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Naringenin and naringin in cardiovascular disease prevention: A preclinical review

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ABSTRACT

Cardiovascular disease is an important cause for morbidity and mortality worldwide. Flavonoids, such as naringin, and naringenin are important natural phytochemicals in the treatment or prevention of various disorders such as obesity, cardiac diseases, diabetes, and metabolic syndrome. Naringin and naringenin have significant therapeutic potential in several diseases through anti-oxidative, anti-inflammatory, and anti-apoptotic actions; these flavonoids play a protective role in human pathophysiology. In this review, based on the latest evidence, we present a summary of the impact of naringin, and naringenin on cardiovascular disease, and analyze and discuss the basic roles of naringin and naringenin and their mechanisms of actions in cardiovascular disease and other vascular dysfunction. The data collected in this review may serve as a comprehensive reference for the effects of naringin, and naringenin in cardiovascular disease, which may be beneficial for further research and for the design of naringin and naringenin analogs as new therapeutic options for cardiovascular diseases.

1. Introduction

Cardiovascular disease is one of the leading causes of death and disability in recent decades worldwide. In the United States, in 2006, more than $400 billion spent on health care and lost productivity and efficiency from cardiovascular disease (Mensah and Brown, 2007; Niu et al., 2019; Wang et al., 2019). There is considerably current interest in the potential of natural products directly and indirectly via synthetic derivatives to provide agents for the prevention and treatment of cardiovascular disease.

All plants make phytochemicals that give them an evolutionary advantage, such as defending against herbivores; as a model salicylic acid, is a hormone in plant defenses (Hayat and Ahmad, 2007). Phytochemicals, as chemicals derived from plant sources, have the considerable potential for utilization as drugs, and various important pharmacological activities of these substances have been reported. Alkaloids, glycosides, polyphenols, and terpenes are the major classes of pharmacologically active phytochemicals, which are produced by a large variety of plants. Phytochemicals show a wide range of pharmacological activities such as antimalarial, antibacterial, antiasthma, anticancer, anti-Alzheimer, vasodilatory, anti-inflammatory, antiarrhythmic, analgesic, and antihyperglycemic activities (Adebayo and Krettli, 2011; Bryzgalov et al., 2018; Chen, 2011; D'Onofrio et al., 2017; Ezekiel et al., 2013; Maqbool et al., 2019; Ravishankar et al., 2013). Many of these compounds are used in medicine and have been utilized as chemical starting points for new drug discovery. Flavonoids are a large important category of secondary metabolites that pertain to the polyphenol class. Flavonoids are the most common group of the

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polyphenolic components that exist in different plant species, and chemically disparate flavonoids can be found in vegetables, flowers, and fruits. Flavonoid compounds show considerable potential and advantages for cancer prevention, cardiovascular diseases, and diabetes mellitus, mostly postulated to be due to their antioxidant effects (Raffa et al., 2017; Ravishankar et al., 2013; Wang et al., 2000). Naringenin is a flavanone flavonoid that can be found in two forms. Its glycosidic form called naringin and its aglycol form, naringenin. Naringin has a disaccharide neohesperidose attached to position 7 via a glycosidic bond (Alam et al., 2014).

Several studies have reported significant protective effects of naringin, and naringenin on various cardiovascular diseases such as myocardial ischemia and cardiac hypertrophy (R Vasanthi et al., 2012). In this paper, recent advances in the use of naringin, and naringenin for the treatment of cardiovascular diseases have been reviewed.

2. Cardiovascular disease (CVD): prevalence, pathophysiology, and risk factors

Cardiovascular disease (CVD) is one of the important issues for human health with high morbidity and mortality rates that can affect the majority of adults past the age of 60 years around the world. CVD mortality was appraised at 17.3 and 17.9 million representing 30% and 31% of all global deaths, in 2008 and 2016, respectively. The majority of the deaths arise from ischemic stroke and coronary heart disease. It is predicted that by 2030, more than 23.3 million people will die annually from CVD (Vilahur et al., 2014). CVD has been mentioned as one of the 15 conditions, which leads to the cause of functional disability and influences the individual's quality of life. CVD covers four important areas which are: i) coronary heart disease (CHD) which is presented as angina pectoris, lethal or non-lethal myocardial infarction, and/or heart failure; ii) peripheral artery disease which occurs as limb ischemia and intermittent claudication; iii) cerebrovascular disease which occurs as lethal or non-lethal strokes and transient ischemic attacks; iv) aortic atherosclerosis and thoracic or abdominal aortic aneurysm (Mendis et al., 2011). One-third to one-half of the total cases of CVD consists of CHD.

Hypercholesterolemia, diabetes, tobacco smoking, hypertension, abdominal obesity, diet, heavy use of alcohol, and physical inactivity are among the most important risk factors for CVD (Raffa et al., 2017; Stewart et al., 2017). These risk factors, are modifiable and should be considered for intervention in all patients. The underlying pathological mechanisms of CVD are variable depending on the disease. Atherosclerosis, one of the primary underlying pathological processes and the main reason for CVD, starts as early as adolescent years and leads to acute coronary syndrome and heart attacks in later years. Coronary atherosclerosis is a common cause of heart failure (HF). Risk factors listed above facilitate the initiation of mechanisms such as inflammation and oxidation in the artery wall that gives rise to the formation of fatty-fibrous lesions over time. Gradually, these lesions can rupture causing serious problems, such as heart attack and stroke (Scott, 2004).

