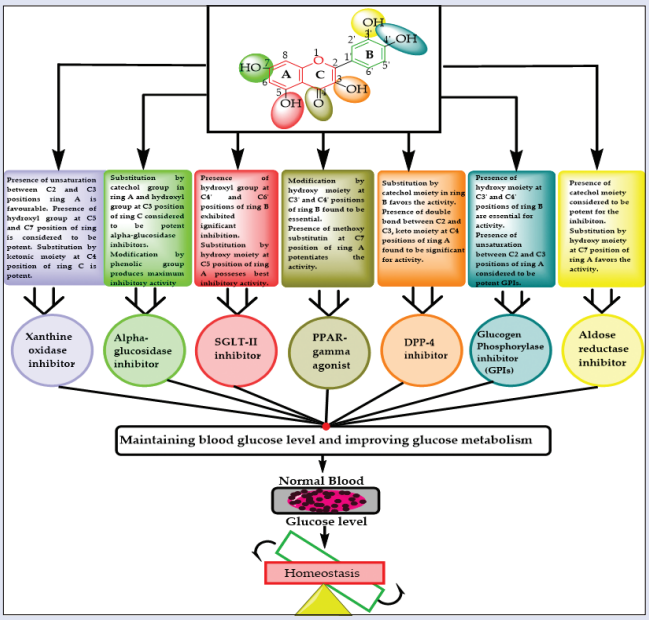
Diabetes is a metabolic complication distinguished mainly by persistent hyperglycemia and is involved in the formation of reactive oxygen species, thereby causing oxidative stress, which is the major culprit for diabetic complications in different organs, including the vascular system. Controlling blood glucose is the most effective strategy for preventing diabetes and its complications. Currently, the available antidiabetic therapy is associated with several side effects, thus inexhaustible attention has been paid toward the development of natural compounds. The present review highlights the different types of flavonoids as potent antidiabetic agents along with their structure–activity relationship (SAR) studies, which will definitely aid in designing innovative molecules with improved antidiabetic efficacy. The type of substitution in the flavonoid core structure decides their bindings at different biological targets involved in diabetes development such as xanthine oxidase inhibitors, SGLT-II inhibitors, α-glucosidase inhibitors, PPAR-γ agonists, DPP-4 inhibitors, and glycogen phosphorylase inhibitors. Based on SAR investigation, a double bond between C_2 and C_3 positions, hydroxy substitutions at C_5 and C_7 positions of ring A, and substitution by the ketonic group at the C_4 position were considered as lead modifications in the bioactivity of flavonoids for potent antidiabetic activity.

Key words: Anthocyanins, catechins, chalcone, diabetes, flavanol, flavanone, flavone, flavonoids, isoflavonoids

SUMMARY

- Flavonoids possess amazing potential to attenuate blood glucose levels in diabetes owing to their diverse mechanisms, viz., the ability to suppress oxidative stress, improve insulin sensitivity, regulation of various processes such as glycolysis, gluconeogenesis, and enzymes such as α-glucosidase, xanthine oxidase, DPP, etc. Flavonoids from different classes possessing antidiabetic effectiveness have been isolated from plants that can be further modified to get novel molecules with improved efficacy.

Abbreviations used: GLUT-4: Glucose Transporter Type-4; DPP: Dipeptidyl Peptidase; SGLT: Sodium-Glucose Linked Transporter; PPAR: Peroxisome Proliferator-Activated Receptor; GPIs: Glycogen Phosphorylase Inhibitors; ARIs: Aldose Reductase Inhibitors.



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INTRODUCTION

Diabetes is considered the world's utmost healthcare issue, affecting about 9% (475 million) of the population worldwide, and is one of the significant reasons for increased mortality, which, if not controlled, will increase to around 11% (700 million) by 2045.[1-3] It is a metabolic disorder leading to insufficient production or utilization of insulin and is associated with an escalated chance of macrovascular and microvascular defects in various organs, including the heart, kidneys, retina, and brain.[4,5] Behavioral factors, including inappropriate diet, sedentary lifestyle, and smoking, further exaggerate the disease. Currently, available therapies have only a temporary antihyperglycemic effect and thus fail to prevent further diabetic complications.[6] Moreover, their adverse effects such as weight gain, gastrointestinal disturbances, fluid retention, insulin resistance, atherosclerosis, unregulated levels of postprandial glucose and glycosylated hemoglobin (HbA_{1c}), and drug resistance, further limit their use.[7,8] It is therefore of great importance to explore novel antidiabetic molecules, which can guard patients against diabetic complications. Natural products, predominantly of plant origin, are the foremost choice for exploring promising hypoglycemic agents because of their ready availability, cost-effectiveness, and low toxicity. Plants possess diverse phytoconstituents such as flavonoids, alkaloids, terpenoids, saponins, and glycosides, which are responsible for their various pharmacological activities, including anticancer, antimalarial, antiviral, anti-inflammatory, and antidiabetic.[6,9-11] Flavonoids (Latin word flavus, meaning yellow), Figure 1, are polyphenolic compounds identified from an array of diverse plant constituents due to their various pharmacological activities such as antidiabetic,[12-14] anticancer,[15-19] anti-inflammation,[20-24] antiviral,[25,26] antimicrobial,[27-29] antimalarial,[30] immunomodulatory,[31] and anti-obesity.[32,33] They are synthesized by the phenylpropanoid pathway[34] and are ubiquitous in nature, found abundantly in various families such as Polygonaceae, Rutaceae, Leguminosae, and Umbelliferae. Citrus fruits such as oranges, grapefruits, lemons, mandarins, and bergamots (*Citrus bergamia*) are rich sources of flavonoids. More than 5,000 flavonoids have been identified such as luteolin, apigenin, tangeretin, quercetin, kaempferol, myricetin, hesperidin, fisetin, galangin, genistein, isorhamnetin, baptigenin, pachypodol, taxifolin, naringenin, epigallocatechin gallate, glycitein, and daidzein,[35] several of which are accountable for imparting attractive colors to various plant parts mainly leaves, flowers, and fruits.[36] Due to their protective effects against various diseases, they are considered health-promoting and disease-preventing dietary supplements.[37] The core scaffold of flavonoids comprises a skeleton of 15-carbon atoms, abbreviated as C6-C3-C6, having two aromatic rings (A and B) connected by 3-carbon containing ring C [Figure 1].

Extensive research has already been done in exploring the anti-diabetic properties of various classes of flavonoids[12,38]; therefore, the present study has been intended to collate all relevant information highlighting the role of flavonoids in diabetes with their associated structure–activity relationship (SAR), which will be beneficial to the keen researchers working in this area in designing novel compounds with significant hypoglycemic potential.

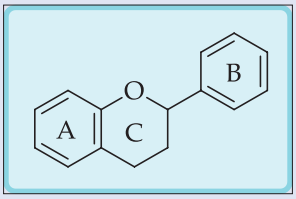


Figure 1: Basic core structure (scaffold) of flavonoids

CLASSIFICATION OF FLAVONOIDS

Flavonoids are the most widely recognized polyphenols in the human regime, accounting for more than 60% of all polyphenols utilized. A large variety of flavonoids identified[39] has been further categorized chemically into numerous subclasses based on the location of ring B, along with the level of unsaturation and oxidation of the C ring. For instance, in isoflavones, the B ring is attached to the C ring at position-3, whereas in neo-flavonoids, the B ring is attached to the 4-position of the C ring. However, flavonoids in which the B ring is attached at position-2 of the C ring are further characterized into several subclasses, viz. flavones, isoflavone, flavonols, flavan-3-ol, flavanones, neoflavonoid, flavanonols, catechins, isoflavan, anthocyanins, and chalcone, depending upon the structural parameters of the C ring[40][Figure 2].

Flavonoids as antidiabetic agents

Flavanones

Naringin (I) and its aglycone portion naringenin (II), hesperidin (III), and taxifolin (IV) are flavanones found in citrus fruits, mainly grapefruits (highest amount), oranges, lime juice, tomatoes, wine, bergamot, and in tea, grass, and wine.[41] Flavanones are reported to exhibit significant hypoglycemic effects[7,42-45] owing to their potential to ameliorate insulin sensitivity by suppressing oxidative stress, receptor for advanced glycation end products (RAGE)/NF–κB mediated mitochondrial apoptosis, and activation of the IR/PDK1 pathway along with the regulation of glycolysis, gluconeogenesis, and α-glucosidase activity [Table 1].

Flavones

Flavones such as tangeretin (**V**), nobiletin (**VI**), luteolin (**VII**), and apigenin (**VIII**) are widely found in citrus fruits, celery, parsley, chamomile, mint, red pepper, apple, onion, cabbage, carrot, tomato skin, and many herbs.[73] Their hypoglycemic tendency[74-79] may be attributed to their different mechanisms, including stimulation of the AMPK pathway, PPARγ, and GLUT-4 expression, and inhibition of the MAPK pathway, as well as oxidative stress, as depicted in Table 2.

Flavonols

Flavonols, the structural blocks of proanthocyanins, are flavonoids with a hydroxyl group at position 3 of the C ring. Kaempferol (IX), quercetin (X), fisetin (XI), and myricetin (XII) are the most significant flavonols obtained from a variety of sources, viz., onion, kale, lettuce, apple, berries, scallions, tomatoes, apple, grapes, tea, red wine, and berries. Flavonols possess extensive health benefits, including their anticancer potential, antioxidant activity as well as reduced risk of vascular disease.[90] Their α-glucosidase, glucose-6-phosphatase, and DPP-4 inhibitory activity, glucokinase and GLP-I agonistic activity, and antioxidant nature make flavonols effective antihyperglycemic agents,[91-94] as evident from different studies [Table 3].

Isoflavonoids

Isoflavonoids, viz., daidzein (**XIII**) and genistein (**XIV**) are the leading and unique subclasses of flavonoids, yet holding a diminutive identification in the plant world, primarily in soybeans or leguminous plants. Some are, however, also present in microbes, where they help in the growth of phytoalexins during plant–microbe interactions.[40] Numerous studies have demonstrated the role of isoflavones as an antidiabetic[110,111] due to their tremendous actions on β-cell proliferation, insulin secretion, and α-glucosidase inhibition [Table 4].

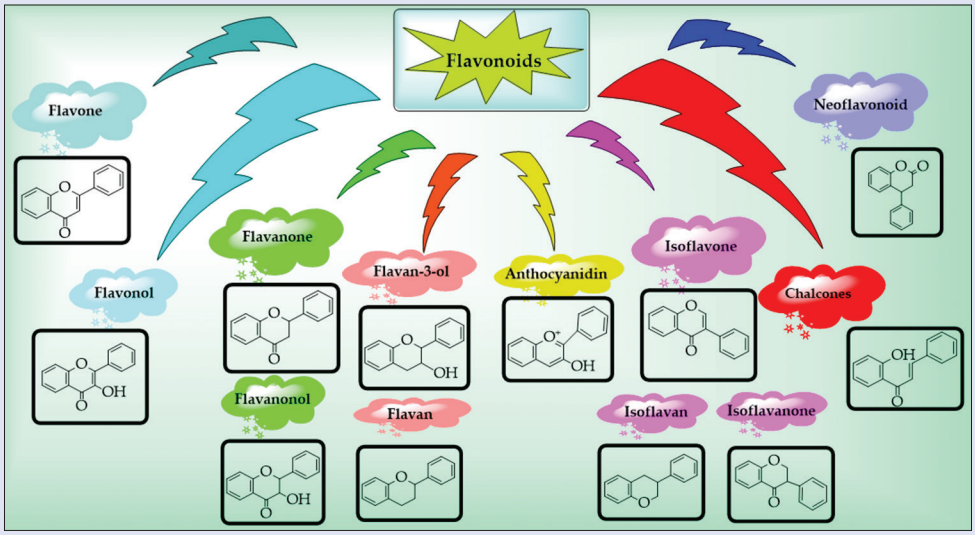


Figure 2: Types of flavonoids

Catechins

Catechins (**XV**) are flavonols with no keto group at the C_3 position and are essentially found in various fruits such as black grapes, strawberries, and also in tea, cocoa, and chocolate, mainly as monomers (epicatechin and catechin) or oligomers (proanthocyanins). The antidiabetic efficacy of catechins[114] is largely attributed to their potential to regulate oxidative stress [Table 5].

