

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

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ABSTRACT

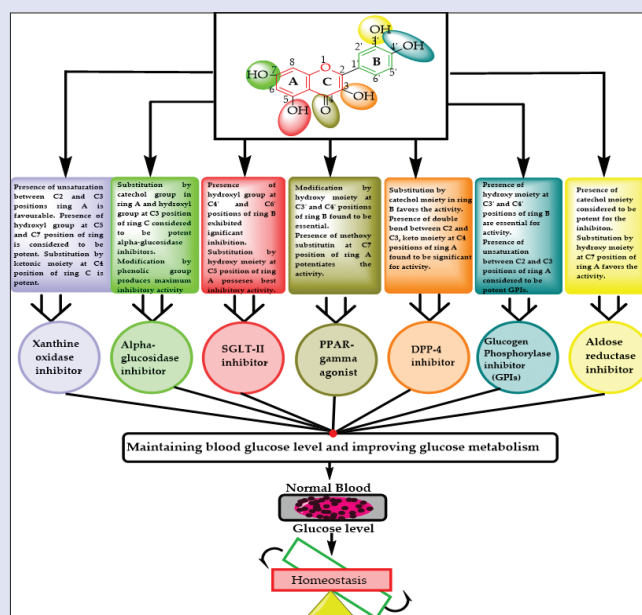
Diabetes is a metabolic complication distinguished mainly by persistent hyperglycemia and is involved in the formation of reactive oxygen species, thereby causing oxidative stress, which is the major culprit for diabetic complications in different organs, including the vascular system. Controlling blood 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 C₂ and C₃ positions, hydroxy substitutions at C₅ and C₇ positions of ring A, and substitution by the ketonic group at the C₄ 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.

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- κ B 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, PPAR γ , 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].