3. Structure, metabolism, sources, and bioavailability of naringin and naringenin

Flavonoids are phenolic secondary metabolites generally synthesized in plants. Prenylated flavonoids showed a wide range of biological activities, including antioxidant, antitumor, and antibacterial activities (Heller and Forkmann, 2017; Panche et al., 2016; Raffa et al., 2017). The most known and important flavonoids amongst plant compounds are naringenin (naringetol) and naringin (naringenin 7-O-neohesperidoside). Flavonoids are defined by a fifteen-carbon structure containing two fused rings (A and C) attached to an aromatic ring (B) via a carbon-carbon bond (Fig. 1) (Panche et al., 2016). The addition of three hydroxy groups at the 4′, 5, and 7 carbons in the main structure of flavonoids results in the formation of naringenin (Nouri et al., 2019; Szoboszlay et al., 2016). The molecular formula of naringenin is $C_{15}H_{12}O_5$, and that has 5,7-Dihydroxy-2-(4-hydroxyphenyl)chroman-4-one IUPAC name (Nouri et al., 2019).

In nature, naringenin is available in two forms: aglycosylated (naringenin) and glycosylated (naringin or naringenin-7-O-glucoside). Naringenin is a colorless and flavorless flavanone derived from the rapid metabolism of naringin by the liver enzymes called naringinase (Ribeiro, 2011). Naringinase exists in yeasts, plants, and fungi it is commonly available in the genus *Aspergillus* and hydrolyzes the naringin into naringenin, rhamnose, glucose, and prunin (Ribeiro, 2011). The naringenin biosynthetic and its hydrolysis pathway by naringinase is provided in Fig. 2. Also, naringin has a chemical formula of $C_{27}H_{32}O_{14}$ and its melting point is 166 °C, the bitter taste of the fruit is due to its presence. The LD_{50} of this compound is about 2000 mg/kg and it is present in grapefruit juice at a concentration of 400 mg/L. Due to the inhibitory effects of naringin on liver enzymes (cytochrome P450 enzymes), the consumption of grapefruit juice can inhibit the metabolism or increase the concentration of drugs that are metabolized in the liver can alter the pharmacokinetics and lead to toxicity (Fuhr and Kummert, 1995; Yusof et al., 1990).

Naringenin and naringin with different ratios that depend on the source can be found in a diversity of fruits, vegetables, and nuts, such as grapefruit, tomatoes, beans, Greek oregano, sour orange, cocoa, water mint, bergamot, tart cherries, and beverages such as red wine, tea, coffee (Ahmed et al., 2017; Burkina et al., 2016; Erlund, 2004; Gattuso et al., 2007; Ho et al., 2000; Ribeiro and Ribeiro, 2008; Silva et al., 2014; Vallverdu-Queralt et al., 2012). Although they show various biological effects, naringenin and naringin suffer from poor pharmacokinetic profiles (low oral bioavailability),which critically limit their clinical potential. It seems that the aglycone form of naringenin has more appropriate bioavailability than the naringenin-7-glucoside form (Choudhury et al., 1999). The use of nano-formulations is one of the suggested solutions to improve the bioavailability of these compounds (Ahmad et al., 2020; Wang et al., 2017; Yen et al., 2009).

Some studies have investigated the comparative pharmacokinetics of naringin and its aglycone, naringenin. To find a pharmacokinetic basis for the detected difference, naringenin and naringin were administered orally (25 mg/kg) and (225 mg/kg) in rabbits, respectively. After oral administration of naringenin and naringin to rabbits, mean concentration-time profiles in serum were calculated. The maximum serum concentration of naringin and its conjugates occurred after almost 90 min, whereas for naringenin administration, it occurred after 10 min. Since a similar flavonoid glycoside such as rutin demonstrated delayed absorption than its aglycone, naringin was poor to be absorbed than naringenin (Hsiu et al., 2002). It was reported that the binding constant

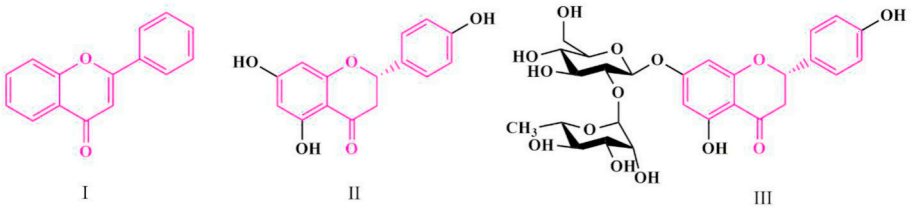

Fig. 1. Structures of flavonoid skeleton (I), naringenin (II), and naringin (III).

