Review Article

Antiartherosclerotic Effects of Plant Flavonoids

**Shamala Salvamani, Baskaran Gunasekaran, Noor Azmi Shaharuddin,
Siti Aqlima Ahmad, and Mohd Yunus Shukor**

*Department of Biochemistry, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia,
43400 Serdang, Selangor, Malaysia*

Correspondence should be addressed to Mohd Yunus Shukor; mohdyunus@upm.edu.my

Received 13 November 2013; Revised 11 May 2014; Accepted 11 May 2014; Published 27 May 2014

Academic Editor: Senthil K. Venugopal

Copyright © 2014 Shamala Salvamani et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Atherosclerosis is the process of hardening and narrowing the arteries. Atherosclerosis is generally associated with cardiovascular diseases such as strokes, heart attacks, and peripheral vascular diseases. Since the usage of the synthetic drug, statins, leads to various side effects, the plants flavonoids with antiatherosclerotic activity gained much attention and were proven to reduce the risk of atherosclerosis *in vitro* and *in vivo* based on different animal models. The flavonoids compounds also exhibit lipid lowering effects and anti-inflammatory and antiatherogenic properties. The future development of flavonoids-based drugs is believed to provide significant effects on atherosclerosis and its related diseases. This paper discusses the antiatherosclerotic effects of selected plant flavonoids such as quercetin, kaempferol, myricetin, rutin, naringenin, catechin, fisetin, and gossypetin.

1. Introduction

Being a chronic inflammatory disease, atherosclerosis is becoming the leading cause of death in most of the developed countries [1]. Cardiovascular diseases (CVDs) like myocardial infarction (heart attack), acute coronary syndrome, or stroke arise through the development of plaques and lesions inside the arteries [2–5]. Hypercholesterolemia, hypertension, and obesity give high risks for the progression of CVDs. Statins are widely used as the clinical treatment for atherosclerosis due to its excellent efficacy in reducing the low density lipoprotein (LDL) level [6, 7]. Statins competitively inhibit the HMG-CoA reductase enzyme that plays a great role in catalyzing the rate-limiting step in the biosynthesis of cholesterol [8]. The increase in hepatic LDL receptors' expression is triggered by the reduction of hepatocyte cholesterol concentration and helps to clear LDL from the circulation [9, 10].

However, the consumption of statins causes adverse health effects such as liver injury and muscle toxicity [10, 11]. The other side effects include myopathy, rhabdomyolysis, and acute renal failure [12]. Thus, attention is now directed to the natural products from plant origin that possess antiatherosclerotic activity and can promote human health.

This can eventually avoid possible health effects due to the long period consumption of statins. Many researches on bioactive compounds and their possible medicinal attributes have been studied during the past decades [13–15]. Plant and plant by-products can be used for isolating health-promoting bioactive compounds since there are substantial plant sources which are relatively inexpensive. The bioactive compound from plant extracts has shown plentiful health-promoting effects in both *in vitro* and *in vivo* studies, such as antioxidant [16, 17], hypoglycemic [18–20], hypotensive [21], and hypocholesterolemic [22–24] effects. The aim of this review is to provide the reader with some important evidence on the antiatherosclerotic activity of selected flavonoids that are mostly found in plants.

2. Flavonoids

Flavonoids represent a broad family of more than 4000 secondary plant metabolites. The four predominant classes are 4-oxoflavonoids (flavones and flavonols), isoflavones, anthocyanins, and flavan-3-ol derivatives (tannins and catechin) [25–27]. For centuries, preparations that contain flavonoids are applied as the primary physiologically active components

that have been used for treating human diseases [28]. Epidemiological studies have shown that the risk of heart diseases can be reduced through the consumption of flavonoid-rich diets [29]. Flavonoids may inhibit the vascular diseases' development through alteration in endothelial cell eicosanoid production [30]. Flavonoids also showed blood pressure lowering effect in hypertensive and normotensive subjects while flavonoids may have beneficial actions in obesity due to their capacity to regulate fatty oxidation and improve adipocyte functionality [31]. Besides, food derived flavonols (quercetin, kaempferol, and myricetin) have been reported to exhibit various biological functions and medicinal properties such as antioxidant, antithrombotic, anti-inflammatory, anti atherogenic, antiatherosclerotic, and cardioprotective effects [32–35]. The plants like *Garcinia cambogia* [36], *Mangifera indica* [37], *Hypericum perforatum* L [38], and *Asparagus racemosus* [39] that contain flavonoids have been proven to significantly lower the risk of atherosclerosis and CVD.

2.1. Quercetin. Flavonoids such as quercetin (3',4',3,5,7-pentahydroxyflavone) have gained considerable attention mainly due to their broad spectrum of health beneficial effects for the treatment of CVDs. Quercetin has been reported to improve endothelium-dependent vasorelaxation in aorta, decreases systolic blood pressure, and reduces cardiac hypertrophy and proteinuria in hypertensive rats [40, 41]. Sánchez et al. [42] reported that enhancement of endothelial nitric oxide synthase (eNOS) activity and reduction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated superoxide production with downregulation of p47^{phox} expression showed the antihypertensive effects of quercetin. Besides that, quercetin has been proven to improve dyslipidemia, decrease oxidative stress through stimulation of lipolysis activity, and upregulate the adipocytes genes expression which increases the lipids beta oxidation [43, 44]. Quercetin treatment in obesity animal models showed reduction in body weight, visceral and subcutaneous adipose tissue, and liver fat accumulation. Moreover, quercetin also suppressed the peroxisome proliferator-activated receptor γ (PPAR γ) and sterol regulatory element-binding proteins (SREBP) expression. The reduction in the expression of PPAR γ indicates reduction in adipogenesis [45–47]. On the other hand, *Morus alba* L leaves containing quercetin 3-(6-malonylglucoside) (Q3MG) as their major flavonol attenuated the development of atherosclerotic lesion in LDL receptor-deficient mice through LDL resistance enhancement to oxidative modification and the atherosclerotic lesion in *M. alba*-treated mice was significantly reduced by 52% [48]. Kleemann et al. [35] reported on the anti-inflammatory and antiatherogenic effects of the quercetin and have shown that short-term treatment for 14 days with dietary quercetin managed to completely quench the cytokine-induced expression of human C-reactive protein (CRP) in transgenic mice. The elevating level of CRP is an inflammation marker that increases the risk of CVDs [35, 49]. Bhaskar et al. [50] investigated the antiatherosclerotic property of quercetin and found notable regression of atherosclerosis in the histopathological examination of the aorta in

hypercholesterolemic rabbits supplemented with quercetin. This suggests the potential of quercetin as an alternative therapeutic agent for atherosclerosis and CVDs as well as for hypertension and obesity that can lead to CVDs [50–52]. *Camellia chinensis* [53, 54], *Allium fistulosum* and *Calamus scipionum* [54], *Moringa oleifera* [17, 55], *Centella asiatica* [56], *Hypericum hircinum* [57], and *Hypericum perforatum* [58] have been reported to have high content of quercetin.

2.2. Kaempferol. Numerous researches have been conducted on kaempferol (3,4',5,7-tetrahydroxyflavone) and studies have shown that consumption of kaempferol-rich foods reduced the risk of developing cardiovascular diseases [59, 60]. Kaempferol has been reported to increase endothelium relaxation in coronary artery of porcine [61]. Xiao et al. [62] investigated kaempferol's protective effects against endothelial damage and found that kaempferol improves the nitric acid production and reduces asymmetric dimethylarginine level which enhances the endothelium-dependent vasorelaxation, preventing endothelium injuries and oxidative damage in cells. The ability of kaempferol in reducing oxidative stress can be the beneficial effect in CVDs [63]. Kaempferol also prevents arteriosclerosis by the inhibition of LDL oxidation and formation of platelets. Kowalski et al. [64] demonstrated that the monocyte chemoattractant protein (MCP-1) is inhibited by kaempferol in an *in vitro* study. MCP-1 involves in the initial stage of plaque formation in arteriosclerosis. Kong et al. [65] evaluated the effect of kaempferol on atherosclerosis induced rabbit models, and upon 10-week treatment of kaempferol with high cholesterol diet, the expression of intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and MCP-1 in the rabbits' aorta has been significantly downregulated. This indicates that kaempferol can alleviate vascular inflammation to prevent atherosclerosis. *Moringa oleifera* constitutes kaempferol as one of its major bioactive compound [17, 55] which was proven to possess antiatherosclerotic and hypolipidemic properties and has therapeutic potential in the treatment of hyperlipidemia, atherosclerosis, and cardiovascular diseases [66, 67]. Therefore, kaempferol can be considered to be an effective and potent agent against atherosclerosis. The presence of kaempferol has been identified in many other plants and some of them are *Centella asiatica* [56], *Euonymus alatus* [68], *Kaempferia galanga* L [69], *Ginkgo biloba*, *Equisetum* spp., *Tilia* spp., *Sophora japonica*, and *propolis* [60].