Anthocyanins

Anthocyanins, an important class of flavonoids, are responsible for imparting color to plants and are known for their antioxidative tendency as well as reported antidiabetic potential[118-120] mainly due to their PPARγ agonistic activity and α-glucosidase, and GSH antagonistic activity [Table 6]. Cyanidin (**XVI**), delphinidin (**XVII**), malvidin (**XVIII**), peonidin (**XIX**), and pelargonidin (**XX**) are the chiefly recognized anthocyanins found abundantly in various fruits such as cranberries, blackcurrants, and blackberries.[121]

Chalcones

Chalcones, mainly phloridzin (**XXI**), arbutin (**XXII**), and phloretin (**XXIII**), are open-chain flavonoids with no C ring in their structure. Tomatoes, blueberries, pears, strawberries, and various wheat products are rich sources of chalcones that impart high nutritional and pharmacological benefits. Chalcones have an astonishing tendency to act on different therapeutic targets such as DPP-4, GLUT-4, SGLT-2, α-amylase, α-glucosidase, aldose reductase, PPAR-γ, and AMP-activated protein kinase, confirming their role in maintaining glucose levels in diabetic patients[133,134] [Table 7].

SAR of Flavonoids toward Antidiabetic Activity

Flavonoids undoubtedly act as potent hypoglycemics via various mechanisms. With an approach for designing and refinement polyphenolic compounds, a structural modification technique has been discussed, which is generally known to be SAR studies. This is a term that refers to the association between chemical structures and the biological activity relationship of compounds. Moreover, understanding a drug's mechanism of action is imperative for successfully using this approach. Based on the literature available, almost all positions of flavonoid scaffolds can be structurally changed. Several structural alterations by various types of medicinally important substituents have been discussed, which has inspired and attracted confront researchers to design novel flavonoids with improved activity[139] [Figure 3].

Flavonoids as xanthine oxidase inhibitors

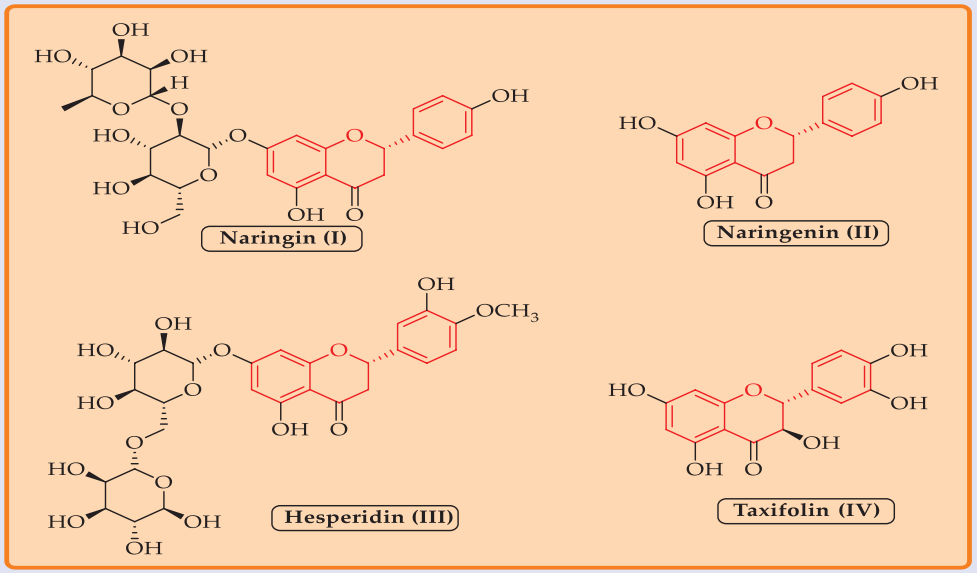
Because of the ability to prevent free radical generation, xanthine oxidase inhibitors have significant therapeutic potential for the management of diabetes.[140] Many of the planar flavonoids such as flavones and flavonols, including luteolin, kaempferol, quercetin, myricetin, and silybin, act as good inhibitors of xanthine oxidase, whereas non-planar flavonoids such as isoflavones and anthocyanidins were found least effective.[141] SAR studies indicated that hydrophobicity along with planar structure (coplanarity of ring B with rings A and C), unsaturation between C_2 and C_3, and a hydroxyl group at C_5 and C_7 of ring A or C_3 and C_4 of ring B are some of the essential requirements responsible for interaction with xanthine oxidase. Hydroxylation increases the electrostatic interaction with the enzyme, resulting in an enhanced activity. In addition, the substitution of the keto group at the C_4 position is considered optimum for activity, as discussed in Figure 4. However, the presence of a bulky sugar moiety, methyl group, and hydroxyl group at C_3 and C_6 positions (ring A) of the flavonoid core structure was considered unfavorable for its binding at the target site.[142,143]

Various studies have been reported to explore the antidiabetic potential of flavonoids possessing inhibition toward the xanthine oxidase enzyme. In view of this, Guimaraes *et al.*[144] discussed the role of rutin (flavonoid) against myocardial dysfunction in diabetic rats by inhibiting this enzyme leading to decreased oxidative stress. Furthermore, the SAR study was also performed, which suggested that the presence of a dihydroxyl group at the C_5 and C_7 positions of ring A, modification by the catechol system in ring B, and ketone moiety at the C_4 position of ring C with unsaturation in between C_2 and C_3 positions retard the absorption of glucose via the inhibition of xanthine oxidase enzyme.[144]

Flavonoids as α-glucosidase inhibitors

Inhibitors of α-glucosidase, being the most promising compounds in reducing postprandial hyperglycemia, serve as another imperative target for designing novel flavonoids such as antidiabetic agents due to their potential in reducing this enzyme activity. Flavonoids such as isorhamnetin, luteolin, naringenin, apigenin, kaempferol, isoquercetin, rutin, chalcone, and chrysin are reported as successful α-glucosidase inhibitors.[145] Like xanthine oxidase inhibitors, SAR studies reveal the presence of unsaturation at C_2 and C_3 positions, a catechol group in

Table 1: Flavanones with significant antidiabetic potential



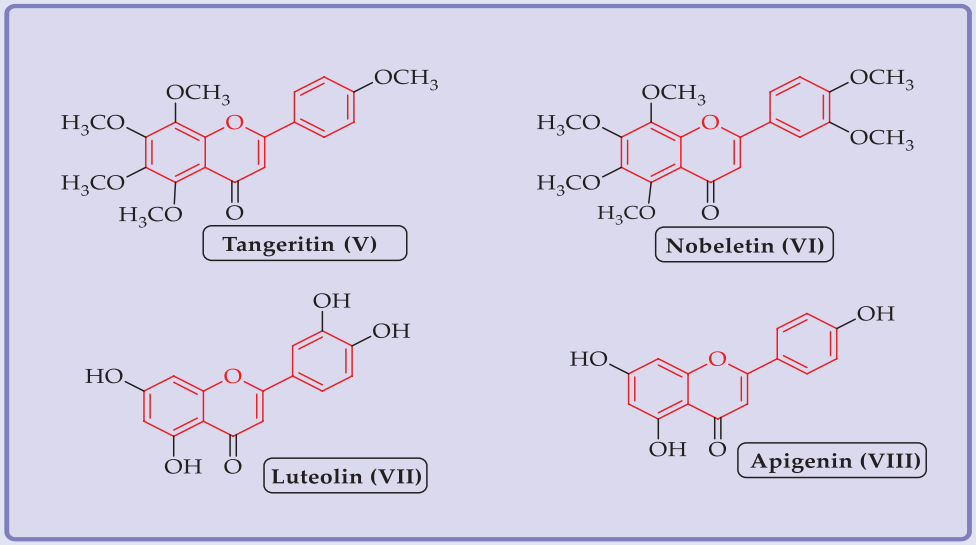
Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Naringin (2S)-5-Hydroxy-2-(4-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-chromen- 7-yl 2-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside ($C_{27}H_{32}O_{14}$; 580.4 g/mol)	*Citrus maxima*, *Carissa carandas*	100 mg/kg/8 weeks/oral	T2DM-induced steatohepatitis	Impedes RAGE/NF-κB-dependent mitochondrial apoptosis	[46]
		100 mg/kg/8 weeks/oral	STZ-induced diabetes	Improves β-cell proliferation by upregulating FoxM1 transcription factor	[47]
		100 mg/kg/8 weeks/oral	STZ-induced diabetes	Increases insulin gene expression and secretion via PDX-1 gene upregulation	[48]
		100 mg/kg/4 weeks/oral	Fructose-induced diabetes in rats	Improves insulin resistance and oxidative stress	[49,50]
		50 mg/kg/oral	STZ-induced diabetes	Improves ketoacidosis and lipid peroxidation	[51]
		50 mg/kg/7 days/intraperitoneal	Alloxan induced diabetes	Reduces oxidative stress	[52]
Naringenin (S)-5,7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one ($C_{15}H_{12}O_5$; 272.26 g/mol)	*Salvia leriifolia*	100 mg/kg (daily)/4 weeks/oral	Gestational diabetic mice model	Restores TNF-α-induced insulin resistance via AMPK	[53]
	Drynaria fortune	150 mg (thrice a day)/8 weeks	Human adipocytes	Increases insulin Sensitivity	[54]
	Alpinia katsumadai	From Gestational day 10–17/ intraperitoneal	Heterozygous db/+ mice	Improves insulin sensitivity by suppressing nuclear factor κB activation	[55]
	Lignum dalbergia	5 and 10 mg/kg (once a day)/10 weeks/oral	STZ-induced diabetes	Alters oxidative stress by downregulation of TGF-β1 and IL-1 cytokines expression and apoptotic events.	[56]
	Cudraniacochinchinensis	50 mg/kg (daily)/21 days/oral	STZ-induced diabetes	Improves oxidative stress	[57]
		50 mg/kg (daily)/5 days	NIDDM rat model	Suppress intestinal carbohydrate absorption and thus reduces the postprandial glucose rise	[58]

Contd...

Table 1: Contd...

