The potential of sweet orange (Citrus sinensis) in cardiovascular health: A literature review

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Consumption of fast food and sedentary lifestyles has recently developed in society. This activity is one of the causes of various degenerative diseases, including cardiovascular disease. Therefore, efforts are needed to prevent it. Sweet orange (Citrus sinensis) is one of the most common types of citrus fruit, with total production reaching 70% of all types. This type of fruit is the most widely produced and consumed by the world's population. Sweet orange is known for its bioactive compounds that have many benefits in cardiovascular health, such as alkaloids, flavonoids, tannins, phenols, vitamins C, B1, B2, and B3, glycosides, coumarin glycosides, folic acid, some organic acids, essential oils, and saponins. Flavonoids are components of secondary metabolites that play a role in the cardiovascular system. The main components of these compounds are hesperidin and naringenin. Various studies have shown that these compounds are active in reducing hyperlipidemia, improving endothelial function, acting as an anti-inflammatory and anti-atherosclerotic agent, preventing myocardial infarction, and preventing cardiac hypertrophy through various mechanisms with low toxicity.

INTRODUCTION

Globalisation changes people's lifestyles that are in line with economic, socio-cultural, and technological growth. Those lifestyles negatively impact health, such as smoking behaviour, drinking alcohol, wrong diet patterns, lack of physical activity, and obesity. An unhealthy lifestyle causes a shift in disease patterns, from infection to degenerative diseases, including cardiovascular disease. Besides, people tend to consume fast food that contains high calories, fat, sugar, and sodium (Na) and is low in fibre, vitamins A, B, C, and calcium. Consumption of a high-fat diet will affect low-density lipoprotein (LDL) levels, which...
causes the blood to clot quickly by activating the endothelial cell, recruiting more monocytes, and forming foam cells. Besides, saturated fatty acids can damage the walls of the arteries, causing a narrowing of the wall of the artery.\textsuperscript{1,2}

Increasing the blood lipid profiles, including total cholesterol, LDL, triglycerides, and the decreasing high-density lipoprotein (HDL), is known as hyperlipidemia. This condition is a significant risk factor for atherosclerosis in arteries and cardiovascular disease, especially coronary heart disease (CHD). According to the World Health Organisation (WHO), CHD is one of the leading causes of mortality globally. Meanwhile, data from the Ministry of Health of the Republic of Indonesia reports that the prevalence of death caused by CHD in Indonesia is relatively high, reaching 1.25 million per 250 million people.\textsuperscript{3,4}

Currently, chemical-based medicines are the principal treatment for hyperlipidemia. Statins are the first-line therapy in treating hyperlipidemia and the primary prevention of atherosclerosis. This drug works by inhibiting the 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme’s action in fat biosynthesis in the body. However, statins have side effects on several body systems, such as the digestive, musculoskeletal, kidney, skin, and central nervous systems. Statins should also not be given to pregnant and lactating women. Therefore, a therapeutic solution is needed using ingredients with minimal side effects, one of which is natural ingredients.\textsuperscript{5,6}

Plants have been used as traditional medicines in developed and developing countries since ancient times. WHO estimates that over 80% of the world’s population still relies on herbal medicines to treat various diseases. This is due to their widespread availability, lower costs, and minimal side effects, making them an attractive alternative to conventional medicine.\textsuperscript{7}

Citrus is one of the world’s most extensively grown and consumed fruits. Citrus production is relatively high in Indonesia, with an expected yield of 2,772.63 tons in 2020. As an agricultural country, Indonesia boasts 255 varieties of Citrus, including sweet oranges (Citrus sinensis), mandarin oranges (Citrus reticulata), tangerines (Citrus nobilis Lour.), sour oranges (Citrus aurantium), pomelo (Citrus maxima (Burm. F.) Merr), limes, lemons, and so on.\textsuperscript{8-10}

