REVIEW ARTICLE

GMJ.2022;11:e2535
www.gmj.ir

Received 2022-07-31
Revised 2022-08-23
Accepted 2022-08-31

The Functionality of Apigenin as a Novel Cardioprotective Nutraceutical with Emphasize on Regulating Cardiac Micro RNAs

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Abstract

Cardiovascular diseases (CVDs) are considered the most common disorder and the leading cause of mortality globally. The etiology of CVDs depends on a variety of genetic and acquired parameters. Nowadays, a dramatic surge appeared in published reports to find the association between microRNAs (miRNAs) and CVDs in order to understand the cause of the disease, rapid diagnosis with the introduction of valid biomarkers, and target as a therapeutic approach. Apigenin is a novel nutraceutical flavonoid that cardioprotective properties are suggested. The current review aimed to evaluate the beneficial features of this phytochemical against CVDs with an emphasis on its ability to regulate the miRNAs. The findings demonstrated that Apigenin could regulate cardiac miRNAs, including miR-103, miR-122-5p, miR-15b, miR-155, and miR-33. Consequently, preventing CVDs is possible through different effects such as the promotion of cholesterol efflux, prevention of hyperlipidemia, alteration in ATP Binding Cassette Subfamily A Member 1 (ABCA1) levels, reducing of cardiocytes apoptosis, and retarding myocytes fibrosis. Also, it can regulate signaling pathways, protect against endothelial dysfunction, maintain oxidative balance, and decrease inflammatory factors and reactive oxygen species. Hence, apigenin regulatory characteristics affecting miRNAs expression could introduce this flavonoid as a novel cardioprotective phytochemical against different CVDs.

[GMJ.2022;11:e2535] DOI:10.31661/gmj.v11i.2535

Keywords: Cardiovascular Diseases; MicroRNAs; Antioxidants; Reactive Oxygen Species; Apigenin

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Introduction

Cardiovascular diseases (CVDs) remain the most common non-communicable disease and the leading cause of mortality and disability worldwide, as per the world health organization, expected to cause more or less 23 million deaths by 2030 [1-4]. In addition to the high level of mortality rates, CVDs cause decrement in quality of life at the micro-level in patients and their families, as well as a result in a crucial financial burden on the health budget of countries, particularly those with low- and middle-incomes, at the macro-level [5-7]. Indeed, CVDs refer to all disorders related to the heart and blood vessels, including hypertension, atherosclerosis, cerebrovascular disease, peripheral vascular disease, deep vein thrombosis, pulmonary embolism, cardiac arrhythmias, myocardial fibrosis, and heart diseases such as coronary heart disease, rheumatic and congenital heart disease, and cardiomyopathies [7, 8].

Significantly, in recent decades, both social changes (e.g., more sedentary jobs instead of physical demands, prolonged office work times, and decreased leisure and recreation time for frivolous accomplishments) and lifestyle changes (e.g., reduced physical activities, high fat and calories rich diets, smoking, and alcoholism) contributed to exponential development in CVDs cases [9-11]. CVDs risk factors are divided into two main categories, modifiable risks such as smoking, undesirable lipid profile, obesity, hyperglycemia, high blood pressure, prolonged stressful state, alcoholism, and reduced physical activities, and non-modifiable risks, including gender, age, and familial history [12-14].

Non-coding RNAs refer to a class of epigenetically functional RNAs, transcribed from DNA but translated into no proteins, including microRNAs (miRNAs), short interfering RNAs, PIWI-interacting RNAs, and long non-coding RNAs [15, 16]. Among them, miRNAs, a subclass of small non-coding RNA molecules, are made of approximately 22 nucleotides and modify gene expression negatively at the post-translational stage and positively in subcellular organelles like the mitochondria and nucleus [17, 18]. Many recent studies determined the involvement of miRNAs in the pathogenesis of different types of CVDs, including hypertension, congenital heart disease, arrhythmia, diabetic cardiomyopathy, and heart failure. Therefore, miRNAs are considered novel biomarkers as well as therapeutic targets [9, 19-21]. Indeed, some evidence has demonstrated numerous signaling pathways involved in the underlying mechanisms of CVDs, in which miRNAs act as nodes of signaling networks that regulate the progression of CVDs [22, 23]. Despite the determination of the potential function of some miRNAs, most of the performed studies are preliminary; thereby, there is a significant absence of high-quality information and in-depth mechanistic insight into CVDs caused by altered miRNAs.