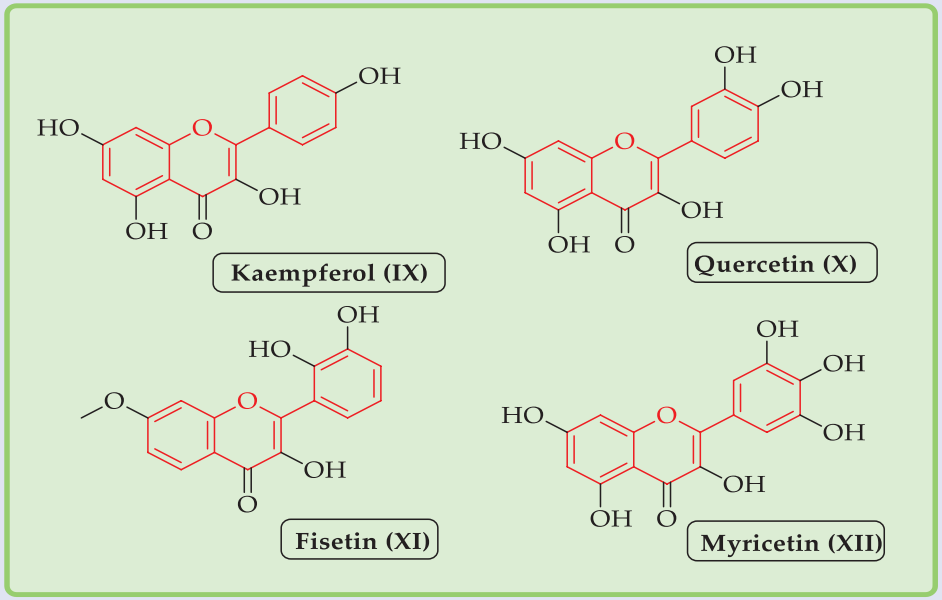
Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Hespiridin	*Citrus reticulate*	100 mg/kg/35 days/oral	Alloxan-induce d type-2 diabetes	Activates IR/PDK1 pathway and regulate glycolysis and gluconeogenesis	[59]
(2S)-5-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4-oxo-3,4-dihydro-2H-chromen-7-yl-6-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside ($C_{28}H_{34}O_{15}$; 610.189 g/mol)	*Citrus sinensis*	55 mg/kg (daily)	HFD-induced obese rats	Regulates insulin resistance by controlling inflammatory responses	[60]
		100 mg/kg (daily) 4 weeks	STZ-induced diabetes	Enhances insulin release, insulin action, and antioxidant defense system	[61]
		100 mg/kg/4 weeks/oral	STZ-induced diabetes in rats	Anti-oxidant effect	[62]
		-	STZ-induced diabetes gestational diabetes in rats	Reduces oxidative stress, inflammatory signaling pathways and RAGE-related gene expression	[63]
		100 mg/kg/4 weeks/ intraperitoneal	STZ-induced diabetes	Down-regulation of free radical generation and pro-inflammatory cytokines release	[64]
		500 mg/day/8 weeks	Type-II diabetic patients	Improve insulin resistance and glycemic control	[65]
		50, 100, and 200 mg/ kg/4 weeks/oral	STZ-induced diabetes	Improves oxidative stress	[66]
		10 mg/kg/4 weeks	STZ-induced diabetes	Controls glucose-regulating enzyme action	[67]
Hesperidin and naringin		50 mg/kg/30 days/oral	STZ-induced type-II diabetes	Reduces oxidative stress, enhances insulin secretion, and decreases gluconeogenesis thereby regulating blood sugar	[68]
		50 mg/kg (daily) hesperidin/ naringin/4 weeks	STZ-induced type-II diabetes	Potentiate antioxidant activity and suppresses production of pro-inflammatory cytokine	[69]
Taxifolin (2R,3R)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one ($C_{15}H_{12}O_7$; 304.25 g/mol)	*Pseudotsuga taxifolia*	500 mg/kg	Sprague-Dawley (SD) rat model	Inhibits carbohydrate-hydrolyzing enzyme activity	[70]
	Taxus chinensis *Garcinia epunctata* *Catha edulis* *Cedrus brevifolia* *Lyrics iberica*	100 mg/kg (daily)/30 days/ intragastrical	Alloxan-induced diabetes	Regulates α-amylase activity	[71]
		10 or 20 mg/kg (daily)/4 weeks/ intragastrical	STZ-induced diabetes	Reduces NF-κB pathway expression	[72]

Table 2: Flavones as antidiabetic agents



Component	Plant source	Dose/duration/ route	Model	Experimental outcome	Reference
Tangeretin 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl) -4H-chromen-4-one ($C_{20}H_{20}O_7$; 372.37 g/mol)	*Citrus sinensis*	100 mg/kg/30 days	STZ-induced diabetes	Enhances insulin secretion	[80]
	Citrus depressa	200 mg/kg	High-fed diet-induced diabetes	Enhances glucose uptake stimulating AMPK pathway	[81]
	Citrus reticulata	25/50 mg/kg		Enhances liver insulin sensitivity by MEK-ERK 1/2 pathway suppression	[82]
Nobiletin 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxy-4H-chromen-4-one ($C_{21}H_{22}O_8$; 402.39 g/mol)	*Poncirus trifoliate*	50 mg/kg (daily)	Gestational diabetic model	Improves glucose uptake (TNF-impaired) in skeletal muscle and inhibits Akt-Erk activation in the placenta	[83]
		10 µM	Type 2 diabetes	Increases glucose-induced insulin secretion	[84]
		200 mg/kg/5 weeks	Obese diabetic ob/ob mice	Regulates Glut 1 and Glut 4 expression	[85]
Luteolin 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one ($C_{15}H_{10}O_6$; 286.24 g/mol)	*Aloe vera*		KK-A (y) mice	Ameliorates insulin resistance and liver TNF-α mRNA expression	[86]
	Eclipta alba				
	Salvia tomentosa	200 mg/kg	STZ-induced diabetes	Anti-oxidative action	[87]
	Lonicera japonica		3T3-L1 adipocytes	Enhances PPARγ expression	[88]
	Justicia acuminatissima				
	Cyperus alopecuroides				
	Bacopa monnieri				
Apigenin 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one ($C_{15}H_{10}O_5$; 270.05 g/mol)	*Portulaca oleracea*	20 mg/kg/oral	STZ-induced diabetes	Suppress oxidative stress and inhibits MAPK pathway	[89]
	Clerodendrum viscosum				
	Justicia gendarussa				
	Allium fistulosum				
	Apium graveolens				
	Gentiana veitchiorum				
	Macaranga gigantifolia				

Table 3: Flavonols with significant antidiabetic potential



Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Kaempferol	*Andrographis paniculata*		C57BL/6J mice	Downregulation of PPAR-γ and SREBP-1c.	[95]
3,5,7-trihydroxy-2-(4-hydroxyphenyl) -4H-chromen-4-one ($C_{15}H_{10}O_6$; 286.23 g/mol)	*Psidium guajava*	200 mg/kg	Alloxan-induced diabetes	Hypoglycemic effect	[96]
	Camellia oleifera	100 mg/kg (daily)/45 days	STZ-induced diabetes	Activate glucose transport system and increases insulin binding to the receptor	[97]
	Lens culinaris	Oral	Alloxan-induced diabetes	Hypoglycemic effect	[98]
	Sophora japonica	800 mg/kg/15 days/oral	Alloxan-induced diabetes	Inhibits α-glucosidase	[99]
	Euphorbia pekinensis	100 mg/kg/8 weeks/oral	STZ-induced diabetes	Antioxidant potential mediated by Nrf-2/HO-1 axis upregulation	[100]
	Ginkgo biloba				
	Neocheiropteris palmatopedata				
	Acalypha indica				
Quericetin	*Ridax procumbens*	50, 100, 150 mg/kg/30 days/oral	STZ-induced diabetes	-	[101]
2-(3,4-dihydroxyphenyl)-3,5,7- trihydroxy-4H-chromen-4-one ($C_{15}H_{10}O_7$; 302.23 g/mol)	*Lens culinaris*	75 mg/kg	STZ-induced diabetes	Enhances insulin sensitivity via α-glucosidase inhibition	[102]
	Aesculus indica				
	Rubus fruticosus	15 mg/kg/21 days/ intraperitoneal	STZ-induced diabetes	Increase glucokinase activity with simultaneous reduction in glucose-6-phosphatase and stress proteins expression	[103]
	Trigonella foenum				
	Lagerstroemia speciosa				
	Butea frondosa	10, 15 mg/kg/10 days	STZ-induced diabetes	Increases insulin release	[104]
	Azadirachta indica				
	Betula pendula				
	Phyllanthus emblica				

Contd...

Table 3: Contd...

Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Fisetin	*Elaeagnus indica*	2.5, 5, and 10 mg/kg, 6 weeks/oral	STZ-induced diabetes	Inhibits glycaemia induced oxidative stress	[105]
2-(2,3-dihydroxyphenyl) -3-hydroxy- 7-methoxy-4H-chromen-4-one ($C_{15}H_{10}O_6$; 286.23 g/mol)	*Rhus cotinus* *Gossypium indicum Elaeagnus indica* *Rhus cotinus* *Gossypium indicum*	10 mg/kg/30 days/oral	STZ-induced diabetes	Improves glucose homeostasis through gluconeogenic enzyme inhibition	[106]
Myricetin 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)- 4H-chromen-4-one ($C_{15}H_{10}O_8$; 318.23 g/mol)	*Myristica fragrans*	20 mg/kg	STZ-induced diabetes	Enhances GLP-1 and insulin levels by inhibiting DPP-4	[107]
		250 µg/kg/oral	Type 2 diabetes	GLP-1R agonist	[108]
		100 mg/kg/7 weeks/oral	STZ-induced diabetes	Inhibits α-glucosidase activity	[109]

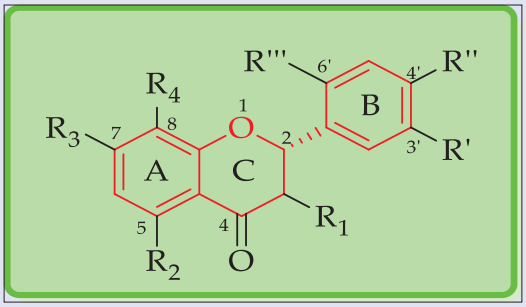


Figure 3: Substitution of flavonoids toward antidiabetic activity

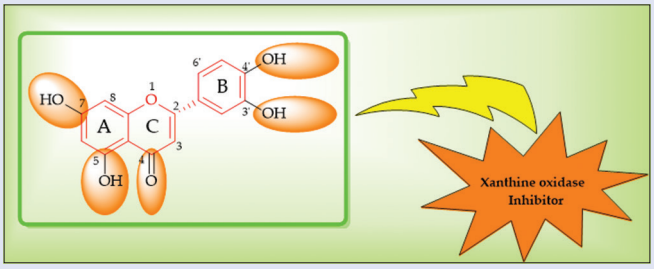


Figure 4: Potent substitutions on flavonoids for the inhibition of xanthine oxidase

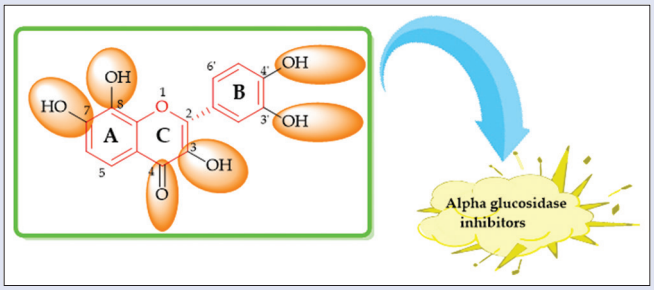


Figure 5: Potent substitutions on flavonoids for the inhibition of xanthine oxidase

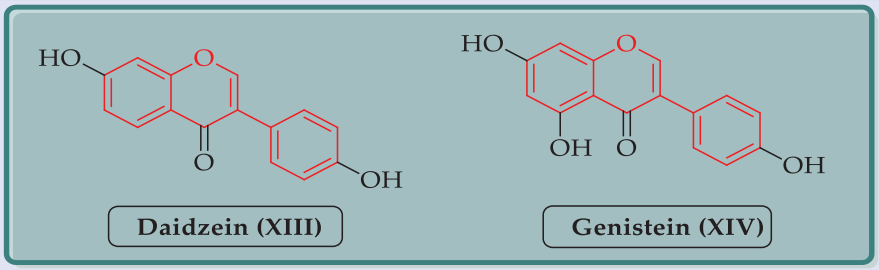
rings A (C_7 and C_8 positions) and B ($C_{3'}$ and $C_{4'}$ positions) along with a hydroxyl group (C_3 position) in ring C, carbonyl group at C_4 position potentiate the activity, as cited in Figure 5. Sugar substitution in any ring decreases the activity, but substitution by a phenolic group increases the inhibitory effect.[135,146]

To verify the above facts, Tang *et al.*[147] performed molecular simulation studies, which established a strong interaction between flavonoids against the α-glucosidase enzyme. This inhibition is further increased due to the presence of catechol moiety at ring B and hydroxyl substitution at C_3, C_7, and C_8 positions as confirmed by SAR studies.[147] Similarly, Sarian *et al.*[148] also reported the significant role of flavonoids in the treatment of diabetes mellitus due to the presence of two crucial structural elements, i.e. the double bond between C_2-C_3 and the C_4 ketonic group.[148]