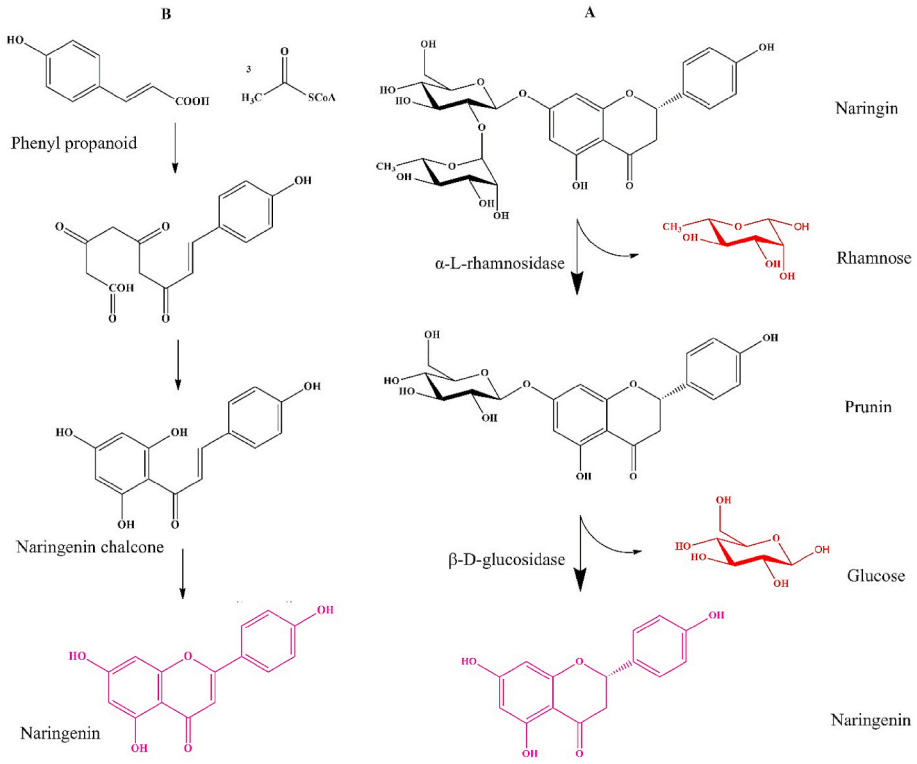

Fig. 2. Biosynthesis of naringenin and its hydrolysis pathway by naringinase. The figure provides two different pathways of naringenin synthesis. Pathway A, naringin with the assistance of the naringinase enzyme turns into naringenin, naringinase is an enzyme mixture containing both β-d-glucosidase and α-L-rhamnosidase, which at the first step, hydrolyzes the naringin to prunin and rhamnose and then hydrolyzes prunin to naringenin and glucose. Pathway B, the combination of acylpolymalonate and shikimic acid leads to the biosynthesis of naringenin's basic structure, in this pathway phenylpropane in combination with acetyl-CoA forms an intermediate compound that converts to naringenin chalcone. Eventually, naringenin chalcone via the chalcone isomerase becomes to the naringenin.

values of the naringenin were found more than four times higher than naringin to human serum albumin (Liu et al., 2012). The experimental result demonstrated that naringenin generates a stronger antioxidant effect and hydroxyl and superoxide radicals-scavenging capacity than naringin (Cavia-Saiz et al., 2010).

4. Cardiovascular actions of naringenin and naringin: pharmacological effects and potential therapeutic targets

Naringenin and naringin are pharmaceutically active flavonoids with significant medicinal importance and its advantageous properties have been largely investigated in the literature with studies *in vitro* and *in vivo* (Bharti et al., 2014; Salehi et al., 2019). The present review focuses on current researches delineating the therapeutic potential and mechanism (s) of action for naringenin and naringin in the cardiovascular system. Pharmacological effects of naringin and naringenin on CVD in experimental animal and cultured cells are summarized in Table 1 and Fig. 3.

4.1. Effects of naringenin and naringin on atherosclerosis and coronary artery disease

Hypercholesterolemia is the most common risk factor for CVD and atherosclerosis (Alam et al., 2014). Atherosclerosis, as a chronic inflammatory disease, is characterized by the initial deposition of lipoproteins in the vessel wall which are bound and trapped by modified proteoglycans (Getachew et al., 2010; Little et al., 2008) followed by the accumulation of cholesterol and low-density lipoprotein (LDL) into macrophages in the arterial wall (Ruparelia et al., 2017). This disease leads to luminal narrowing, disturbs the basic structure of vessels or thrombus formation which may lead to partial and/or complete occlusion of arteries (Ambrose and Singh, 2015). Various studies both *in vitro* and *in vivo* models have demonstrated positive effects of naringenin on inhibition of atherosclerosis progression. In a study, beneficial effects of naringin and naringenin as potent anti-atherogenic compounds were observed in rabbits fed a high-cholesterol diet. Male rabbits were selected for this study and were categorized into 3 groups. For 8 weeks, animals received a 1% cholesterol diet, or a 1% cholesterol diet containing either 0.1% naringin or 0.05% naringenin. It has been found that anti-atherogenic effect is mainly associated with a decreased hepatic acyl-coenzyme A: cholesterol acyltransferase activity, downregulation of monocyte chemotactic protein-1 (MCP-1), and vascular cell adhesion molecule-1 (VCAM-1) genes. In rabbits fed on high cholesterol diets, results showed that treatment with naringin and naringenin reduced the levels of MCP-1 and VCAM-1 gene expression in the segment of aorta and inhibited the formation of aortic fatty streaks (Lee et al., 2001). No significant difference was observed between effects of naringenin and naringin. In another study, the anti-atherogenic effects of naringin were examined on diet-induced hypercholesterolemia in wild-type mouse models for 18 weeks. Wild-type mice were divided into two groups, fed a high-fat/high-cholesterol diet and apolipoprotein E-deficient mice fed a semisynthetic diet. The effect of naringin at 0.02% (w/w) showed that the extension of atherosclerotic lesions varied considerably between the two groups. In mice fed a high-fat/high-cholesterol diet, in contrast to the apolipoprotein E-deficient mice, naringin affects the atherogenic lipoprotein profile, and reduced plaque progression. It was also observed that naringin reduced the concentration of plasma non-high-density lipoprotein in addition to improved endothelial function (Chanet et al., 2012). Another series of experiments were conducted to investigate the effect of naringenin on heart tissue in a hypercholesterolemic rat model. Rats on a hypercholesterolemic diet showed a significant increase in nitric oxide (NO) level, creatine kinase (CK) activities and serum lactate dehydrogenase (LDH), and cardiac lipid profile. Naringenin (50 mg/kg) was administered orally for 3 months. All the above-mentioned biochemical parameters were normalized in naringenin-treated rats (Chtourou et al., 2015).

