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PHARMACOTHERAPEUTIC POTENTIAL OF FLAVONOIDS IN THE MITIGATION OF CARDIOVASCULAR DISEASES

Fatima[*1], Fatima Rehman[2], Rushda Fatima[3], Ariba Ilyas[4], *Laiba Naz*[5]

*[*1,2,3,4]Department of Zoology, Wildlife & Fisheries, University of Agriculture Faisalabad, Pakistan*
[5]School of Biochemistry and Biotechnology, University of Punjab Lahore

[*1]fatimanaseer795@gmail.com

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Fatima

Abstract

Cardiovascular diseases (CVDs) including myocardial failure, coronary artery disease, angina, cerebrovascular disease, hypertension and stroke, are leading causes of morbidity as well as mortality worldwide. Recent drugs used for CVDs treatment can induce toxicity, diets abundant in plant-based food have been reported to reduce the risk of developing CVDs. Flavonoids, a wide variety of polyphenolic compounds, derived from plants are abundantly present in human diet including dairy products, tea, grains, fruits & vegetables. Flavonoids are categorized into six subclasses based on their chemical composition: anthocyanidins, isoflavones, flavan-3-ols, flavonols, flavones, and flavanones. Flavonoids are considered crucial elements in a variety of cosmetic, nutraceutical, and pharmacological formulations due to their potential health benefits and therapeutic value. These compounds exhibit antioxidant, anti-inflammatory, anti-apoptotic, and anti-atherogenic properties. Flavonoids help mitigate oxidative stress by scavenging free radicals, thus contributing to their antioxidant effects. In cases of prolonged inflammation, cytokines that promote inflammation can damage heart, leading to conditions like heart attacks and reduced oxygen supply to heart

muscle cells, ultimately causing cell death. This review summarizes flavonoids, potential therapeutic effects on health in various diseases, highlighting their diverse redox-active cardio-protective processes, including antioxidant effects.

Introduction

Cardiovascular diseases (CVD), which include a variety of disorders including atherosclerosis, aortic aneurysm, congenital heart disease, cerebrovascular disease, rheumatic heart disease, myocardial infarction, angina, etc., continue to be the leading cause of illness rate and fatality rate in both developing and developed countries (Coady *et al*., 2001; Pala *et al*., 2020). In 2017, heart diseases predicted to cause around 1.6-1.7 million deaths throughout globe. Dietary risks account for approximately 11 million deaths and 250-255 million disability-adjusted life years (DALYs), making them one of the leading altered risk factors worldwide. Aging plays a crucial role in the increased incidents of cardiovascular diseases due to the rising plasma cholesterol, arterial rigidity also vascular resistance (Ball, 2020). Gender-related patterns of CVD show that men under the age of 50 face a five-fold greater incidence of CVD, while women over the age of 50 experience a notable rise in CVD occurrence. Other risk factors for CVD include high cholesterol, genetic factors, a sedentary lifestyle, obesity, tobacco use, alcohol consumption, high blood pressure, diabetes, and dyslipidemia (Curry *et al*., 2018).

Cardiovascular diseases are recognized as multifactorial conditions. Elevated concentrations of LDL (low-density lipoprotein) cholesterol in the blood are strongly linked to the risk of coronary heart disease, although this association is relatively weaker in relation to stroke risk. Recent drugs used for CVDs treatment mainly include cardiac rhythm regulators, hyperlipidemia medications, anti-hypertensive drugs, heart strengthening medications, and antiplatelet agents. However, these common medicines can have toxic effects as well as side effects like muscular pain, hepatic disease, and muscle breakdown to the patients during treatment of diseases (Angelino *et al*., 2019).

Epidemiological studies have consistently shown that diets rich in plant-based foods can significantly reduce the risk of cardiovascular disease (CVD) (Angelino *et al*., 2019). Based on current data, public health campaigns are promoting healthier eating habits to significantly reduce the global impact of cardiovascular disease (Martini *et al.,* 2017). Apart from their nutrients and dietary fiber content, these food categories are familiar for their comparatively high levels of phytochemicals (Del *et al*., 2013), which are biologically active compounds with

varied chemical composition, bio-absorption, and 1 metabolism in the gut microbiome, resulting in the formation of smaller phenolic and aromatic acids (Del *et al.,* 2013).