Flavonoids as SGLT-II inhibitors

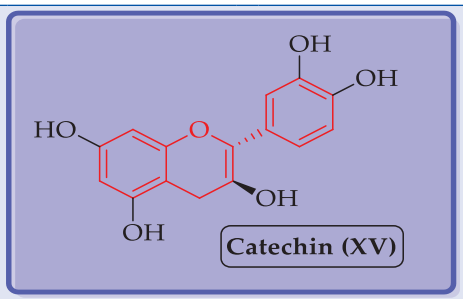
Phlorizin or phloridzin, a dihydrochalcone isolated from *Malus domestica*, was the first flavonoid reported to possess antidiabetic potential due to its ability to inhibit sodium-dependent glucose transporters I and II. Due to its various drawbacks such as poor absorption and gastrointestinal disturbances, various analogs were synthesized chemically, keeping

Table 4: Isoflavonoids with significant antidiabetic potential



Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Daidzein 7-hydroxy-3-(4-hydroxyphenyl) -4H-chromen-4-one ($C_{15}H_{10}O_4$; 254.23 g/mol)	*Chenopodium quinoa* *Acacia Arabica* *Glycine max*	100, 200, 400 mg/kg	STZ-induced diabetes	Inhibits α-glucosidase activity	[112]
Genistein 5,7-dihydroxy-3-(4-hydroxyphenyl)- 4H-chromen-4-one ($C_{15}H_{10}O_5$; 270.24 g/mol)	*Chenopodium quinoa* *Glycine max* *Butea monopermea*	10 nmol/L-5 μmol/L	INS-1 and MIN6 (insulin-secreting cell lines) and mouse pancreatic islets	Insulinotropic effect due to cAMP/PKA signaling cascade activation	[113]

Table 5: Catechins with antidiabetic potential



Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Catechins 2-(3,4-dihydroxyphenyl)-4H-chroman-3,5,7-triol ($C_{15}H_{10}O_6$; 290.26 g/mol)	*Camellia sinensis*	20, 40, 80 mg/kg	STZ-induced diabetes	Controls oxidative stress	[115]
	Elaeagnus umbellate	10 mg/kg (daily)/21 days/oral	STZ-induced diabetes	Stimulates peripheral glucose utilization and enhance glycolysis	[116]
	Bridelia ferruginea *Acacia catechu*	100 mg/kg/14 days/oral	STZ-nicotinamide induced diabetes	Increase insulin sensitivity and reduce oxidative stress	[117]

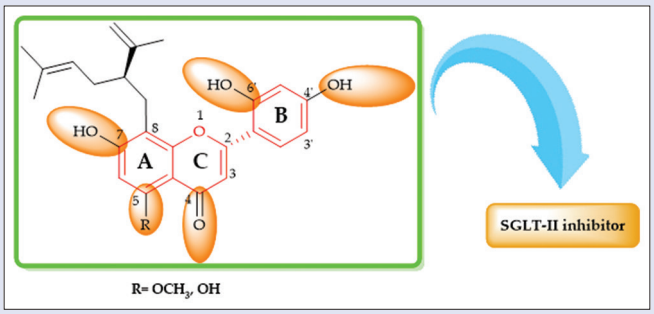


Figure 6: Flavonoids as SGLT-II inhibitors

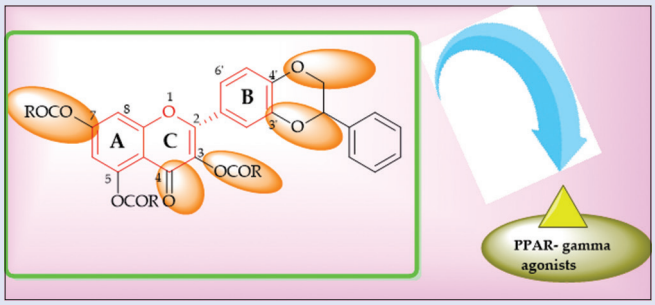


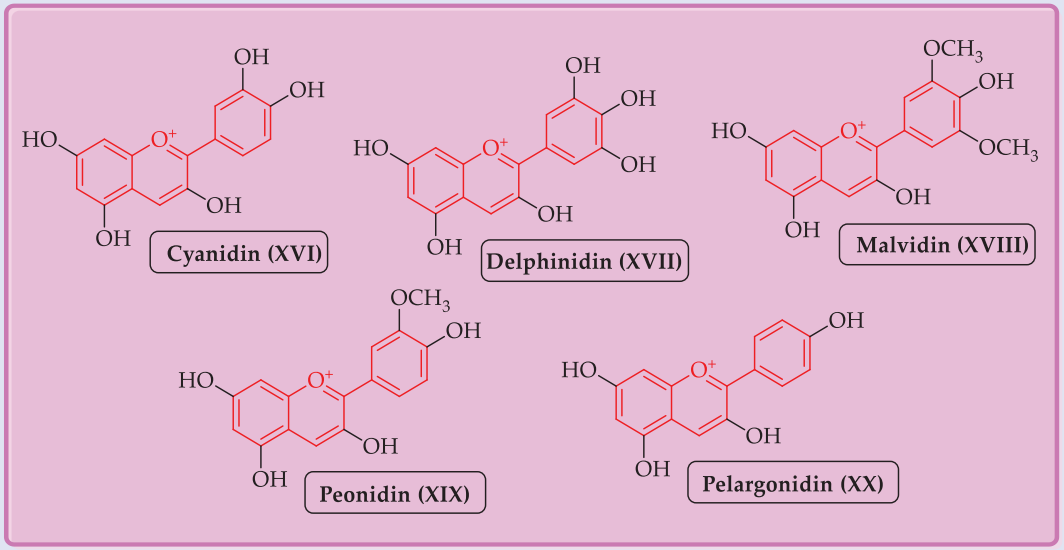
Figure 7: SAR approach toward flavonoids as PPAR-γ agonists

phlorizin as a prototype, which was found clinically successful. Epigallocatechin, quercetin, apigenin, and myricetin also ameliorate hyperglycemia by inhibiting SGLT-I.[149] Later, natural flavonoids with selective SGLT-II inhibitory activity were also isolated from methanolic extracts of *Sophora flavescens*, viz., formononetin, sophoraflavanone, and kurarinone. The presence of hydroxyl groups at $C_{4'}$ and $C_{6'}$ positions of ring B and the carbonyl group at the C_4 position favors SGLT inhibition. Methoxy or hydroxyl groups at the C_5 position of ring A, alkyl chain, especially lavandulyl at C_8, increase the SGLT-I inhibitory action, whereas replacement of this alkyl chain by the sugar moiety and substitution of the hydroxy group at the C_7 position of the ring A increase the selective SGLT-II inhibitory activity [Figure 6] as reported previously.[150,151]

Flavonoids as PPAR-γ agonists

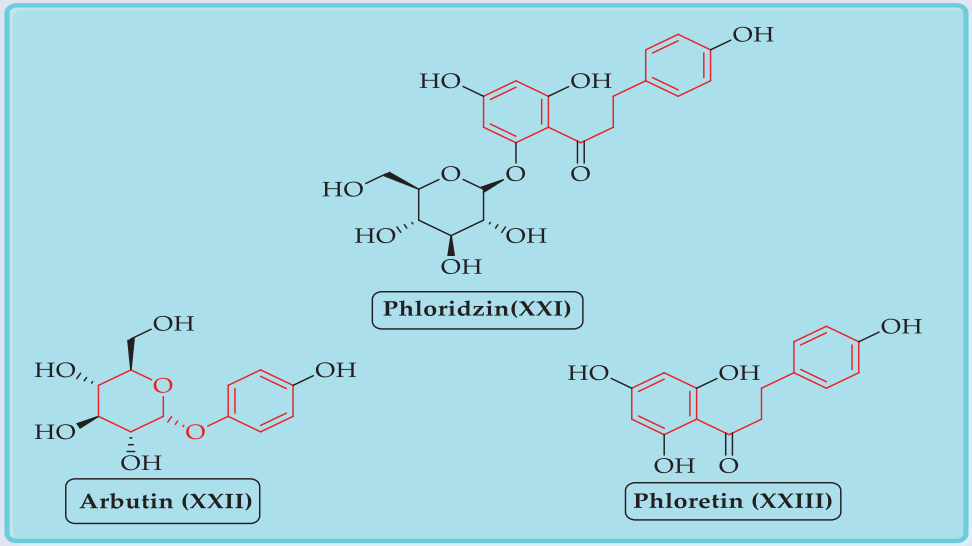
Flavonoids, by virtue of their peroxisome proliferator-activated receptor (PPAR-γ) agonistic activity, also act as a potent antidiabetic agent. They improve glucose homeostasis by escalating glucose transporter

Table 6: Anthocyanins with antidiabetic potential



Component	Plant source	Dose	Model	Experimental outcome	Reference
Cyanidin 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromenylium flavylium ($C_{15}H_{11}O_6^+$; 287.24 g/mol)	*Morus alba*	50 mg/kg (daily)	Diabetic mice	Activates PPARs	[122]
	Glycine max	20 mg/kg (daily)	Diabetic mice	GSH synthesis inhibition	[123]
	Vaccinium corymbosum	50 µmol/L	Human omental adipocytes	PPARγ activity upregulation	[124]
		10 mg/kg	STZ-induced diabetes	Inhibits α-glucosidase activity	[125]
		2 mg/kg	Diabetic rats	Downregulation of retinol-binding protein-4 expression	[126]
Delphinidin 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl) chromenylium ($C_{15}H_{11}O_7$; 303.24 g/mol)	*Ribes nigrum*	50 µM	Mice jejunal tissue and human intestinal cells	Inhibits glucose absorption in an FFA1-dependent manner	[127]
		5 mg/kg/intraperitoneal	Diabetic rat	Stimulate GLP-1 secretion	[128]
Malvidin 3,5,7-trihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl) chromenylium ($C_{17}H_{15}O_7^+$; 331.29 g/mol)	*Vaccinium angustifolium*	300 mg/kg	Type-II diabetic mice	Anti-oxidant	[129]
	Daucus carota				
Peonidin 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromenylium ($C_{16}H_{13}O_6^+$; 301.27 g/mol)	*Ipomoea batatas*	-	Type-II diabetic mice	Downregulation of NF-κB expression	[130]
Pelargonidin 3,5,7-trihydroxy-2-(4-hydroxyphenyl) chromenylium ($C_{15}H_{11}O_5^+$; 271.24 g/mol)	*Rubus occidentalis*	150 mg/kg	Diabetic rats	Induce autophagy and modulate gut microbiota	[131]
		3 mg/kg BW	STZ-induced diabetes	Lowers glycation level	[132]

Table 7: Chalcones with antidiabetic potential



Component	Plant source	Dose	Model	Experimental outcome	Reference
Phloridzin 3,5-Dihydroxy-2-[3-(4-hydroxyphenyl) propanoyl] phenyl β-D-glucopyranoside ($C_{21}H_{24}O_{10}$; 436.41 g/mol)	*Malus domestica*	5, 10, 20 and 40 mg/kg	STZ-induced diabetes	Inhibits intestinal (SGLT1) and kidney (SGLT2) sodium-glucose co-transporter	[135]
		25 mg/kg	STZ-induced diabetes	Attenuate oxidative stress (hyperglycemia mediated)	[136]
		100 mg/kg/intraperitoneal	STZ-induced diabetes	Stimulation of GLUT4 translocation and expression	[137]
Arbutin4-hydroxyphenyl β-D-glucopyranoside ($C_{12}H_{16}O_7$; 272.25 g/mol)	*Arctostaphylos uvaursi* *Pyrus biossieriana*	100 mg/mL	*In vitro* enzymatic model	Inhibit α-glucosidase activity	[138]
Phloretin 3-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl) propan-1-one ($C_{15}H_{14}O_5$; 274.26 g/mol)	*Rubus occidentali*	100 mg/kg	STZ-induced diabetes	Translocation of GLUT4 in L6 myotubes	[139]
		5, 10, 40 mg/kg	STZ-induced diabetes	Inhibits renal glucose reabsorption and promotes glucose excretion	[140]

expression (especially GLUT-4) as well as adiponectin, thereby enhancing insulin sensitivity.[152,153] SAR studies indicated that ring B having a hydroxy group at $C_3$and $C_{4'}$ positions is essential for the activity, and its replacement with any heterocyclic moiety such as thiazole, pyridine, and oxazole, decreases the activity. Esterification of the ketonic group at C_3 and C_4 positions increases the activity; however, ether substitution decreases the activity. The presence of a methoxy group at C_7 and isopentyl group at the C_6 position of ring A, along with the double bond between C_2 and C_3 in ring C, also potentiates the PPAR-γ agonistic activity [Figure 7].