The inhibition of vascular smooth muscle cell (VSMC) proliferation may retard the development of atherosclerosis (Hasanov et al., 2017). In one experiment, researchers have examined the relationship between molecular mechanisms of the naringin effects and $VSMC_S$. Naringin reduces VSMC proliferation through activation of the Ras/Raf/ERK pathway, also results pointed out that ERK activation is an important mediator of naringin-induced cell growth inhibition (Lee et al., 2008).

Table 1
Effects of naringin and naringenin on CVD in animal and cell studies.

Derivative and dose	Model	Experimental outcome	Ref
Naringin			
0.02% wt/ wt diet	Diet-induced hypercholesterolemia in mice	Reduced atherosclerotic lesions Decreased plasma total cholesterol, soluble E-selectin and ICAM-1 concentrations	Chanet et al. (2012)
0–150 μM	VSMCs	Activated Ras/Raf/ ERK signaling Decreased CDKs levels Reduced VSMCs proliferation	Lee et al. (2008)
100 mg/kg	fructose-fed rats	Increased nitric oxide levels through enhanced eNOS activity Improved endothelial function	Malakul et al. (2018)
80 μM 100 mg/kg	H9c2 rat myoblastic cell High-fructose diet mice of cardiac hypertrophy	Suppressed the increased ROS production Attenuated the increased HW/BW ratio Inhibition of cardiomyocyte hypertrophy by regulating the AMPK-mTOR signaling axis	Park et al. (2018)
10, 20, 40 mg/kg	ISO-induced MI in rats	Decreased total, Ester, and Free Cholesterol in Serum and Heart Decreased serum LDL, VLDL, Increased HDL Increased serum Triglycerides, Free Fatty Acids and Phospholipids	Rajadurai and Stanely Mainzen Prince (2006)
10, 20, 40 μM	Anoxia/reoxygenation induced apoptosis in H9c2 cells	Decreased the activity of MDA, SOD, CAT, and GSH-Px Increased the GCLC, HO-1 Increased Nrf2 activation and phosphorylation of ERK1/2, PKCδ, and AKT	Chen et al. (2015)
5 μM	high glucose -induced cardiomyocyte apoptosis	Inhibited cardiomyocyte apoptosis by preventing the p38 activation	Huang et al. (2013)
10–160 μM	High Glucose -induced injuries in H9c2 Cardiac Cells	Inhibited the oxidative stress and ROS-activated MAPK pathway	Chen et al. (2014)
80 μM	Hyperglycemia-induced injuries in H9c2 cardiac cells	Decreased p65 mRNA level and KATP channel protein levels Inhibited ROS generation Inhibited p38 MAPK and NF-κB pathway	You et al. (2016)
25–100 mg/ kg	Streptozotocin-induced type 2 diabetic rats		
50 mg/kg	Hyperglycemia-induced cardiac fibrosis in rats	Decreased cardiac fibrosis, oxidative stress, NADPH oxidase activity	Adebiyi et al. (2016)
Naringenin			
0.05 % wt/ wt diet	High Cholesterol-Fed Rabbits	Inhibited foam cell development in vascular wall, MCP-1 and VACM-1 expressions	Lee et al. (2001)
0, 10, 50, 100 μM	Angiotensin II-Induced VSMCs	Increased SOD Activity Inhibited the VSMCs migration and neointimal hyperplasia Decreased NADPH oxidase activity	Xu et al. (2013)
25 or 100 μM	TNF-a induced VSMCs	Increased heme oxygenase-1, Inhibited ROS generation and VSMC activation	Chen et al. (2012)
100 mg/kg	Overload-induced cardiac hypertrophy in mice	Decreased cardiac interstitial fibrosis Decreased cardiac interstitial fibrosis Inhibited the activation of JNK, ERK and PI3K/Akt signaling	Zhang et al. (2015)
100 mg/kg	Left ventricular hypertrophy in rats	Decreased ACE1 and Ang II levels in myocardial tissue	Gao et al. (2018)
1.25, 2.5, 5, 10, 20, 40 μM	I/R injury rats	Increased coronary blood flow after reperfusion, SOD activity Decreased lactate dehydrogenates in coronary effluent, malondialdehyde Reduced MI area	Meng et al. (2016)
50 mg/kg 40,80,160 μM	MI/R injury rats H9c2 cells	Reduced oxidative stress and ER stress via cGMP-PKGIα signaling	Yu et al. (2019b)
40, 80 and 160 μM	Hypoxia/reoxygenation model of MI/R injury in H9c2 myocardial cells	Decreased expressions of ER stress and apoptosis Increased cells viability, expressions of ER stress by activating ATF6, PERK and IRE1α signaling	Tang et al. (2017)
100 mg/kg	I/R injury in 1 year old rats	Reduced ischemic area size and I/R injured areas Decreased calcium up-take in the mitochondria	Testai et al. (2017)
4 and 40 μM	Aged myocardial cells	Increased the calcium retention capacity, Modulated levels of released estradiol and mitochondrial potassium channels	Da Pozzo et al. (2017)
100 mg/kg	High-fat diet-induced apoE−/− mice	Increased cholesterol efflux in lipid-loaded macrophage Inhibited ER stress-ATF6 signaling	Xu et al. (2019)
0, 10, 20, 30, 40, 50 μM	Factor β1-induced cardiac fibroblast	Inhibited cardiac fibroblast transformation and proliferation	Liu et al. (2017)