2.3. Myricetin. Myricetin (3,3',4',5,5',7-hexahydroxyflavone) is a natural flavonol found in vegetables, fruits, berries, tea, and medicinal plants [70]. Various health related studies on myricetin from plant sources have been demonstrated which revealed the antioxidant, antiviral, anticarcinogenic, antiplatelet, hypoglycemic, and cytoprotective properties of myricetin [59, 71–76]. Myricetin also possesses antihypertensive action. Godse et al. [77] reported that myricetin prevent the progression of high blood pressure and reversed the metabolic alterations in fructose-induced rats. Besides, myricetin was proven to suppress body weight gain and fat accumulation by increasing oxidation of fatty acids which

is due to upregulation of hepatic peroxisome proliferator activated receptor (PPAR α) and downregulation of hepatic sterol regulatory element-binding proteins (SREBPs) expressions in high fat-induced rats. These results revealed the antiobesity and antihyperlipidemic effects of myricetin [78]. Myricetin also was proven to possess protective effects on the oxidation of LDL in blood [79, 80]. Ha et al. [79] reported that *Ampelopsis cantoniensis* has myricetin as its main constituent and managed to inhibit the LDL oxidation induced by metal ion (Cu²⁺) and free radical (AAPH), and therefore the *A. cantoniensis* extract can be utilized as a natural remedy to prevent the oxidation of LDL which is involved in the formation atherosclerotic lesion. Lian et al. [80] revealed that besides preventing the LDL from oxidation, myricetin also blocks the oxidized LDL uptake by macrophages and plays an essential role in preventing atherosclerosis. *In vivo* studies on antiatherosclerotic effects of myricetin could further provide better knowledge and understanding of its role in ameliorating atherosclerosis. High content of myricetin has been also reported in these plants: *Myrica cerifera* L [81], *Calamus scipionum* [54], *Chrysobalanus icaco* L [82], *Moringa oleifera*, and *Aloe vera* [17].

2.4. Rutin. Rutin (quercetin-3-rutinoside) is a bioflavonoid commonly found in buckwheat bran, black tea, and citrus fruits [83]. Rutin contributes to many positive health effects such as powerful antioxidant [84], protects against free radicals [85], possess anti-inflammatory properties [86, 87], and suppresses aldose reductase activity [88]. Endothelial dysfunction plays a major role in the development of CDVs and it is found in conditions such as hypertension, hypercholesterolemia, and atherosclerosis. Rutin in buckwheat extract decreases body weight, improves capillary fragility to maintain blood pressure, and significantly reduced nitrotyrosine immunoreactivity in endothelial cells of aorta [89]. Rutin has been proven to exhibit antiobesity effect via suppression of oxidative stress, dyslipidemia, and hepatosteatosis in obese rats. Rutin decreases liver and adipose tissue weight, suppresses hepatic triacylglycerol and cholesterol level, and enhances antioxidant enzymes (superoxide dismutase and glutathione peroxidase) activities in obese rats [90]. On the other hand, rutin plays a great role in preventing atherosclerosis and the evidence for its antiatherosclerotic effects is available in *in vivo* studies: rabbits [91], rat [92], and hamsters [93]. Voskresensky and Bobyrev [91] showed that rutin delays the hypercholesterolemia development and inhibits the atherosclerotic formation in rabbits' aorta. While, Santos et al. [92] researched into the effects of rutin on controlling lipid metabolism and found that rutin reduced the cholesterol levels and has the lowest level of triacylglycerol in hypercholesterolemia rats. In addition, rutin extracted from *Dimorphandra mollis* showed decreases in the level of plasma triglyceride of hypercholesterolemia induced hamsters without changing the high-density lipoprotein (HDL) cholesterol and total cholesterol levels. Rutin was also proven to be nontoxic and no notable changes were observed in total white bloods cells and mononuclear and granulocytes cells compared to the untreated control group [93]. Therefore,

rutin can be developed as an alternative drug for the treatment of atherosclerosis. Other plants that constitute rutin compound are *Flos hippocastani* [94], *Ruta graveolens* [95], *Rhus cotinus* [96], and *Phyllanthus amarus* [97].

2.5. Naringenin. Naringenin (4',5,7-trihydroxyflavanone) has been widely studied in issues related to atherosclerosis. Naringenin was reported to have poor antioxidant properties compared to other flavanoids but it is still able to be a potential inhibitor in cholesterol biosynthesis [98, 99]. Borradaile et al. [100] claimed that naringenin regulates apolipoprotein B secretion by HepG2 cells directly through inhibition of cholesterol ester synthesis. Naringenin also reported to affect lipid metabolism through inhibition of acyl coenzyme A: cholesterol O-acyltransferase and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase in rats [101, 102]. Study on higher animal models, rabbits, was conducted by Kurowska et al. [103] whereby the results obtained showed decrease in hepatic cholesterol and LDL levels. Meanwhile, studies performed on hypercholesterolemic human subjects showed increase in HDL levels after consumption of naringenin rich orange juices [104]. Lee et al. [105] demonstrated that (2S)-naringenin, isolated from *Typha angustata*, inhibits the vascular smooth muscle cells (VSMCs) proliferation while Mulvihill et al. [106] reported that naringenin-treated mice showed about 60% reduction of aortic cholesterol and decreases the level of hepatic cholesteryl ester, very low-density lipoprotein (VLDL) and low density lipoprotein (LDL). These lead to the reduction in cholesterol and triglyceride accumulation within the arterial wall and ameliorates atherosclerosis. Besides, naringenin also prevents accumulation of adipose, adipocyte hypertrophy, and dyslipidemia [106]. Other biological activities of naringenin include anti-inflammatory, anticancer, and positive effects on sex metabolism through binding to estrogen receptors [107–112]. Naringenin is a potential flavonoid to be explored further especially in atherosclerosis since it has numerous health benefits. Some of the plant sources that are rich in naringenin are *Solanum lycopersicum* and citrus fruits [113, 114], *Mentha aquatica* L [115], immature fruit of *Citrus aurantium* [116], and flowers of *Acacia podalyriifolia* [117].

2.6. Catechin. Catechin [(2R,3S)-3',4',5,7-tetrahydroxyflavan-3-ol] has been reported to effectively inhibit lipid peroxidation and scavenge free radicals [118, 119]. Catechin is known to possess preventive effect in CVDs due to its involvement in oxidative process in atherogenesis [120]. Being antioxidant, catechin is able to modulate cellular signaling pathways that lead to elevation of vascular reactivity, platelet aggregation, and reduction of inflammation [121–124]. Diverse studies have been conducted using tea (*Camellia sinensis*) which contains catechin believed to play a major role as cardio-protective plant source [123]. Almost 50–80% of the total catechin from tea is epigallocatechin-3-gallate (EGCG) and it is considered to be the most effective bioactive component in cholesterol lowering [125]. Proinflammatory cytokine and tumor necrosis factor-alpha (TNF α) commonly exist in

atherosclerotic lesions which have direct effect on monocyte chemotactic protein-1 (MCP-1) stimulation and vascular endothelial cells. MCP-1 plays an important role in the monocytes' recruitment in developing inflammatory CVDs. EGCG inhibits TNF α activation and resulted in reduction of MCP-1 production in coronary vascular endothelial cell [126]. Furuyashiki et al. [127] demonstrated that EGCG at low concentration (5 μ M) is able to suppress intracellular lipid accumulation in an *in vitro* model suggesting that the cholesterol lowering effect of EGCG is due to the influence on intestinal lipid absorption. Clinical studies done by Potenza et al. [128] in hypertensive rats suggested that EGCG was shown to reduce blood pressure, raise adiponectin levels, protect against myocardial injury, and improve endothelial function which was proven to reduce the CVDs risk. Another study done by Bursill and Roach [129] confirmed that EGCG lowers the cholesterol and triglyceride absorption in rats. Studies conducted on humans by Widlansky et al. [130] claim that EGCG can reverse endothelial dysfunction and improve dilation of brachial artery in patients with coronary artery disease. These studies suggest the efficiency of EGCG as a potential agent for treating CVD. Other plant sources that are rich in catechins are *Betula pubescens* and *Betula pendula* [131], *Cocos nucifera* [132], fruit pulp of *Argania spinosa* [133], and *Cassia fistula* [134].

