Review

Dietary Flavonoids: Cardioprotective Potential with Antioxidant Effects and Their Pharmacokinetic, Toxicological and Therapeutic Concerns

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Abstract: Flavonoids comprise a large group of structurally diverse polyphenolic compounds of plant origin and are abundantly found in human diet such as fruits, vegetables, grains, tea, dairy products, red wine and so on. Major classes of flavonoids include flavonols, flavones, flavanones, flavanols, anthocyanidins, isoflavones, and chalcones. Owing to their potential health benefits and medicinal significance, flavonoids are now considered as an indispensable component in a variety of medicinal, pharmaceutical, nutraceutical, and cosmetic preparations. However, flavonoids play a significant role in preventing cardiovascular diseases (CVDs), which could be mainly due to their antioxidant, antiatherogenic, and antithrombotic effects. Epidemiological and in vitro/in vivo evidences of antioxidant effects support the cardioprotective function of dietary flavonoids. Further, the inhibition of LDL oxidation and platelet aggregation following regular consumption of food containing flavonoids and moderate consumption of red wine might protect against atherosclerosis and thrombosis. A study suggests that daily intake of 100 mg of flavonoids through diet may reduce the risk of developing morbidity and mortality due to coronary heart disease (CHD) by approximately 10%. This review summarizes dietary flavonoids with their sources and potential health implications in CVDs including various redox-active cardioprotective (molecular) mechanisms with antioxidant effects. Pharmacokinetic (oral bioavailability, drug metabolism), toxicological and therapeutic aspects of dietary flavonoids are also addressed herein with future directions for the discovery and development of useful drug candidates/ therapeutic molecules.

Keywords: dietary flavonoids; cardioprotective effects; ROS scavenging; myocardial dysfunction; bioavailability and drug metabolism; toxicity; drug discovery

1. Introduction

The introduction should briefly place the study in a broad context and highlight Cardiovascular diseases (CVDs) are the most protuberant cause of death across the world. Over three quarters of deaths due to CVDs take place in low- and middle-income

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countries. An estimated 17.9 million people died from CVDs in 2016, constituting 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke [1]. Most of the CVDs can be prevented by tackling behavioural risk factors for instance tobacco use, insalubrious diet and obesity, physical inactivity and long consumption of alcohol using population-wide approaches. In the United States, for example, lack of awareness towards leading a healthy lifestyle contributes to nearly half of all cardiometabolic disorders [2]. In India, premature mortality because of CVDs has increased from 37 million in 2010 to 52 million in 2020. In Western populations only 23% of CVD deaths occur before the age of 70 years while in India this number is 52% [3]. The World Health Organisation (WHO) estimation demonstrates that over 75% of premature CVD is preventable and associated risk factors betterment can help decrease the mounting CVD burden on both people and healthcare workers [4]. Autopsy evidence suggests that the progression of CVDs in later years is not foreseeable, thus management is crucial. The INTERHEART study explicated the consequences of CVD risk factors including dyslipidemia, hypertension, diabetes, abdominal obesity, smoking, at the same time as it demonstrated the shielding effects of consumption of nutritious fruits and vegetables, and regular exercise. People with cardiovascular disease or who are at high cardiovascular risk including those having an already established disease like hypertension, diabetes, hyperlipidaemia etc. require early recognition and management using appropriate counselling and medications [5].

Diet and lifestyle have an eminent effect on LDL-cholesterol levels and CVD risk. Patients with CVDs should be counselled about lifestyle modifications to reduce fat and cholesterol ingestion, to duck tobacco products and to maintain the caloric level in our body by ensuring appropriate physical activity in order to maintain a healthy BMI. A body mass index (BMI) > 25 is a risk factor for CVD with lowest probability at BMI 20-25 but, Although BMI < 20 are not routinely recommended [6]. In the prevailing years, this has been reported that the majority of cardiovascular diseases occur due to an imbalance between the formation of reactive oxygen species (ROS) and ROS-degrading antioxidant systems. This disparity results in accrual of superoxide, hydrogen peroxide, and other by products such as peroxynitrite and hypochlorous acid which leads to oxidative damage of vital cell structures and essential biomolecules including lipids, membranes, proteins and DNA. This phenomenon causes deactivation of essential metabolic enzymes and also destruct signal transduction pathways [7]. Oxidative stress (OS) has been linked to a variety of diseases, including neurodegenerative disorders, autoimmune diseases, complex lifestyle diseases, and cancer, and it is implicated in the pathogenesis of over 100 inflammatory disorders, including diabetes, rheumatoid arthritis, periodontitis, stroke, CVDs, and alveolar inflammations. In general, there are numerous molecular mechanisms involving sources of ROS and their respective targets. The intracellular ROS generation takes place in the mitochondrial electron transport chain due to leakage of a small fraction of electrons to oxygen. Antioxidants present in the mitochondria including superoxide dismutase (SOD) and glutathione sequester ROS to reduce their reactivity [8]. Cardiac tissues hold a large number of mitochondria but the antioxidant capacity is not sufficient enough for sequestering ROS which results in cardiac dysfunction or

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mitochondrial cellular oxidative stress. It has been proven that oxidised low-density lipoprotein (ox-LDL) increases the development of reactive oxygen species [9] in human umbilical vein endothelial cells (HUVECs). Angiotensin II and uremic toxin indoxylsulfate-induced endothelial cell dysfunction are two other recognised causes of ROS noticed in CVDs [10].

It has been well established via previous reports that sugars are involved in the development of atherosclerosis, hypertension, peripheral vascular disease, coronary artery disease, cardiomyopathy, heart failure and cardiac arrhythmias and that these effects of added sugars are mediated through ROS as glucose can produce ROS via various pathways including the sorbitol pathway, insulin pathway, NADPH-oxidase (Nox). Noxsignalling is crucial for normal physiology, but overstimulated Nox enzymes contribute to oxidative stress and cardiovascular disease [11]. In AT-II-induced hypertension, NOX-2 activation induces Sirt3 S-glutathionylation which causes acetylation of vascular SOD2 and reduces SOD2 activity, which further results in increased mitochondrial superoxide levels and lessened endothelial nitric oxide bioavailability which acts as an antioxidant in-vivo [11, 12].

Diets low in saturated fat and high in fruits, vegetables, and essential fatty acids, as well as moderate wine intake, appear to protect against the production and progression of CVDs, according to epidemiological evidence.Long term metabolic studies have shown that the fatty acid composition of the diet, rather than the overall amount of fat consumed, predicts serum cholesterol levels. Saturated fatty acids (SFA) and transfatty acids are the ones associated with elevated cardiovascular risk however monounsaturated fatty acids (MUFA, omega-9) and polyunsaturated fatty acids (PUFA, omega-3, omega-6) explicit decreased risk of coronary heart disease (CHD) [13]. The activity of enzymes involved in the desaturation of fatty acids in the body is highly influenced by dietary fat quality. Plant sterols and stanols (saturated form of sterols) are natural elements of plants structurally related to cholesterol. Plant stanols lessen cholesterol absorption in the GIT thereby dipping plasma LDL concentrations. These stanols are found abundantly in vegetable oils, olive oil, fruits and nuts. Recent progressions in food technology have perceived the emergence of nutrition products such as margarine, milk, yoghurt, and cereal products being supplemented with plant sterols/stanols and encouraged as a food that can help lower serum cholesterol [14]. It has been found via clinical studies that serum LDL cholesterol was significantly dropped when stanols were added to milk (15.9%) and yoghurt (8.6%), but significantly less when added to bread (6.5%) and cereal (5.4%). Nonetheless, routine consumption of phytosterols has emerged as an effective strategy in the management of hypercholesterolemic patients in the clinical situation. Alternatively, red yeast rice (Monascuspurpureus) is natural compound capable of reducing cholesterol levels. This fermented rice holds plentiful monacolins that are naturally occurring HMG-CoA reductase inhibitors [15]. The commercial preparations of this traditional supplement possess a beneficial lipid lowering effect. Several studies including cohort studies have suggested a J-shaped relationship between salt intake and CVD risk. As per the recommendation of WHO, Gradual salt reduction in one's diet relics an attainable, cost

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effective, and efficient strategy to prevent CVD worldwide. The INTERSALT study (an international study of electrolyte excretion and BP) confirmed a direct association between salt intake and the increase in BP with age [16].

2. Dietary Flavonoids

2.1. Dietary Occurrence

Flavonoids are secondary metabolites located in the vacuoles of the plants. Approximately 10,000 flavonoids have been reported in the literature positioning them in the third place of the most abundant bioactive compounds in plants. The main function of flavonoids in plants is protecting themselves against pathogens, UV radiation, and participates in pollination by being recognized by pollinators [17]. Flavonoids basic chemical structure consist of 15 carbon atoms (C_6-C_3-C_6) conforming the two aromatic ring A and B linked by a C ring conformed by 3 carbon atoms (**Figure 1**).