Sweet orange is the most commonly produced and consumed citrus fruit worldwide, accounting for 70% of total production. Sweet orange contains flavonoid polyphenol compounds, particularly hesperidin and naringenin, which have been found to have potent anti-hyperglycemic and anti-hyperlipidemic effects in high-fat or streptozocin-induced diabetic myocardial infarction rats. Additionally, a study has revealed that hesperidin supplementation can improve endothelial function, reduce circulating biomarkers of inflammation, and improve lipid profiles in patients with metabolic syndrome. It has also been shown to reduce blood pressure in individuals with pre or stage-1 hypertension.\textsuperscript{11-16}

METHODS

This literature review summarises relevant studies on the theme of sweet oranges and cardiovascular health. Several databases were searched to retrieve articles, including ScienceDirect, PubMed, ResearchGate, Taylor & Francis, Hindawi, and Google Scholar. The keywords used in this study were “Citrus sinensis”, “Flavonoids”, “Hesperidin”, and “Naringenin”. The research articles were obtained and screened based on inclusion and exclusion criteria, such as publication date (2013-2021),
language (Indonesian or English), and article type (research articles or review journals, not seminar proceedings or books). The selected articles were then identified for further analysis.

Sweet orange

Sweet orange is a small plant from the Rutaceae family that initially grows in southern China. It is an evergreen blooming plant that grows in tropical, semitropical, and warm regions. The plant grows to 9-10 meters, with huge spines on the branches. The plant’s leaves are 3-5 mm wide and 6.5-15 cm long, elliptical or oval in shape, bluntly serrated, and have a distinct citrus scent due to the presence of oil. The flowers of sweet orange consist of five white petals and 20-25 yellow stamens. The fruits, which are round or oval, range in width from 6.5 to 9.5 cm and turn orange or yellow when they mature.

Biochemical ingredients of sweet orange and its functions on the cardiovascular system

Sweet orange contains bioactive compounds such as alkaloids, flavonoids, tannins, phenols, vitamins C, B1, B2, and B3, glycosides, coumarin glycosides, folic acid, other organic acids, essential oils, and saponins. Flavonoids consisting of flavanones, flavones, and flavonols are secondary metabolites in plants with broad health benefits. Hesperidin and its aglycones, naringin, eriodictol, and isosacuranethin are a group of flavones found in sweet oranges. Meanwhile, the flavone group consists of diosmetin, and the flavonol group consists of quercetin and kaempferol.

The main flavonoids present in the peel of sweet oranges are hesperidin and naringenin. The content of hesperidin in sweet orange ranges from 99.9-119 mg/100 g serving, while the content of naringenin ranges from 1.06-40.2 mg/100 g serving. Several studies have demonstrated that these compounds have a role in cardiovascular maintenance, including improving endothelial function, reducing insulin resistance, combating oxidative stress, and lowering lipid profiles.

Other flavonoids possessed by sweet oranges, such as ferritin, ferulic acid, nobiletin, and hesperidin, also have anti-atherosclerotic and anti-platelet aggregation effects. The combination of flavonoids, vitamin C, and coumarin-xanthoxyletin compounds can inhibit platelet aggregation through the activity of the cyclooxygenase and lipoxygenase pathways. Inhibit platelet aggregation causes a decrease in fibrinogen which functions to activate aggregation. The details on the study design and pharmaceutical of sweet orange’s bioactive compound and its role in the cardiovascular system are shown in Table 1.

Hesperidin and naringenin of sweet orange role in lowering lipid profile

Hesperidin is a flavanone glycoside found abundantly in sweet oranges. It consists of hesperetin, a flavanone aglycon, bonded to rutinose and glucose via a disaccharide bond, specifically 6-O-(α-L-Rhamnopyranosyl)-D-glucopyranose and 6-O-(α-L-Rhamnosyl)-D-glucose. Hesperidin is commonly referred to as a β-7-rutinoside of hesperetin. The unique

![Figure 2. Flavonoids in sweet orange](image-url)
Table 1. Bioactive compounds of Citrus sinensis and its role in cardiovascular system