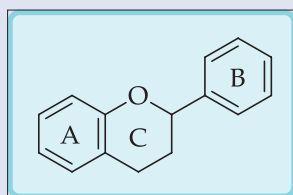


Figure 1: Basic core structure (scaffold) of flavonoids

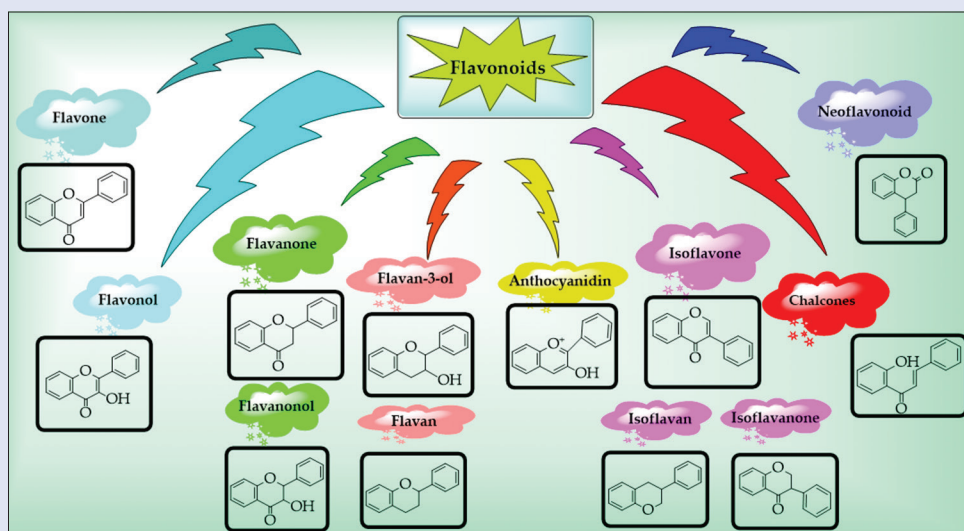


Figure 2: Types of flavonoids

Catechins

Catechins (XV) are flavonols with no keto group at the C₃ 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 PPAR γ 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 C₂ and C₃, and a hydroxyl group at C₅ and C₇ of ring A or C₃ and C₄ 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 C₄ 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 C₃ and C₆ 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 C₅ and C₇ positions of ring A, modification by the catechol system in ring B, and ketone moiety at the C₄ position of ring C with unsaturation in between C₂ and C₃ 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 C₂ and C₃ 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 ₁₆ ; 580.4 g/mol)	<i>Citrus maxima</i>	100 mg/kg/8 weeks/oral	T2DM-induced steatohepatitis	Impedes RAGE/NF-κB-dependent mitochondrial apoptosis	[46]
	<i>Carissa carandas</i>	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]
Naringenin (S)-5,7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one (C ₁₅ H ₁₂ O ₃ ; 272.26 g/mol)	<i>Salvia leirifolia</i>	50 mg/kg/oral	STZ-induced diabetes	Improves ketoacidosis and lipid peroxidation	[51]
	<i>Drynaria fortune</i>	50 mg/kg/7 days/intraperitoneal	Alloxan induced diabetes	Reduces oxidative stress	[52]
	<i>Alpinia katsumadai</i>	100 mg/kg (daily)/4 weeks/oral	Gestational diabetic mice model	Restores TNF-α-induced insulin resistance via AMPK	[53]
	<i>Lignum dalbergia</i>	150 mg (thrice a day)/8 weeks From Gestational day 10-17/intraperitoneal	Human adipocytes	Increases insulin Sensitivity	[54]
	<i>Cudrania cochinchinensis</i>	5 and 10 mg/kg (once a day)/10 weeks/oral	Heterozygous db/+ mice	Improves insulin sensitivity by suppressing nuclear factor κB activation	[55]
		50 mg/kg (daily)/21 days/oral	STZ-induced diabetes	Alters oxidative stress by downregulation of TGF-β1 and IL-1 cytokines expression and apoptotic events.	[56]
		50 mg/kg (daily)/5 days	STZ-induced diabetes NIDDM rat model	Improves oxidative stress Suppress intestinal carbohydrate absorption and thus reduces the postprandial glucose rise	[57] [58]

Naringin (II)

Naringenin (III)

Hesperidin (IV)

Taxifolin (V)

Contd...

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Table 1: Contd...

Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Hesperidin (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)	<i>Citrus reticulata</i> <i>Citrus sinensis</i>	100 mg/kg/35 days/oral 55 mg/kg (daily) 100 mg/kg (daily) 4 weeks 100 mg/kg/4 weeks/oral	Alloxan-induced d type-2 diabetes HFD-induced obese rats STZ-induced diabetes STZ-induced diabetes in rats STZ-induced diabetes gestational diabetes in rats	Activates IR/PDK1 pathway and regulate glycolysis and gluconeogenesis Regulates insulin resistance by controlling inflammatory responses Enhances insulin release, insulin action, and antioxidant defense system Anti-oxidant effect Reduces oxidative stress, inflammatory signaling pathways	[59] [60] [61] [62] [63]
Hesperidin and naringin		100 mg/kg/4 weeks/intraperitoneal 500 mg/day/8 weeks 50, 100, and 200 mg/kg/4 weeks/oral 10 mg/kg/4 weeks 50 mg/kg/30 days/oral	STZ-induced diabetes Type-II diabetic patients STZ-induced diabetes STZ-induced diabetes STZ-induced type-II diabetes	Down-regulation of free radical generation and pro-inflammatory cytokines release Improve insulin resistance and glycemic control Improves oxidative stress Controls glucose-regulating enzyme action Reduces oxidative stress, enhances insulin secretion, and decreases gluconeogenesis thereby regulating blood sugar	[64] [65] [66] [67] [68]
Taxifolin (2R,3R)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one (C ₁₅ H ₁₂ O ₇ ; 304.25 g/mol)	<i>Pseudotsuga taxifolia</i> <i>Taxus chinensis</i> <i>Garcinia epunctata</i> <i>Catha edulis</i> <i>Cedrus brevifolia</i> <i>Lyrics iberica</i>	50 mg/kg (daily) hesperidin/naringin/4 weeks 500 mg/kg 100 mg/kg (daily)/30 days/intragastrical 10 or 20 mg/kg (daily)/4 weeks/intragastrical	STZ-induced type-II diabetes Sprague-Dawley (SD) rat model Alloxan-induced diabetes STZ-induced diabetes	Potentiate antioxidant activity and suppresses production of pro-inflammatory cytokine Inhibits carbohydrate-hydrolyzing enzyme activity Regulates α -amylase activity Reduces NF- κ B pathway expression	[69] [70] [71] [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 Citrus depressa Citrus reticulata	100 mg/kg/30 days 200 mg/kg 25/50 mg/kg	STZ-induced diabetes High-fed diet-induced diabetes	Enhances insulin secretion Enhances glucose uptake stimulating AMPK pathway Enhances liver insulin sensitivity by MEK-ERK 1/2 pathway suppression	[80] [81] [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 trifoliata	50 mg/kg (daily)	Gestational diabetic model	Improves glucose uptake (TNF-impaird) in skeletal muscle and inhibits Akt-Erk activation in the placenta Increases glucose-induced insulin secretion	[83] [84]
Luteolin 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one (C ₁₅ H ₁₀ O ₆ ; 286.24 g/mol)	Aloe vera Eclipta alba Salvia tomentosa Lonicerajaponica Justicia acuminatissima Cyperus alopecuroides Bacopa monnieri Portulaca oleracea Clerodendrum viscosum Justicia gendarussa Allium fistulosum Apium graveolens Gentiana veitchiorum Macaranga gigantifolia	10 µM 200 mg/kg/5 weeks 200 mg/kg	Type 2 diabetes Obese diabetic ob/ob mice KK-A (y) mice STZ-induced diabetes 3T3-L1 adipocytes	Regulates Glut 1 and Glut 4 expression Ameliorates insulin resistance and liver TNF-α mRNA expression Anti-oxidative action Enhances PPARγ expression	[85] [86] [87] [88]
Apigenin 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (C ₁₅ H ₁₀ O ₃ ; 270.05 g/mol)		20 mg/kg/oral	STZ-induced diabetes	Suppress oxidative stress and inhibits MAPK pathway	[89]