Using a novel method for regioselective modification of silybin, Zhang *et al.*[154]developed strong PPAR-targeting agonists against diabetes. Based on research findings, it was concluded that the presence of an esteric moiety such as a lipophilic side chain at C_3, C_5, and C_7 positions considered to be significant PPARγ agonists even the substitution by aromatic substitution through oxygen linker was also reported to be potent.[154]

Flavonoids as a DPP-4 inhibitor

Recently, DPP-4 inhibitors have gained a lot of popularity due to their inhibitory action on endogenously released GLP-1 and GIP, leading to enhanced insulin and decreased glucagon secretion after meals. Various flavonoids such as quercetin, kaempferol, and hypolaetin, act as successful DPP-4 inhibitors as a result of catechol or hydroxyl groups present in the required configuration on ring B, the double bond between C_2 and C_3, and a keto group at the C_4 position [Figure 8].[148,155]

With the aim of exploring the antidiabetic activity of flavonoids, Pan *et al.*[156]elucidated the SAR-based therapeutic efficacy of flavonoids with kinetics and interaction mechanism. SAR analysis showed that introducing a hydroxyl moiety at C_3 and $C_4$and ketonic at C_4 positions of flavonoid core structure was reported to be beneficial for increasing their inhibitory efficiency against DPP-4.[156]

Flavonoids as insulin secretagogues

Flavonoids, especially anthocyanins, act as insulin secretagogues due to the presence of a hydroxyl group in ring B, which increases their ability to secrete insulin. The activity further increases with an increase in the number of hydroxyl groups in ring B [Figure 9].[157]

Based on considerable evidence, Zhang *et al.*[158]discovered that kaempferol, a plant-derived flavonol acts as an antidiabetic compound by enhancing pancreatic β-cell viability and insulin secretory function. In context to this, SAR analysis was also performed, which suggested that the presence of a hydroxy substitution at C_3 and $C_{4'}$positions with ketonic modification at the C_4 position was reported to be significant for the antidiabetic effect.[158]

Flavonoids as potent glycogen phosphorylase inhibitors (GPIs)

Another promising strategy for attenuating hyperglycemia involves the inhibition of glycogen phosphorylase,[159]an enzyme leading to glycogen breakdown to glucose-1-phosphate for glycolysis leading to energy production.[160] Flavonoids, viz., 6-hydroxyluteolin, rutin, and hypolaetin are identified as good inhibitors of enzyme glycogen phosphorylase.[12,161] SAR studies [Figure 10] further indicated that the double bond between C_2 and C_3 (C ring), and the presence of hydroxy groups at C_3 and $C_{4'}$ positions of the B ring are essential requirements for flavonoids to act as effective GPIs. Hydroxylation at the C_5 and C_7 positions of ring A decreases the activity; however, the activity increases if the OH group is present at C_6 and C_8 positions of the ring. Deoxygenation of the $C_{3'}$ position of ring B decreases the activity, further confirming the importance of the hydroxy group at the $C_{3'}$position.[161]

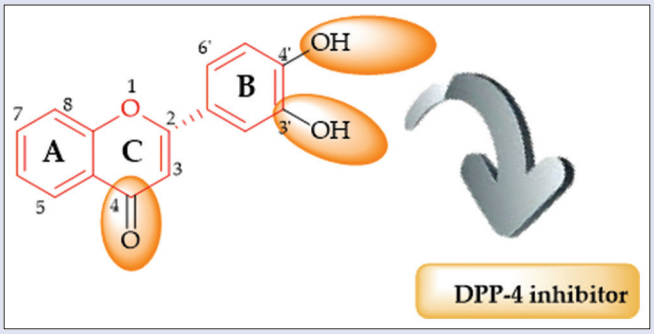


Figure 8: Potent modifications on flavonoids as DPP-4 inhibitors

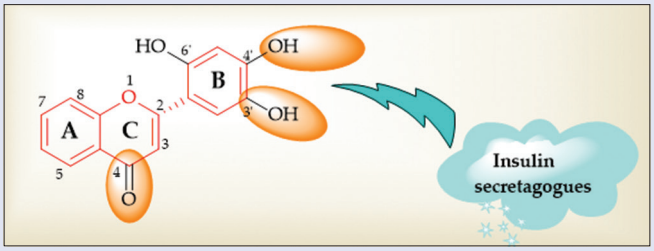


Figure 9: Effect of substitutions on flavonoids as insulin secretagogues

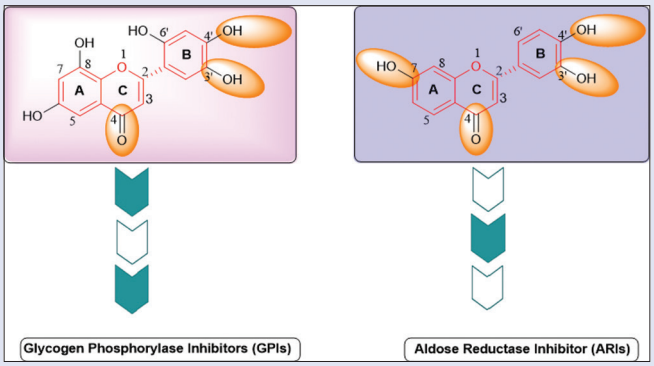


Figure 10: SAR study of flavonoids as GPI and ARI inhibitors

Flavonoids as aldose reductase inhibitors(ARIs)

Aldose reductase inhibitors, by inhibiting glucose breakdown via a specific metabolic pathway such as the polyol pathway, mainly prevent the development of secondary complications due to diabetes.[162]Flavonoids such as kaempferol, hispidulin, and cirsimarin are reported to possess an aldose reductase inhibitory effect. The SAR studies [Figure 10] suggested that the substitution by a hydroxy group at the C_7 position, the presence of unsaturation between C_2 and C_3 positions, and the 3',4'-catechol nucleus of ring B imparts strong activity. The hydroxy group at C_3 and an o-glucosyl moiety at the C_7 position, however, decrease the activity.[163] Kim *et al.*[164] isolated a number of phenolic compounds from ethanolic extract of *Paulownia coreana* bark and evaluated their significant role as potent aldose reductase inhibitors in the treatment of diabetic complications. Furthermore, the investigated compounds with the 3',4'-dihydroxy moiety on their B rings show more potent inhibition of aldose reductase in diabetes.[164] The correlation between structural requirements and the mode of action of flavonoids for antidiabetic effect [Figure 11].

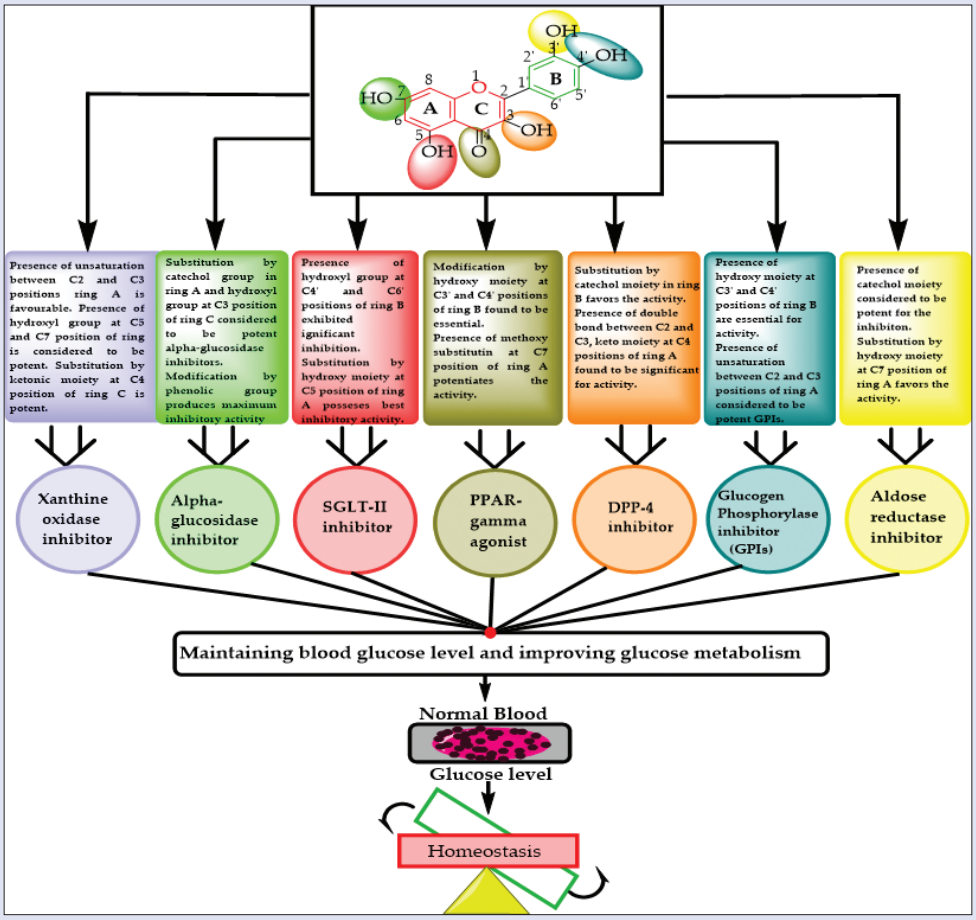


Figure 11: Correlation of structural requirements and mode of action of flavonoids for antidiabetic effect

CONCLUSION

As with the growing diabetes complications, the continuous emergence of toxicity and resistance issues clearly demands an effective therapeutic agent. With relevance to polyphenolic compounds, the flavonoid is considered a more reliable scaffold with limited toxicity. From the above study, it can be concluded that flavonoids possess amazing potential to attenuate blood glucose levels in diabetes owing to their diverse mechanisms, viz., the ability to suppress oxidative stress, improve insulin sensitivity, regulation of various processes such as glycolysis, gluconeogenesis, and enzymes such as α-glucosidase, xanthine oxidase, and DPP.

Flavonoids from different classes possessing antidiabetic effectiveness have been isolated from plants that can be further modified to get novel molecules with improved efficacy. Various SAR studies were also performed, which concluded that the major structural modifications on flavonoids include the presence of unsaturation between C_2 and C_3 positions of ring A, and the catechol moiety in rings A and B is considered as the significant substitution for maintaining blood glucose level, thereby showing a substantial increase in the antidiabetic potential of flavonoids. These findings showed the exploration of flavonoids glucose SAR as a promising approach for the development of novel antidiabetic agents.

Author contributions

Conceptualization, K.N.V., J.C., V.S., A.J., M.K., D.S., P.S., B.E.A., P.K.D., and M.A.M.; resources, K.N.V., B.E.A., P.K.D., R.V., O.I.A., M.K., W.E-D., and V.M.; writing—original draft preparation, K.N.V., J.C., V.S., A.J., M.K., D.S., P.S., B.E.A., P.K.D., R.V., O.I.A., M.A., A.B.N., N.S., M.K., C.T., W.E-D., M.H., M.F.M., V.M. and M.A.M.; writing—review and editing, K.N.V., J.C., V.S., A.J., M.K., D.S., P.S., B.E.A., P.K.D., R.V., O.I.A., M.A., A.B.N., N.S., M.K., C.T., W.E-D., M.H., M.F.M., V.M. and M.A.M.; project administration, K.N.V.; funding acquisition, K.N.V., P.S., M.A., A.B.N., N.S., and M.A.M.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, *et al.* Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from

the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843.