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Benefits in the cardiovascular system</th>
<th>Mechanism of action</th>
<th>Subject</th>
<th>Formulation and intervention</th>
<th>Result</th>
<th>Toxicity</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Hesperidin</td>
<td>Hyperlipidemia</td>
<td>Stimulates LDLR gene expression in HepG2 cells through increased phosphorylation of PI3K and ERK1/2 and SREBP-2 mRNAs</td>
<td>Group K1: high-fat diet ad libitum + CMC-Na 1% + aquadest ad libitum</td>
<td>Group K2: high-fat diet ad libitum + CMC-Na 1% dose 500 mg/kg BW + aquadest ad libitum</td>
<td>Group K3: high-fat diet ad libitum + CMC-Na 1% dose 750 mg/kg BW + aquadest ad libitum</td>
<td>CMC-Na 1% dose 500 mg/kg BW and CMC-Na 1% dose 750 mg/kg BW for six weeks could significantly decrease total cholesterol, LDL-C, and TG; however, they cannot increase HDL-C levels</td>
<td>No toxicity</td>
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<td></td>
<td>Pre- or stage-1 hypertensive individuals</td>
<td>Inhibits the activity of the enzyme HMG-CoA reductase</td>
<td>Intake of hesperidin in group 2 decreases systolic blood pressure, and intake of hesperidin in group 3 decreases systolic and diastolic blood pressure after sustained consumption in 12 weeks</td>
<td>Group 2: orange juice containing 690 mg/L of hesperidin (the natural hesperidin content)</td>
<td>Group 3: enriched orange juice containing 1200 mg/L hesperidin</td>
<td>Intake of hesperidin in group 2 decreases systolic blood pressure, and intake of hesperidin in group 3 decreases systolic and diastolic blood pressure after sustained consumption in 12 weeks</td>
<td>No toxicity</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Inhibits secretion of apolipoprotein B</td>
<td>Hypertensive male Sprague-Dawley rats (Rattus norvegicus)</td>
<td>Group 1: control drink</td>
<td>Group 2: two-kidney, one-clip (2K-1C) in a renal artery (hypertensive rats)</td>
<td>Group 3: 2K-1C+ hesperidin 20 mg/kg BW</td>
<td>Group 4: 2K-1C+ hesperidin 40 mg/kg BW</td>
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<td></td>
<td>Vasodilation of blood vessels</td>
<td></td>
<td>Patient with metabolic syndrome</td>
<td>Group 1: Placebo</td>
<td>Group 2: hesperidin 500 mg/day</td>
<td>Daily oral consumption of hesperidin for three weeks improved endothelial function, reduced circulating biomarkers of inflammation, and favourably altered lipid profiles in subjects with metabolic syndrome.</td>
<td>[16]</td>
</tr>
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</table>
| Hesperidin  | Inflammation                         | Inhibits the release of cytokines TNF- 
and cyclooxygenase (COX), which play a role in the release of prostaglandins | Adult male Wistar rats (Rattus norvegicus) with induction of inflammation | Group 1: non-inflamed rats with no intervention  
Group 2: inflamed rats with aquades intervention  
Group 3: inflamed rats with prednisolone 0.7 mg/kg BW  
Group 4: inflamed rats with 2 ml/kg BW Citrus sinensis  
Group 5: inflamed rats with 5 ml/kg BW Citrus sinensis  
Group 6: inflamed rats with 8 ml/kg BW Citrus sinensis  
Group 7: inflamed rats with 0.1 ml/kg BW Citrus paradisi  
Group 8: inflamed rats with 0.3 ml/kg BW Citrus paradisi  
Group 9: inflamed rats with 0.5 ml/kg BW Citrus paradisi  
Group 10: inflamed rats with a combination of 2 ml/kg BW Citrus sinensis juice + 0.1 ml/kg BW Citrus paradisi  
Group 11: inflamed rats with a combination of 5 ml/kg BW Citrus sinensis juice + 0.3 ml/kg BW Citrus paradisi | Citrus paradisi at high doses, Citrus sinensis in a dose-dependent manner, and 5 ml/kg C. sinensis juice + 0.3 ml/kg C. paradisi exhibit maximum protective role against inflammation | Citrus paradisi at high doses, Citrus sinensis in a dose-dependent manner, and 5 ml/kg C. sinensis juice + 0.3 ml/kg C. paradisi exhibit maximum protective role against inflammation | No toxicity | [31] |
| Hesperidin  | Atherosclerosis/ 
Anticoagulation | Inhibits platelet aggregation by activating Protein and thrombin antithrombin (TAT) complex in plasma  
Ameliorate insulin resistance, increase the level of HDL-c and decrease the serum levels of TG, TC, and LDL-c, decreases the expression of AGG and FAS | White healthy rabbits | Group 1: Citrus sinensis 2 ml/kg BW  