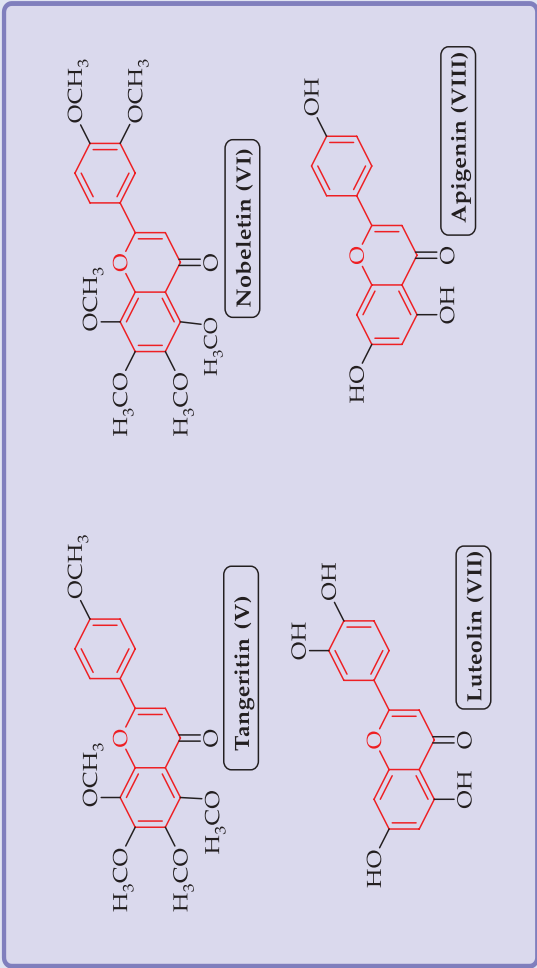


Table 3: Flavonols with significant antidiabetic potential

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

Contd...

Table 3: Contd...

Component	Plant source	Dose/duration/route	Model	Experimental outcome	Reference
Fisetin	<i>Elaeagnus indica</i>	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	<i>Rhus cotinus</i>	10 mg/kg/30 days/oral	STZ-induced diabetes	Improves glucose homeostasis through gluconeogenic enzyme inhibition	[106]
(C ₁₅ H ₁₀ O ₆ ; 286.23 g/mol)	<i>Gossypium indicum</i>				
Myricetin 3,5,7-trihydroxy-2-(3,4,5- trihydroxyphenyl)-4H-chromen- 4-one (C ₁₅ H ₁₀ O ₈ ; 318.23 g/mol)	<i>Rhus cotinus</i>				
	<i>Gossypium indicum</i>	20 mg/kg	STZ-induced diabetes	Enhances GLP-1 and insulin levels by inhibiting DPP-4	[107]
	<i>Myristica fragrans</i>	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]