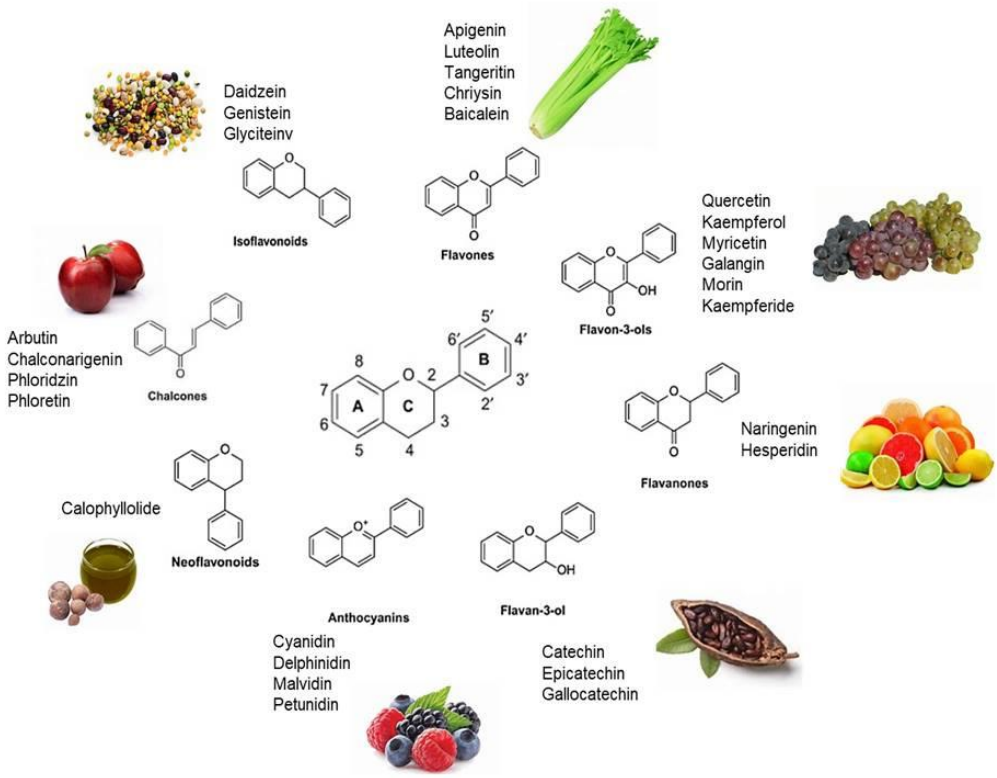

Figure 1. Dietary sources of flavonoids

The classification of flavonoids can be according to the position of the carbon in the B ring linked with the C ring. Thus, the flavonoids linked in the position 3 of the ring C are denominated isoflavones. the ones linked in position 4 are neoflavonoids, and finally those linked to position 2 are subdivided into different subgroups (flavones, flavonols, flavanones, flavanonols, flavanols, anthocyanins and chalcones) depending on the structural characteristics of the C ring [18]. Flavonols, such as quercetin, kaempferol and myricetin are one of the most common flavonoids found in fruits and vegetables, for example, apples, grapes, berries, tomatoes, onions, lettuce, etc. The chemical structure of flavonols is characterized to have a ketone group, and a hydroxyl group located in the

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position 3 of the C ring, that can have different glycosylation patterns and for this reason are the largest subgroups present in plants and foods [19].

On the other hand, the most well-known compounds in flavanones group are hesperidin, naringenin and eriodyctiol, regularly found in the white part of the peel of citrus fruits such as lemon, orange, and grapefruit. Structurally, those compounds are very similar to flavonols, the only difference is the saturation of C ring in the 2 and 3 position [19].

Isoflavonoids are less distributed on plants, and are usually present in lentils, beans, soybean, and other leguminous plants. The most important bioactive compounds on this group are genistein and daidzein, well known as a phytoestrogen due to their osteogenicactivity[18].

Neoflavonoids are a less studied group, their structure is characterized to have a 4-phenylchromen backbone with no hydroxyl group substitution at position 2. The hydroxyl group is bound to position 3 of the C ring [18]. One of the neoflavone is calophyllolide from Calophylluminophyllum seeds, found in other plants and flowers [20]. Flavanols also known as catechins, are abundantly distributed in berries, bananas, peaches, and apples.

Anthocyanins are a flavonoids class widely studied, their notable blue, black, red, and pink colours depend on the pH as well as by the methylation or acylation in the hydroxyl groups on A and B rings. This characteristic produced high interest in the food industry in a variety of applications. The well-known anthocyanins are cyanidin, delphinidin, malvidin, pelargonidin and peonidin. Those compounds are present in strawberries, raspberries, blueberries, blackberries, blue corn, black beans, among others (**Table 1**) [18]. The structures of dietary flavonoids are represented in **Figure 2a-c**.

Table 1. Dietary flavonoids with their natural sources and health benefits [18, 21, 22]

Flavonoids	Major Flavonoids	Major Source	Health Benefits
Flavonols	Isorhamnetin Kaempferol Myricetin Quercetin	Onions, Broccoli, Tea, apple, blueberries.	Regulates systolic blood pressure, glycemic levels and BMI.
Flavones	Apigenin Luteolin	Parsley, celery, chamomile tea, fenugreek, onion, garlic, pepper, citrus fruits,	Regulates blood glucose levels.
Flavanones	Eriodictyol Hesperetin Naringenin	Citrus Fruits, Mint, Tomatoes.	Lowers risk of ischaemic stroke.
Flavanols	Catechins Epicatachins	Apricots, Cocoa, Chocolates, Red Grapes, Red Wine, Tea	Reduces mean arterial pressure Improves

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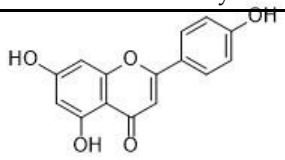
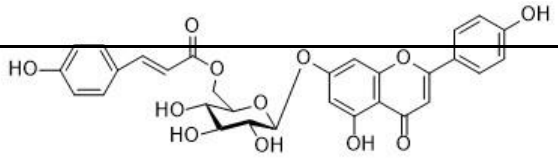
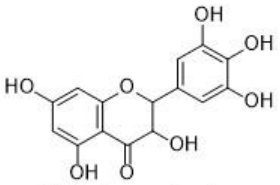
			Insulin resistance and LDL-C, HDL-C levels.
Procyanidins	Theaflavins Thearubigins	Cocoa, Apples, Grapes, Red Wine, Chocolates	Regulates Blood pressure.
Anthocyanidins	Cyanidin Delphinidin Malvidin Pelargonidin Peonidin Petunidin	Berries, Red Wine, Red cabbage, bright coloured fruits, cherries, cranberries	Lowers risk of Myocardial infarctions.
Isoflavones	Daidzein Genistein Glycitein	Soyabean, dairy products, egg, meat	Beneficial for T2DM.



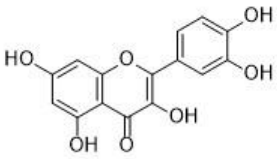
Apigenin



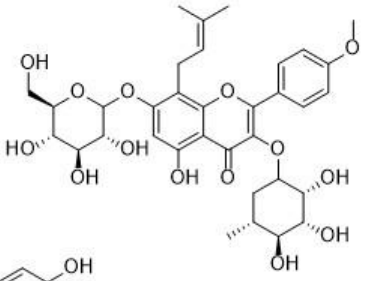
Apigenin-7-O-b-D-(-6''-p-coumaroyl)-glucopyranoside