Group 2: Citrus sinensis 5 ml/kg BW  
Group 3: Citrus sinensis 8 ml/kg BW  
Group 4: Received saline equivalent to their body weights  
Group 5: Received warfarin 5mg/kg BW in first three days and 10mg/kg BW in next three days  
Group 1: ad libitum food and water  
Group 2: Citrus sinensis 2 ml/kg BW  
Group 3: Citrus sinensis 5 ml/kg BW  
Group 4: Citrus sinensis 8 ml/kg BW  
Group 5: Citrus sinensis 10 ml/kg BW  
Group 4: Received saline equivalent to their body weights  
Group 5: Received warfarin 5mg/kg BW in first three days and 10mg/kg BW in next three days  
Group 1: ad libitum food and water  
Group 2: Citrus sinensis 2 ml/kg BW  
Group 3: Citrus sinensis 5 ml/kg BW  
Group 4: Citrus sinensis 8 ml/kg BW  
Group 5: Citrus sinensis 10 ml/kg BW | The significant effect of C. sinensis on PT in groups 2 and 3 was almost similar to the effect of heparin; aPTT was also prolonged significantly at all three doses of C. sinensis, and significant inhibition of platelet aggregation | The significant effect of C. sinensis on PT in groups 2 and 3 was almost similar to the effect of heparin; aPTT was also prolonged significantly at all three doses of C. sinensis, and significant inhibition of platelet aggregation | No toxicity | [25] |
| Naringenin  | Hyperlipidemia                        | Suppresses carnitine palmitoyl-O-transferase (CPT), peroxisomal acyl-CoA oxidase, cyanide insensitive carnitine palmitoyl-CoA oxidase, carnitine, enoyl-CoA hydratase, 3-ketoacyl-CoA thiolase in vivo | Male Long-Evans hooded healthy rats | Group 1: ad libitum food and water  
Group 2: Citrus sinensis 2 ml/kg BW  
Group 3: Citrus sinensis 5 ml/kg BW  
Group 4: Citrus sinensis 8 ml/kg BW  
Group 5: Citrus sinensis 10 ml/kg BW  
Group 4: Received saline equivalent to their body weights  
Group 5: Received warfarin 5mg/kg BW in first three days and 10mg/kg BW in next three days  
Group 1: ad libitum food and water  
Group 2: Citrus sinensis 2 ml/kg BW  
Group 3: Citrus sinensis 5 ml/kg BW  
Group 4: Citrus sinensis 8 ml/kg BW  
Group 5: Citrus sinensis 10 ml/kg BW  
Group 4: Received saline equivalent to their body weights  
Group 5: Received warfarin 5mg/kg BW in first three days and 10mg/kg BW in next three days  
Group 1: ad libitum food and water  
Group 2: Citrus sinensis 2 ml/kg BW  
Group 3: Citrus sinensis 5 ml/kg BW  
Group 4: Citrus sinensis 8 ml/kg BW  
Group 5: Citrus sinensis 10 ml/kg BW | Dietary naringenin exerts hypolipidemic and anti-adiposity effects in vivo at physiologically relevant concentrations. | Dietary naringenin exerts hypolipidemic and anti-adiposity effects in vivo at physiologically relevant concentrations. | No toxicity | [29] |
| Naringenin  | Hyperlipidemia                        | Inhibits the activity of the enzyme HMG-Co-A reductase | Adult male Wistar rats with ethanol-induced toxicity | Group 1: isocaloric glucose  
Group 2: isocaloric glucose + 50 mg/kg BW/day  
Group 3: 20% ethanol  
Group 4: 20% ethanol + 50 mg/kg BW/day | Administration of naringenin to ethanol-fed rats can significantly prevent the rise in plasma lipids, lipoproteins and tissue lipids during ethanol-mediated tissue injury. Thus, this study shows that naringenin at 50 mg/kg BW/day effectively protects the tissues against ethanol-induced hyperlipidemia. | Administration of naringenin to ethanol-fed rats can significantly prevent the rise in plasma lipids, lipoproteins and tissue lipids during ethanol-mediated tissue injury. Thus, this study shows that naringenin at 50 mg/kg BW/day effectively protects the tissues against ethanol-induced hyperlipidemia. | No toxicity | [32] |
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| Naringin and naringenin | Endothelial Function | Increases eNOS, NOx, and p-eNOS | Fructose-fed male Sprague-Dawley rats | Group 1: normal drinking water  
Group 2: fructose solution + 0.1 % CMC Na  
Group 3: fructose solution and naringenin (100 mg/kg BW/day) | The study demonstrated that treating fructose-fed rats with naringenin (100 mg/kg/d) for four weeks improved the impaired endothelial-dependent relaxation in aortic rings and increased serum NO level. | No toxicity | [33] |