Over the past two decades, despite the remarkable advances in the treatment of CVDs, such as coronary artery disease and acute myocardial infarction, the mortality rate remains on the rise [24]. Nowadays, many studies have proposed novel pharmaceuticals and/or dietary antioxidants as a solution with minimal adverse effects for the treatment of various acute and chronic disorders such as cancer [25, 26], infertility [27-29], diabetes [30], endometriosis [31], viral infections [32], and CVDs [33, 34]. Apigenin is one of the dietary flavonoids that, in addition to its favorite properties (such as anti-inflammatory, antioxidant, anti-tumor, and anti-apoptotic effects), represents the ability to prevent/alleviate CVDs by regulating the expression of miRNAs. Hence, the current review aims to provide information regarding apigenin role in relieving CVDs, and describe apigenin-induced mechanisms related to the modification of miRNAs expression.

Apigenin, a Widespread Flavonoid, Is Capable of Alleviating CVDs Through Different Mechanisms

Flavonoids are a class of naturally-occurring phytochemicals with various functions abundantly found in almost all plant tissues. Basically, flavonoids are divided into different subclasses, such as flavones, flavans, flavonols, flavanones, flavan-3-ols, flavanonols,

anthocyanidins, etc., based on their chemical structure [35, 36]. Overall, normalizing endothelial dysfunction, increasing vasodilation, and reducing oxidative stress are the main mechanisms by which these natural antioxidants exhibit their cardioprotective properties. Flavonoids could modify the endothelial nitric oxide synthase and sirtuin-1 pathways, for example, which are intracellular targets capable of maintaining the endothelial function by regulating miRNAs expression, suggesting that regulation of miRNAs by flavonoids is a promising approach to alleviate CVDs [37]. Furthermore, it is well established that the level of several miRNAs, such as miR-19b, miR-155, miR-146amiR-10b, miR-33a, miR-33b, and miR-378, along with the levels of ATP Binding Cassette Subfamily A Member 1 (ABCA1) and ABCG1, two major receptors involved in cholesterol metabolism, and expression of signaling pathways like nuclear factor-κB (NF-κB), nuclear factor erythroid 2–related factor 2 (Nrf2) signaling, and PI3K/AKT could be modified by natural antioxidants leading to inhibition of atherosclerosis, a widespread fatal type of CVDs [38].

Apigenin (4′,5,7-trihydroxyflavone) is one of the most widespread flavonoids that belongs to the flavone sub-class [39]. The name of this dietary antioxidant is derived from the genus Apium. Dietary fruits and vegetables such as celery seeds, marjoram, Italian oregano, spinach, chamomile, parsley, sage, and pistachio are considered the enrichest sources of apigenin [39]. It is documented that the main sources of apigenin are the plants belonging to the *Asteraceae* family, such as those belonging to *Artemisia, Matricaria, Achillea,* and *Tanacetum* genera [40, 41]. Biogenetically, apigenin is produced by the phenylpropanoid pathway and can be obtained from both L-tyrosine and L-phenylalanine amino acids [42]. In this regard, both amino acids convert to *p*-coumaric acid but with different pathways. Upon the activation of *p*-coumaric acid with Coenzyme-A (CoA) and condensation with three residues of malonyl-CoA, the chalcone synthase enzyme performs the aromatization process to form chalcone. By the next stage, chalcone isomerase converts chalcone to naringenin, which is further oxidized by a flavanone synthase to form apigenin. Interestingly, apigenin is considered one of the most renowned nutraceuticals among all the phenolic compounds, which exerts countless nutritional and organoleptic properties [43, 44].

Like other flavonoids, apigenin and similar compounds such as naringenin, kaempferol, hesperidin, ellagic acid, and oleuropein can modulate the expression of miRNAs and also have cardioprotective properties [39]. Indeed, the large number of studies have claimed the palliative effects of apigenin on CVDs through the modification of various mechanisms. The peroxisome proliferator-activated receptor-γ (PPAR-γ) is one of the targets that apigenin could induce its activation results in the restoration of the left ventricular function, prevention of hemodynamic perturbations, and maintenance of the balanced redox status in the diabetic rat's myocardium; hence, protecting against myocardial infarction through attenuating edema, myonecrosis, apoptosis, and oxidative stress [45]. Similarly, Liu *et al.* demonstrated that the administration of apigenin alleviated diabetic cardiomyopathy via inhibition of cardiac remodeling, improvement of cardiac function, reducing cardiac interstitial fibrosis, suppression of cardiac oxidative stress, and prevention of cardiocytes apoptosis, all of which were caused by inhibition of NF-κB/p65 translocation and consequent inflammation [46]. In addition, Cardenas *et al*. suggested that the reduction in the activity of the NF-κB pathway, along with halting leukocyte infiltration and restoring normal metabolic function, are the main mechanisms by which dietary apigenin reveals its immune-regulatory properties [47]. Moreover, the downregulation of the NF-κB pathway is believed to contribute to the protection against abdominal aortic aneurysms, a multifactorial vascular disease caused by elastin degradation, chronic inflammation, and vascular smooth muscle cell phenotypic modulation through attenuation of pathological expansion of the aorta, preservation of the elastic fiber, and reduction in vascular inflammation [48].