2. Al-Lawati JA. Diabetes mellitus: A local and global public health emergency! Oman Med J 2017;32:177-9.
3. Hameed I, Masoodi SR, Mir SA, Nabi M, Ghazanfar K, Ganai BA. Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. World J Diabetes 2015;6:598-612.
4. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, UribeK B, *et al.* Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 2020;21:6275.
5. Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab 2016;20:546-51.
6. Salehi B, Ata A, V Anil Kumar N, Sharopov F, Ramírez-Alarcón K, Ruiz-Ortega A,*et al.* Antidiabetic potential of medicinal plants and their active components. Biomolecules 2019;9:551.
7. Manandhar Shrestha JTM, Shrestha H, Prajapati M, Karkee A, Maharjan A. Adverse effects of oral hypoglycemic agents and adherence to them among patients with type 2 diabetes mellitus in Nepal. J Lumbini Med Coll 2017;5:34-40.
8. Rath D, Kar B, Pattnaik G. Preventive role of naringinin diabetes mellitus and its mechanism of action: A review. Plant Arch 2020;2:7806-12.
9. Chiocchio I, Mandrone M, Tomasi P, Marincich L, Poli F. Plant secondary metabolites: An opportunity for circular economy. Molecules 2021;26:495.
10. Jain C, Khatana S, Vijayvergia R. Bioactivity of secondary metabolites of various plants: A review. Int J Pharm Sci Res 2019;10:494-504.
11. Seca AML, Pinto DCGA. Biological potential and medical use of secondary metabolites. Medicines (Basel)2019;6:66.
12. Al-Ishaq RK, Abotaleb M, Kubatka P, Kajo K, Büsselberg D. Flavonoids and their anti-diabetic effects: Cellular mechanisms and effects to improve blood sugar levels. Biomolecules 2019;9:430.
13. Jasmin V, Jaitak V. A review on molecular mechanism of flavonoids as antidiabetic agents. Mini Rev Med Chem 2019;19:762-86.
14. Vinayagam R, Xu B. Antidiabetic properties of dietary flavonoids: A cellular mechanism review. Nutr Metab (Lond) 2015;12:60.
15. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J. Flavonoids as anticancer agents. Nutrients 2020;12:457.
16. Raffa D, Maggio B, Raimondi MV, Plescia F, Daidone G. Recent discoveries of anticancer flavonoids. Eur J Med Chem 2017;142:213-28.
17. Batra P, Sharma AK. Anti-cancer potential of flavonoids: Recent trends and future perspectives. 3 Biotech 2013;3:439-59.
18. Kandaswami C, Lee LT, Lee PP, Hwang JJ, Ke FC, Huang YT, *et al.* The antitumor activities of flavonoids. In Vivo 2005;19:895-909.
19. Ren W, Qiao Z, Wang H, Zhu L, Zhang L. Flavonoids: Promising anticancer agents. Med Res Rev 2003;23:519-34.
20. Maleki SJ, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. Food Chem 2019;299:125124.
21. Choy KW, Murugan D, Leong XF, Abas R, Alias A, Mustafa MR. Flavonoids as natural anti-inflammatory agents targeting nuclear factor-kappa B (NFκB) signaling in cardiovascular diseases: A mini review. Front Pharmacol 2019;10:1295.
22. Verri WAJr, Vicentini FTMC, Baracat MM, Georgetti SR, Cardoso RDR, Cunha TM, *et al.* Flavonoids as anti-inflammatory and analgesic drugs: Mechanisms of action and perspectives in the development of pharmaceutical forms. Stud Nat Prod Chem 2012;36:297-330.
23. Serafini M, Peluso I, Raguzzini A. Flavonoids as anti-inflammatory agents. Proc Nutr Soc 2010;69:273-8.
24. Rathee P, Chaudhary H, Rathee S, Rathee D, Kumar V, Kohli K. Mechanism of action of flavonoids as anti-inflammatory agents: A review. Inflamm Allergy Drug 2009;8:229-35.
25. Badshah SL, Faisal S, Muhammad A, Poulson BG, Emwas AH, Jaremko M. Antiviral activities of flavonoids. Biomed Pharmacother 2021;140:111596.
26. Lalani S, Poh CL. Flavonoids as antiviral agents for Enterovirus A71 (EV-A71). Viruses 2020;12:184.
27. Biharee A, Sharma A, Kumar A, Jaitak V. Antimicrobial flavonoids as a potential substitute for overcoming antimicrobial resistance. Fitoterapia 2020;146:104720.
28. Górniak I, Bartoszewski R, Króliczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. Phytochem Rev 2019;18:241-72.
29. Xie Y, Yang W, Tang F, Chen X, Ren L. Antibacterial activities of flavonoids: Structure–activity relationship and mechanism. Curr Med Chem 2015;22:132-49.
30. Rudrapal M, Chetia D. Plant flavonoids as potential source of future antimalarial leads. Syst Rev Pharm 2016;8:13-8.
31. Hosseinzade A, Sadeghi O, NaghdipourBiregani A, Soukhtehzari S, Brandt GS, Esmaillzadeh A. Immunomodulatory effects of flavonoids: Possible induction of T CD4+ regulatory cells through suppression of mTOR pathway signaling activity. Front Immunol 2019;10:51.
32. Rufino AT, Costa VM, Carvalho F, Fernandes E. Flavonoids as antiobesity agents: A review. Med Res Rev 2021;41:556-85.
33. García-Barrado MJ, Iglesias-Osma MC, Pérez-García E, Carrero S, Blanco EJ, Carretero-Hernández M, *et al.* Role of flavonoids in the interactions among obesity, inflammation, and autophagy. Pharmaceuticals (Basel)2020;13:342.
34. Rana AC, Gulliya B. Chemistry and pharmacology of flavonoids-a review. Indian J Pharm Educ Res 2019;53:8-20.
35. Kocic B, Kitic D, Brankovic S. Dietary flavonoid intake and colorectal cancer risk: Evidence from human population studies. J BUON 2013;18:34-43.
36. Iwashina T. Contribution to flower colors of flavonoids including anthocyanins: A review. Nat Prod Commun 2015;10:529-44.
37. Rupasinghe HPV. Special Issue "flavonoids and their disease prevention and treatment potential": Recent advances and future perspectives. Molecules 2020;25:4746.
38. Bai L, L i X, He L, Zheng Y, Lu H, Li J, *et al.* Antidiabetic potential of flavonoids from traditional Chinese medicine: A review. Am J Chin Med 2019;47:933-57.
39. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. Sci World J 2013;2013:1-17.
40. Panche AN, Diwan AD, Chandra SR. Flavonoids: An overview. J Nutr Sci 2016;5:e47. Doi: 10.1017/jns.2016.41.
41. Alam MA, Subhan N, Rahman MM, Uddin SJ, Reza HM, Sarker SD. Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action. Adv Nutr 2014;5:404-17.
42. Raja Kumar S, Mohd Ramli ES, Abdul Nasir NA, Ismail NHM, Mohd Fahami NA. Preventive effect of naringin on metabolic syndrome and its mechanism of action: A systematic review. Evid Based Complement Alternat Med 2019;2019:9752826.
43. Den Hartogh DJ, Tsiani E. Antidiabetic properties of naringenin: A citrus fruit polyphenol. Biomolecules 2019;9:99.
44. Mahmoud AM, Hussein O. Hesperidin as a promising antidiabetic flavonoid: The underlying molecular mechanism. Int J Food Nutr Sci 2016;3:1-2.
45. Mahmoud A, Hussein O. Anti-Diabetic effect of naringin: Insights into the molecular mechanism. Plant Biol 2016;8:324-8.
46. Syed AA, Reza MI, Shafiq M, Kumariya S, Singh P, Husain A, *et al.* Naringin ameliorates type 2 diabetes mellitus-induced steatohepatitis by inhibiting RAGE/NF-κB mediated mitochondrial apoptosis. Life Sci 2020;257:118118.
47. Subramanian M, Thotakura B, Chandra Sekaran SPC, Jyothi AK, Sundaramurthil. Naringin ameliorates streptozotocin-induced diabetes through forkhead Box M1-Mediated Beta Cell Proliferation. Cells Tissues Organs 2018;206:242-53.
48. Subramanian M, Thotakura B, Chandra Sekaran SP, Jyothi AK, Sundaramurthi I. Naringin (4′, 5, 7-trihydroxyflavanone 7-rhamnoglucoside) attenuates β-cell dysfunction in diabetic rats through upregulation of PDX-1. Cells Tissues Organs 2018;206:133-43.
49. Malakul W, Pengnet S, Kumchoom C, Tunsophon S. Naringin ameliorates endothelial dysfunction in fructose-fed rats. Exp Ther Med 2018;15:3140-6.
50. Malakul W, Pengnet S. Effect of naringin on insulin resistance and oxidative stress in fructosefedrats. Sci Technol (NUJST) 2018;26:10-8.
51. Murunga AN, Miruka DO, Driver C, Nkomo FS, Cobongela SZ, Owira PM. Grapefruit derived flavonoid naringin improves ketoacidosis and lipid peroxidation in type 1 diabetes rat model. PLoS One 2016;11:e0153241. Doi: 10.1371/journal.pone.0153241.
52. Sirovina D, Oršolić N, Ivić I, Novak S, Gajski G, Garaj-Vrhovac V, *et al.* Antioxidative and antidiabetic effects of naringin and curcumin *in vitro* and *in vivo*. Int J Phytomed 2015;7:176-84.
53. Li S, Zhang Y, Sun Y, Zhang G, Bai J, Guo J, *et al.* Naringenin improves insulin sensitivity in gestational diabetes mellitus mice through AMPK. Nutr Diabetes 2019;9:28.
54. Murugesan N, Woodard K, Ramaraju R, Greenway FL, Coulter AA, Rebello CJ. Naringenin increases insulin sensitivity and metabolic rate: A case study. J Med Food 2020;23:343-8.
55. Nguyen-Ngo C, Willcox JC, Lappas M. Anti-diabetic, anti-inflammatory, and anti-oxidant effects of naringenin in an *in vitro* human model and an *in vivo* murine model of gestational

diabetes mellitus. Mol Nutr Food Res 2019;63:e1900224. Doi: 10.1002/mnfr.201900224.