1. Flavonoids: chemistry, classification & dietary sources

Flavonoids are polyphenolic compounds derived from plant natural occurring in crops, cereals, veggies, tubers, dinghy, blossoms, branches, herbal tea, and grape drink (Zeinali *et al*., 2017). Similarly, non-flora natural products like mushrooms and nectar, flora extracts, herbal juices, botanical powders, and extracted oils, had demonstrated anti-inflammatory properties, with many organic products containing phenolics as essential components (Khalil and Sulaiman, 2010; Azab *et al*., 2016). Flavonoids comprise an enormous group of poly phenolic composites, chemically defined by the presence of 2-phenyl-4H-1-benzopyrane skeleton, also called as 2-phenyl-4H-chromene (Ververidis *et al*., 2007). Flavonoids divided into six subclasses reliant on their chemical structures: flavones, flavonols, flavanones, isoflavones, flavan-3-ols, and anthocyanidins (Panche et al., 2016). Copious in flowers, fruits, and leaves such as red peppers, celery, parsley, chamomile, mint, and ginkgo biloba (Manach et al., 2004), flavones are mainly represented by luteolin, apigenin, and tangeritin (Manach et al., 2004). Flavonols such as rutin, quercetin, myricetin, and kaempferol are widespread in diverse nutriments (Pollastri and Tattini, 2011) (Table 1).

Table 1. Flavonoid subclasses, representative compounds & dietary sources

Subclass	Representative compounds	Main dietary sources
Flavones	Luteolin, apigenin, tangeritin	Parsley, celery, red peppers, chamomile, mint
Flavonols	Quercetin, kaempferol, rutin, myricetin	Onions, kale, apples, berries, tea, red wine
Flavanones	Naringenin, hesperetin, eriodictyol	Citrus fruits
Isoflavones	Genistein, daidzein	Soy products
Flavan-3-ols	Catechin, epicatechin, epigallocatechin gallate	Tea, cocoa, apples, pears, blueberries
Anthocyanidins	Cyanidin, delphinidin, malvidin, pelargonidin, peonidin	Berries, red grapes

2. Flavonoids and Cardiovascular diseases

Various researches highlighted the significant benefits involving different classes of flavonoid compounds and plant extracts rich in flavonoids for cardiovascular health. These benefits include reducing cellular oxidative damage, combating swelling and regulating diverse signaling channels within cell (Gross, 2004; Siow and Mann, 2010). A recent systematic review has also pointed potential recommendations concerning the function of these phytochemical compounds in supporting cardiovascular health (Parmenter *et al.,* 2021). Furthermore, there is evidence of a positive relationship between the utilization of flavonoids and depletion of cardiovascular diseases (Feliciano *et al*., 2015) (Table 2).

Table 2. Classification of flavonoids and their reported cardiovascular health benefits

Flavonoids	*Reported cardiovascular effects*	*Key references*
Flavones	Higher intake linked to lower coronary disease risk in meta-analysis	Manach *et al.,* 2004; Micek *et al*., 2021
Flavonols	Antihypertensive action via endothelial nitric oxide (kaempferol); lower coronary artery disease risk (quercetin)	Pollastri and Tattini, 2011; Leeya *et al*., 2010; Micek *et al.,* 2021
Flavanones	Lower blood pressure, less vascular dysfunction, anti-atherosclerotic and anti-inflammatory effects	Barreca *et al*., 2017; Ikemura *et al*., 2012; Yamamoto *et al*., 2013
Isoflavones	Antihypertensive effects; protection of LDL from peroxy-nitrite mediated oxidation in vitro	Marzocchella *et al*., 2011; Lai and Yen, 2002
Flavan-3-ols	Blood pressure reduction and improved vascular function	Osakabe, 2013; Igarashi *et al*., 2007 (rats); Ried *et al*., 2012
Anthocyanidins	Endothelium-mediated vasorelaxation; lower risk of	Khoo *et al*., 2017; Cassidy, 2018

	myocardial infarction in cohort data

3. Mechanisms of Flavonoid-Mediated Cardio protection

The cardiovascular system is particularly susceptible to oxidative stress prompted by spontaneously generated reactive oxygen species (ROS) which can arise from factors such as high-calorie diets, medications, and other foreign substances. Prolonged utilization of a high calorie diet alone can diminish myocardial antioxidant status as well as contribute to chronic issues like endothelial damage, tissue hypoxia and enlarged heart (Figure 1). Flavonoids exhibit anti-oxidant, anti-inflammatory, anti-apoptotic, anti-hypertensive properties (Janabi *et al*., 2020).