(continued on next page)

Table 1 (*continued*)

Derivative and dose	Model	Experimental outcome	Ref
		Inhibited CTGF synthesis	
25 or 75 mg/kg	High-fat feeding combined with streptozotocin -induced diabetic mice in cardiac hypertrophy model	Decreased fasting blood glucose, LVHI, LV/BW, ANF mRNA expression Increased EETs, PPARs	Zhang et al. (2018)
3 or 30 μM	High glucose in endothelial cells	Increased eNOS activity, nitric oxide level Inhibited ROS production, PKCβII expression	Qin et al. (2016)
0–100 μM	Human umbilical vein endothelial cells	Enhanced HO-1 expression by Nrf2 activation Increased Akt, ERK, and JNK pathway	Feng et al. (2019)
50 mg/kg	High Cholesterol-Fed rats	Increased heart mitochondrial enzymes, enzymatic and nonenzymatic antioxidants, Inhibited ROS production	Chtourou et al. (2015)
80 μM	H9c2 cardiomyoblast cells	Reduced infarction size, myocardial apoptosis index, PGC-1α and SIRT3 signaling Activated AMPK phosphorylation	Yu et al. (2019a)
100 μM	Microglia and macrophage cell	Inhibited iNOS, COX-2, nitric oxide synthase	Chao et al. (2010)

Abbreviations: ICAM-1, intercellular adhesion molecule-1; ERK, extracellular signal-regulated kinase; CDK, cyclin/cyclin-dependent kinase; VSMCs, vascular smooth muscle cells; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; HW/BW, heart-to-body weight ratio; mTOR, mammalian target of rapamycin: AMPK,AMP-activated protein kinase; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; HDL, High-density lipoprotein; MDA, malondialdehyde; CAT, catalase; SOD, superoxide dismutase; GSH-Px, Glutathione peroxidase; HO-1, heme oxygenase; GCLC, glutamate cysteine ligase; Nrf2, nuclear factor erythroid 2-related factor 2; PKCδ, protein kinase C-delta; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; KATP, ATP-sensitive potassium; NF-κB, nuclear factor kappa B; NADPH, Nicotinamide adenine dinucleotide phosphate; MCP-1, monocyte chemotactic protein; VCAM-1,vascular cell adhesion molecule-1; PKCβII, phosphorylation of protein kinase C βII; ISO, isoproterenol; MI, myocardial infarction; MI/R, myocardial ischemia/reperfusion; ER, endoplasmic reticulum; ATF6, activating transcription factor 6; PERK, phosphorylation levels of phospho-extracellular regulated protein kinases; IRE1α,inositol-requiring enzyme-1 α; Ang II,angiotensin II; ACE, angiotensin-converting enzyme; apoB, apolipoprotein B; CTGF, connective tissue growth factor; TNF-a, tumor necrosis factor alpha; LVHI, left ventricular hypertrophy index; ANF, atrial natriuretic factor; LV, left ventricle; PPARs, peroxisome proliferator-activated receptors; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2.

The effects of antioxidant property of naringenin in angiotensin II (Ang II) -treated VSMCs were assessed using the rat model of carotid artery balloon injury. The main enzymes responsible for the regulation of reactive oxygen species (ROS) production include NADPH oxidase and superoxide dismutase (SOD). Naringenin decreased NADPH oxidase activity and increased SOD activity, so there was a significant decrease in the level of Ang II -induced ROS production. In addition, naringenin inhibited VSMC proliferation and migration *in vitro* and neointimal hyperplasia *in vivo* by regulating MAPK/NF-κB signaling pathway and oxidative stress (Xu et al., 2013).

Heme oxygenase-1 (HO-1) is a cytoprotective and antioxidant enzyme that protects VSMCs from oxidative injury and also assists the prevention of vascular inflammation, atherosclerosis, and endothelial dysfunction (Kishimoto et al., 2019; Ruparelia et al., 2017). Evidence suggests that tumor necrosis factor-alpha (TNF-α) causes chronic inflammatory diseases and insulin resistance in human. Naringenin and naringin decrease TNF-α and its associated abnormalities. In a study, VSMC proliferation and migration were induced by TNF-αand the outcome of naringenin on HO-1 activity as well as ROS generation in treated rats was evaluated. Naringenin suppressed VSMC proliferation via decreasing ERK/MAPK (see note above) and Akt pathways and increasing HO-1 expression (Chen et al., 2012). Inducible nitric oxide synthase (iNOS) expression leads to abnormal cardiac function by promoting pro-inflammatory cytokine production and mitochondrial dysfunction (Cannon, 1998). Several findings have supported the notion that inflammation plays a key role in coronary artery disease and iNOS expression is deleterious in the heart and blood vessels (Bian et al., 2008). Chao and coworkers demonstrated the anti-inflammatory effects of naringenin. by showing that naringenin inhibited nitrite production and cyclooxygenase-2 (COX-2) and iNOS expression in lipopolysaccharide-induced microglia and macrophage cells (Chao et al., 2010).