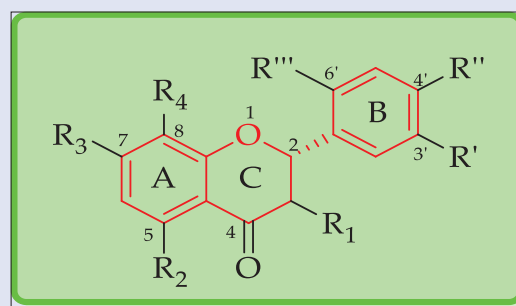


Figure 3: Substitution of flavonoids toward antidiabetic activity

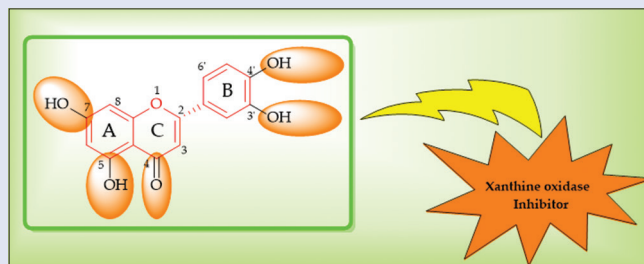


Figure 4: Potent substitutions on flavonoids for the inhibition of xanthine oxidase

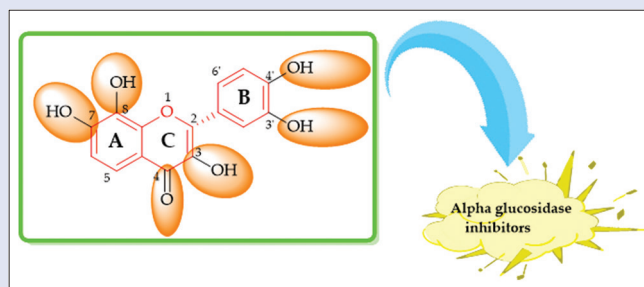


Figure 5: Potent substitutions on flavonoids for the inhibition of xanthine oxidase

rings A (C₇ and C₈ positions) and B (C_{3'} and C_{4'} positions) along with a hydroxyl group (C₃ position) in ring C, carbonyl group at C₄ 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 C₃, C₇, and C₈ 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 C₂-C₃ and the C₄ ketonic group.^[148]

Flavonoids as SGLT-II inhibitors

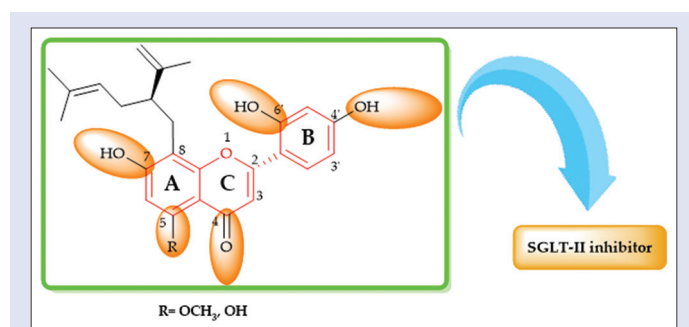
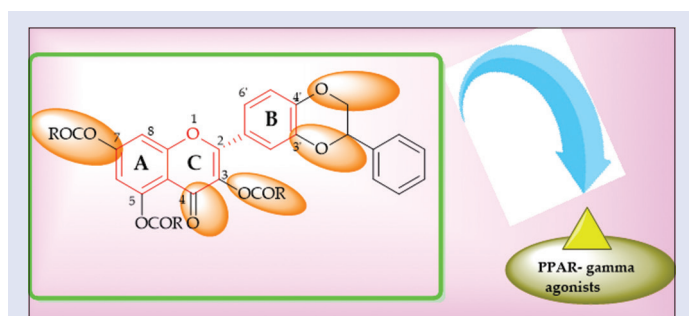
Phlorizin or phloridzin, a dihydrochalcone isolated from *Malus domestica*, was the first flavonoid reported to possess antidiabetic potential due to its ability to inhibit sodium-dependent glucose transporters I and II. Due to its various drawbacks such as poor absorption and gastrointestinal disturbances, 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)	<i>Chenopodium quinoa</i> <i>Acacia Arabica</i> <i>Glycine max</i>	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)	<i>Chenopodium quinoa</i> <i>Glycine max</i> <i>Butea monopermea</i>	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	<i>Camellia sinensis</i>	20, 40, 80 mg/kg	STZ-induced diabetes	Controls oxidative stress	[115]
2-(3,4-dihydroxyphenyl)-4H-chroman-3,5,7-triol (C ₁₅ H ₁₀ O ₆ ; 290.26 g/mol)	<i>Elaeagnus umbellata</i> <i>Bridelia ferruginea</i> <i>Acacia catechu</i>	10 mg/kg (daily)/21 days/oral 100 mg/kg/14 days/oral	STZ-induced diabetes STZ-nicotinamide induced diabetes	Stimulates peripheral glucose utilization and enhance glycolysis Increase insulin sensitivity and reduce oxidative stress	[116] [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 C₄ and C₆ positions of ring B and the carbonyl group at the C₄ position favors SGLT inhibition. Methoxy or hydroxyl groups at the C₅ position of ring A, alkyl chain,