56. Roy S, Ahmed F, Banerjee S, Saha U. Naringenin ameliorates streptozotocin-induced diabetic rat renal impairment by downregulation of TGF-β1 and IL-1 via modulation of oxidative stress correlates with decreased apoptotic events. Pharm Biol 2016;54:1616-27.
57. Annadurai T, Muralidharan AR, Joseph T, Hsu MJ, Thomas PA, Geraldine P. Antihyperglycemic and antioxidant effects of a flavanone, naringenin, in streptozotocin–nicotinamide-induced experimental diabetic rats. J Physiol Biochem 2012;68:307-18.
58. Ortiz-Andrade RR, Sánchez-Salgado JC, Navarrete-Vázquez G, Webster SP, Binnie M, García-Jiménez S, *et al.* Antidiabetic and toxicological evaluations of naringenin in normoglycaemic and NIDDM rat models and its implications on extra-pancreatic glucose regulation. Diabetes Obes Metab 2008;10:1097-104.
59. Peng P, Jin J, Zou G, Sui Y, Han Y, Zhao D, *et al.* Hesperidin prevents hyperglycemia in diabetic rats by activating the insulin receptor pathway. Exp Ther Med 2021;21:53.
60. Rehman K, Munawar SM, Akash MSH, Buabeid MA, Chohan TA, Tariq M, *et al.* Correction: Hesperidin improves insulin resistance via down-regulation of inflammatory responses: Biochemical analysis and *in silico* validation. PLoS One 2020;15:e0229348. Doi: 10.1371/journal.pone.0229348.
61. Ali AM, Gabbar MA, Abdel-Twab SM, Fahmy EM, Ebaid H, Alhazzal M, *et al.* Antidiabetic potency, antioxidant effects, and mode of actions of Citrus reticulata fruit peel hydroethanolic extract, hesperidin, and quercetin in nicotinamide/streptozotocin-induced Wistar diabetic rats. Oxid Med Cell Longev 2020;2020:1730492.
62. Rekha SS, Pradeepkiran JA, Bhaskar M. Bioflavonoid hesperidin possesses the anti-hyperglycemic and hypolipidemic property in STZ induced diabetic myocardial infarction (DMI) in male Wister rats. J Nutr Intermed Metab 2019;15:58-64.
63. Wang Y, Wang L, Xu G, Wei D. Hesperidin exerts the gestational diabetes mellitus via AGEs-RAGE signalling pathway. Int J Pharmacol 2019;15:604-15.
64. Visnagri A, Kandhare AD, Chakravarty S, Ghosh P, Bodhankar SL. Hesperidin, a flavanoglycone attenuates experimental diabetic neuropathy via modulation of cellular and biochemical marker to improve nerve functions. Pharm Biol 2014;52:814-28.
65. Eghtesadi S, Mohammadi M, Vafa M, Heidari I, Salehi M, Khadem HH, *et al.* Effects of hesperidin supplementation on glycemic control, lipid profile and inflammatory factors in patients with type 2 diabetes: A randomized, double-blind and placebo-controlled clinical trial. Endocr Abstr 2016;43:OC16. Doi: 10.1530/endoabs.43.OC16.
66. Jain DP, Somani RS. Hesperidin ameliorates streptozotocin and high-fat diet induced diabetic nephropathy in rats. J ExpIntegr Med 2014;4:261-7.
67. Akiyama S, Katsumata S, Suzuki K, Ishimi Y, Wu J, Uehara M. Dietary hesperidin exerts hypoglycemic and hypolipidemic effects in streptozotocin-induced marginal type 1 diabetic rats. J Clin Biochem Nutr 2010;46:87-92.
68. Ahmed OM, Mahmoud AM, Abdel-Moneim A, Ashour MB. Antidiabetic effects of hesperidin and naringin in type 2 diabetic rats. Diabetol Croat 2012;41:53-67.
69. 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;26:483-90.
70. Yoon KD, Lee JY, Kim TY, Kang H, Ha KS, Ham TH, *et al. In vitro* and *in vivo* anti-hyperglycemic activities of taxifolin and its derivatives isolated from pigmented rice (Oryzae sativa L. cv. Superhongmi). J Agric Food Chem 2020;68:742-50.
71. Rehman K, Chohan TA, Waheed I, Gilani Z, Akash MSH. Taxifolin prevents postprandial hyperglycemia by regulating the activity of α-amylase: Evidence from an *in vivo* and *in silico* studies. J Cell Biochem 2019;120:425-38.
72. Zhao Y, Huang W, Wang J, Chen Y, Huang W, Zhu Y. Taxifolin attenuates diabetic nephropathy in streptozotocin-induced diabetic rats. Am J Transl Res 2018;10:1205-10.
73. Hostetler GL, Ralston RA, Schwartz SJ. Flavones: Food sources, bioavailability, metabolism, and bioactivity. Adv Nutr 2017;8:423-35.
74. Gandhi GR, Vasconcelos ABS, Wu DT, Li HB, Antony PJ, Li H, *et al.* Citrus flavonoids as promising phytochemicals targeting diabetes and related complications: A systematic review of *in vitro* and *in vivo* studies. Nutrients 2020;12:2907.
75. El Barky AR, Ezz Aah, El-Said KS, Sadek ME, Mohamed TM. Anti-diabetic activity of Egyptian celery apigenin. Asian J Dairy Food Res 2019;38:341-6.
76. Barky A, Ezz A, Mohammed T. The Potential role of apigenin in diabetes mellitus. Int J Clin Case Rep Rev 2020;3:32.
77. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, *et al.* The therapeutic potential of apigenin. Int J Mol Sci 2019;20:1305.
78. Sangeetha R. Luteolin in the management of type 2 diabetes mellitus. Curr Res Nutr Food Sci J 2019;7:393-8.
79. Huang H, Li L, Shi W, Liu H, Yang J, Yuan X, *et al.* The multifunctional effects of nobiletin and its metabolites *in vivo* and *in vitro.* Evid Based Complement Alternat Med 2016;2016:2918796.
80. Sundaram R, Shanthi P, Sachdanandam P. Effect of tangeretin, a polymethoxylated flavone on glucose metabolism in streptozotocin-induced diabetic rats. Phytomedicine 2014;21:793-9.
81. Kim MS, Hur HJ, Kwon DY, Hwang JT. Tangeretin stimulates glucose uptake via regulation of AMPK signaling pathways in C2C12 myotubes and improves glucose tolerance in high-fat diet-induced obese mice. Mol Cell Endocrinol 2012;358:127-34.
82. Guo J, Chen J, Ren W, Zhu Y, Zhao Q, Zhang K, *et al.* Citrus flavone tangeretin is a potential insulin sensitizer targeting hepatocytes through suppressing MEK-ERK1 / 2 pathway. Biochem Biophys Res Commun 2020;529:277-82.
83. Nguyen-Ngo C, Salomon C, Quak S, Lai A, Willcox JC, Lappas M. Nobiletin exerts anti-diabetic and anti-inflammatory effects in an *in vitro* human model and *in vivo* murine model of gestational diabetes. Clin Sci (Lond)2020;134:571-92.
84. K. Kaneko Y, Kan T, Ishikawa T. [Citrus flavonoids as a target for the prevention of pancreatic β-cells dysfunction in diabetes]. [Nihon Yakurigaku Zasshi] Folia Pharmacol Jpn 2020;155:209-13.
85. Lee YS, Cha BY, Saito K, Yamakawa H, Choi SS, Yamaguchi K, *et al.* Nobiletin improves hyperglycemia and insulin resistance in obese diabetic ob/ob mice. Biochem Pharmacol 2010;79:1674-83.
86. Zang Y, Igarashi K, Li Y. Antidiabetic effects of luteolin and luteolin-7-O-glucoside on KK-A y mice. Biosci Biotechnol Biochem 2016;80:1580-6.
87. Wang GG, Lu XH, Li W, Zhao X, Zhang C. Protective effects of luteolin on diabetic nephropathy in STZ-induced diabetic rats. Evid Based Complement Alternat Med 2011;2011:323171.
88. Ding L, Jin D, Chen X. Luteolin enhances insulin sensitivity via activation of PPARγ transcriptional activity in adipocytes. J Nutr Biochem 2010;21:941-7.
89. Malik S, Suchal K, Khan SI, Bhatia J, Kishore K, Dinda AK, *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 Ren Physiol 2017;313:F414-22. Doi: 10.1152/ajprenal.00393.2016.
90. Hollman PC, Katan MB. Health effects and bioavailability of dietary flavonols. Free Radic Res 1999;31(Suppl):S75-80.
91. Salehi B, Machin L, Monzote L, Sharifi-Rad J, Ezzat SM, Salem MA, *et al.* Therapeutic potential of quercetin: New insights and perspectives for human health. ACS Omega 2020;5:11849-72.
92. Ren J, Lu Y, Qian Y, Chen B, Wu T, Ji G. Recent progress regarding kaempferol for the treatment of various diseases. Exp Ther Med 2019;18:2759-76.
93. Sivaraj S, Kannayiram G, Dasararaju G. Evaluation of antidiabetic activity of different extracts of Myristica fragranshoutt: *In vitro* and *in silico* studies. Evaluation 2017;10:275-7.
94. Babu PVA, Liu D, Gilbert ER. Recent advances in understanding the anti-diabetic actions of dietary flavonoids. J Nutr Biochem 2013;24:1777-89.
95. Zang Y, Zhang L, Igarashi K, Yu C. The anti-obesity and anti-diabetic effects of kaempferol glycosides from unripe soybean leaves in high-fat-diet mice. Food Funct 2015;6:834-41.
96. de Sousa E, Zanatta L, Seifriz I, Creczynski-Pasa TB, Pizzolatti MG, Szpoganicz B, *et al.* Hypoglycemiceffect and antioxidant potential of kaempferol-3, 7-O-(α)-dirhamnoside from Bauhinia f orficata Leaves. J Nat Prod 2004;67:829-32.
97. Chandramohan G, Al-Numair KS, Alsaif MA, Veeramani C. Antidiabetic effect of kaempferol a flavonoid compound, on streptozotocin-induced diabetic rats with special reference to glycoprotein components. Prog Nutr 2015;17:50-7.
98. Ramasamy R. Evaluation of antidiabetic activity of kaempferol isolated from Cardiospermum halicacabum leaf extract in alloxan induced diabetic rats. Int J Pharm Biol Sci 2019;10:1-7.
99. Yin P, Wang Y, Yang L, Sui J, Liu Y. Hypoglycemic effects in alloxan-induced diabetic rats of the phenolic extract from Mongolian oak cups enriched in ellagic acid, kaempferol and their derivatives. Molecules 2018;23:1046.
100. Alshehri AS. Kaempferol attenuates diabetic nephropathy in streptozotocin-induced diabetic rats by a hypoglycaemic effect and concomitant activation of the Nrf-2/Ho-1/antioxidants axis. Arch Physiol Biochem 2021:1-14. Doi: https://doi.org/10.1080/13813455.2021.1890129.
101. Shaikhomar OA, Bahattab OS. Physiological effect of quercetin as a naturalflavonoid to be used as hypoglycemicagent in diabetes mellitus Type II rats. Saudi J Biomed Res 2021;6:10-7.
102. Srinivasan P, Vijayakumar S, Kothandaraman S, Palani M. Anti-diabetic activity of quercetin extracted from Phyllanthus emblicaL. fruit: *In silico* and *in vivo* approaches. J Pharm Anal 2018;8:109-18.