2.7. Fisetin. Fisetin (3,7,3',4'-tetrahydroxyflavone) together with morin and myricetin is structural related flavan-3-ol and is commonly distributed in vegetables and fruits such as apple, strawberry, grape, persimmon, cucumber, and onion at concentrations of 2–160 μ g/g [135]. Fisetin is known for its strong antioxidative [136], anti-inflammatory [137], anti-cancer [138], antiproliferative [139], and antihyperglycemic [140] activities. Increase in adipocyte cell number (hyperplasia) is an essential therapeutic target for the prevention of obesity [141]. Jung et al. [142] demonstrated that fisetin ameliorates diet-induced obesity by inhibition of mammalian target of rapamycin complex I (mTORC1) signalling which is central mediator for lipid biosynthesis, cellular growth, and proliferation. Fisetin supplementation in high-fat diet-induced mice regulated fat accumulation in adipose tissue and suppresses adipogenesis during the adipocyte differentiation via downregulation of related gene and thus the study proves that fisetin can be an effective antiobesity agent [142]. The development of atherosclerotic lesion is induced by the elevated concentrations of LDL, blood cholesterol, and triglycerides [143]. Macrophages play an essential role in the development of atherosclerosis by accumulating cholesterol in foam cells [144]. Fisetin inhibits LDL oxidation by macrophages and plays a role as free radical scavenger in LDL which also inhibits the oxidative enzymes from macrophage [145]. Thiobarbituric acid-reactive substances assay (TBARS), electrophoretic mobility, and conjugated diene formation analyses by Lian et al. [80] have shown that fisetin inhibits Cu²⁺ mediated LDL oxidation stronger than morin and myricetin. Binding of CD36 (class B scavenger receptor) to oxidized LDL causes the formation of atherosclerotic lesion. Fisetin blocks macrophage's oxidized LDL uptake by reducing

the CD36 expression on the macrophages [80]. However, the study of fisetin *in vivo* atherosclerosis models is still lacking. The participation of fisetin in ameliorating atherosclerosis can further be confirmed in animal model studies for future flavonoids-based drugs. Plants like *Butea frondosa*, *Gleditsia triacanthos*, *Quebracho colorado* [146], *Curcuma longa* [147], *Rhus verniciflua* [148], *Acacia greggii*, and *Acacia berlandieri* [149] are rich sources of fisetin.

2.8. Gossypetin. Gossypetin (3,5,7,8,3',4'-hexahydroxyflavone) was originally isolated from *Hibiscus spp.* [151]. Gossypetin suppressed the oxidation of LDL [143] and was able to modify the LDL in a form accepted by macrophage through elevated affinity process in a nonoxidative mechanism [154]. Lin et al. [150] reported that gossypetin is an important flavonoid from *Hibiscus sabdariffa* and has been shown to prevent atherosclerosis, reduce oxidative stress, and neutralize agents that cause cancer. *H. Sabdariffa* extract revealed the potential of gossypetin in inhibiting atherosclerosis in hyperlipidemic rabbits [150]. Chen et al. [151] published the first report on the antiatherosclerotic activity of gossypetin in *in vitro* study and demonstrated that gossypetin inhibits both lipoprotein oxidation and lipid peroxidation. Gossypetin functions against oxidative LDL and accumulation of intracellular lipid through the regulation of peroxisome proliferator-activated receptor (PPAR) signals which stimulated the cholesterol to be removed from macrophages and retard the atherosclerosis process [151]. The findings mentioned strongly suggest the development of gossypetin as an antiatherosclerotic agent. *H. Sabdariffa* extract has been used as antihypertensive agent since it decreases systolic blood and pulse pressure [155]. Villalpando-Arteaga et al. [156] reported that *H. Sabdariffa* aqueous extract possesses antilipidemic, antiobesity, and hepatoprotective effects. Studies on the role of gossypetin against hypertension and obesity can further reveal its beneficial effects and pharmacological activities. Besides *H. Sabdariffa*, gossypetin also is present in *H. vitifolius*, *H. esculentus*, *Empetrum nigrum* and *Acacia constricta* [152], *H. rosa-sinensis*, *Chiranthodendron pentadactylon*, *Fremontia californica*, *Thespesia populnea*, and *Fagonia cretica* [153].

3. Conclusion

The summary of reported plant flavonoids is shown in Table 1. Various flavonoids compounds that are available in plants exhibit numerous effects that can prevent the progression of atherosclerosis and diseases such as hypercholesterolemia, hypertension, and obesity that can lead to CVDs. *In vivo* studies on myricetin and fisetin could give better view on its potential as an antiatherosclerotic agent. Investigation of potential effects of gossypetin against hypertension and obesity is suggested. Future research can be focused on the role of plant flavonoids in human metabolism and signaling pathway involved during the therapy of atherosclerosis. This could help to determine the strategies of improving the alternatives therapeutic approaches for atherosclerosis and other related diseases. Since there is an urge for alternatives

TABLE 1: Summary of reported plant flavanoids.

Flavonoid	Bioavailability	Plant
Quercetin	Anti-inflammatory [35]	<i>Morus alba</i> L [48]
	Antihypertensive [40]	<i>Camellia chinensis</i> [53, 54]
	Vasodilator effects [41]	<i>Allium fistulosum</i> and <i>Calamus scipionum</i> [54]
	Antiobesity [47]	<i>Moringa oleifera</i> [17, 55]
	Antihypercholesterolemic and antiatherosclerotic [50]	<i>Centella asiatica</i> [56]
		<i>Hypericum hircinum</i> [57]
Kaempferol		<i>Hypericum perforatum</i> [58]
	Enhances endothelium vasorelaxation [61]	<i>Moringa oleifera</i> [17, 55]
	Protective effects against endothelial damage [62]	<i>Centella asiatica</i> [56]
	Reduce oxidative stress [63]	<i>Ginkgo biloba</i> , <i>Equisetum</i> spp., <i>Tilia</i> spp., <i>Sophora japonica</i> , and <i>propolis</i> [60]
	Antiatherosclerotic [65]	<i>Euonymus alatus</i> [68]
	Antihyperlipidemic [67]	<i>Kaempferia galanga</i> L [69]
Myricetin	Antiplatelet [75]	<i>Calamus scipronum</i> [54]
	Cytoprotective effects [76]	<i>Moringa oleifera</i> and <i>Aloe vera</i> [17]
	Antihypertensive [77]	<i>Ampelopsis cantoniensis</i> [79]
	Antiobesity and antihyperlipidemic [78]	<i>Myrica cerifera</i> L [81]
	Antiatherosclerotic [80]	<i>Chrysobalanus icaco</i> L [82]
Rutin	Anti-inflammatory [86, 87]	<i>Dimorphandra mollis</i> [93]
	Improves capillary fragility and antihypertensive [89]	<i>Flos hippocastani</i> [94]
	Suppresses oxidative stress and antiobesity [90]	<i>Ruta graveolens</i> [95]
	Antiatherosclerotic [91]	<i>Rhus cotinus</i> [96]
	Antihypercholesterolemic [93]	<i>Phyllanthus amarus</i> [97]
Naringenin	Antihypercholesterolemic [104]	<i>Typha angustata</i> [105]
	Antitherogenic and antiobesity [106]	<i>Solanum lycopersicum</i> and <i>citrus fruits</i> [113, 114]
	Anti-inflammatory [111]	<i>Mentha aquatica</i> L [115]
		<i>Citrus aurantium</i> [116]
Catechin		<i>Acacia podalyriifolia</i> [117]
	Antiplatelet and anti-inflammatory [121–124]	<i>Camellia sinensis</i> [123, 125–130]
	Cardioprotective effects [123]	<i>Betula pubescens</i> and <i>Betula pendula</i> [131]
	Antiatherosclerotic [126]	<i>Cocos nucifera</i> [132]
	Antihypercholesterolemic [127]	<i>Argania spinosa</i> [133]
	Antihypertensive [128]	<i>Cassia fistula</i> [134]
Fisetin	Antioxidative [136]	<i>Butea frondosa</i> , <i>Gleditsia triacanthos</i> , and <i>Quebracho colorado</i> [146]
	Anti-inflammatory [137]	<i>Curcuma longa</i> [147]
	Antiproliferative [139]	<i>Rhus verniciflua</i> [148]
	Antiobesity [142]	<i>Acacia greggii</i> and <i>Acacia berlandieri</i> [149]
	Antiatherosclerotic [80]	
Gossypetin		<i>Hibiscus</i> spp. [151]
	Suppresses LDL oxidation [143]	<i>Hibiscus sabdariffa</i> [150]
	Reduces oxidative stress [150]	<i>Hibiscus vitifolius</i> , <i>Hibiscus esculentus</i> , <i>Empetrum nigrum</i> , and <i>Acacia constricta</i> [152]
	Antihyperlipidemic [150]	<i>Hibiscus rosa-sinensis</i> , <i>Chiranthodendron pentadactylon</i> , <i>Fremontia californica</i> , <i>Thespesia populnea</i> , and <i>Fagonia cretica</i> [153]
	Antiatherosclerotic [151]	

natural treatment due to the side effects of statins, flavonoid-based drugs can be utilized for the prevention and treatment of atherosclerosis and CVDs.