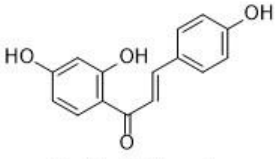
Dihydromyricetin



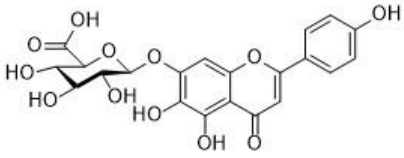
Quercetin



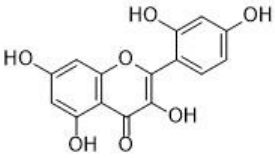
Icarin



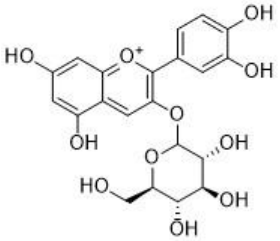
Isoliquiritigenin



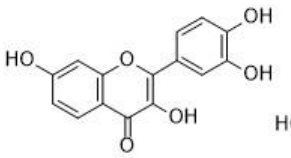
Scutellarin



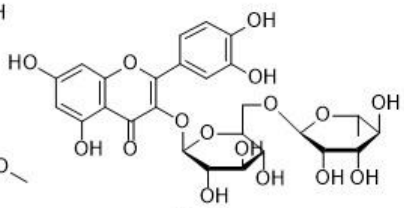
Morin



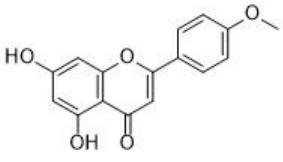
Cyanidin-3-glucoside



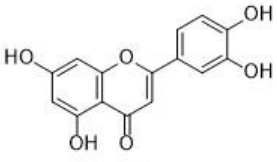
Fisetin



Rutin

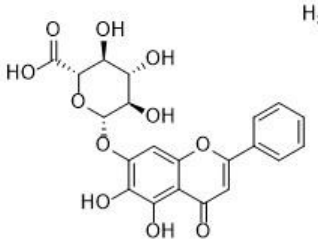


Acacetin

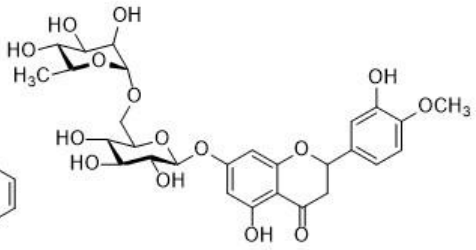


Luteolin

Baicalein



Baicalin



Fisetin

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Figure 2a. Structures of dietary flavonoids

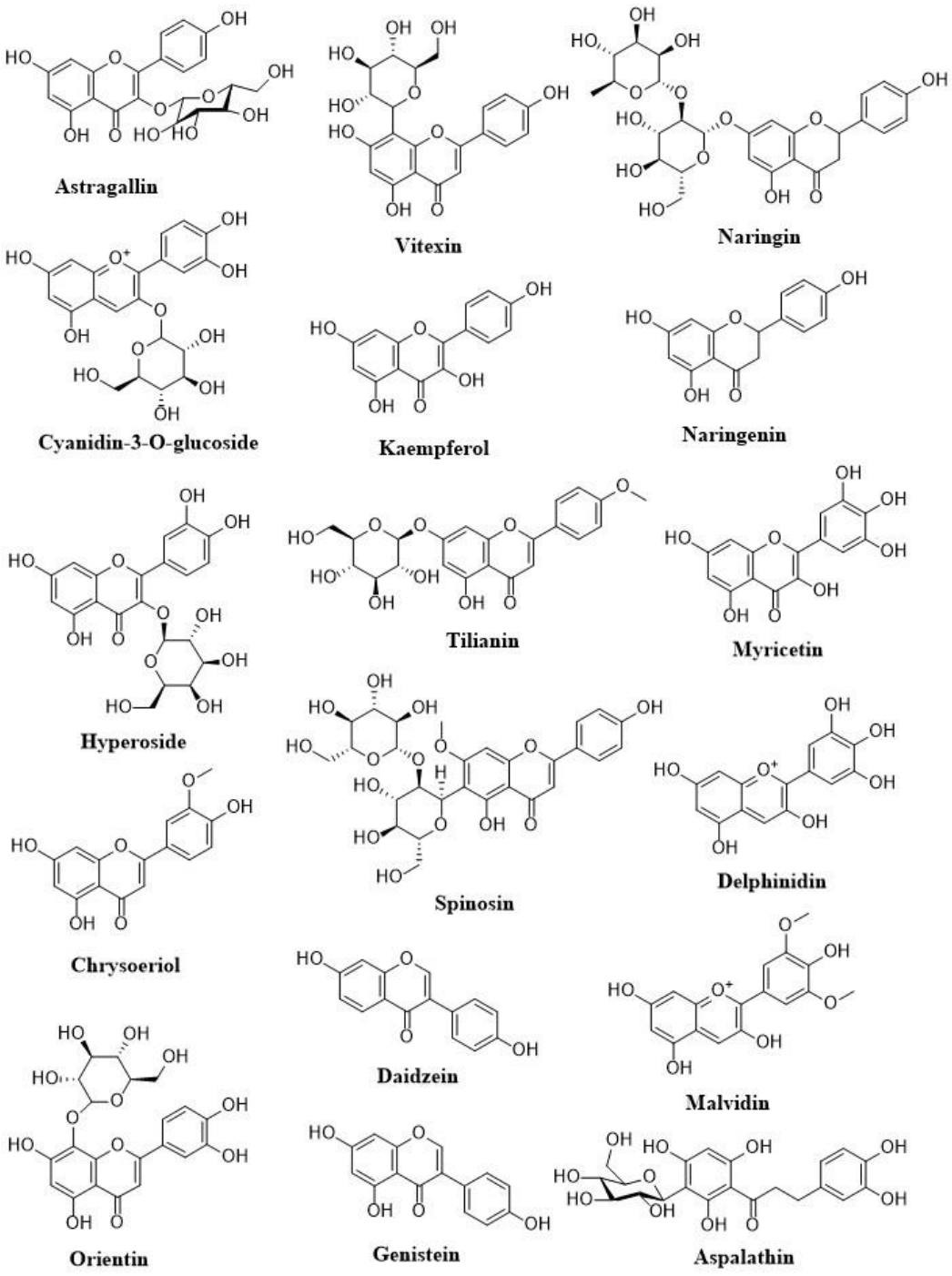

Figure 2b. Structures of dietary flavonoids

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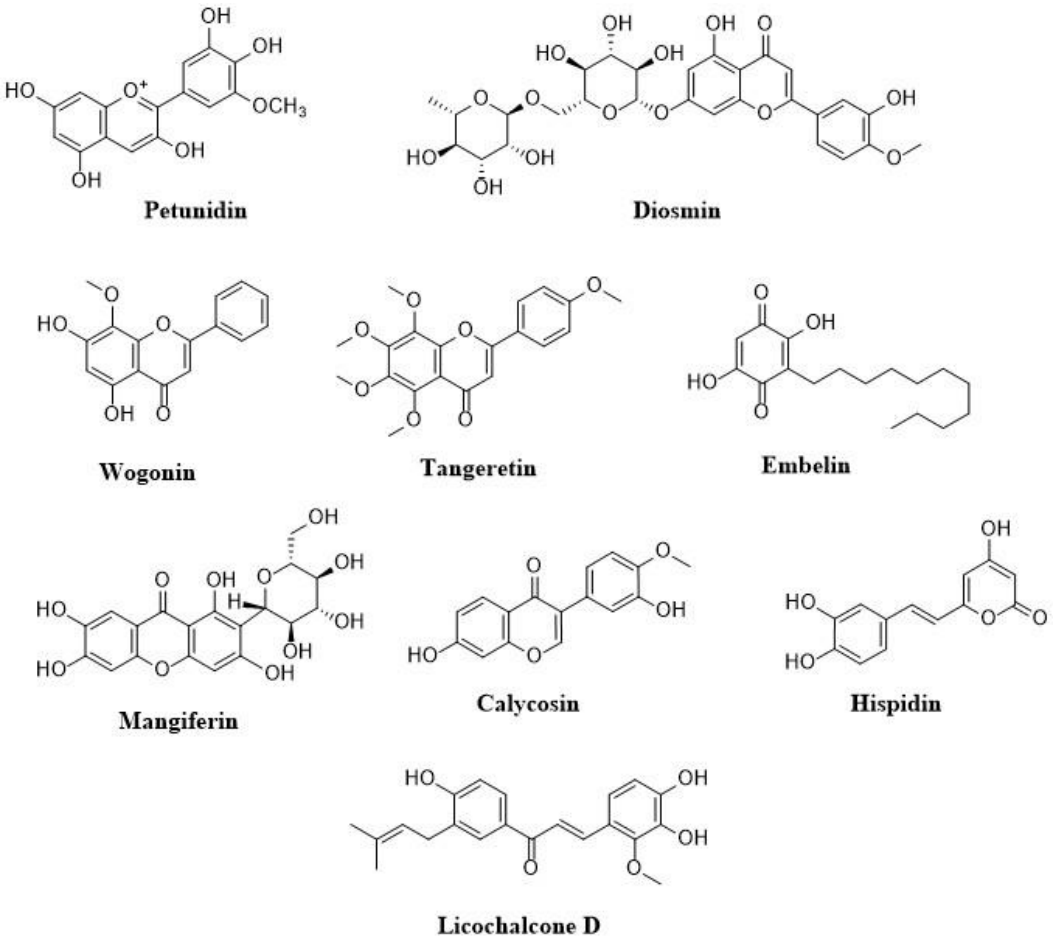

Figure 2c. Structures of dietary flavonoids

2.2. Health benefits, Medicinal Significance and Nutraceutical Importance

Flavonoid-rich foods are widely studied and considering as potent bioactive compounds with different biological activities, participating in different important signalling pathways related to chronic disease [23]. Herbal supplements enriched with flavonoidsare frequentlyreported for their ameliorative effects in the management of metabolic syndrome including CVDs and diabetes mellitus. Anthocyanins, like cyanidin and delphinidin 3-glucoside, have shown to improve insulin resistance, insulin production and hepatic glucose uptake during type 2 diabetes mellitus [24]. Many flavonoids, specifically flavanols, are well-known for their antihypertensive effect and endothelialprotectionby lowering triglycerides and detrimentallipid accumulation.