| | Myocardial ischemia | Protects against MI/R injury by inhibiting oxidative stress and ER stress via activation of cGMP-PKGα signalling | Male Sprague-Dawley induced myocardial ischemia-reperfusion injury rats | Group 1: non-myocardial ischemia rats  
Group 2: myocardial ischemia-reperfusion with no intervention  
Group 3: myocardial ischemia-reperfusion with naringenin at a dose of 50 mg/kg BW/day  
Group 4: myocardial ischemia-reperfusion with naringenin at a dose of 50 mg/kg BW/day and KT5823 at a dose of 2 mg/kg BW | Naringenin effectively improved heart function while it attenuated myocardial apoptosis and infarction. Naringenin significantly activated myocardial cGMP-PKGα signalling while inhibiting PKG signalling with KT5823 (in vivo) or siRNA (in vitro). | No toxicity | [34] |
| | Cardiac hypertrophy | Activates myocardial cGMP-PKGα signalling to decrease oxidative stress and ER stress levels | Male C57BL/6 mice with pressure overload-induced cardiac hypertrophy | Group 1: non-cardiac hypertrophy mice + 100 mg/kg BW/day naringenin  
Group 2: aortic banding (AB) to make cardiac hypertrophy + 100 mg/Kg BW/day naringenin  
Group 3: non-cardiac hypertrophy mice  
Group 4: AB | The results of the study demonstrated that naringenin exerts a pharmacological effect against the progression of cardiac hypertrophy induced by pressure overload. | No toxicity | [35] |
| | | Inhibits ROS-dependent ATM-mediated p53 signalling pathway | Male C57BL/6 juvenile mice with high fructose-induced cardiac hypertrophy | Group 1: The control diet contained 536 g/kg BW starch and 100 g/kg BW sucrose  
Group 2: control diet + 100 mg/kg BW/day naringenin  
Group 3: 60% high fructose diet contained 36 g/kg BW starch and 600 g/kg BW fructose  
Group 4: high fructose diet + naringenin 100 mg/kg BW/day | Naringenin protects against fructose-induced cardiac hypertrophy | | [36] |
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</thead>
<tbody>
<tr>
<td>Naringin and naringenin</td>
<td>Atherosclerosis</td>
<td>Decreases NADPH-oxidase, HO-1, MCP-1, and NF-kB</td>
<td>Rat embryonic cardiomyoblast-derived H9c2 cell</td>
<td>Group 1: control group without any treatment</td>
<td>Naringenin can protect A/R-induced H9c2 cells from death or apoptosis by alleviating oxidative stress injury, which may be mediated by the phosphorylation of ERK1/2, PKCδ, and AKT</td>
<td>No toxicity</td>
<td>[37]</td>
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<td>Group 2: the anoxia/reoxygenation group (A/R model group), which was cultured under OGD for four h and then under recovery conditions for 24 h</td>
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<td>Group 3: the A/R cell + Naringenin at concentrations of 10 μg/ml</td>
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<td>Group 4: the A/R cell + Naringenin at concentrations of 20 μg/ml</td>
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<td>Group 5: the A/R cell + Naringenin at concentrations of 40 μg/ml</td>
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<td>Quercetin</td>
<td>Metabolic syndrome</td>
<td>Vasodilation of denuded endothelium by activating potassium channels</td>
<td>Obese Zucker Rats</td>
<td>Group 1: Quercetin 2mg/kgBW mixed with 1 ml of 1% methylcellulose</td>
<td>The results show for the first time that the chronic daily administration of both 2 and 10mg/kg BW of quercetin reduces insulin resistance, dyslipidemia, and hypertension in the experimental model of metabolic syndrome of obese Zucker rats</td>
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<td>[38]</td>
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<td></td>
<td>Group 2: Quercetin 10mg/kgBW mixed with 1 ml of 1% methylcellulose</td>
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<td></td>
<td></td>
<td></td>
<td>Group 3: 1 ml of 1% methylcellulose</td>
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</table>
placement of hydroxyl groups in the aromatic rings of flavanones produces essential changes in their biochemical structure, which are crucial for their beneficial effects. Hesperidin has demonstrated a range of positive effects, including anti-tumour, anti-oxidant, anti-inflammatory, hypocholesterolemic, and hypoglycemic effects. These effects have been shown to improve chronic pathologies such as cancer, neurodegenerative diseases, and cardiovascular diseases.\textsuperscript{26,27}