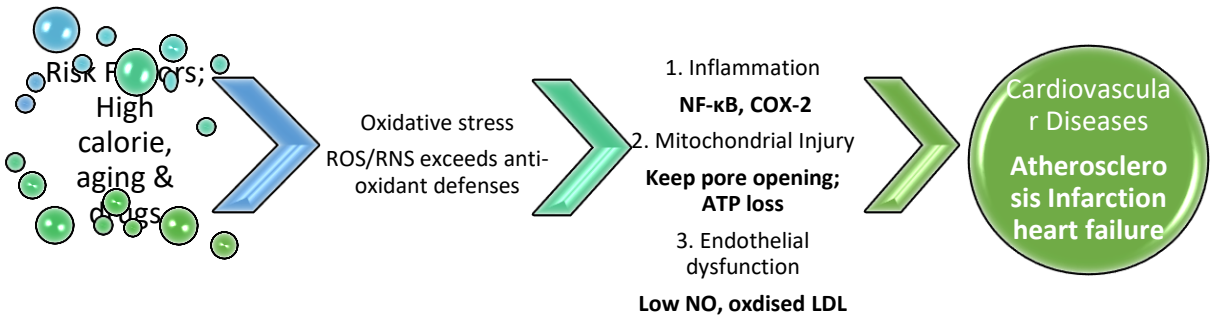


Figure 1. Oxidative stress drives inflammation, mitochondrial injury and endothelial dysfunction, which converge on cardiovascular diseases.

Flavonoids have been demonstrated to have significant positive impact on mitigating damage caused by reactive oxygen species and other oxidative radicals within body. Their beneficial effects are primarily attributed to their potent antioxidant activity. Flavonoids primarily function as antioxidants by being oxidized themselves by free radicals, leading to the formation of more stable, less reactive radical (Panche *et al*., 2016). The hydroxyl group in the flavonoids is highly reactive and aids in neutralizing free radicals. Certain flavonoids can straightly neutralize superoxide, while others can target the greatly reactive oxygen free radicals like peroxynitrite ions (Kackov *et al*., 2013). The protective role of these phenols against heart diseases has been extensively discussed. Their antioxidant activity plays a key role in reducing oxidative imbalances to cellular elements and in regulating heart cells death (Santos *et al*., 2017; Corcoran *et al*., 2012).

3.1. Oxidative stress and direct antioxidant action

Oxidative stress (OS) plays a critical role in the development of cardiovascular diseases (CVDs), including heart injury and heart tissue diseases, leading to severe complications like heart muscle disorder and infarction. This oxidative damage occurs due to an imbalance between the progression of reactive oxygen species or reactive nitrogen species (ROS/RNS) and the body's natural antioxidant defense mechanisms. The excessive generation and accumulation of ROS and RNS trigger apoptosis in cells of heart and vascular cells (Siti *et al*., 2015). Flavonoids act as scavengers for a broad range of free radicals including oxygen, chlorine as well nitrogen reactive species. When flavonoids interact with these reactive species, they become oxidized themselves, resulting in a stabilized, least reactive radical (Korkina and Afanas'ev, 1996). Certain flavonoids, like genistein and daidzein, straightly target greatly reactive oxygen-based radicals such as peroxynitrite (Lai and Yen, 2002).