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Several flavanoid molecules have been established for their wide range of therapeutic benefits in CVDs including endothelial dysfunction, coronary artery disease, cardiac fibrosis, myocardial infarction, ischemic reperfusion injury etc. [9, 25].

A study suggests that regular consumption of 100 mg of total flavonoids in a day may reduce the risk of developing morbidity as well as fatality due to CVDs by approximately 10% [26]. Due to the presence of multiple hydroxyl groups (-OH) in the flavanoid structure, they exert as strong antioxidant and neutralizes the oxidative insult during various pathological events [18]. Flavanoids also often reported as strong inhibitor of DNA damage due to oxidative stress. Nevertheless, flavonoids have also been explored for their positive impact in neurological health and found to be effective in neural regeneration and counter inflammation in the nerve cells. A study indicated that [6]-Epigallocatechingallate, a flavonoid mainly found in green tea, can produce microglial activation and protects against inflammation in Alzheimer's disease [27]. Now-a-daysflavanoids are increasingly being recognized in the field of nutraceuticals for management of chronic life style related disorders and maintenance of healthy aging. Several herbal beverages enriched with high content of flavanoids are commercially available as anti-aging, antidiabetic and antiobesity and blood pressure lowering purposes. For example, hibiscus tea, blue motcha tea, green tea, red tea, rose wine, kiwi wine, red wine are the most popular beverages commercially available and widely acclaimed for their scientifically proven beneficial health effects.

2.3. Antioxidant Potential of Dietary Flavonoids in OS-induced CVDs

Cardiovascular system is the one, which being most prevalent to be affected by the oxidative stress triggered by spontaneously generated ROS due to the intake of high calorie diet, drugs and other xenobiotics. Mostly the high calorie diet intake longer period of time alone can lead to the depletion of myocardial antioxidantstatus and also allows developing chronic abnormalities like endothelial dysfunction, ischemia and cardiac hypertrophy [28]. Flavonoids consumption have been proven to exhibitnoticeablepositiveinfluencein preventing damages produced by ROS and other free radicals in the human body. The beneficial effects of flavonoids have been mostly linked to their strong antioxidant activity. The basic antioxidant mechanism of flavonoids consists in the oxidation of flavonoids by free radicals, resulting in a more stable, less-reactive radical [17]. The high reactivity of the hydroxyl group of the flavonoids produces inactivation of the free radicals. Some of the flavonoids can directly scavenge superoxide, whereas other flavonoids can scavenge the highly reactive oxygen-derived radical like peroxynitrite ions [29]. The preventive action of flavonoids on cardiovascular diseases has been one of the most studied topics. It is well known that the antioxidant activity of these compounds is responsible for diminution of the oxidative damages of cellular components and induction of cardiomyocytes apoptosis [16, 25]. Moreover, other mechanism action of flavonoids is the vasodilation by maintaining the action of Renin-angiotensin aldosterone system and eNOS in the blood vessel [30]. Flavanoids also have been reported for their anti-apoptotic function on the cardiomyocytes during oxidative insult. Noticeably, fruits and vegetables rich in flavanoids like anthocyanins

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and other flavanoids like quercetin, rutin, apigenin etc. administration to the experimental animals exhibited remarkable improvement of the myocardial antioxidant status during drugs (doxorubicin) and chemical (isoproterenol) induced cardiac dysfunction[25,27,28].

3. Cardioprotective Potential of Dietary Flavonoids

3.1. Dietary Flavonoids and Their Health Implications in CVDs

Flavonoids are naturally occurring organic compound groups generated by plants as secondary metabolites. In a metanalysis of prospective cohort studies, regular diets containing flavonoids were accompanying with a lesser risk of CVD mortality. Additionally, consumption of 200 mg/day of total flavonoids is associated with reduced danger of all-cause mortality [31]. Chemically, flavonoids contain a C_6-C_3-C_6 skeleton and consist of 2 aromatic rings (A and B ring). Based on their binding functional group, they are further classified as the subspecies flavonols, flavones, flavanols, flavanones, anthocyanidins, procyanidins and isoflavones. The hydroxyl radical of flavonoids scavenges free radicals and intercedes antioxidant effects associated with numerous health benefits[17, 30]. In the West, the main dietary sources of flavonoids are tea, chocolate, cocoa, vegetables, fruits, red wine, and legumes. In Asian countries such as Japan, soybean-derived isoflavone is the major source besides tea, coffee and legumes [32].

The structural variation in the flavonoid types contributes to their specific activities modulated by their definite molecular pathway. This affects their ADME profile after consumption thereby altering their bioavailability, target site and metabolites produced in-vivo. Flavonoids having high absorption are well distributed in multiple tissues while those having limited absorption or distribution exhibit their systemic effects by interaction with microbiota [33]. Colonic microbiota present in our gut can enzymatically break flavonoids into small phenolic acids and aromatic metabolites. These microbiota-generated metabolites curbed production of cytokines more efficiently when compared with their parent flavonoids. Many of these microbial derived flavonoid metabolites also provided protection against pancreatic β-cell dysfunction and platelet and monocyte adhesion to the arterial wall [34, 35]. Overall, in-vitro and in-vivo studies suggest that flavonoids exhibit a long range of activities such as antihypertensive effect by inhibiting ACE, potentiating bradykinin effects, decreasing endothelin levels and increasing NO mediated vasodilation; anti apoptotic activity which lowers the risk of myocardial infarctions; antithrombotic activity; prevent LDL oxidation thereby inhibiting the progression of arteriosclerosis [30, 36].

3.2. Cardioprotective Mechanisms of Dietary Flavonoids

Over the decade growing interest of scientific research regarding flavonoid con sumption to prevent CVDs and to improve vascular health has been noticed. Several studies have shown the advantageous propensities of various classes of flavonoid compounds and flavonoid enriched plant extracts on cardiovascular system by balancing the cellular oxidative stress, counter inflammation, and modulation of various intracellular

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signalling pathways [9, 24]. Some important molecular mechanisms of the cardiovascular protective function of flavonoids are described below (**Table 2**).

Table 2. Cardioprotective effects of dietary flavonoids in OS-induced CVDs

Flavanoids	**Oxidative stress model**	**Molecular Mechanism**	**Reference (s)**
Apigenin	Myocardial ischemia-reperfusion injury in h9C2 cardiomyocytes; adriamycin-induced cardiotoxicity in Kunming mice	↑PI3K/AKT/mTOR pathway	[37, 38]
Apigenin-7-O-b-D-(-6''-p-coumaroyl)-glucopyranoside	Primary neonatal cardiomyocyte (C57/6J) ischemic reperfusion model in-vitro	↑PKCe translocation signalling ↑Nrf2/HO-1 pathway ↓NF-kB signalling Pathway	[39]
Dihydromyricetin	Doxorubicin induced cardiotoxicity	↑SIRT1 ↓NLRP3 inflammosome	[40]
Quercetin	Isoproterenol induced cardiac fibrosis	↑Nrf2-HO; ↓LDL receptor expression; ROS scavenger	[41]
Icarin	High glucose and adenovirus induced cardiomyopathy in neonatal C57 mice	↑Apelin/Sirt3	[42]
Isoliquiritigenin	Hypoxia induced contractile dysfunction in cardiomyocytes	↑AMPK and ERK signalling pathways; ROS scavenger	[43]
Scutellarin	Isoproterenol induced myocardial infarction in SD rats	↓α-SMA ↑CD31, Jagged1, Notch 1, and Hes1	[44]
Cyanidin-3-glucoside	Wistar rats induced by STZ	↑TIMP-1 ↓MMP-9,.TGF-b, p-MEK1/2, CTGF, P-ERK1/2, FGF2	[45]
Morin	Isoproterenol induced	Restored the	[46,47]