Disclosure

The authors declare that the original paper has not been previously published and that it is not being considered elsewhere for publication and that, if accepted, it will not be

published in all forms and media, without the consent of the editor and publisher. All authors agree to submit the paper and agree that the corresponding author acts on their behalf throughout the review and publication process.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Shamala Salvamani and Baskaran Gunasekaran contributed equally to this work.

References

- [1] C. Margaret, "Burden: mortality, morbidity and risk factors," Global Status Report on Non Communicable Diseases, 2010.
- [2] M. Navab, J. A. Berliner, A. D. Watson et al., "The Yin and Yang of oxidation in the development of the fatty streak," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 16, no. 7, pp. 831–842, 1996.
- [3] R. Ross, "Atherosclerosis—an inflammatory disease," *The New England Journal of Medicine*, vol. 340, no. 2, pp. 115–126, 1999.
- [4] D. Steinberg and J. L. Witztum, *Lipoproteins, Lipoprotein, Oxidation, and Atherogenesis*, WB Saunders, Philadelphia, Pa, USA, 1999.
- [5] J. F. Keaney Jr., "Atherosclerosis: from lesion formation to plaque activation and endothelial dysfunction," *Molecular Aspects of Medicine*, vol. 21, no. 4-5, pp. 99–166, 2000.
- [6] A. L. Gould, J. E. Rossouw, N. C. Santanello, J. F. Heyse, and C. D. Furberg, "Cholesterol reduction yields clinical benefit: impact of statin trials," *Circulation*, vol. 97, no. 10, pp. 946–952, 1998.
- [7] K. K. Ray and C. P. Cannon, "The potential relevance of the multiple lipid-independent (Pleiotropic) effects of statins in the management of acute coronary syndromes," *Journal of the American College of Cardiology*, vol. 46, no. 8, pp. 1425–1433, 2005.
- [8] A. Endo, Y. Tsujita, M. Kuroda, and K. Tanzawa, "Inhibition of cholesterol synthesis in vitro and in vivo by ML 236A and ML 236B, competitive inhibitors of 3 hydroxy 3 methylglutaryl Coenzyme A reductase," *European Journal of Biochemistry*, vol. 77, no. 1, pp. 31–36, 1977.
- [9] M. S. Brown and J. L. Goldstein, "A receptor-mediated pathway for cholesterol homeostasis," *Science*, vol. 232, no. 4746, pp. 34–47, 1986.
- [10] D. J. Maron, G. P. Lu, N. S. Cai et al., "Cholesterol-lowering effect of a theaflavin-enriched green tea extract: a randomized controlled trial," *Archives of Internal Medicine*, vol. 163, no. 12, pp. 1448–1453, 2003.
- [11] R. H. Bradford, C. L. Shear, A. N. Chremos et al., "Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia," *Archives of Internal Medicine*, vol. 151, no. 1, pp. 43–49, 1991.
- [12] L. R. Pierce, D. K. Wysowski, and T. P. Gross, "Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy," *Journal of the American Medical Association*, vol. 264, no. 1, pp. 71–75, 1990.
- [13] S. Agarwal and A. V. Rao, "Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study," *Lipids*, vol. 33, no. 10, pp. 981–984, 1998.
- [14] C. Auger, P.-L. Teissedre, P. Gérain et al., "Dietary wine phenolics catechin, quercetin, and resveratrol efficiently protect hypercholesterolemic hamsters against aortic fatty streak accumulation," *Journal of Agricultural and Food Chemistry*, vol. 53, no. 6, pp. 2015–2021, 2005.
- [15] W. M. Loke, J. M. Proudfoot, J. M. Hodgson et al., "Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein e-knockout mice by alleviating inflammation and endothelial dysfunction," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 4, pp. 749–757, 2010.
- [16] M. Škerget, P. Kotnik, M. Hadolin, A. R. Hraš, M. Simonič, and Ž. Knez, "Phenols, proanthocyanidins, flavones and flavonols in some plant materials and their antioxidant activities," *Food Chemistry*, vol. 89, no. 2, pp. 191–198, 2005.
- [17] B. Sultana and F. Anwar, "Flavonols (kaempferol, quercetin, myricetin) contents of selected fruits, vegetables and medicinal plants," *Food Chemistry*, vol. 108, no. 3, pp. 879–884, 2008.
- [18] D. M. Ribnicky, P. Kuhn, A. Poulev et al., "Improved absorption and bioactivity of active compounds from an anti-diabetic extract of *Artemisia dracuncululus* L.," *International Journal of Pharmaceutics*, vol. 370, no. 1-2, pp. 87–92, 2009.
- [19] R. Patil, R. Patil, B. Ahirwar, and D. Ahirwar, "Isolation and characterization of anti-diabetic component (bioactivity-guided fractionation) from *Ocimum sanctum* L. (Lamiaceae) aerial part," *Asian Pacific Journal of Tropical Medicine*, vol. 4, no. 4, pp. 278–282, 2011.
- [20] J. Wainstein, T. Ganz, M. Boaz et al., "Olive leaf extract as a hypoglycemic agent in both human diabetic subjects and in rats," *Journal of Medicinal Food*, vol. 15, no. 7, pp. 605–610, 2012.
- [21] N. Tabassum and F. Ahmad, "Role of natural herbs in the treatment of hypertension," *Pharmacognosy Reviews*, vol. 5, no. 9, pp. 30–40, 2011.
- [22] S. I. Koo and S. K. Noh, "Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect," *Journal of Nutritional Biochemistry*, vol. 18, no. 3, pp. 179–183, 2007.
- [23] D. K. Singh, S. Banerjee, and T. D. Porter, "Green and black tea extracts inhibit HMG-CoA reductase and activate AMP kinase to decrease cholesterol synthesis in hepatoma cells," *The Journal of Nutritional Biochemistry*, vol. 20, no. 10, pp. 816–822, 2009.
- [24] M. Ismail, G. Al-Naqeeq, and K. W. Chan, "Nigella sativa thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats," *Free Radical Biology and Medicine*, vol. 48, no. 5, pp. 664–672, 2010.
- [25] M. J. C. Rhodes and K. R. Price, "Analytical problems in the study of flavonoid compounds in onions," *Food Chemistry*, vol. 57, no. 1, pp. 113–117, 1996.
- [26] G. Dinelli, A. Bonetti, M. Minelli, I. Marotti, P. Catizone, and A. Mazzanti, "Content of flavonols in Italian bean (*Phaseolus vulgaris* L.) ecotypes," *Food Chemistry*, vol. 99, no. 1, pp. 105–114, 2006.
- [27] N. E. Rocha-Guzmán, A. Herzog, R. F. González-Laredo, F. J. Ibarra-Pérez, G. Zambrano-Galván, and J. A. Gallegos-Infante, "Antioxidant and antimutagenic activity of phenolic compounds in three different colour groups of common bean cultivars (*Phaseolus vulgaris*)," *Food Chemistry*, vol. 103, no. 2, pp. 521–527, 2007.
- [28] B. Havsteen, "Flavonoids, a class of natural products of high pharmacological potency," *Biochemical Pharmacology*, vol. 32, no. 7, pp. 1141–1148, 1983.
- [29] M. G. L. Hertog, D. Kromhout, C. Aravanis et al., "Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study," *Archives of Internal Medicine*, vol. 155, no. 4, pp. 1184–1195, 1995.
- [30] D. D. Schramm and J. B. German, "Potential effects of flavonoids on the etiology of vascular disease," *The Journal of Nutritional Biochemistry*, vol. 9, no. 10, pp. 560–566, 1998.