The ability of individual flavonoids to scavenge reactive oxygen species (ROS) and act as antioxidants can vary based on their structural arrangement, the number and placement of hydroxyl groups (-OH), and the linkage of other functional groups to their molecular structure (Akhlaghi and Banday, 2009; Ciumărnean *et al*., 2020). For instance, rutin as well as epicatechin exhibit a potent scavenging effect on hydroxyl radicals (OH) that is 300 times stronger than mannitol, a hydroxyl scavenger. They also hinder the generation of superoxide anions in systems like the hypoxanthine-xanthine oxidase system (Hanasaki *et al*., 1994). By neutralizing free radicals, flavonoids can impede decreased cholesterol oxidation in laboratory settings (Kerry and Abbey, 1997), thus safeguarding LDL particles and potentially offering preventive effects against arteriosclerosis. During swelling, the substantial production of nitric oxide by inducible nitric oxide synthase in macrophages can lead to oxidative harm. In such scenarios, stimulated macrophages significantly elevate the concurrent production of nitric oxide and superoxide anions. Nitric oxide reacts with free 5 radicals, resulting in the formation of the highly destructive peroxynitrite, which can directly oxidize LDL, causing irreversible damage to cell membranes (Haenen *et al*., 1997). When flavonoids are employed as antioxidants, they scavenge free radicals, preventing their reaction with NO and thus minimizing cellular damage (Shutenko *et al*., 1999). Moreover, flavonoids can directly scavenge nitric oxide molecules, as nitric oxide itself can be considered a radical (Vanacker *et al*., 1995).

3.2. Activation of endogenous antioxidant defenses through Nrf2

In vivo experiment, flavonoids don't rely only on scavenging free radicals like in the vitro. Instead, they activate antioxidant signaling channels within cell boosting the formation of endogenous antioxidants like catalase, SOD along with GSH. (Clifford *et al*., 2021). The body uses diverse mechanisms, including nuclear factor erythroid 2 (Nrf2), to manage oxidative stress by releasing these anti-oxidants. Nrf2 normally couples with KEAP1 protein but dissociates under mild oxidative stress, moving up to nucleus to up regulate antioxidant genes (Satta *et al*., 2017; Clifford *et al*., 2021; Satta *et al*., 2017). Flavonoid compounds hinder Nrf2-KEAP1 protein-protein connections in the cytosol, preventing Nrf2 degradation as well as promoting its movement to nucleus where it triggers genes like HO1 and NQO1 (Satta *et al*., 2017). Activation of these proteins straightly increases antioxidant genes like GSH, SOD, and catalase. This pathway activation seen with flavonoids such as quercetin and luteolin helps protect the heart (Satta *et al*., 2017; Suraweera *et al*., 2020).

3.3. Anti-inflammatory effects

In the development of a various cardiovascular diseases (CVDs), inflammation is considered a significant aggravating factor, affecting everything from endothelial damage to myocardial cell death (Sugamura *et al*., 2011). This inflammation arises due to the elevated oxidative imbalance and increased level of reactive oxygen species triggered by adverse stimuli, coupled to many difficult signaling pathways. During chronic inflammation, pro-inflammatory cytokines including TNF-α, IL-1 along with IL-6 cause damage to myocardial and endothelial tissue, causing conditions like myocardial infarction and reduced oxygen supply in cells of heart vessels, ultimately leading to accidently death of cells (Ciumărnean *et al*., 2020; Sugamura *et al*., 2011).

Citrus flavonoids have demonstrated anti-inflammatory effects in diverse in vivo as well as in vitro experiments. During inflammation, several pro-inflammatory modulators including interleukin-1b (IL-1b), tumor necrosis factor-a (TNF-a), prostaglandin E2 (PGE2) as well as nitric oxide are produced (Kim *et al*., 2004). Certain regulatory enzymes like lipoxygenase, nitric oxide synthase, cyclooxygenase-2 as well as phospholipase are pivotal in the generation of pro-inflammatory mediators like PGE2 and NO (Kim *et al.,* 2004). Citrus flavonoids have the ability to reduce the expression of COX-2 and iNOS, thereby suppressing the production of associated pro-inflammatory mediators (Benavente-Garcia and Castillo, 2008). Moreover, other anti-inflammatory mechanisms of flavonoids linked to heart related oxidative stress involve the upregulation of genes like GSK3, pAkt, VEGF-B, SIRT3 along with SIRT1 and the

downregulation of genes like Bax, Caspase, ET-1, FAK, COX-2, COX-1 as well as TLR-4 (Choy *et al*., 2019).