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	myocardial infarction; doxorubicin induced cardiac fibrosis	mitochondrial function and improvement of mitochondrial antioxidant enzymes; ↓myocardial; Apoptosis; ↑Bcl-2	
Fisetin	Isoproterenol induced cardiac ischemia	↓RAGE and NF-κB; ↓Bax, caspase-3, cytochrome-c; ↑Bcl-2; ↓Myocardial apoptosis	[48]
Rutin	Cobalt chloride-induced hypoxic injury in H9c2 cells	Modulation of Akt, p-Akt, p38 and p-p38; ↓of HIF-1α, BAX and caspase	[49]
Acacetin	Doxorubicin induced cardiomyopathy	↑Sirt1/pAMPK pathway ↑AMPK/Nrf2 signal pathway	[50]
Hesperidin	Nitric oxide deficiency-Induced Cardiovascular remodelling	↓TNF-R1 and TGF- β1 protein expression; ↓MMP-2 and MMP-9	[51]
Luteolin	Doxorubicin-induced cardiotoxicity	↑AKT/Bcl-2 signalling pathway; ↑Nrf2/HO-1 pathway; ↑eNOS/Nrf2 signaling pathway	[52,53]
Baicalein	t-BHP induced oxidative stress; H2O2 and ischemia/reperfusion (I/R) stress	↑Nrf2/Keap1 pathway; ↓KLF4-MARCH5-Drp1 pathway	[54,55]
Baicalin	Hypoxia induced oxidative stress in cardiomyocytes; Angiotensin-II induced	↑Nrf2/HO-1 signalling pathway; ↓NF-kB	[56,57]

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	endothelial dysfunction	signalling pathway; ↓iNOS protein expression	
Astragallin	Myocardial ischemia/reperfusion (I/R) injury in isolated rat heart	↓ROS; ↓ Inflammation; ↓Myocardial apoptosis; ↑Bcl-2	[58]
Cyanidin-3-O-glucoside	Myocardial Ischemia-Reperfusion Injury in SD rats and H9c2 cells	↓USP19, Beclin1, NCOA4, and LC3II/LC3I; ↓LC3II/LC3I; ↓TfR1 expression; ↑FTH1 and GPX4; ↓Ferroptosis promoter RSL3	[59]
Hyperoside	High glucose induced oxidative stress in cardiac cells	↑ p-AKT/AKT and p-Nrf2/Nrf2; ↓Myocardial apoptosis and levels of ROS and MDA	[60]
Chrysoeriol	Doxorubicin-induced toxicity in cardiomyocytes	↓ROS, MDA; ↑GSH, SOD	[61]
Orientin	Myocardial ischemia reperfusion injury	↑AMPK,Akt and Bcl-2; ↓mTOR and Raptor, Beclin 1	[62]
Vitexin	Myocardial ischemia/reperfusion (I/R) injury	↓phospho-c-Jun; ↑phospho-ERK; ↓inflammatory cytokines and ↓MAPK pathway.	[63]
Kaempferol	Cardiac hypertrophy by aorta banding	↓ASK1/JNK1/2/p38 signaling pathway; ↓ASK1/MAPK signaling pathways (JNK1/2 and p38)	[64]
Naringin	High-cholesterol diet induced endothelial dysfunction and oxidative stress in rats	↓LOX-1, NADPH oxidase subunits (p47phox, Nox2, and Nox4), and iNOS	[65]

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Naringenin	H2O2 induced oxidative stress in cardiomyocytes	↓ROS; ↑Nrf2 signalling pathway	[66]
Tilianin	Myocardial ischemia/reperfusion injury in rats	↑AMPK, pAMPK, SIRT1, PGC-1alpha, NRF1, TFAM and FOXO1 proteins	[67]
Spinosin	Myocardial ischemia/reperfusion injury in rats	↓GSK3β; ↑PGC-1α; ↑Nrf2/HO-1 pathway	[68]
Myricetin	Myocardial ischemia/reperfusion injury in rats	↓STAT1	[69]
Delphinidin	Myocardial ischemia/reperfusion injury in rats	↓STAT1	[69]
Daidzein	Isoproterenol-induced apoptosis in H9c2 cardiomyoblast	↑Akt activation	[70]
Genistein	Doxorubicin-induced cardiotoxicity	↑Nrf2/HO-1 signalling pathway; ↓DNA damage	[71]
Malvidin	Isoproterenol-induced apoptosis in H9c2 cardiomyoblast	↑Nrf2/HO-1 signalling pathway; ↓NF-κB signalling pathway activation	[72]
Petunidin	Myocardial ischemia/reperfusion injury in rats	↑Bcl-2 protein expression, ↓ NOX4 and Bax expression, ↓cytoplasmic cytochrome c expression; ↓ROS	[73]
Aspalathin	Doxorubicin-induced cardiotoxicity in cardiomyocytes	↓ROS; ↓ Myocardial apoptosis	[74]
Diosmin	Myocardial	↑Bcl-2 expression;	[75]

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	ischemia/reperfusion injury in rats	↑antioxidant enzyme activities; ↓LPO	
Wogonin	Isoproterenol-induced myocardial infarction	↑Nrf2/HO-1 signalling pathway; ↓Inflammation	[76]
Tangeretin	Isoproterenol-induced myocardial infarction	↑PI3K/Aktsignalling pathway	[77]
Embelin	Isoproterenol-induced myocardial injury	↑Bcl-2; ↓Bax, Cytochrome c, cleaved-caspase-3 & 9 and PARP;	[78]
Neferin	Isoproterenol-induced myocardial injury	↓Inflammation; ↑ Tissue antioxidant status	[79]
Mangiferin	Myocardial ischemia/reperfusion injury in rats	↓Phosphorylation of p38 and JNK, phosphorylation of ERK1/2; ↓TGF-β, ↓MAPK	[80]
Calycosin	H2O2 induced oxidative stress in cardiomyocytes	↓ Apoptosis; ↑ ER/ and Akt	[81]
Licochalcone D	Myocardial ischemia/reperfusion (I/R) injury in cardiomyocytes	↓ Caspase 3 and PARP; ↓ IL-6, NF-kB and p38 MAPK	[82]
Hispidin	H_2O_2 induced oxidative stress in cardiomyocytes	↓ Apoptosis, ROS, DNA damage, caspase 3 and Bax expression ↑ HO-1, CAT, Bcl-2, Akt/GSK3 and ERK ½	[83]

3.2.1. ROS Scavenging Mechanism

Oxidative stress (OS) plays key role in the development of CVDs including myocardial injury, ischemic heart diseases leading to fatal complications like cardiomyopathy and heart attack etc. Oxidative insult in the myocardium and endothelial wall occurs due an imbalance between the generation of ROS/RNS and the clean-up mechanisms of endogenous antioxidant defencesystem. Spontaneous generation and accumulation of reactive species (ROS and RNS) accelerating the apoptosis of cardiomyocytes and endothelial cells [84]. Many experimental studies

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evident that the antioxidant mechanism of various naturally occurring flavanoids or their active metabolites to counter oxidative stress and protects heart tissue during toxic insult [24, 85]. However, the ROS scavenging and antioxidant mechanism of individual flavanoids may vary depending on their structural orientation, number and position of hydroxyl groups (-OH) and linkage of the other functional groups to the structural skeleton [30, 85].

Flavanoids may quench ROS by several mechanisms: direct neutralization of the different type (superoxide radical, OH., peroxynitrite radical) of free radicals or ROS; metal chelation property; increase production of endogenous antioxidant enzymes like GSH, SOD and catalase etc. and inhibition of cellular ROS generating enzymes like xanthine oxidase, myeloperoxidase, NADPH oxidase etc. [30, 86]. Various flavanoids which exhibit antioxidant and radical scavenging mechanism in OS associated cardiovascular dysfunction are mentioned in the **Table 2**. The basic mechanisms involved in the cardioprotection of dietary flavanoids in OS associated CVDs is displayed in **Figure 3**.