In addition, excessive amounts of free fatty acids are acknowledged as the main cause of obesity and similar consequences such

as hyperlipidemia, which in turn extensively disrupts the physiological function of vascular endothelium, the most immediately exposed tissue to the drastic effects of hyperlipidemia [49, 50]. More importantly, the dysfunction of the vascular endothelium is considered the initial step of CVDs in patients with obesity [51]. It is suggested by Miao *et al.* that apigenin is capable of protecting against lipotoxicity in human aortic endothelial cells via increasing cell viability, improving mitochondrial membrane potential, elevating nitric oxide production, and preserving proteomic content all of which through modification of regulatory pathways such as Foxo, inflammatory responses (including IL-17 and tumor necrosis factor), cell adhesion, and endoplasmic reticulum protein processing [52]. Furthermore, in human endothelial cells exposed to trimethylamine-n-oxide and the induced vascular inflammation, which is related to endothelial dysfunction, atherosclerosis, and elevated risk of CVDs, apigenin exerted alleviative effects on the expression of genes associated with arteriosclerosis, inflammasomes, and endothelial dysfunction including *LOX-1, SR-PSOX, SREC, NLRP3, TXNIP, VCAM-1, ASC, ICAM-1,* and *MCP-1*, as well as suppressed leukocyte adhesion and reduced the uptake levels of acetylated low-density lipoprotein [35]. So, it suggests that apigenin can retard vascular endothelium dysfunction by modifying the expression of scavenger receptors and uptake of the acetylated form of low-density lipoprotein, expression of adhesion molecules, and the formation of NLRP3 inflammasomes [53].

Apigenin Could Alleviate CVDs Through Modification of Regulatory miRNAs

Considering the current interest of researchers in determining and introducing miRNAs as the main factors involved in disease etiology, therapeutic targets, and diagnostic biomarkers in CVDs, several studies have investigated the possibility of modifying the expression of these regulatory molecules by apigenin, and as a result, prevention/alleviation of CVDs have been suggested. In the following, some miRNAs and its role were investigated.

miR-103

Several studies have suggested that miR-103 is involved in different types of CVDs. In atherosclerosis, Jiang *et al*. discovered that miR-103 contributes to the disease's progression as its inhibition is followed by attenuation in the inflammation and endoplasmic reticulum stress through disruption of the PTEN-mediated MAPK signaling pathway [54]. Furthermore, it is established that miR-103, along with miR107, targets Fas-associated protein with death domain (FADD) and thereby regulates programmed cardiac necrosis and myocardial ischemia/reperfusion injury [55]. Similarly, the inhibition of miR-103 resulted in the cardioprotection against myocardial infarction by affecting on FADD/RIPK pathway [56]. Cardiac hypertrophy is another CVD in which miR-103 is believed to be capable of affecting this disorder through the inactivation of autophagic flux via targeting TRPV3, a non-selective cationic channel [57]. Interestingly, Wang *et al.* [58] revealed that apigenin could attenuate the cardiomyocyte injury caused by myocardial infarction through the regulation of miR-103-1-5p. In this regard, the findings demonstrated that the administration of apigenin to mouse myocardial cells that underwent acute myocardial infarction was accompanied by downregulation of miR-103-1-5p, which was followed by overexpression of Parkin, increment of the level of mitochondrial autophagy, and restoration of myocardial injury caused by hypoxia/reoxygenation [58].

miR-122-5p

In many studies, miR-122-5p has been related to different types of CVDs. Badacz *et al*. conducted a 6-year prospective evaluation of cardiovascular disease/ myocardial infarction/ ischemic stroke (CVD/MI/IS) in 142 patients with acute ischemia that was caused by carotid and/or coronary artery stenosis and these patients underwent revascularization for the symptomatic lesion [59]. The findings demonstrated that miR-122-5p was associated

with peripheral artery disease, myocardial infarction, and creatine levels suggesting this miRNA is a potential risk factor for secondary cardiovascular events [59]. Furthermore, Šatrauskienė *et al.* described that miR-122-5p is associated with metabolic syndrome-related subclinical aortic atherosclerosis [60]. In addition, miR-122-5p is reported to inhibit Hand2 and thereby be the inducer of mitochondria-dependent cardiomyocyte apoptosis and subsequent heart failure [61]. Moreover, the contribution of this miRNA to cardiovascular fibrosis and related diseases has been described previously [62].