The inner layer of the blood vessel wall is the endothelium and it is a target for the therapy of CVD. The pathological state of the endothelium is generally known as “endothelial dysfunction” which is linked to the initiation and development of atherosclerosis (Dinh et al., 2017). Endothelial dysfunction induced by fructose feeding in a rat model and the treatment effect of the naringin (100 mg/kg/d) on animals was investigated for 4 weeks. Naringin significantly enhanced nitrate/nitrite (NOx) levels, phosphorylated eNOS (p-eNOS), and aortic expression of endothelial nitric oxide synthase (eNOS) while high-fructose diets reduced these levels. Thus, it can be summarized that naringin reduces the severity of endothelial dysfunction through the modulation of NO bioavailability and oxidative stress (Malakul et al., 2018).

4.2. *Effects of naringenin and naringin on hypertension and cardiac hypertrophy*

Heart failure is a systemic disease caused by divergent regulatory mechanisms to compensate for the heart’s inability to pump enough blood to the systems and organs of the human body. Cardiac hypertrophy is a major risk factor for heart failure. Several causative factors underlie cardiac hypertrophy, such as hypertension, familial hypertrophy, congenital malformations, myocarditis, and dilated cardiomyopathies (Tham et al., 2015). Many researchers have investigated the effects of naringin and naringenin against heart failure in various animal models. *In vivo & in vitro* models, Park et al. evaluated the effects of naringin treatment on fructose-induced cardiac hypertrophy and studied the mechanisms of action. Mitochondrial dysfunction and myocardial ROS production are suppressed by naringin in cardiomyocyte exposed to fructose, also cardiomyocyte hypertrophy is decreased via AMPK/mTOR pathway. Furthermore, it was observed that fructose-induced cardiomyocyte apoptosis was counteracted by naringin through inhibition of ROS-dependent ATM-mediated p53 signaling pathway. This study provides a novel approach in protective pathological cardiac hypertrophy for naringin (Park et al., 2018). In experiments where cardiac hypertrophy was induced by aortic banding (AB) in mice, it was observed that naringenin treatment inhibits ERK, JNK, and PI3K/Akt signaling pathway. As a result of naringenin treatment, interstitial fibrosis and cardiac hypertrophy were attenuated and cardiac function was improved (Zhang et al., 2015). Hypertension in rats was induced by administering NG-nitro-L-arginine methyl ester (L-NAME) for 8 weeks. The results suggest that the effects of naringenin treatment against cardiac hypertrophy may be associated with decreasing angiotensin-converting enzyme 1 (ACE1) and Ang II expression in heart

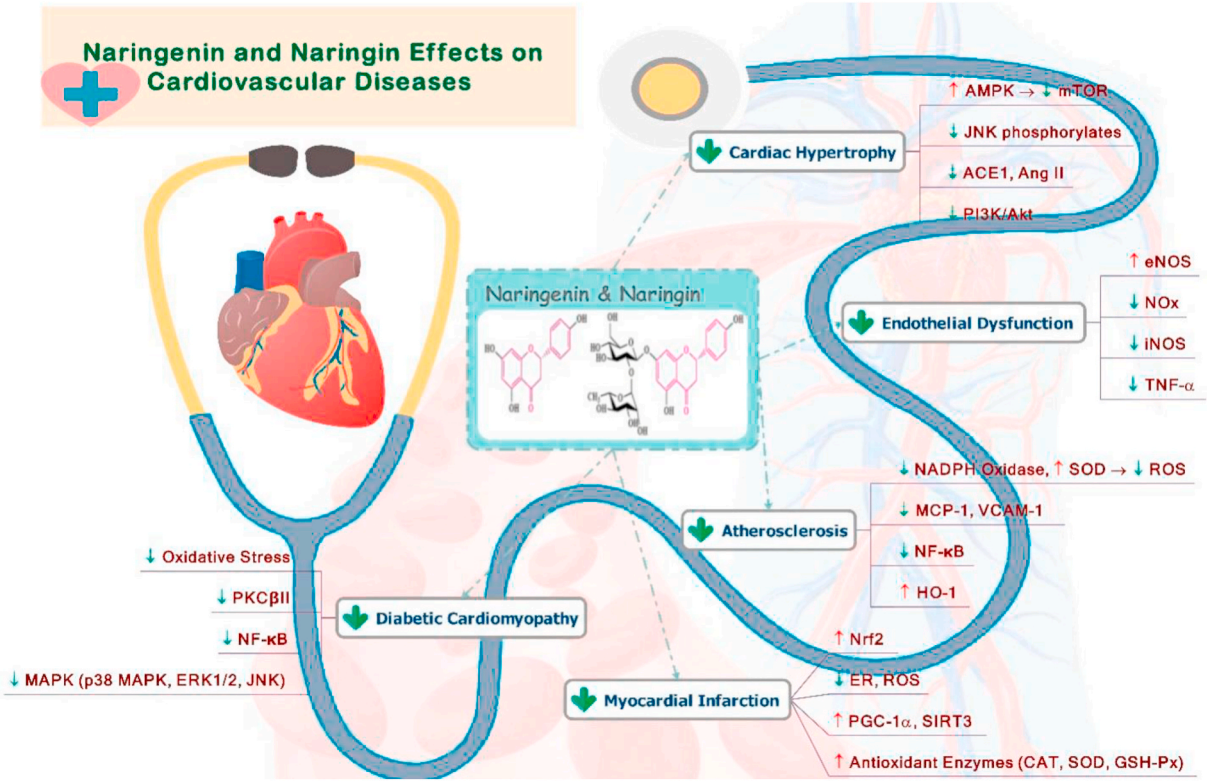

Fig. 3. Cardiovascular actions and molecular targets of naringin and naringenin.

tissues (Gao et al., 2018).