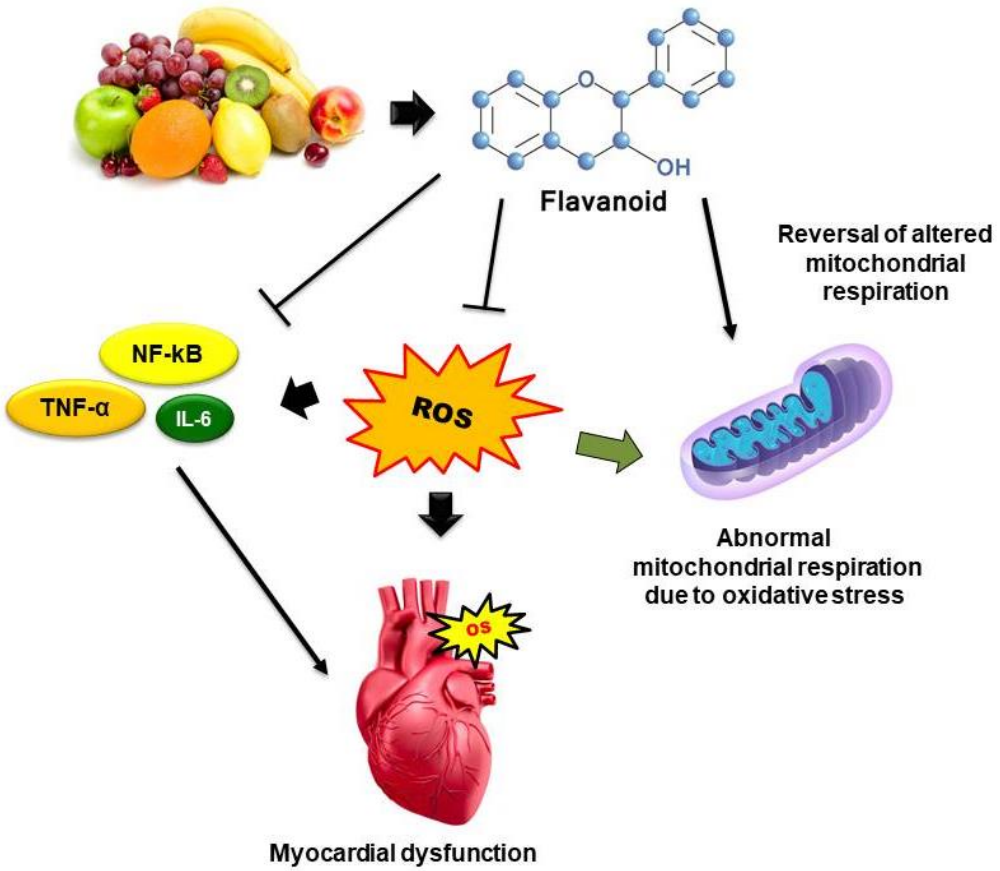

Figure 3. Mechanisms involved in the cardioprotection of dietary flavanoids in OS associated CVDs. Dietary flavanoids counter myocardial OS via inhibition of endogenous ROS production, down-regulation of inflammatory cytokines (IL-6, TNF-α, NFkB) and reversal of mitochondrial respiratory chain reactions.

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3.2.2. Intracellular Antioxidant Signalling Pathways

Unlike the in-vitro environment, antioxidative mechanisms of flavanoids in the in-vivo system often do not work only on the principle of scavenging free radicals. Rather flavanoids have been found to activate intracellular antioxidant signalling pathways to accelerate the production of endogenous antioxidants like GSH, SOD, and catalase etc. [87]. Physiological system comprises of various machinery to control the oxidative stress by accelerating the release of endogenous antioxidants. Nuclear factor erythroid 2 commonly known as Nrf2 is one of such important cellular machinery responsible for the production of endogenous antioxidants during oxidative stress condition. In normal physiological condition Nrf2 couples with KEAP1 protein in the Kelch domainof KEAP1 and spontaneously undergoes degradation in the cytosol [88]. Whereas, mild to moderate oxidative stress triggers dissociation of Nrf2-KEAP1 complex and translocation of Nrf2 in the nucleus and stimulates upregulation of antioxidant responsive genes like HO1, NQO1 etc. which further accelerates the production and release of endogenous antioxidants like GSH, SOD, and catalase etc. to control oxidative stress [87, 88].

Flavanoid compounds have been reported to inhibit Nrf2-KEAP1 protein-protein interactions in the cytosol and diminish thespontaneous degradation of Nrf2 protein. Flavanoids competitively bind with the Keap1 protein in the Nrf2 binding site resulting translocation of Nrf2 protein into the nucleus and activates the downstream protein HO1 and NQO1 [88]. Activation of these downstream proteins directly influences the up-regulation of antioxidant genes like GSH, SOD, catalase (**Figure 4**). For example, flavanoids like quercetin, luteolin, baicalin, genistein, wogonin etc. have been found to protect heart via activation of Nrf2 pathway during chemical induced myocardial infarction and cardiotoxicity [88, 89].

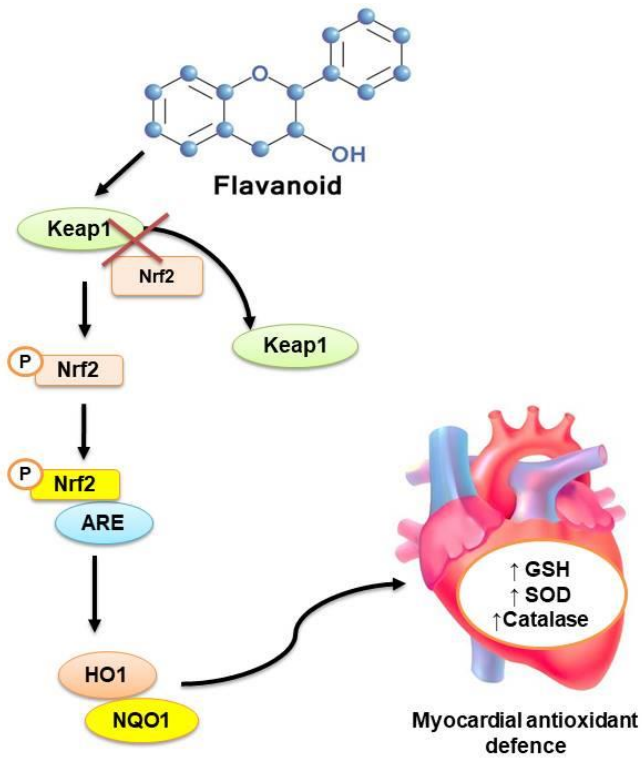

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Figure 4. Activation of Nrf2 mediated antioxidant signalling cascade by dietary flavanoids. Nrf2 and Keap1 ubiquitously coupled in the cytosol and leads to the spontaneous destruction of Nrf2. Dietary flavanoids inhibits the Nrf2-Keap1 protein-protein interaction, which results free Nrf2 to get phosphorylated and bind with the ARE which activates the downstream antioxidant signalling via up-regulation of HO1 and NQO1.

3.2.3. Counter Inflammatory Pathways

Inflammation is thought to be one of the most aggravating factors in the progression of a variety of CVDs, from endothelial dysfunction to myocardial apoptosis [90]. Inflammation occurs due to the increased oxidative stress and elevated level of ROS in response to injurious stimuli and comprises with the multiple complex signalling pathways. A short term inflammation is the result of immunological response to the body; however chronic inflammation in the cardiovascular system leads to the development of pathological incidentsin myocardial tissue and blood vessels. During chronic inflammation, pro-inflammatory cytokines such as IL-1, IL-6, and TNF- cause damage to the myocardial and vascular tissue, resulting in myocardial infarction and hypoxia in cardiomyocytes, which leads to apoptosis. Similarly, increased inflammation substantially damages the endothelial wall resulting development of ischemic condition [85, 90]. Oral flavonoids supplementation extensively reported to observe decreased inflammatory cell invasion, lowered levels of pro-inflammatory cytokines and tissue fibrosis, and increased cell survival and function, according to epidemiological studies. Inhibition of signalling through NF-kB (nuclear factor-B) seemed to be a central pathway that seemed to mediate the anti-inflammatory effect of several flavonoids [85,91]. Many flavanoids, in general, can exert cardioprotective effects by modulating multiple targets and genes involved in major pathways such as MAPK/ERK/JNK/p38 impairment, modulation of PI3K-Akt-eNOS, STAT3 pathway, and AMPK-mTOR pathway [30, 85]. Other anti-inflammatory mechanismsof flavanoids involved during cardiovascular oxidative stress are up-regulation of SIRT1, SIRT3, VEGF-B, pAkt, GSK3, and Bcl-2 genes while down-regulation of TLR-4, COX-1,COX-2, FAK, ET-1, Caspase 9, and Bax genes [92].

3.2.4. Mitochondrial and Intracellular Pathways

Mitochondria plays vital role in the normal functioning of cardiomyocytes and endothelial cells. Synthesis of ATP by catabolism of carbon rich sources via oxidative phosphorylation is one of the major roles of mitochondria. Integrity of inner mitochondrial membrane is very much essential to have the normal physiological and biophysical functioning[93]. Mitochondrial damage during oxidative insult like accumulation of cardiotoxins or due to ischemia/reperfusion is considered as a key event leading to cardiomyocytes dysfunction and apoptosis[94]. In this regard, protective potential of various flavonoids on mitochondrial functions have been widely investigated. The mechanism of action of certain flavonoids on mitochondrial targets may be another reason for the cardioprotective effect, which is enabled by maintaining

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mitochondrial ATP output and calcium homeostasis, as well as preserving mPTP opening and subsequent cell apoptosis [94,95]. Many flavanoid compounds for example epigallocatechin3-gallate, baicalein, puerarin, naringenin etc. have been reported to exhibit cardioprotection during oxidative stress via activation of mitochondrial ion channels present in the inner mitochondrial membrane like mitoK, mitoKATP channels [96, 97]. Other study suggested that the dietary flavanoid consumption also acts as cardioprotective agents by activation of Ca^{+2} channels and modulation of mitochondrial Ca^{2+} uptake [94].