- [31] M. Galleano, V. Calabro, P. D. Prince et al., "Flavonoids and metabolic syndrome," *Annals of the New York Academy of Sciences*, vol. 1259, no. 1, pp. 87–94, 2012.
- [32] J. A. Vinson, Y. A. Dabbagh, M. M. Serry, and J. Jang, "Plant flavonoids, especially tea flavonols, are powerful antioxidants using an in vitro oxidation model for heart disease," *Journal of Agricultural and Food Chemistry*, vol. 43, no. 11, pp. 2800–2802, 1995.
- [33] P. C. H. Hollman, J. M. P. Van Trijp, M. N. C. P. Buysman et al., "Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man," *FEBS Letters*, vol. 418, no. 1-2, pp. 152–156, 1997.
- [34] C. Manach, A. Mazur, and A. Scalbert, "Polyphenols and prevention of cardiovascular diseases," *Current Opinion in Lipidology*, vol. 16, no. 1, pp. 77–84, 2005.
- [35] R. Kleemann, L. Verschuren, M. Morrison et al., "Anti-inflammatory, anti-proliferative and anti-atherosclerotic effects of quercetin in human *in vitro* and *in vivo* models," *Atherosclerosis*, vol. 218, no. 1, pp. 44–52, 2011.
- [36] A. S. Koshy, L. Anila, and N. R. Vijayalakshmi, "Flavonoids from *Garcinia cambogia* lower lipid levels in hypercholesterolemic rats," *Food Chemistry*, vol. 72, no. 3, pp. 289–294, 2001.
- [37] L. Anila and N. R. Vijayalakshmi, "Antioxidant action of flavonoids from *Mangifera indica* and *Emblica officinalis* in hypercholesterolemic rats," *Food Chemistry*, vol. 83, no. 4, pp. 569–574, 2003.
- [38] Y. Zou, Y. Lu, and D. Wei, "Hypocholesterolemic effects of a flavonoid-rich extract of *Hypericum perforatum* L. in rats fed a cholesterol-rich diet," *Journal of Agricultural and Food Chemistry*, vol. 53, no. 7, pp. 2462–2466, 2005.
- [39] N. P. Visavadiya and A. V. R. L. Narasimhacharya, "Asparagus root regulates cholesterol metabolism and improves antioxidant status in hypercholesteremic rats," *Evidence-Based Complementary and Alternative Medicine*, vol. 6, no. 2, pp. 219–226, 2009.
- [40] J. Duarte, R. Pérez-Palencia, F. Vargas et al., "Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats," *British Journal of Pharmacology*, vol. 133, no. 1, pp. 117–124, 2001.
- [41] M. F. García-Saura, M. Galisteo, I. C. Villar et al., "Effects of chronic quercetin treatment in experimental renovascular hypertension," *Molecular and Cellular Biochemistry*, vol. 270, no. 1-2, pp. 147–155, 2005.
- [42] M. Sánchez, M. Galisteo, R. Vera et al., "Quercetin downregulates NADPH oxidase, increases eNOS activity and prevents endothelial dysfunction in spontaneously hypertensive rats," *Journal of Hypertension*, vol. 24, no. 1, pp. 75–84, 2006.
- [43] A. Abbass, "Efficiency of some antioxidants in reducing cardiometabolic risks in obese rats," *Journal of American Science*, vol. 7, pp. 1146–1159, 2011.
- [44] K.-H. Lee, E. Park, H.-J. Lee et al., "Effects of daily quercetin supplementation on cardiometabolic risks in male smokers," *Nutrition Research and Practice*, vol. 5, no. 1, pp. 28–33, 2011.
- [45] L. K. Stewart, J. L. Soileau, D. Ribnicky et al., "Quercetin transiently increases energy expenditure but persistently decreases circulating markers of inflammation in C57BL/6J mice fed a high-fat diet," *Metabolism: Clinical and Experimental*, vol. 57, no. 1, pp. S39–S46, 2008.
- [46] E. Ohkoshi, H. Miyazaki, K. Shindo, H. Watanabe, A. Yoshida, and H. Yajima, "Constituents from the leaves of *Nelumbo nucifera* stimulate lipolysis in the white adipose tissue of mice," *Planta Medica*, vol. 73, no. 12, pp. 1255–1259, 2007.
- [47] M. Kobori, S. Masumoto, Y. Akimoto, and H. Oike, "Chronic dietary intake of quercetin alleviates hepatic fat accumulation associated with consumption of a Western-style diet in C57/BL6J mice," *Molecular Nutrition and Food Research*, vol. 55, no. 4, pp. 530–540, 2011.
- [48] B. Enkhmaa, K. Shiwaku, T. Katsube et al., "Mulberry (*Morus alba* L.) leaves and their major flavonol quercetin 3-(6-malonylglucoside) attenuate atherosclerotic lesion development in LDL receptor-deficient mice," *Journal of Nutrition*, vol. 135, no. 4, pp. 729–734, 2005.
- [49] P. M. Ridker, "C-reactive protein: a simple test to help predict risk of heart attack and stroke," *Circulation*, vol. 108, no. 12, pp. e81–e85, 2003.
- [50] S. Bhaskar, K. S. Kumar, K. Krishnan, and H. Antony, "Quercetin alleviates hypercholesterolemic diet induced inflammation during progression and regression of atherosclerosis in rabbits," *Nutrition*, vol. 29, no. 1, pp. 219–229, 2013.
- [51] S. Jużwiak, J. Wójcicki, K. Mokrzycki et al., "Effect of quercetin on experimental hyperlipidemia and atherosclerosis in rabbits," *Pharmacological Reports*, vol. 57, no. 5, pp. 604–609, 2005.
- [52] S. Bhaskar, V. Shalini, and A. Helen, "Quercetin regulates oxidized LDL induced inflammatory changes in human PBMCs by modulating the TLR-NF- κ B signaling pathway," *Immunobiology*, vol. 216, no. 3, pp. 367–373, 2011.
- [53] M. G. L. Hertog, P. C. H. Hollman, and B. Van de Putte, "Content of potentially anticarcinogenic flavonoids of tea infusions, wines, and fruit juices," *Journal of Agricultural and Food Chemistry*, vol. 41, no. 8, pp. 1242–1246, 1993.
- [54] K. H. Miesan and S. Mohamed, "Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants," *Journal of Agricultural and Food Chemistry*, vol. 49, no. 6, pp. 3106–3112, 2001.
- [55] P. Siddhuraju and K. Becker, "Antioxidant properties of various solvent extracts of total phenolic constituents from three different agroclimatic origins of drumstick tree (*Moringa oleifera* Lam.) leaves," *Journal of Agricultural and Food Chemistry*, vol. 51, no. 8, pp. 2144–2155, 2003.
- [56] M. Bajpai, A. Pande, S. K. Tewari, and D. Prakash, "Phenolic contents and antioxidant activity of some food and medicinal plants," *International Journal of Food Sciences and Nutrition*, vol. 56, no. 4, pp. 287–291, 2005.
- [57] F. Chimenti, F. Cottiglia, L. Bonsignore et al., "Quercetin as the active principle of *Hypericum hircinum* exerts a selective inhibitory activity against MAO-A: extraction, biological analysis, and computational study," *Journal of Natural Products*, vol. 69, no. 6, pp. 945–949, 2006.
- [58] B. Silva, P. J. Oliveira, A. Dias, and J. O. Malva, "Quercetin, kaempferol and biapigenin from *hypericum perforatum* are neuroprotective against excitotoxic insults," *Neurotoxicity Research*, vol. 13, no. 3-4, pp. 265–279, 2008.
- [59] P. Knekt, J. Kumpulainen, R. Järvinen et al., "Flavonoid intake and risk of chronic diseases," *American Journal of Clinical Nutrition*, vol. 76, no. 3, pp. 560–568, 2002.
- [60] J. M. Calderon-Montano, E. Burgos-Morón, and M. López-Lázaro, "A review on the dietary flavonoid kaempferol," *Mini Review in Medicinal Chemistry*, vol. 11, pp. 298–344, 2011.
- [61] Y. C. Xu, D. K. Y. Yeung, R. Y. K. Man, and S. W. S. Leung, "Kaempferol enhances endothelium-independent and dependent relaxation in the porcine coronary artery," *Molecular and Cellular Biochemistry*, vol. 287, no. 1-2, pp. 61–67, 2006.