4.3. *Protective effects of naringenin and naringin in myocardial infarction and ischemic stroke*

Myocardial Infarction (MI) is a common and lethal manifestation of CVD which can lead to loss of heart muscle cell volume, changes in ventricular function and structure, and scar formation (Hashmi and Al-Salam, 2015). A very recent study reported that ischemia/reperfusion (I/R) injury impaired cardiovascular function also caused cellular apoptosis and MI. Naringenin treatment provided protection against I/R injury by stimulating mitochondrial biogenesis and preserving mitochondrial function through the AMPK-SIRT3 signaling pathway (Yu et al., 2019a). In a related study, the beneficial effects of naringin and its potential for altering lipoproteins, lipids, and lipid metabolizing enzymes were investigated in isoproterenol-induced MI in Wistar rats. It was reported that there was a significant reduction in the levels of total and free cholesterol, free fatty acids, cholesterol ester, and triglycerides in serum, heart and elevated phospholipids in heart. Naringin pretreatment inhibits the activity of HMG-CoA reductase which can lead to its cholesterol-lowering effect. These findings confirmed that naringin protects the myocardium against lipid accumulation (Rajadurai and Stanely Mainzen Prince, 2006). Meng et al. (2016) reported I/R rat heart treated with naringenin (above 2.5 μmol/L) had functional improvements in recovery of left ventricular (LV) function via activation of K_{ATP} channels. In addition, lactate dehydrogenase (LDH) in coronary effluent was decreased and myocardial antioxidation capacity was increased in animals treated with naringenin.

Oxidative stress and endoplasmic reticulum (ER) stress play a significant role in myocardial damage and cardiomyocyte death (Choy et al., 2018). In a corroborating study, naringenin activates myocardial cGMP-PKGIα signaling *in vitro* and *in vivo* which resulted in decreased oxidative stress and ER stress levels as well as inhibited myocardial apoptosis during I/R condition. (Yu et al., 2019b). For investigating the myocardial protective effect of naringenin, researchers used cardiomyocytes to simulate I/R injury using hypoxia/reoxygenation (H/R) assay in H9c2 myocardial cells. Substantial evidence indicated that inhibition of ER stress signaling pathways including ATF6, PERK and IRE1α by naringenin leads to its cardioprotection against I/R injury (Tang et al., 2017). In a study, the naringin pretreatment protects H9c2 cardiomyocytes from anoxia/reoxygenation (A/R) injury for its capability to activate Nrf2 signaling pathway. The data indicated that naringin could prevent acute myocardial infarction by increasing phosphorylation of PKC, AKT, and ERK1/2 which subsequently activated the Nrf2 signaling. Moreover, the apoptosis rate was reduced by increasing endogenous antioxidative enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) (Chen et al., 2015).

4.4. *Benefits of naringenin and naringin against other cardiovascular diseases*

Decreased cardiac function, which is widely associated with mitochondrial failure in cell death increases with age, and the ageing heart is vulnerable to apoptosis. It was documented that naringenin consumption was presented to elevate cardioprotective activity against I/R injury in the aged rat heart. These protective actions were observed in both *in vivo* and *ex vivo* I/R models. According to the finding in 1-year-old rats, naringenin protected the heart through the activation of mitochondrial large-conductance calcium-activated potassium channel (mitoBK) and could confer cardioprotection in senescent H9c2 cardiomyoblasts (Testai et al., 2017).

Cardiac aging is often caused by ROS, such as superoxide radicals and hydrogen peroxide (H_2O_2) (Nita and Grzybowski, 2016). Pozzo et al. evaluated the efficacy and pharmacological mechanism involved in the anti-aging effect of naringenin in H_2O_2-induced senescence in H9c2 cells. Naringenin has a potential protective effect on the myocardial cells against age-related damage through modulating the ROS levels, the estrogen-associated pathway, and mitochondrial potassium channels (Da Pozzo et al., 2017).

Cholesterol efflux capacity, the main index of HDL functions in humans, transfers cholesterol from macrophages to HDL particles. Several epidemiological studies have documented that cholesterol efflux capacity is an indicator of coronary heart disease events (Shea et al., 2019). Naringenin has a significant ability to increase cholesterol efflux and improve the lipoprotein profile. Naringenin performs this function by increasing the PI3K/AKT pathway that occurs due to inhibition of ER stress-ATF6 activity and thereby resulting in decreased cholesterol efflux in macrophages (Xu et al., 2019). . In the context of CVD, the role of cardiac fibrosis as myocardial scarring is arousing growing attention since it is correlated with heart failure, hypertension, arrhythmia, and death due to sudden cardiac arrest (Hinderer and Schenke-Layland, 2019). Furthermore, an *in vitro* study indicated that the anti-fibrotic capacity of naringenin inhibited the proliferation of cardiac fibroblasts stimulated with transforming growth factor-β1. (Liu et al., 2017).