Oxidative phosphorylation and maintenance of respiratory chain or electron transport chain are the vital functions of mitochondria. However, due to oxidative insult in the cardiac tissue hampers the complex formation (Complex I) and subsequently release cytochrome C [94, 96]. Notably anthocyanin flavanoidslike cyanidin 3-O-glucoside and delphidin 3-O-glucoside have been found to reduce oxidative stress in cardiac cells by restoration of mitochondrial bioenergetics and safeguard the preservation of normal functioning of complex I [98]. Flavonoids have also been found to suppress the generated ROS due to mitochondrial respiration by directly inhibiting enzymes and chelating the trace elements involved in ROS generation[94]. Evidently flavanoids prototypes like quercetin, kaempferol, and epicatechin etc. has been found to inhibit H_2O_2 production in isolated rat heart mitochondria [99].

4. Pharmacokinetic and Toxicological Issues

4.1. Bioavailability and Biotransformations of Dietary Flavanoids

Although flavonoids have shown countless health benefits, however their low oral bioavailability has been a major concern in the drug development. Absorption and distribution of flavanoids and their metabolites from the gut to the blood stream are the important phenomena to achieve the optimum therapeutic efficacy. Also,to understand the bioactivity and mechanism of action of dietary flavonoids in the body, it is fundamental to determine how much and which chemical forms they reach in systemic circulation, as these would be the physiologically active forms [100]. The most important factors which are associated with the absorption and bioavailability of dietary flavanoids aretheir types, number and position of sugar linkage, metabolism via phase II metabolic enzymes and gut microbiota [101]. In foods, flavonoids are often present in their glycosylated form, but once are ingested; the sugar moiety is removed before the absorption phase. This mechanism is carried out in the brush border of the small intestine by the enzyme lactase phlorizin hydrolase (LPG) that produces the hydrolyzation of the structure and the sugar is removed to release the aglycone to enter in the epithelial cells by passive diffusion. Organic anion transporter (OAT) families SLC22A, SLC21A, and MRP are also responsible of the absorption and delivery of flavonoids around the body as well as their excretion in urine [102].

Food matrix and where they exist in the dietary sources plays an important role in the absorption and bioavailability of various flavonoids. Evidently ethanol present in the red wine enhances the absorption of anthocyanins from the gut [102]. Flavanoid for example quercetin co-administration with carbohydrate containing food exhibited

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enhanced absorption from intestine and bioavailability. Fatty matrix can increase the uptake of flavanoids and slow down their clearance. On the other hand, protein co-administration and flavanoid protein interactions significantly reduce oral bioavailability of many flavonoids [103].

The aglycones of flavanoid glycosides undergoes metabolicconversion or modificationbefore passing into the blood stream presenting sulfate, glucuronide conjugate and/or methylated metabolites through the action of sulfotransferases, uridine-5′-diphosphate glucuronosyltransferases (UGT), and catechol-O-methyltransferases (COMT), and glutathione transferees [104]. When metabolites reach the bloodstream, are subjected to phase II metabolismwith transformations taking place in the liver, prior to urinary excretion. Cytochrome P450 (CYP450) superfamily in the liver microsomal enzymes mostly bear the responsibilities of phase II metabolism. Mostly CYP1A2 and CYP3A4 are demonstrated to be the key enzymes in human liver mediating the oxidative de-methylation of many flavanoid compoundsin the A- and B-ring [105].

Another important mechanism of non-absorbed flavonoids in the small intestine consists in the pass of flavonoids into the distal colon where the intestinal microbiota makessome changes and produce phenolic acids and aromatic compounds that can enter in the phase II metabolism and are excreted in the urine [106]. Recently it has been proven that gut microbiota plays significant role in the metabolic conversion of many flavanoids as well as other phenolic compounds present in the dietary sources. Beneficial microorganisms like lactobacillus in the gut releases enzyme like phenolase, glucosidase etc. which eventually transforms the parent compounds into several newer metabolites with high bioavailability [107]. Biotransformation not only caters the clearance of the flavanoids from the human body but also facilitates the molecular interactions with the therapeutic target. It is also proven that the therapeutic properties exert by the many naturally occurring flavanoids and phenolics are because of their metabolites but not the actual compounds due to their several biopharmaceutical limitations. A schematic of bioavailability and metabolism/ biotransformation reactions of dietary flavanoids is depicted in **Figure 5**.

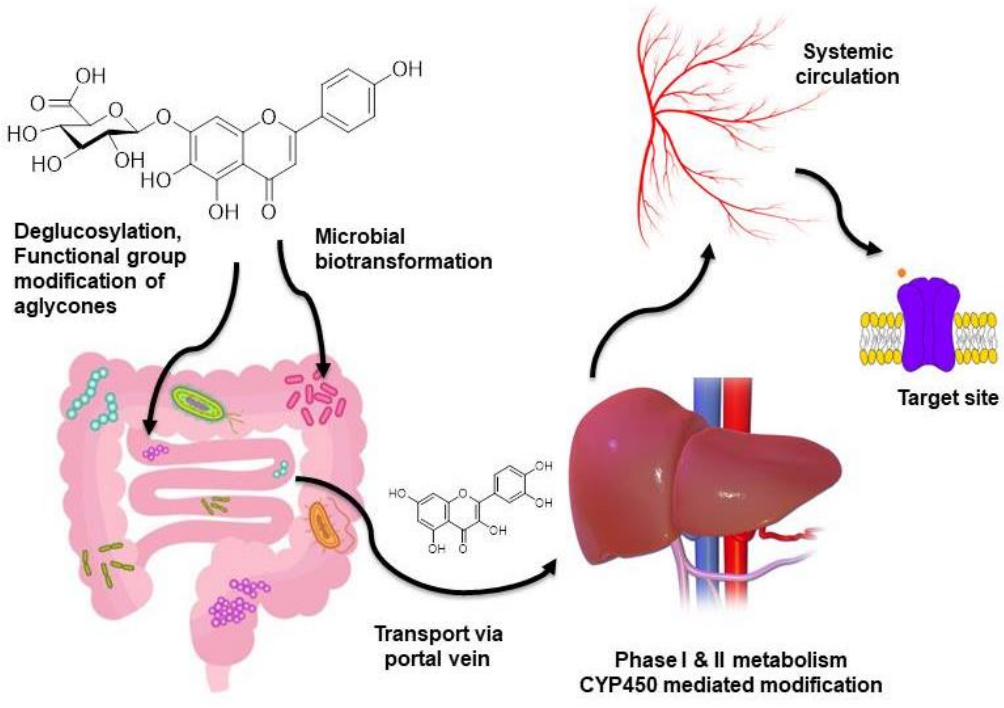

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Figure 5. Schematic of bioavailability and metabolism of dietary flavanoids. Flavanoids from dietary sources after ingestion goes through de-glycosylation and modifications like sulphate conjugation, glucuronide conjugation etc. in the small intestine and enter to the liver via portal vein. Hepatic microsomal enzymes (CYP450 isoforms) take major responsibility to convert the flavanoid aglycones into the simpler form. After hepatic first-pass metabolism metabolites reaches to the systemic circulation and finally bind to the target site. Colonic gut microbiota also plays similar role in the de-glycosylation and biotransformation trhough microbial enzymes.

4.2 Toxicities and Interactions with Drugs/Foods/Herbs

In contrast to the beneficial effects of flavanoids, the toxic effects and interactions with drugs/ foods/ herbs and other phytochemicals have been less explored. Nevertheless, scientific interest to uncover the toxicity profile and chemical/ physicochemical/ biological interactions of flavanoids and their possible metabolites are continuously increasing. A wide variety of flavanoid compounds have been exhibited cytotoxic effect to various cancercells and inhibit tumor progression substantially by acting as pro-oxidants and inducing mitochondrial oxidative stress and also leading to DNA damage [108]. Many vegetables, fruits and medicinal herbs enriched with flavanoids are also found to exhibit anti-proliferative properties against cancer cells. On the contrary, flavanoids and flavanoid enriched foods/ herbal extracts often demonstrated no or mild cytotoxicity in normal cells only with a very high concentration. A possible explanation for these conflicting phenomena is may bedue to the selective toxicity of flavonoids to cancer cells and differences in their cellular physiology and biochemical events than the normal cells [109].