3.4. Mitochondrial protection

Mitochondria are essential for the proper working of cardiomyocytes and vascular cells, primarily through generating ATP via oxidative phosphorylation via carbon rich sources. The intactness of the inner mitochondrial membrane is crucial for normal physiological and biophysical functioning (Kicinska and Jarmuszkiewicz, 2020). Mitochondrial damage caused by oxidative damage like the collection of heart toxins or due to reperfusion is a critical event leading to cardiomyocytes damage and apoptosis (Crow *et al*., 2004). Consequently, the protective effects of diverse flavonoids (cinnamic acid and ferulic acid) on mitochondrial functions had been broadly investigated. Another reason for the cardio-protective effect of flavonoids is their impact on mitochondrial targets.

Flavonoids regulate ATP output and calcium balance, as well as prevent the opening of the mitochondrial permeability transition pore, which can lead to cell death (Crow *et al*., 2004; Testai, 2015). Numerous flavonoids compounds such as, epigallocatechin3-gallate, baicalein, and naringenin, etc. have been reported to express cardio-protection during oxidative damage by stimulating mitochondrial ion passages found in the inner mitochondrial layer-like mitoK, mitoKATP channels (Montero *et al*., 2004; Bednarczyk *et al*., 2017). Recent studies suggested that flavonoid intake also serves as a cardio-protective agent by initiation of calcium ions channels and regulation of mitochondrial Ca2+ uptake (Crow *et al.,* 2004).

3.5. Endothelial, vascular, lipid and platelet effects

Flavonoids have the potential to mitigate cardiovascular disease through a number of processes, including enhanced endothelial function, controlling blood pressure and reducing plasma concentrations of lipoprotein (Lee *et al*., 2005). Flavonoids exhibit a diverse array of functions, including a hypotensive effect, anti-cell death activity, which reduces the likelihood of a heart attack, anticoagulant effects, and the prevention of low-density cholesterol oxidation, thereby impeding the production of arteriosclerosis (Akhlaghi and Bandy, 2009).

Table 3. Mechanisms of flavonoid-mediated cardio protection and the level of supporting evidence

Mechanism	Molecular targets	Representative flavonoids	Main level of evidence

Direct radical scavenging and metal chelation	Superoxide, hydroxyl radical, peroxynitrite, nitric oxide	Rutin, epicatechin, genistein, daidzein	Mostly in vitro
Nrf2–KEAP1 pathway activation	Nrf2, HO-1, NQO1; downstream SOD, catalase, GSH	Quercetin, luteolin	Cell and animal studies; human trials limited
Anti-inflammatory action	NF-κB, COX-2, iNOS, TNF-α, IL-1β, IL-6, PGE2	Citrus flavonoids, others	In vitro and in vivo
Mitochondrial protection	Permeability transition pore, mitoK(ATP) channel, calcium uniporter, ATP output	Epigallocatechin gallate, baicalein, naringenin	Experimental
Endothelial, vascular and hemostatic effects	Endothelial nitric oxide, smooth muscle Ca^{2+} and K^{+} channels, LDL oxidation, platelet aggregation	Kaempferol, hesperetin, naringenin, quercetin	Mixed: experimental and some human data

4. Evidence from epidemiological and clinical studies

Prospective cohorts, meta-analyses, and a few randomized trials provide the majority of the human evidence (Table 4). A greater intake of overall flavonoids and several subclasses was linked to a lower risk of cardiovascular disease (CVD), according to a dose-response meta-analysis. Flavonols and flavones were linked to a lower risk of coronary disease, flavanones to a lower risk of stroke, and catechins to favorable outcomes across heart outcome measures (Micek *et al*., 2021). According to a review, consuming 100 mg of flavonoids daily reduces the incidence of coronary heart disease by roughly 10% (Khan *et al.,* 2021). However, this estimate is based on observation data and should be interpreted with precaution.

There is less uniformity in trial evidence. Heterogeneous effects between subclasses and foods were discovered in a meta-analysis of randomized trials; certain foods, such cocoa and soy, had advantages for blood pressure levels, LDL cholesterol, and flow-mediated dilation, but not consistently (Hooper *et al*., 2008). Anthocyanin trials enhanced lipid profiles primarily in individuals with risk variables (Wallace *et al*., 2016), while reviews of flavanol-rich tea and cocoa suggest vascular benefits but emphasize small studies and different dosages (Grassi *et al*., 2009). Flavonols may lower CVD risk factors, according to reviews of phenolic substances more generally, although additional proof is required (Rangel-Huerta *et al*., 2015).