Hesperidin has several mechanisms for managing hyperlipidemic conditions. It acts through three primary mechanisms: inhibiting HMG-CoA reductase and acetyl-coenzyme A acetyl-transferase (ACAT) enzymes, stimulating the expression and transcription of LDL receptor genes, and inhibiting the secretion of apolipoprotein B in the liver. Hesperidin inhibits HMG-CoA, reducing cholesterol synthesis in the liver through a mechanism of action that is similar to statin drugs.\textsuperscript{39,28}

The HMG-CoA reductase is a crucial enzyme in the process of cholesterol biosynthesis. It acts as the rate-limiting factor, catalysing the conversion of HMG-CoA into mevalonate. When HMG-CoA reductase is inhibited by hesperidin, it efficiently reduces the total cholesterol levels by activating the sterol regulatory element-binding protein-2. This protein upregulates both the HMG-CoA reductase and LDL receptor, leading to a reduction in cholesterol levels. Figure 3 illustrates this mechanism.\textsuperscript{40}

Hesperidin stimulates LDLr gene expression by increasing phosphorylation of PI3K and ERK1/2, which enhance mRNA levels of the transcription factors SREBP-1a and SREBP-2 and increase their protein maturation in human hepatoma HepG2 cells. SREBP's regulate plasma lipoproteins and bile micelle synthesis genes. In vivo, cholesterol metabolism genes are activated by SREBP-2, while SREBP-1c activates fatty acid and triglyceride metabolism genes. The enhancement of SREBPs may lead to lower plasma LDL cholesterol. In addition, stimulation of this LDLr gene may also exhibit cardioprotective potential.\textsuperscript{41,42}

Hesperidin treatment has been shown to inhibit apolipoprotein B secretion. Apolipoprotein B is an LDL transport protein produced in the liver to carry LDL to the blood. It is the main protein in atherogenic lipoprotein particles and LDL particles. Hesperidin inhibits the secretion of apolipoprotein B, reducing the amount of LDL transported to the blood.\textsuperscript{43}

Naringin, another flavonoid derivative, has been shown to have anti-atherogenic and hypolipidemic effects. Naringin and its aglycone, naringenin, have been found to decrease the activity of several hepatic enzymes, including HMG-CoA reductase, ACAT, peroxisomal acyl-CoA oxidase, cyanide-insensitive palmitoyl-
CoA oxidase, carnitine palmitoyl-O-transferase (CPT), enoyl-CoA hydratase, 3-hydroxy acyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase. By suppressing plasma CPT, which is involved in the transport of free fatty acids across the mitochondrial membrane during oxidation and ketogenesis, naringin and naringenin could decrease the level of free fatty acids in the blood, leading to a lipid-lowering effect. In male Long-Evans hooded rats, naringenin enhanced the expression of peroxisomal fatty acid oxidation enzymes, such as carnitine octanoyl transferase, acetyl-CoA oxidase, bifunctional enzyme, and 3-ketoacyl-CoA thiolase. Additionally, dietary naringenin was observed to dramatically increase the mRNA expression of microsomal cytochrome P-450 IV A1, which is involved in fatty acid x-oxidation in mice. These previous findings suggest that naringin and naringenin may have potential therapeutic benefits for managing hyperlipidemia and related metabolic disorders.