Although,the interest in using flavonoids as food supplements and/or nutraceuticals alone or together with other prescription medicines are increasing, which may lead to risk of flavonoid-drug/herb/food interactions.According to certain published reports, some dietary flavonoids may have the potential to interact adversely with clinically used drugs.Dietary flavanoids alone or combination present in dietary sources often found to alter pharmacokinetic profile of therapeutic drugs [109, 110]. Many herbal drugs enriched with flavanoid have been reported to accelerate or diminish the rate of absorption of various drugs when co-administered. One of the most studied mechanisms of dietary flavanoids leading to increased or decreased bioavailability of the therapeutic drug is CYP450 enzyme interaction.Dietary flavanoid compounds individually or present in dietary supplements or herbal preparations found to inhibit or induce various isoforms of CYP450 enzyme in the gut and liver and also found to modify the action of xenobiotic efflux in the gut [111, 112]. This phenomenon often found to increase the bioavailability of many drugs, which is of course beneficial for the drugs with low bioavailability or metabolic stability. However, these pharmacokinetic alterations turns negatively for the drugs with extremely narrow therapeutic index like digoxin, lisinopril, captopril etc. [111]. These interactive behaviour of dietary flavanoids and alterations of pharmacokinetics are not always predictable. One of the main reasons behind this effect

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is the individual flavanoids and other non-flavonoid constituents are their concentrations are different in every matrix. Nevertheless, toxicity on the other hand a dose and concentration dependant phenomena. Consumption of dietary flavanoids as food or supplements generally contains low concentrations of flavanoids during daily dietary intake. On the contrary, higher doses in food supplements the same can become pro-oxidants and generates free radicals rather than acting as antioxidants [110]. Hence, it is very important to have a better understanding of the timing and amount of intake of dietary flavanoids in order to maximize the benefits while minimizing the risks. Some important flavonoid-drug intercations are depicted in **Table 3**.

Table 3. Flavanoid-drug interaction [111]

Drugs	**Flavanoid**	**Species in which tested**	**Change in bioavailability**
Diltiazem (15 mg/kg, oral)	Morin (1.5–7.5 mg/kg, oral)	Rat	1.4- to 1.8-fold increases
Talinolol (10 mg/kg, oral)	Naringin (1–20 mg/kg, oral)	Rat	1.5- to 3.0-fold increases
Etoposide (6 mg/kg, oral)	Morin (15 mg/kg, oral)	Rat	1.4-fold increases
Digoxin (0.02 mg/kg, oral)	Quercetin (40 mg/kg, oral)	Pig	1.7-fold increases
Moxidectin (0.2 mg/kg, subcutaneous)	Quercetin (10 mg/kg, subcutaneous)	Sheep	1.8-fold increases
Verapamil (10 mg/kg, oral)	Quercetin (15 mg/kg, oral)	Rabbit	2-fold increases
Paclitaxel (30 mg/kg oral)	Genistein (10 mg/kg, oral)	Rat	1.5-fold increases

4.3 Strategies to Overcome Pharmacokinetic and Toxicological Limitations

The delivery of phytochemicals like flavonoids is challenging due to poor solubility, run-down permeability, low bioavailability, instability in biological environment and extensive first-pass metabolism.Currentlyvarious absorption enhancing techniques have recently been developed and used to improve the oral bioavailability and efficacy of poorly absorbable flavonoids by increasing their solubility or gastrointestinal permeability and preventing metabolic degradation.Researchers across globe have proposed several approaches including structural modifications of parent compound, nano-formulation, matrix complex formation, co-crystal techniqueand dispersion techniquesetc. to enhance the pharmacokinetics and bioavailability of natural active flavanoids and improve their efficacy [113]. Colloidal Drug Delivery System (CDDS) as carriers for phytochemicals have seen an exponential rise, which had also helped in rejuvenation of ancient and forgotten natural molecules by optimizing some unfavourable chemical or physical properties of the natural active compounds, including solubility and the biological stability, while on the other hand, can also improve their

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radical scavenging activity and promote bioavailability [114]. The delivery system is capable of increasing the antioxidant activity of flavonoids by preventing degradation of the formulation due to encapsulation and maintaining the drug concentration over time which in turn increases the antioxidant/radical scavenging activity of the active compound compared to the unloaded one. Furthermore, these also help in compounding sustained and controlled release formulations which can be used for flavonoid targeted therapies [115]. In comparison to the conventional formulation micro or nano-emulsion increase the penetration rate through biological membranes and also enhance their ADME phase thereby decreasing associated toxicities [116]. The use of biopolymers in formulations used for CVDs treatment adds an advantage because of its favourable properties such as biodegradability, good biocompatibility, and attractive biomimetic characteristics [117]. Structural modification of the parent flavanoid compounds also has been proven as one of the successful strategy to overcome poor solubility and GI absorption. Glycosylation and glucuronide conjugation are the useful tailoring reactions which may significantly change the physicochemical properties of hydrophobic flavonoids. Introduction of new polar groups or masking the selective functional groups in the structural skeleton, which is popularly known as pro-drug approach become useful to improve the pharmacokinetic profile of various dietary flavanoids[118]. It is often observed that co-administration of food and flavanoids together serves better absorption flavanoids from the gut. Hence, the complex carrier formation approach like cyclodextrin complex, lipid/carbohydrate-flavanoid conjugate is some of the approaches to overcome pharmacokinetic limitations [104, 112]. Formulation of nanoparticles or nanocrystals is the most common approach to enhance the absorption and bioavailability of flavanoids and found remarkably effective in the cancer chemoprevention [119, 120]. However, all these strategies to improve the pharmacokinetic profile of dietary flavanoids are exclusively depends on the area of their application and most of them are still under experimental investigational phases which need more in-depth studies to make any conclusive statement.

5. Therapeutic Approaches and Future Drug Discovery

Flavonoids are allied with a wide spectrum of health promoting effects and therefore are a requisite component in a variety of nutraceutical, medicinaland cosmetic applications. These compounds exhibit a wide variety of medicinal properties such as anti-mutagenic, anti-atherosclerotic, cardiovascular protective, antidiabetic, insulin sensitizer, anti-carcinogenic, antioxidant, anti-inflammatory, antithrombogenic and antitumour agents [16, 17]. Flavanoid supplementation exhibited positive improvement during neurodegenerative complications like Alzheimer's disease. In the anticancer therapy flavanoids have been extensively used. Flavonoids were used as a single agent or in combination with other therapeutics against hematopoietic/lymphoid or solid cancers in 22 phase II and 1 phase III clinical trials (PubMed, Scopus, and Web of Science) released by January 2019. Quercetin is one of the most studied flavanoid in the mitigation of cancer and related complications [121]. Flavonoids have also been known for their antimicrobial activity and many of them have been isolated and identified having

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properties of antifungal, antiviral and antibacterial activity. Many flavanoid molecules have been used in combination with synthetic and other existing antibiotics to increase the efficacy and overcome drug resistance [122]. Naturally occurring flavanoid scaffolds often caters novel template to design various potent synthetic drugable molecules. For example, phlorizin is a chalcone type of flavanoid which brings the idea of clinically approved SGLT-2 inhibitor gliflozins [123]. The most intriguing properties of flavanoids in the field of disease management are their antioxidant and cytoprotective properties during oxidative stress. Because of this property, flavonoids hold an irreplaceable position in the fields of nutrition, food safety and health. Various flavanoid enriched nutraceuticals like green tea, motcha tea and beverages are gaining global interest. Flavonoids such as quercetin, naringin, hesperetin and catechin possess a higher grade of antiviral activity and they act by affecting the replication and infectivity of certain RNA and DNA viruses [124]. Recently during this COVID-19 pandemic there is an overwhelming scientific interest have been noticed in searching the naturally occurring and synthetic flavanoid compounds to reduced COVID-19 infected cardiovascular malfunctioning by blocking the viral entry at the ACE2 receptor [125].

Despite their broad and multi-potent pharmacological properties, research into the therapeutic efficacy of standardised flavonoid products extracted from plant sources in prospective human studies is still missing.To produce cost-effective flavonoid-based natural health products, scale-up, consumer- and environment-friendly green technologies are needed. Flavonoid supplementation should be performed with caution in cancer patients because it can interfere with radiotherapy and various chemotherapies. There should have a strict monitoring of the flavanoid rich food-drug interactions as well to minimize the unwanted contraindications. To resolve bioavailability issues, targeted delivery, and improvement of the therapeutic efficacy of certain flavonoids, multidisciplinary research collaborations are needed. Biotransformation of flavanoids is also a major concern in their drug development aspects. Microsomal and gut microbiota mediated metabolism of large variety of dietary flavonoid still not well studied, which can give idea to design novel and therapeutically active potent small molecules and also open up newer directions of therapeutic strategies.

6. Conclusions

Dietary flavonoids are bioactive components of fruits and vegetables that may be effective in the prevention of disease such as cancer and cardiovascular diseases (CVDs). Current research trends on flavonoids aim to identify plant-derived/ dietary flavonoids with regard to exploring their medicinal applications and/or biological/pharmacological activities in various chronic disorders. The bioactivity of flavonoids depends primarily upon their pharmacokinetic, metabolism and pharmacodynamic profile in the human body. Due to the lack of adequate information, further research is needed in order to elucidate/ explore the biochemical (molecular) mechanisms of action, bioavailability, metabolism and other pharmacokinetic issues, and toxicities/ safety concerns (in vivo studies) of dietary flavonoids associated with beneficial health effects in CVDs.

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