- [62] H.-B. Xiao, X.-Y. Lu, X.-J. Chen, and Z.-L. Sun, "Protective effects of kaempferol against endothelial damage by an improvement in nitric oxide production and a decrease in asymmetric dimethylarginine level," *European Journal of Pharmacology*, vol. 616, no. 1-3, pp. 213–222, 2009.
- [63] R. Singh, B. Singh, S. Singh, N. Kumar, S. Kumar, and S. Arora, "Anti-free radical activities of kaempferol isolated from *Acacia nilotica* (L.) Willd. Ex. Del," *Toxicology in Vitro*, vol. 22, no. 8, pp. 1965–1970, 2008.
- [64] J. Kowalski, A. Samojedny, M. Paul, G. Pietsz, and T. Wilczok, "Effect of kaempferol on the production and gene expression of monocyte chemoattractant protein-1 in J774.2 macrophages," *Pharmacological Reports*, vol. 57, no. 1, pp. 107–112, 2005.
- [65] L. Kong, C. Luo, X. Li, Y. Zhou, and H. He, "The anti-inflammatory effect of kaempferol on early atherosclerosis in high cholesterol fed rabbits," *Lipids in Health and Disease*, vol. 12, no. 1, pp. 112–115, 2013.
- [66] P. Chumark, P. Khunawat, Y. Sanvarinda et al., "The *in vitro* and *ex vivo* antioxidant properties, hypolipidaemic and antiatherosclerotic activities of water extract of *Moringa oleifera* Lam. leaves," *Journal of Ethnopharmacology*, vol. 116, no. 3, pp. 439–446, 2008.
- [67] M. G. Rajanandh, M. N. Satishkumar, K. Elango, and B. Suresh, "*Moringa oleifera* Lam. A herbal medicine for hyperlipidemia: a pre-clinical report," *Asian Pacific Journal of Tropical Disease*, vol. 2, no. 2, pp. S790–S795, 2012.
- [68] X.-K. Fang, J. Gao, and D.-N. Zhu, "Kaempferol and quercetin isolated from *Euonymus alatus* improve glucose uptake of 3T3-L1 cells without adipogenesis activity," *Life Sciences*, vol. 82, no. 11-12, pp. 615–622, 2008.
- [69] M. R. Sulaiman, Z. A. Zakaria, I. A. Daud, F. N. Ng, Y. C. Ng, and M. T. Hidayat, "Antinociceptive and anti-inflammatory activities of the aqueous extract of *Kaempferia galanga* leaves in animal models," *Journal of Natural Medicines*, vol. 62, no. 2, pp. 221–227, 2008.
- [70] J. M. Harnly, R. F. Doherty, G. R. Beecher et al., "Flavonoid content of U.S. fruits, vegetables, and nuts," *Journal of Agricultural and Food Chemistry*, vol. 54, no. 26, pp. 9966–9977, 2006.
- [71] A. M. Gray and P. R. Flatt, "Nature's own pharmacy: the diabetes perspective," *Proceedings of the Nutrition Society*, vol. 56, no. 1999, pp. 507–517, 1997.
- [72] L. Mira, M. T. Fernandez, M. Santos, R. Rocha, M. H. Florêncio, and K. R. Jennings, "Interactions of flavonoids with iron and copper ions: a mechanism for their antioxidant activity," *Free Radical Research*, vol. 36, no. 11, pp. 1199–1208, 2002.
- [73] T. P. T. Cushnie and A. J. Lamb, "Antimicrobial activity of flavonoids," *International Journal of Antimicrobial Agents*, vol. 26, no. 5, pp. 343–356, 2005.
- [74] Y. Shimmyo, T. Kihara, A. Akaike, T. Niidome, and H. Sugimoto, "Three distinct neuroprotective functions of myricetin against glutamate-induced neuronal cell death: involvement of direct inhibition of caspase-3," *Journal of Neuroscience Research*, vol. 86, no. 8, pp. 1836–1845, 2008.
- [75] N. J. Kang, S. K. Jung, K. W. Lee, and H. J. Lee, "Myricetin is a potent chemopreventive phytochemical in skin carcinogenesis," *Annals of the New York Academy of Sciences*, vol. 1229, no. 1, pp. 124–132, 2011.
- [76] Y. Li and Y. Ding, "Minireview: therapeutic potential of myricetin in diabetes mellitus," *Food Science and Human Wellness*, vol. 1, pp. 19–25, 2012.
- [77] S. Godse, M. Mohan, V. Kasture, and S. Kasture, "Effect of myricetin on blood pressure and metabolic alterations in fructose hypertensive rats," *Pharmaceutical Biology*, vol. 48, no. 5, pp. 494–498, 2010.
- [78] C. J. Chang, T.-F. Tzeng, S.-S. Liou, Y.-S. Chang, and I.-M. Liu, "Myricetin increases hepatic peroxisome proliferator-activated receptor protein expression and decreases plasma lipids and adiposity in rats," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 787152, 11 pages, 2012.
- [79] D. T. Ha, P. T. Thuang, and N. D. Thuan, "Protective action of *Ampelopsis cantoniensis* and its major constituent—myricetin against LDL oxidation," *Journal of Chemistry*, vol. 45, pp. 768–771, 2007.
- [80] T.-W. Lian, L. Wang, Y.-H. Lo, I.-J. Huang, and M.-J. Wu, "Fisetin, morin and myricetin attenuate CD36 expression and oxLDL uptake in U937-derived macrophages," *Biochimica et Biophysica Acta: Molecular and Cell Biology of Lipids*, vol. 1781, no. 10, pp. 601–609, 2008.
- [81] B. D. Paul, G. S. Rao, and G. J. Kapadia, "Isolation of myricadiol, myricitrin, taraxerol, and taraxerone from *Myrica cerifera* L. root bark," *Journal of Pharmaceutical Sciences*, vol. 63, no. 6, pp. 958–959, 1974.
- [82] W. L. R. Barbosa, A. Peres, S. Gallori et al., "Determination of myricetin derivatives in *Chrysobalanus icaco* L., (Chrysobalanaceae)," *Brazilian Journal of Pharmacognosy*, vol. 16, pp. 333–337, 2006.
- [83] S. Kreft, M. Knapp, and I. Kreft, "Extraction of rutin from buckwheat (*Fagopyrum esculentum moench*) seeds and determination by capillary electrophoresis," *Journal of Agricultural and Food Chemistry*, vol. 47, no. 11, pp. 4649–4652, 1999.
- [84] D. Metodiewa, A. Kochman, and S. Karolczak, "Evidence for antiradical and antioxidant properties of four biologically active N,N-diethylamioethyl ethers of flavanone oximes: a comparison with natural polyphenolic flavonoid (rutin) action," *International Union of Biochemistry and Molecular Life*, vol. 41, no. 5, pp. 1067–1075, 1997.
- [85] S. A. Aherne and N. M. O'Brien, "Protection by the flavonoids myricetin, quercetin, and rutin against hydrogen peroxide-induced DNA damage in Caco-2 and Hep G2 cells," *Nutrition and Cancer*, vol. 34, no. 2, pp. 160–166, 1999.
- [86] T. Guardia, A. E. Rotelli, A. O. Juarez, and L. E. Pelzer, "Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat," *Farmaco*, vol. 56, no. 9, pp. 683–687, 2001.
- [87] H. J. Chan, Y. L. Ji, H. C. Chul, and J. K. Chang, "Anti-asthmatic action of quercetin and rutin in conscious guinea-pigs challenged with aerosolized ovalbumin," *Archives of Pharmacological Research*, vol. 30, no. 12, pp. 1599–1607, 2007.
- [88] G. B. Reddy, P. Muthenna, C. Akileshwari, M. Saraswat, and J. M. Petrash, "Inhibition of aldose reductase and sorbitol accumulation by dietary rutin," *Current Science*, vol. 101, no. 9, pp. 1191–1197, 2011.
- [89] W. K. Dae, K. H. In, S. L. Soon et al., "Germinated buckwheat extract decreases blood pressure and nitrotyrosine immunoreactivity in aortic endothelial cells in spontaneously hypertensive rats," *Phytotherapy Research*, vol. 23, no. 7, pp. 993–998, 2009.
- [90] C.-L. Hsu, C.-H. Wu, S.-L. Huang, and G.-C. Yen, "Phenolic compounds rutin and o-coumaric acid ameliorate obesity induced by high-fat diet in rats," *Journal of Agricultural and Food Chemistry*, vol. 57, no. 2, pp. 425–431, 2009.