especially lavandulyl at C₈, increase the SGLT-I inhibitory action, whereas replacement of this alkyl chain by the sugar moiety and substitution of the hydroxy group at the C₇ 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)	<i>Morus alba</i> <i>Glycine max</i> <i>Vaccinium corymbosum</i>	50 mg/kg (daily) 20 mg/kg (daily) 50 µmol/L	Diabetic mice Diabetic mice Human omental adipocytes STZ-induced diabetes	Activates PPARs GSH synthesis inhibition PPARγ activity upregulation Inhibits α-glucosidase activity	[122] [123] [124] [125]
Delphinidin 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl) chromenylium (C ₁₅ H ₁₁ O ₇ ; 303.24 g/mol)	<i>Ribes nigrum</i>	10 mg/kg 2 mg/kg 50 µM	Diabetic rats Mice jejunal tissue and human intestinal cells	Inhibits glucose absorption in an FFA1-dependent manner	[126] [127]
Malvidin 3,5,7-trihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl) chromenylium (C ₁₇ H ₁₅ O ₇ ; 331.29 g/mol)	<i>Vaccinium angustifolium</i>	5 mg/kg/intraperitoneal	Diabetic rat	Stimulate GLP-1 secretion	[128]
Peonidin 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromenylium (C ₁₆ H ₁₃ O ₆ ; 301.27 g/mol)	<i>Daucus carota</i>	300 mg/kg	Type-II diabetic mice	Anti-oxidant	[129]
Pelargonidin 3,5,7-trihydroxy-2-(4-hydroxyphenyl) chromenylium (C ₁₅ H ₁₁ O ₅ ; 271.24 g/mol)	<i>Ipomoea batatas</i> <i>Rubus occidentalis</i>	- 150 mg/kg 3 mg/kg BW	Type-II diabetic mice Diabetic rats STZ-induced diabetes	Downregulation of NF-κB expression Induce autophagy and modulate gut microbiota Lowers glycation level	[130] [131] [132]