Table 4. Summary of Clinical Evidence on the Cardiovascular Benefits of Flavonoids

Source	Design	Main finding	Study limitations
Micek *et al.*, 2021	Dose–response meta-analysis of prospective cohorts	Higher flavonoid intake associated with lower CVD risk; subclass-specific associations	Observational; residual confounding
Hooper *et al*., 2008	Meta-analysis of randomized trials	Effects differ by subclass and food source	Marked heterogeneity; short trials
Wallace *et al*., 2016	Systematic review of anthocyanin trials	Improved lipid profile in people with existing risk factors	Little effect in healthy people; need for longer trials
Rangel-Huerta *et al*., 2015	Systematic review of phenolic compounds in trials	Flavonols may reduce risk factors	Evidence not yet robust
Grassi *et al*., 2009	Review	Cocoa and tea flavanols associated with vascular benefit	Small studies, variable doses
Cassidy, 2018	Review	Anthocyanin-rich foods linked to lower CVD risk in cohorts	Lack of long-term randomized trials
Andra-Iulia *et al*., 2014	Review of dark chocolate studies	Regular dark chocolate linked to lower cardiometabolic risk in at-risk groups	Specific to cocoa products

5. Bioavailability, safety and limitations

The primary barrier to clinical use is bioavailability. Flavonoids have low plasma concentrations, are poorly absorbed, and are extensively conjugated and metabolized by gut bacteria (Thilakarathna and Rupasinghe, 2013; Del Rio *et al*., 2013). For instance, quercetin exhibits variable plasma levels in vivo due to its poor water solubility and instability in biological fluids (Islam *et al*., 2014; Gormaz *et al*., 2015). The question of whether direct antioxidant action is physiologically significant in humans has also been raised by low doses; many cardiovascular benefits may instead be the result of signaling and enzyme modulation (Tattini *et al*., 2013; Mladenka *et al*., 2010; Gupta *et al*., 2016). To increase bioactivity, structural alteration is being investigated (Chen *et al*., 2018).

Anthocyanin experiments showed no negative effects at the tested levels (Wallace *et al*., 2016), and flavonoids are usually considered safe at normal dietary levels (Sánchez *et al*., 2019). Less is known about the safety of high-dose dietary supplements and their interactions with cardiovascular medications. The vast range of chemicals and dosages examined, the predominance of in vitro and rodent evidence, and the challenge of distinguishing the impact of individual flavonoids from the dietary matrix are further limitations of the research.

6. Future perspectives

The following needs stand out:

- Long-term, sufficiently powered randomized trials with hard cardiovascular outcomes, standardized dosages, and identified flavonoid subclasses (Grassi *et al*., 2009; Cassidy, 2018).
- Improved delivery methods and structural equivalents to increase absorption and solubility (Islam *et al*., 2014; Chen *et al*., 2018).
- Research on metabolites of the gut microbiota, which may partially mediate the effect (Del Rio *et al.,* 2013).
- Research on the epigenetic pathways that flavonoids may use, such as long non-coding RNAs (Jiang *et al*., 2022).
- Studies on interactions between flavonoid categories in whole foods that are either antagonistic or synergistic (Grassi *et al*., 2009).

Conclusion

Flavonoids are plant polyphenolic compounds of plant origin that has great involvement in decreasing the threat of cardiovascular diseases (CVDs). Oxidative stress acts as crucial factor in the heart diseases development including heart injury and ischemic heart conditions. These bioactive polyphenols prevent these diseases by scavenging free radicals due to their anti-

oxidant effects. Flavonoids also activate intracellular anti-oxidant signaling pathways, resulting in elevated endogenous anti-oxidants production like catalase, GSH and SOD. Additionally, flavonoids reduce inflammation by modulating NFkB, making them potential agents for CVDs treatment. Flavonoid intake works as cardio-protective agent by activating Calcium ions channels and modulating mitochondrial Ca2+ uptake. Further research is required, to fully comprehend all the processes due to which these phenolic compounds owning advantageous health impacts in many cardiovascular diseases.

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