- [91] O. N. Voskresensky and V. N. Bobyrev, "Effect of ascorbic acid and rutin on the development of experimental peroxide atherosclerosis," *Farmakologiya i Toksikologiya*, vol. 42, no. 4, pp. 378–382, 1979.
- [92] K. F. R. Santos, T. T. Oliveira, T. J. Nagem, A. S. Pinto, and M. G. A. Oliveira, "Hypolipidaemic effects of naringenin, rutin, nicotinic acid and their associations," *Pharmacological Research*, vol. 40, no. 6, pp. 493–496, 1999.
- [93] A. Kanashiro, D. C. O. Andrade, L. M. Kabeya et al., "Modulatory effects of rutin on biochemical and hematological parameters in hypercholesterolemic Golden Syrian hamsters," *Annals of the Brazilian Academy of Sciences*, vol. 81, no. 1, pp. 67–71, 2009.
- [94] B. Buszewski, S. Kawka, Z. Suprynowicz, and T. Wolski, "Simultaneous isolation of Rutin and Esculin from plant material and drugs using solid-phase extraction," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 11, no. 3, pp. 211–215, 1993.
- [95] D. J. Afshar and A. Delazar, "Rutin from *Ruta graveolens* L.," *DARU Journal of Pharmaceutical Sciences*, vol. 4, pp. 1–12, 1994.
- [96] M. Atanassova and V. Bagdassarian, "Rutin in plant products," *Journal of the University of Chemical Technology and Metallurgy*, vol. 44, pp. 201–203, 2009.
- [97] P. Shukla, B. Gopalkrishna, and P. Shukla, "Isolation of rutin from *Phyllanthus amarus*," *International Journal of Pharmaceutical Sciences and Research*, vol. 3, pp. 1198–1201, 2012.
- [98] S.-M. Jeon, S.-H. Bok, M.-K. Jang et al., "Comparison of antioxidant effects of naringin and probucol in cholesterol-fed rabbits," *Clinica Chimica Acta*, vol. 317, no. 1–2, pp. 181–190, 2002.
- [99] F. A. A. Van Acker, O. Schouten, G. R. M. M. Haenen, W. J. F. Van Der Vijgh, and A. Bast, "Flavonoids can replace α -tocopherol as an antioxidant," *FEBS Letters*, vol. 473, no. 2, pp. 145–148, 2000.
- [100] N. M. Borradaile, K. K. Carroll, and E. M. Kurowska, "Regulation of HepG2 cell apolipoprotein B metabolism by the citrus flavanones hesperetin and naringenin," *Lipids*, vol. 34, no. 6, pp. 591–598, 1999.
- [101] S.-H. Lee, T.-S. Jeong, Y. B. Park, Y.-K. Kwon, M.-S. Choi, and S.-H. Bok, "Hypocholesterolemic effect of hesperetin mediated by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and acyl coenzyme A: cholesterol acyltransferase in rats fed high-cholesterol diet," *Nutrition Research*, vol. 19, no. 8, pp. 1245–1258, 1999.
- [102] S. H. Lee, Y. B. Park, K. H. Bae et al., "Cholesterol-lowering activity of naringenin via inhibition of 8-hydroxy-3-methylglutaryl coenzyme A reductase and acyl coenzyme A: cholesterol acyltransferase in rats," *Annals of Nutrition and Metabolism*, vol. 43, no. 3, pp. 173–180, 1999.
- [103] E. M. Kurowska, N. M. Borradaile, J. D. Spence, and K. K. Carroll, "Hypocholesterolemic effects of dietary citrus juices in rabbits," *Nutrition Research*, vol. 20, no. 1, pp. 121–129, 2000.
- [104] E. M. Kurowska, J. D. Spence, J. Jordan et al., "HDL-cholesterol-raising effect of orange juice in subjects with hypercholesterolemia," *American Journal of Clinical Nutrition*, vol. 72, no. 5, pp. 1095–1100, 2000.
- [105] J.-J. Lee, H. Yi, I.-S. Kim et al., "(2S)-Naringenin from *Typha angustata* inhibits vascular smooth muscle cell proliferation via a G0/G1 arrest," *Journal of Ethnopharmacology*, vol. 139, pp. 873–878, 2012.
- [106] E. E. Mulvihill, J. M. Assini, B. G. Sutherland et al., "Naringenin decreases progression of atherosclerosis by improving dyslipidemia in high-fat-fed low-density lipoprotein receptor-null mice," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 4, pp. 742–748, 2010.
- [107] M. F. Ruh, T. Zacharewski, K. Connor, J. Howell, I. Chen, and S. Safe, "Naringenin: a weakly estrogenic bioflavonoid that exhibits antiestrogenic activity," *Biochemical Pharmacology*, vol. 50, no. 9, pp. 1485–1493, 1995.
- [108] G. G. J. M. Kuiper, J. G. Lemmen, B. Carlsson et al., "Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β ," *Endocrinology*, vol. 139, no. 10, pp. 4252–4263, 1998.
- [109] R. S. Rosenberg, L. Grass, D. J. A. Jenkins, C. W. C. Kendall, and E. P. Diamandis, "Modulation of androgen and progesterone receptors by phytochemicals in breast cancer cell lines," *Biochemical and Biophysical Research Communications*, vol. 248, no. 3, pp. 935–939, 1998.
- [110] H. Déchaud, C. Ravard, F. Claustrat, A. B. De La Perrière, and M. Pugeat, "Xenoestrogen interaction with human sex hormone-binding globulin (hSHBG)," *Steroids*, vol. 64, no. 5, pp. 328–334, 1999.
- [111] J. A. Manthey, N. Guthrie, and K. Grohmann, "Biological properties of citrus flavonoids pertaining to cancer and inflammation," *Current Medicinal Chemistry*, vol. 8, no. 2, pp. 135–153, 2001.
- [112] K. Yoon, L. Pallaroni, M. Stoner, K. Gaido, and S. Safe, "Differential activation of wild-type and variant forms of estrogen receptor α by synthetic and natural estrogenic compounds using a promoter containing three estrogen-responsive elements," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 78, no. 1, pp. 25–32, 2001.
- [113] M. Krause and R. Galensa, "Determination of naringenin and naringenin-chalcone in tomato skins by reversed phase HPLC after solid phase extraction," *Zeitschrift für Lebensmittel-Untersuchung und -Forschung*, vol. 194, no. 1, pp. 29–32, 1992.
- [114] S. Kawaii, Y. Tomono, E. Katase, K. Ogawa, and M. Yano, "Quantitation of flavonoid constituents in Citrus fruits," *Journal of Agricultural and Food Chemistry*, vol. 47, no. 9, pp. 3565–3571, 1999.
- [115] H. T. Olsen, G. I. Stafford, J. van Staden, S. B. Christensen, and A. K. Jäger, "Isolation of the MAO-inhibitor naringenin from *Mentha aquatica* L.," *Journal of Ethnopharmacology*, vol. 117, no. 3, pp. 500–502, 2008.
- [116] L. Liu, S. Shan, K. Zhang, Z.-Q. Ning, X.-P. Lu, and Y.-Y. Cheng, "Naringenin and hesperetin, two flavonoids derived from *Citrus aurantium* up-regulate transcription of adiponectin," *Phytotherapy Research*, vol. 22, no. 10, pp. 1400–1403, 2008.
- [117] C. A. de Andrade, J. L. D. S. Carvalho, M. M. Cunico et al., "Antioxidant and antibacterial activity of extracts, fractions and isolated substances from the flowers of *Acacia podalyriifolia* A. Cunn. ex G. Don," *Brazilian Journal of Pharmaceutical Sciences*, vol. 46, no. 4, pp. 715–721, 2010.
- [118] K. Yoshino, Y. Hara, M. Sano, and I. Tomita, "Antioxidative effects of black tea theaflavins and thearubigin on lipid peroxidation of liver homogenates induced by tert-butyl hydroperoxide," *Biological and Pharmaceutical Bulletin*, vol. 17, no. 1, pp. 146–149, 1994.
- [119] N. Salah, N. J. Miller, G. Paganga, L. Tijburg, G. P. Bolwell, and C. Rice-Evans, "Polyphenolic flavanols as scavengers of aqueous phase radicals and as chain-breaking antioxidants," *Archives of Biochemistry and Biophysics*, vol. 322, no. 2, pp. 339–346, 1995.
- [120] K. F. Gey, "Ten-year retrospective on the antioxidant hypothesis of arteriosclerosis: threshold plasma levels of antioxidant micronutrients related to minimum cardiovascular risk," *Journal of Nutritional Biochemistry*, vol. 6, no. 4, pp. 206–236, 1995.