Interestingly, in 2021, researchers revealed that apigenin is able to enhance the expression of miR-122-5p, which is followed by overexpression of Smad7 and downregulation of HIF-1α, Smad2/3, p-Smad2/3, α-smooth muscle actin, and collagen I/III representing the functionality of apigenin in the treatment of cardiac fibrosis through the subsequent downregulation of HIF-1α expression and suppression of the collagen synthesis [63]. Concordantly, a most recent study described that apigenin regulates the expression of miR-122-5p and miR-155-5p, which the second one is discussed later, thereby alleviating myocardial fibrosis [63]. In this regard, the administration of apigenin resulted in the overexpression of miR-122-5p and downregulation of miR-155-5p that was followed by the downregulation of HIF-1α, upregulation of c-Ski, reduction in the levels of NF-κB/TGF-β1 signaling pathway, promotion of antioxidant ability, inhibition of TGF-β1-induced Smad2/3 expression, and overexpression of Smad7 [64].

miR-15b

It is documented that miR-15b, in a cascade involving MALAT1/miR-15b-5p/MAPK1, is able to alter the autophagic flux and the mTOR signaling pathway in endothelial progenitor cells; hence, affecting coronary atherosclerotic heart disease [65]. Moreover, the downregulation of miR15-b could leads to reduced incidence of arrhythmia, infarct size, and cardiomyocyte apoptosis along with suppressed inflammation and oxidative stress via by KNCJ2 overexpression [66]. According to the study conducted by Wang *et al*., the downregulation of miR-15b upon the administration of apigenin resulted in the overexpression of JAK2 and a higher activity of the JAK2-STAT3 pathway, disruption of myocardial apoptosis, and reduction of reactive oxygen species; hence, alleviation myocardial injury caused by ischemia/reperfusion [67].

miR-155

In accordance with other miRNAs, miR-155 has been associated with CVDs. Faccini *et al*. reported that miR-155 is downregulated, suggesting this biomolecule is a novel biomarker for the diagnosis of coronary heart disease [68]. More importantly, the higher alteration in miR-155 expression, the more severe coronary heart disease [69]. Also, Ding *et al*. introduced miR-155, along with some other miRNAs, as a marker for screening of early heart failure diseases that was resulted by evaluating plasma levels in 62 subjects with heart failure [70].

It is reported that the administration of apigenin could alleviate myocardial fibrosis through the downregulation of miR-155-5p, which is accompanied by the overexpression of the c-Ski gene, and a significant downregulation in the levels of collagen I/III, α-smooth muscle actin, Smad2/3, and p-Smad2/3 representing the functionality of apigenin in the inhibition of cardiac fibroblast differentiation and extracellular matrix production via the regulation of miR-155-5p [71]. In addition, it is documented that the inhibition of miR-155-5p could assumed as novel therapy for lipopolysaccharide-induced cardiac apoptosis and septic myocardial dysfunction [72]. Interestingly, apigenin can inhibit the lipopolysaccharide-induced miR-155 overexpression was followed by a significant increment in anti-inflammatory regulators such as FOXO3a and SMAD2 [73]. However, its effectiveness in improving myocardial dysfunction caused by lipopolysaccharide has not been investigated.

miR-33

In concurrence with other mentioned micro-

molecules, miR33 has been recommended as a possible biomarker in patients with coronary heart and artery diseases [74, 75]. In addition, Chen *et al*. reported that miR-33 can promote myocardial fibrosis via the inhibition of MMP16 and the stimulation of the p38/MAPK signaling pathway [76]. Furthermore, it is documented that genetic ablation of miR-33 could disrupt physiological metabolism and elevate the risk of CVDs by increasing food intake and adipose tissue expansion, promoting obesity and insulin resistance [77]. Similarly, miR-33 is believed to be related to atherosclerotic plaques [78]. In this regard, it is documented that apigenin can suppress atherogenesis through the downregulation of miR-33, which results in the augmentation of ABCA1 expression, the enhancement of ABCA1-mediated cholesterol efflux, and the inhibition of inflammatory responses [79].

Conclusion

The findings of the current review study revealed that apigenin is capable of regulating different miRNAs, including miR-103, miR-122-5p, miR-15b, miR-155, and miR-33, which in turn modifies several signaling pathways, inhibits cardiac apoptosis, suppresses oxidative stress, alters autophagic flux, decreases coronary lipotoxicity and improve cholesterol efflux via affecting the expression of ABCA1. Also, it could considerate as a potential nutraceutical to prevent/alleviate different types of cardiovascular disorders.

Conflict of Interest

The authors declare that there is no conflict of interest.

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