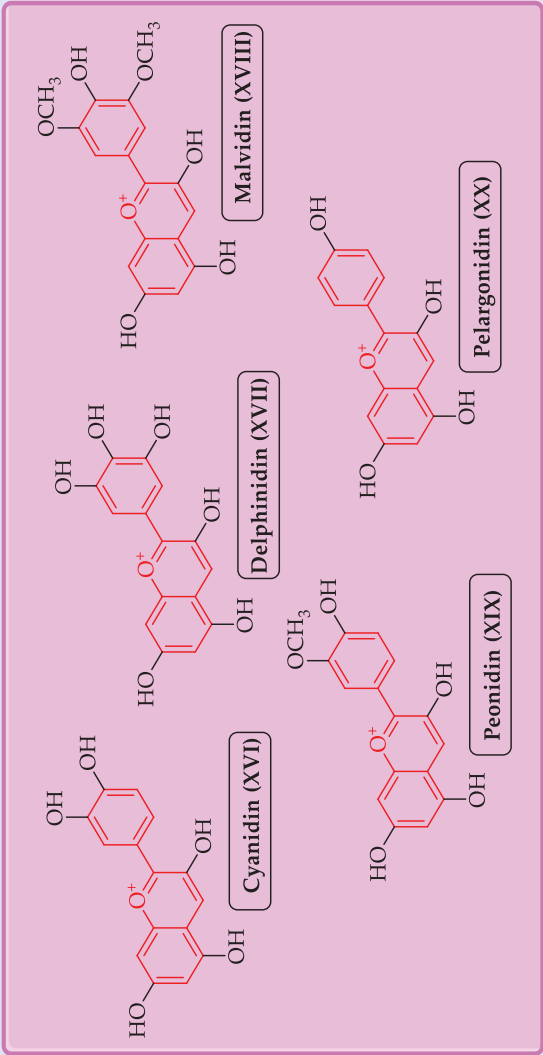


Table 7: Chalcones with antidiabetic potential

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)	<i>Malus domestica</i>	5, 10, 20 and 40 mg/kg	STZ-induced diabetes	Inhibits intestinal (SGLT1) and kidney (SGLT2) sodium-glucose co-transporter	[135]
Arbutin 4-hydroxyphenyl β-D-glucopyranoside (C ₁₂ H ₁₆ O ₇ ; 272.25 g/mol)	<i>Arctostaphylos uvaursi</i> <i>Pyrus brossieriana</i>	25 mg/kg 100 mg/kg/intraperitoneal 100 mg/mL	STZ-induced diabetes STZ-induced diabetes <i>In vitro</i> enzymatic model	Attenuate oxidative stress (hyperglycemia mediated) Stimulation of GLUT4 translocation and expression Inhibit α-glucosidase activity	[136] [137] [138]
Phloretin 3-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one (C ₁₅ H ₁₆ O ₅ ; 274.26 g/mol)	<i>Rubus occidentali</i>	100 mg/kg 5, 10, 40 mg/kg	STZ-induced diabetes STZ-induced diabetes	Translocation of GLUT4 in L6 myotubes Inhibits renal glucose reabsorption and promotes glucose excretion	[139] [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 C₃ and C₄ 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 C₃ and C₄ positions increases the activity; however, ether substitution decreases the activity. The presence of a methoxy group at C₇ and isopentyl group at the C₆ position of ring A, along with the double bond between C₂ and C₃ 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 C₃, C₅, and C₇ positions considered to be significant PPAR γ 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 C₂ and C₃, and a keto group at the C₄ 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 C₃ and C₄ and ketonic at C₄ 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 C₃ and C₄ positions with ketonic modification at the C₄ 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 C₂ and C₃ (C ring), and the presence of hydroxy groups at C₃ and C₄ positions of the B ring are essential requirements for flavonoids to act as effective GPIs. Hydroxylation at the C₅ and C₇ positions of ring A decreases the activity; however, the activity increases if the OH group is present at C₆ and C₈ positions of the ring. Deoxygenation of the C₃ position of ring B decreases the activity, further confirming the importance of the hydroxy group at the C₃ position.^[161]