103. Hemmati M, Mostafavi SE, Zarban A, Hoshyar R. Protective effects of quercetin on hyperglycemia and stress proteins expression in rats with streptozocin-induced diabetes. Mod Care J 2018;15:e64964. doi: 10.5812/odern.64964.
104. Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp Biochem PhysiolC Toxicol Pharmacol 2003;135C:357-64.
105. Kumari S, Kamboj A, Wanjari M, Sharma AK. Protective role of fisetin in STZ induced diabetic nephropathy in rats. J Pharm Res Int 2021;33:97-111.
106. Prasath GS, Pillai SI, Subramanian SP. Fisetin improves glucose homeostasis through the inhibition of gluconeogenic enzymes in hepatic tissues of streptozotocin induced diabetic rats. EurJ Pharmacol 2014;740:248-54.
107. Lalitha N, Sadashivaiah B, Ramaprasad TR, Singh SA. Anti-hyperglycemic activity of myricetin, through inhibition of DPP-4 and enhanced GLP-1 levels, is attenuated by co-ingestion with lectin-rich protein. PLoS One 2020;15:e0231543. Doi: 10.1371/journal.pone.0231543.
108. Li Y, Zheng X, Yi X, Liu C, Kong D, Zhang J, *et al.* Myricetin: A potent approach for the treatment of type 2 diabetes as a natural class BGPCR agonist. FASEB J 2017;31:2603-11.
109. Kang S-J, Park J-HY, Choi H-N, Kim J-I. α-glucosidase inhibitory activities of myricetin in animal models of diabetes mellitus. Food Sci Biotechnol 2015;24:1897-900.
110. Gilbert ER, Liu D. Anti-diabetic functions of soy isoflavone genistein: Mechanisms underlying its effects on pancreatic β-cell function. Food Funct 2013;4:200-12.
111. Behloul N, Wu G. Genistein: A promising therapeutic agent for obesity and diabetes treatment. EurJ Pharmacol 2013;698:31-8.
112. Tian D, Liu J, Liu N, Wang R, Ai Y, Jin L, *et al.* Daidzin decreases blood glucose and lipid in streptozotocin-induced diabetic mice. Trop J Pharm Res 2016;15:2435-43.
113. Liu D, Zhen W, Yang Z, Carter JD, Si H, Reynolds KA. Genistein acutely stimulates insulin secretion in pancreatic β-cells through a cAMP-dependent protein kinase pathway. Diabetes 2006;55:1043-50.
114. Pawar MRV, Karthikeyan E. Role of catechins in diabetes mellitus. Eur J Mol Clin Med 2020;7:2515-826.
115. Samarghandian S, Azimi-Nezhad M, Farkhondeh T. Catechin treatment ameliorates diabetes and its complications in streptozotocin-induced diabetic rats. Dose-Response 2017;15:1559325817691158. Doi: 10.1177 / 1559325817691158.
116. Batomayena B, Benedicte B, Aboudoulatif D, Kwashie E-G, Kodjo A, Messanvi G, *et al.* Catechins as antidiabetic compounds of Brideliaferruginea Benth root bark extract. J Pharmacogn Phytother 2018;10:182-6.
117. Ardiana L, Sauriasari R, Elya B. Antidiabetic activity studies of white tea (Camellia sinensis (L.) O.Kuntze) ethanolic extracts in streptozotocin-nicotinamide induced diabetic rats. Pharmacogn J2017;10:186-9.
118. Les F, Cásedas G, Gómez C, Moliner C, Valero MS, López V. The role of anthocyanins as antidiabetic agents: From molecular mechanisms to *in vivo* and human studies. J Physiol Biochem 2021;77:109-31.
119. Oliveira H, Fernandes A, Brás NF, Mateus N, de Freitas V, Fernandes I. Anthocyanins as antidiabetic agents—*In vitro* and *in silico* approaches of preventive and therapeutic effects. Molecules 2020;25:3813.
120. Sivamaruthi BS, Kesika P, Subasankari K, Chaiyasut C. Beneficial effects of anthocyanins against diabetes mellitus associated consequences-A mini review. Asian Pac J Trop Biomed 2018;8:471-7.
121. Khoo HE, Azlan A, Tang ST, Lim SM. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res 2017;61:1361779.
122. Jia Y, Wu C, Kim YS, Yang SO, Kim Y, Kim JS, *et al.* A dietary anthocyanin cyanidin-3-O-glucoside binds to PPARs to regulate glucose metabolism and insulin sensitivity in mice. Commun Biol 2020;3:514.
123. Qin Y, Zhai Q, Li Y, Cao M, Xu Y, Zhao K, *et al.* Cyanidin-3-O-glucoside ameliorates diabetic nephropathy through regulation of glutathione pool. Biomed Pharmacother 2018;103:1223-30.
124. Scazzocchio B, Varì R, Filesi C, D'Archivio M, Santangelo C, Giovannini 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;60:2234-44.
125. Choi K, Choi S-I, Park MH, Han J-S. Cyanidin-3-O-glucoside ameliorates postprandial hyperglycemia in diabetic mice. J Life Sci 2017;27:32-7.
126. Sasaki R, Nishimura N, Hoshino H, Isa Y, Kadowaki M, Ichi T, *et al.* Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity due to down regulation of retinol binding protein 4 expression in diabetic mice. Biochem Pharmacol 2007;74:1619-27.
127. Hidalgo J, Teuber S, Morera FJ, Ojeda C, Flores CA, Hidalgo MA, *et al.* Delphinidin reduces glucose uptake in mice jejunal tissue and human intestinal cells lines through FFA1/GPR40. Int J Mol Sci 2017;18:750.
128. Tani T, Nishikawa S, Kato M, Tsuda T. Delphinidin 3-rutinoside-rich blackcurrant extract ameliorates glucose tolerance by increasing the release of glucagon-like peptide-1 secretion. Food Sci Nutr 2017;5:929-33.
129. Grace MH, Ribnicky DM, Kuhn P, Poulev A, Logendra S, Yousef GG, *et al.* Hypoglycemic activity of a novel anthocyanin-rich formulation from lowbush blueberry, Vaccinium angustifolium Aiton. Phytomedicine 2009;16:406-15.
130. Hongwei JIAO. Protective effect of peonidin on mice with type 2 diabetes mellitus and nonalcoholic fatty liver disease. Herald Med 2020;39:436-40.
131. Su H, Xie L, Xu Y, Ke H, Bao T, Li 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;68:13025-37.
132. 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;82:1102-10.
133. Rocha S, Ribeiro D, Fernandes E, Freitas M. A systematic review on anti-diabetic properties of chalcones. Curr Med Chem 2020;27:2257-321.
134. Paliwal S, Pathak D. Chalcones in the therapeutics of diabetes mellitus. Scholars Acad J Pharm 2018;7:392-401.
135. Najafian M, Jahromi MZ, Nowroznejhad MJ, Khajeaian P, Kargar MM, Sadeghi M, *et al.* Phloridzin reduces blood glucose levels and improves lipids metabolism in streptozotocin-induced diabetic rats. Mol Biol Rep 2012;39:5299-306.
136. Nithiya T, Udayakumar R. Protective effect of phloretin on hyperglycemia mediated oxidative stress in experimental diabetic rats. Integr Food Nutr Metab 2017;5:1-6.
137. Yousefi F, Mahjoub S, Pouramir M, Khadir F. Hypoglycemic activity of Pyrus biossieriana Buhse leaf extract and arbutin: Inhibitory effects on alpha amylase and alpha glucosidase. Caspian J Intern Med 2013;4:763-7.
138. Shen X, Zhou N, Mi L, Hu Z, Wang L, Liu X, *et al.* Phloretin exerts hypoglycemic effect in streptozotocin-induced diabetic rats and improves insulin resistance *in vitro*. Drug Des Dev Ther 2017;11:313-24.
139. Şöhretoğlu D, Sari S. Flavonoids as alpha-glucosidase inhibitors: Mechanistic approaches merged with enzyme kinetics and molecular modelling. Phytochem Rev 2020;19:1081-92.
140. Desco MC, Asensi M, Márquez R, Martínez-Valls J, Vento M, Pallardó FV, *et al.* Xanthine oxidase is involved in free radical production in type 1 diabetes: Protection by allopurinol. Diabetes 2002;51:1118-24.
141. Nagao A, Seki M, Kobayashi H. Inhibition of xanthine oxidase by flavonoids. Biosci Biotechnol Biochem 1999;63:1787-90.
142. Lin S, Zhang G, Liao Y, Pan J, Gong D. Dietary flavonoids as xanthine oxidase inhibitors: Structure–affinity and structure–activity relationships. J Agric Food Chem 2015;63:7784-94.
143. Mathew B, Suresh J, Mathew G, Rasheed S, Vilapurathu J, Jayaraj P. Flavonoids: An outstanding structural core for the inhibition of xanthine oxidase enzyme. Curr Enzyme Inhib 2015;11:108-15.
144. Guimaraes JF, Muzio BP, Rosa CM, Nascimento AF, Sugizaki MM, Fernandes AA, *et al.* Rutin administration attenuates myocardial dysfunction in diabetic rats. Cardiovasc Diabetol 2015;14:90.
145. Chen J, Mangelinckx S, Adams A, Wang ZT, Li WL, De Kimpe N. Natural flavonoids as potential herbal medication for the treatment of diabetes mellitus and its complications. Nat Prod Commun 2015;10:187-200.
146. Proença C, Freitas M, Ribeiro D, Oliveira EFT, Sousa JLC, Tomé SM, *et al.* α-glucosidase inhibition by flavonoids: An *in vitro* and *in silico* structure–activity relationship study. J EnzymeInhib Med Chem 2017;32:1216-28.
147. Tang H, Huang L, Sun C, Zhao D. Exploring the structure–activity relationship and interaction mechanism of flavonoids and α-glucosidase based on experimental analysis and molecular docking studies. Food Funct 2020;11:3332-50.
148. Sarian MN, Ahmed QU, Mat So'ad SZ, Alhassan AM, Murugesu S, Perumal V, *et al.* Antioxidant and antidiabetic effects of flavonoids: A structure–activity relationship based study. Bio Med Res Int 2017;2017:8386065.
149. Kim JS, Kwon CS, Son KH. Inhibition of alpha-glucosidase and amylase by luteolin, a flavonoid. Biosci Biotechnol Biochem 2000;64:2458-61.
150. Choi CI. Sodium-glucose cotransporter 2 (SGLT2) inhibitors from natural products: Discovery of next-generation antihyperglycemic agents. Molecules 2016;21:1136.

151. Sato S, Takeo J, Aoyama C, Kawahara H. Na+-glucose cotransporter (SGLT) inhibitory flavonoids from the roots of Sophora flavescens. Bioorg Med Chem 2007;15:3445-9.
152. Noruddin NAA, Hamzah MF, Rosman Z, Salin NH, Shu-Chien AC, Muhammad TST. Natural Compound 3β, 7β, 25-trihydroxycucurbita-5, 23. Molecules 2021;26:2682.
153. Bermúdez V, Fino IF, Parra N, Parra M, Pérez A, Peñaranda L, *et al.* PPAR-γ agonists and their role in type 2 diabetes mellitus management. Am J Ther 2010;17:274-83.
154. Zhang Z, Meng Y, Wang Z, Mei Y, Gao S, Wu Y, *et al.* Discovery of potentglucokinase and PPARγdual-targetagonists through an innovativescheme for regioselectivemodification of silybin. ACS Omega 2022;7:3812-22.
155. Proença C, Ribeiro D, Freitas M, Carvalho F, Fernandes E. A comprehensive review on the antidiabetic activity of flavonoids targeting PTP1B and DPP-4: A structure–activity relationship analysis. Crit Rev Food Sci Nutr 2022;62:4095-151.
156. Pan J, Zhang Q, Zhang C, Yang W, Liu H, Lv Z, *et al.* Inhibition of dipeptidyl peptidase-4 by flavonoids: Structure–activity relationship, kinetics and interaction mechanism. Front Nutr 2022;9:892426.
157. Pinent M, Castell A, Baiges I, Montagut G, Arola L, Ardévol A. Bioactivity of flavonoids on insulin-secreting cells. Compr Rev Food Sci Food Saf 2008;7:299-308.
158. Zhang Y, Liu D. Flavonol kaempferol improves chronic hyperglycemia-impaired pancreatic beta-cell viability and insulin secretory function. Eur J Pharmacol 2011;670:325-32.
159. Jakobs S, Fridrich D, Hofem S, Pahlke G, Eisenbrand G. Natural flavonoids are potent inhibitors of glycogen phosphorylase. Mol Nutr Food Res 2006;50:52-7.
160. Rath VL, Ammirati M, Danley DE, Ekstrom JL, Gibbs EM, Hynes TR, *et al.* Human liver glycogen phosphorylase inhibitors bind at a new allosteric site. Chem Biol 2000;7:677-82.
161. Kato A, Nasu N, Takebayashi K, Adachi I, Minami Y, Sanae F, *et al.* Structure–activity relationships of flavonoids as potential inhibitors of glycogen phosphorylase. J Agric Food Chem 2008;56:4469-73.
162. Ghamali M, Chtita S, Hmamouchi R, Adad A, Bouachrine M, Lakhlifi T. The inhibitory activity of aldose reductase of flavonoid compounds: Combining DFT and QSAR calculations. J Taibah Univ Sci 2016;10:534-42.
163. Matsuda H, Morikawa T, Toguchida I, Yoshikawa M. Structural requirements of flavonoids and related compounds for aldose reductase inhibitory activity. Chem Pharm Bull (Tokyo) 2002;50:788-95.
164. Kim J-K, Lee Y-S, Lim S-S, Bae Y-S. Aldose reductase inhibition effect of phenolicv compounds isolated from paulownia Coreana bark. J Korean Wood Sci Technol 2010;38:159-64.