5. Cardioprotective effects of naringenin and naringin in the diabetic hearts

There is a close association between CVD and diabetes mellitus. Heart disease is the most common cause of mortality in people with diabetes mellitus (Leon and Maddox, 2015). Therefore, targeting appropriate control of the hyperglycemia and general treatment of diabetes mellitus and its complications along with management of all CVD risk factors is important to minimize the progression and prevalence of diabetes mellitus and CVD (Haas and McDonnell, 2018). Peroxisome proliferator-activated receptors (PPARs) as nuclear receptors play a significant role in the treatment of disorders such as inflammation, hypertension, dyslipidemia, and diabetes. One of the main flavonoids for increasing PPARs is naringenin that improves diabetes and its complications such as diabetic cardiomyopathy (Zhang et al., 2018). Naringenin and naringin improve cardiac function and structure in the diabetic state. To demonstrate the role of naringin in cardiac apoptosis in diabetes, the researchers used H9c2 cell apoptosis under high glucose stimulation as an *in vitro* model. Naringin modulates the activity of the p38 signaling pathway and attenuates mitochondrial dysfunction which can lead to inhibition of cardiomyocyte apoptosis in H9c2 cells in high glucose conditions (Huang et al., 2013). Additionally, naringin provided cardiac protection against the effects of high glucose-induced injury in H9c2 cardiac cells by inhibiting the activation of mitogen-activated protein kinase (MAPK) and oxidative stress pathway (Chen et al., 2014). Another series of experiments in streptozotocin-induced diabetic rats and in H9c2 cardiac cells, naringin upregulates ATP-sensitive potassium channels (K_{ATP}) *in vitro* and inhibits the nuclear factor kappa B (NF-κB) pathway *in vivo* and *in vitro*. Thus, naringin provides protection against hyperglycemia-induced injury, via anti-apoptosis, anti-oxidant, anti-mitochondrial, anti--fibrosis, and anti-inflammatory actions (You et al., 2016).

Several risk factors and pathological processes including insulin resistance, atherosclerosis, dyslipidemia, hyperglycemia, and coronary artery disease are common in patients with endothelial dysfunction (Sena et al., 2013). An *in vitro* system placed a focus on the effects of naringenin therapy in the reduction of endothelial dysfunction under high glucose-induced conditions. Naringenin attenuates endothelial dysfunction by reducing ROS accumulation and increasing nitric oxide production in endothelial cells. Moreover, naringenin inhibits the phosphorylation of protein kinase C βII (PKCβII) activation and NF-κB pathway and promotes the phosphorylation of Akt that leads to myocardial protection (Qin et al., 2016).

Studies targeting cardiac hypertrophy have shown that diabetes mellitus alters cardiovascular function and structure by promoting fibrosis and hypertrophy (Spector, 1998). Naringenin appears to be beneficial in diabetic cardiomyopathy by elevating EETs-PPARs activation and regulating CYP2J3 protein expression in diabetic cardiac hypertrophy model (Zhang et al., 2018). Feng et al. demonstrated anti-apoptotic effects of naringenin by increasing HO-1 expression via activation of Nrf2 in high glucose-induced injury in human umbilical vein endothelial cells (HUVECs). In fact, naringenin has been shown to increase the expression of HO-1, through upregulating Nrf2 and PI3K/Akt or JNK signaling pathway (Feng et al., 2019).

Myocardial fibrosis is one of the main structural changes in the diabetic hearts which leads to heart failure (Candido et al., 2003). A series of experiments were performed in the hearts of rats with Type 1 diabetes that showed naringin regulates the progression of myocardial fibrosis by relieving oxidative stress. The antioxidant ability of naringin leads to the modulation of protein kinase C (PKC)-β and p38 expression, and reduction of the activity of NADPH oxidase in cardiac tissue by reducing concentrations of myocardial ROS. There was a significant reduction in the fibrotic area by approximately 67% in the naringin-treated group compared with the untreated group (Adebiyi et al., 2016). Given the results of these trials, naringenin and naringin may be potential agents to treat CVD patients coexisting with diabetes. The effects of naringin and naringenin on CVD in animal and cultured cells are summarized in Table 1 and Fig. 3.

6. Conclusions and future perspectives

The protective effects of naringenin and naringin have been extensively investigated in the treatment of CVD. Both flavonoid compounds show promise for treating a variety of heart diseases because of their antioxidant and anti-inflammatory activities. In addition, there is growing evidence that naringenin and naringin have potential effects in the protection against many cardiovascular complications of diabetes. Clearly, controlled clinical trials are needed to fully assess the therapeutic potential of naringin and naringenin. Despite the huge amount of data on the utilization of nanoparticle formulation in cardiovascular technology, there are no studies available on naringenin or naringin nanoparticle system as a treatment to improve the pharmacokinetic properties and allow substantial room for a full evaluation of these interesting phytochemicals.

CRediT authorship contribution statement

Reza Heidary Moghaddam: Writing - original draft, Writing - review & editing. **Zeinab Samimi:** Writing - original draft, Writing - review & editing. **Seyed Zachariah Moradi:** Writing - original draft, Writing - review & editing. **Peter J. Little:** Writing - original draft, Writing - review & editing. **Suowen Xu:** Writing - original draft, Writing - review & editing. **Mohammad Hosein Farzaei:** Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest during the writing the manuscript.

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