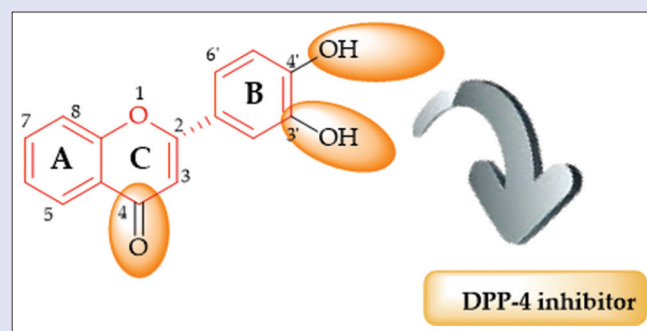


Figure 8: Potent modifications on flavonoids as DPP-4 inhibitors

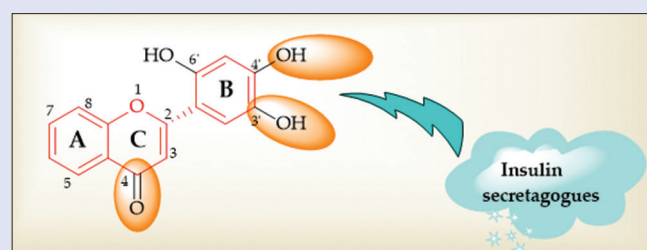


Figure 9: Effect of substitutions on flavonoids as insulin secretagogues

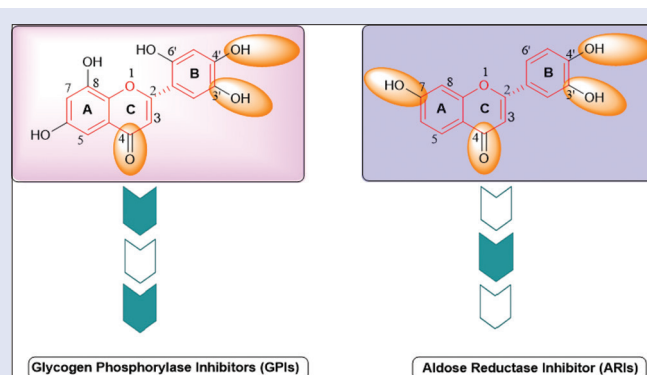


Figure 10: SAR study of flavonoids as GPI and ARI inhibitors

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 C₃ position, the presence of unsaturation between C₂ and C₃ positions, and the 3',4'-catechol nucleus of ring B imparts strong activity. The hydroxy group at C₃ and an o-glucosyl moiety at the C₇ 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].

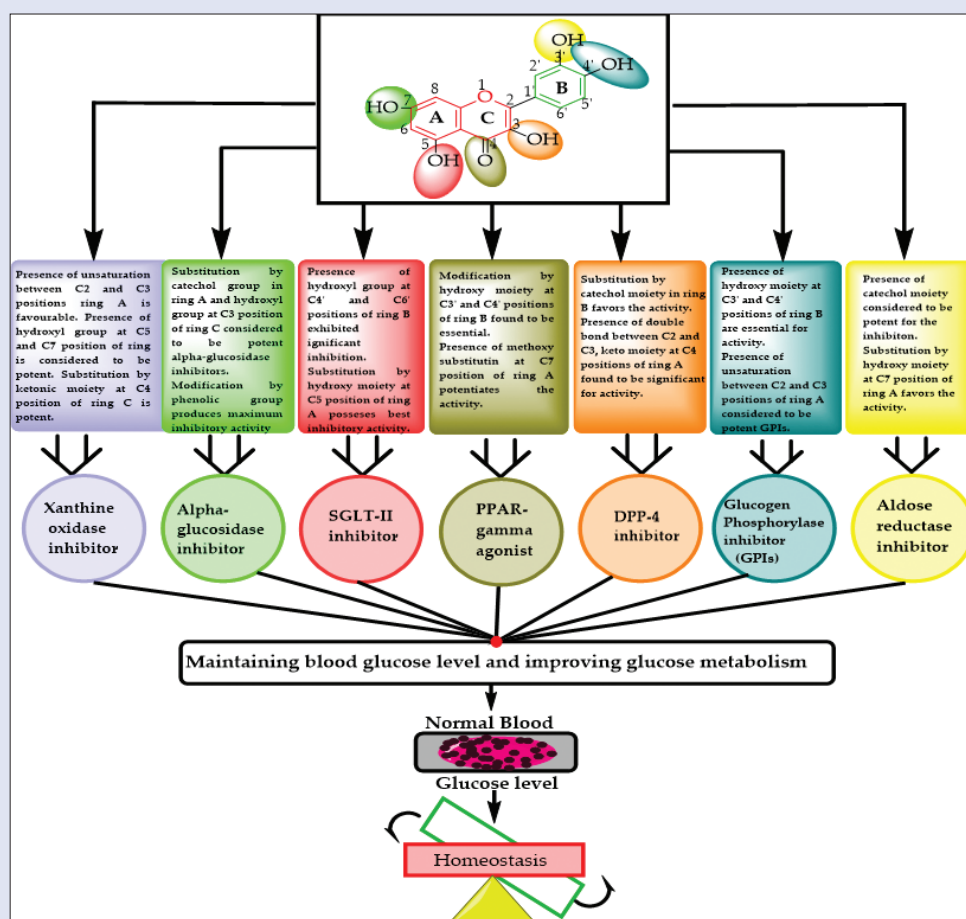


Figure 11: Correlation of structural requirements and mode of action of flavonoids for antidiabetic effect

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 C₂ and C₃ 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.

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