- [121] J. A. Vita, "Tea consumption and cardiovascular disease: effects on endothelial function," *Journal of Nutrition*, vol. 133, no. 10, pp. 3293s–3297s, 2003.
- [122] V. Stangl, M. Lorenz, and K. Stangl, "The role of tea and tea flavonoids in cardiovascular health," *Molecular Nutrition and Food Research*, vol. 50, no. 2, pp. 218–228, 2006.
- [123] V. Stangl, H. Dreger, K. Stangl, and M. Lorenz, "Molecular targets of tea polyphenols in the cardiovascular system," *Cardiovascular Research*, vol. 73, no. 2, pp. 348–358, 2007.
- [124] S. M. Shenouda and J. A. Vita, "Effects of flavonoid-containing beverages and EGCG on endothelial function," *Journal of the American College of Nutrition*, vol. 26, no. 4, pp. 366s–372s, 2007.
- [125] N. Khan and H. Mukhtar, "Tea polyphenols for health promotion," *Life Sciences*, vol. 81, no. 7, pp. 519–533, 2007.
- [126] H. Y. Ahn, Y. Xu, and S. T. Davidge, "Epigallocatechin-3-O-gallate inhibits TNF α -induced monocyte chemotactic protein-1 production from vascular endothelial cells," *Life Sciences*, vol. 82, no. 17–18, pp. 964–968, 2008.
- [127] T. Furuyashiki, H. Nagayasu, Y. Aoki et al., "Tea catechin suppresses adipocyte differentiation accompanied by down-regulation of PPAR γ 2 and C/EBP α in 3T3-L1 cells," *Bioscience, Biotechnology and Biochemistry*, vol. 68, no. 11, pp. 2353–2359, 2004.
- [128] M. A. Potenza, F. L. Marasciulo, M. Tarquinio et al., "EGCG, a green tea polyphenol, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR," *American Journal of Physiology: Endocrinology and Metabolism*, vol. 292, no. 5, pp. E1378–E1387, 2007.
- [129] C. A. Bursill and P. D. Roach, "A green tea catechin extract upregulates the hepatic low-density lipoprotein receptor in rats," *Lipids*, vol. 42, no. 7, pp. 621–627, 2007.
- [130] M. E. Widlansky, N. M. Hamburg, E. Anter et al., "Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease," *Journal of the American College of Nutrition*, vol. 26, no. 2, pp. 95–102, 2007.
- [131] V. Ossipov, K. Nurmi, J. Loponen, E. Haukioja, and K. Pihlaja, "High-performance liquid chromatographic separation and identification of phenolic compounds from leaves of *Betula pubescens* and *Betula pendula*," *Journal of Chromatography A*, vol. 721, no. 1, pp. 59–68, 1996.
- [132] C. Kirszberg, D. Esquenazi, C. S. Alviano, and V. M. Rumjanek, "The effect of a catechin-rich extract of *Cocos nucifera* on lymphocytes proliferation," *Phytotherapy Research*, vol. 17, no. 9, pp. 1054–1058, 2003.
- [133] Z. Charrouf and D. Guillaume, "Phenols and polyphenols from *Argania spinosa*," *American Journal of Food Technology*, vol. 2, no. 7, pp. 679–683, 2007.
- [134] P. Daisy, K. Balasubramanian, M. Rajalakshmi, J. Eliza, and J. Selvaraj, "Insulin mimetic impact of Catechin isolated from *Cassia fistula* on the glucose oxidation and molecular mechanisms of glucose uptake on Streptozotocin-induced diabetic Wistar rats," *Phytomedicine*, vol. 17, no. 1, pp. 28–36, 2010.
- [135] Y. Arai, S. Watanabe, M. Kimira, K. Shimoi, R. Mochizuki, and N. Kinae, "Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration," *Journal of Nutrition*, vol. 130, no. 9, pp. 2243–2250, 2000.
- [136] R. P. Constantin, J. Constantin, C. L. S. Pagadigorria et al., "Prooxidant activity of fisetin: effects on energy metabolism in the rat liver," *Journal of Biochemical and Molecular Toxicology*, vol. 25, no. 2, pp. 117–126, 2011.
- [137] F. Y. Goh, N. Upton, S. Guan et al., "Fisetin, a bioactive flavonol, attenuates allergic airway inflammation through negative regulation of NF- κ B," *European Journal of Pharmacology*, vol. 679, no. 1–3, pp. 109–116, 2012.
- [138] P.-M. Yang, H.-H. Tseng, C.-W. Peng, W.-S. Chen, and S.-J. Chiu, "Dietary flavonoid fisetin targets caspase-3-deficient human breast cancer MCF-7 cells by induction of caspase-7-associated apoptosis and inhibition of autophagy," *International Journal of Oncology*, vol. 40, no. 2, pp. 469–478, 2012.
- [139] N. Khan, F. Afaq, D. N. Syed, and H. Mukhtar, "Fisetin, a novel dietary flavonoid, causes apoptosis and cell cycle arrest in human prostate cancer LNCaP cells," *Carcinogenesis*, vol. 29, no. 5, pp. 1049–1056, 2008.
- [140] G. S. Prasath and S. P. Subramanian, "Modulatory effects of fisetin, a bioflavonoid, on hyperglycemia by attenuating the key enzymes of carbohydrate metabolism in hepatic and renal tissues in streptozotocin-induced diabetic rats," *European Journal of Pharmacology*, vol. 668, no. 3, pp. 492–496, 2011.
- [141] Y. Lee and E. J. Bae, "Inhibition of mitotic clonal expansion mediates fisetin-exerted prevention of adipocyte differentiation in 3T3-L1 cells," *Archives of Pharmacal Research*, vol. 36, pp. 1377–1384, 2013.
- [142] C. H. Jung, H. Kim, J. Ahn, T.-I. Jeon, D.-H. Lee, and T.-Y. Ha, "Fisetin regulates obesity by targeting mTORC1 signaling," *The Journal of Nutritional Biochemistry*, vol. 24, no. 8, pp. 1547–1554, 2013.
- [143] J. Reed, "Cranberry flavonoids, atherosclerosis and cardiovascular health," *Critical Reviews in Food Science and Nutrition*, vol. 42, no. 3, pp. 301–316, 2002.
- [144] D. Steinberg, S. Parthasarathy, T. E. Carew, J. C. Khoo, and J. L. Witztum, "Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity," *The New England Journal of Medicine*, vol. 320, no. 14, pp. 915–924, 1989.
- [145] C. V. De Whalley, S. M. Rankin, J. R. S. Hoult, W. Jessup, and D. S. Leake, "Flavonoids inhibit the oxidative modification of low density lipoproteins by macrophages," *Biochemical Pharmacology*, vol. 39, no. 11, pp. 1743–1750, 1990.
- [146] M. Gábor and E. Eperjessy, "Antibacterial effect of fisetin and fisetinidin," *Nature*, vol. 212, no. 5067, p. 1273, 1966.
- [147] J. Lako, V. C. Trenerry, M. Wahlqvist, N. Wattanapenpaiboon, S. Sotheeswaran, and R. Premier, "Phytochemical flavonols, carotenoids and the antioxidant properties of a wide selection of Fijian fruit, vegetables and other readily available foods," *Food Chemistry*, vol. 101, no. 4, pp. 1727–1741, 2007.
- [148] J.-D. Lee, J.-E. Huh, G. Jeon et al., "Flavonol-rich RVHxR from *Rhus verniciflua* stokes and its major compound fisetin inhibits inflammation-related cytokines and angiogenic factor in rheumatoid arthritic fibroblast-like synovial cells and in vivo models," *International Immunopharmacology*, vol. 9, no. 3, pp. 268–276, 2009.
- [149] T. D. A. Forbes and B. A. Clement, "Chemistry of *Acacia's* from South Texas," *Texas A&M Agricultural Research and Extension Center*, pp. 4–14, 2010.
- [150] H.-H. Lin, J.-H. Chen, and C.-J. Wang, "Chemopreventive properties and molecular mechanisms of the bioactive compounds in *Hibiscus sabdariffa* linne," *Current Medicinal Chemistry*, vol. 18, no. 8, pp. 1245–1254, 2011.
- [151] J. H. Chen, C. W. Tsai, C. P. Wang, and H. H. Lin, "Anti-atherosclerotic potential of gossypetin via inhibiting LDL oxidation

- and foam cell formation,” *Toxicology and Applied Pharmacology*, vol. 272, pp. 313–324, 2013.
- [152] J. B. Harborne, “Gossypetin and herbacetin as taxonomic markers in higher plants,” *Phytochemistry*, vol. 8, no. 1, pp. 177–183, 1969.
- [153] G. Bendz, *Chemistry in Botanical Classification: Medicine and Natural Sciences*, Science, 2013.
- [154] S. M. Rankin, C. V. De Whalley, J. R. S. Hoult et al., “The modification of low density lipoprotein by the flavonoids myricetin and gossypetin,” *Biochemical Pharmacology*, vol. 45, no. 1, pp. 67–75, 1993.
- [155] H. Mozaffari-Khosravi, B.-A. Jalali-Khanabadi, M. Afkhami-Ardekani, F. Fatehi, and M. Noori-Shadkam, “The effects of sour tea (*Hibiscus sabdariffa*) on hypertension in patients with type II diabetes,” *Journal of Human Hypertension*, vol. 23, no. 1, pp. 48–54, 2009.
- [156] E. V. Villalpando-Arteaga, E. Mendieta-Condado, H. Esquivel-Solís et al., “*Hibiscus sabdariffa* L. aqueous extract attenuates hepatic steatosis through down-regulation of PPAR- γ and SREBP-1c in diet-induced obese mice,” *Food & Function*, vol. 4, pp. 618–626, 2013.