Effects of sweet orange hesperidin and naringenin in lowering blood pressure

Hesperidin and naringenin have been reported to have antihypertensive effects by improving endothelial function and reducing oxidative stress and inflammation. The antihypertensive effect is believed to be mediated through the vascular nitric oxide (NO) synthase pathway. Nitric oxide is a vasodilator that helps regulate vascular tone, blood pressure, and hemodynamics by modulating the cytoplasmic Ca$^{2+}$ concentration and myofibrillar Ca$^{2+}$ sensitivity in vascular smooth muscle cells (VSMCs). The NO/cGMP/cGK signalling pathway increases NO and tetrahydrobiopterin (BH4) in the endothelium, leading to paracrine relaxation of underlying VSMCs and subsequent vasodilation. This reduces blood pressure by lowering the resistance in the blood vessels. Thus, hesperidin and naringenin improve endothelial function by modulating the NO pathway.\textsuperscript{15,27,45,46}

Effects of sweet orange hesperidin and naringenin on atherosclerosis

Atherosclerosis starts when fatty deposits or atheromatous plaques appear in the arteries’ inner layers. It is a chronic vascular disease characterised by focal narrowing and thickening of blood vessel lumens caused by lipid-laden plaques in the arterial wall. Furthermore, atherosclerosis is frequently associated with other metabolic disorders such as insulin resistance and fatty liver, dyslipidemia, an imbalanced redox status, or elevated circulating pro-inflammatory factors.\textsuperscript{47,48}

Reverse cholesterol transport (RCT) is a cholesterol metabolism pathway that ensures the removal of cholesterol from lipid-containing macrophages in the arterial wall and its transport back to the liver for final excretion. RCT is an important defence mechanism in atherogenesis. This release of cholesterol from macrophages is mediated by various membrane transporters, such as the G1 and A1 ATP-binding cassette transporters (ABCG1 and ABCA1) on the macrophage membrane. ABCG1 mediates cholesterol and phospholipid efflux to HDL particles, while ABCA1 induces cholesterol efflux to lipid-poor apolipoprotein A-I (apoA-I). In this case, hesperidin can increase the expression of ABCA1 and ABCG1 genes responsible for activating RCTs. In addition, the role of hesperidin in increasing HDL and lowering blood triglyceride levels, total cholesterol, and LDL also plays a role in the prevention of atherosclerosis.\textsuperscript{47}

Hesperidin could inhibit blood coagulation, which is another anti-atherosclerosis mechanism. Multiple studies have demonstrated that hesperidin has a similar effect to heparin, a commonly used anticoagulant medication. Specifically, hesperidin prolongs the time it takes for thrombin, prothrombin, and thromboplastin to form clots in the blood, as it reduces the levels of intrinsic coagulation factors. Also, hesperidin increases protein C levels and the thrombin-antithrombin complex (TAT), which play crucial roles in preventing thrombosis. Protein C deficiency can lead to macro and microvascular thrombosis, while the TAT complex serves as a significant marker to measure the amount of inhibited thrombin by combining with anti-thrombin III.\textsuperscript{25}

Meanwhile, naringenin reduces the proliferation of VSMCs to inhibit the development of atherosclerosis. Naringenin mechanism occurs through activating the Ras/Raf/ERK pathway. Naringenin inhibits VSMC proliferation and migration in vitro and neointimal hyperplasia in vivo by regulating the MAPK/NF-κB signalling pathway.
pathway and oxidative stress due to reactive oxygen species (ROS) production. NADPH oxidase and superoxide dismutase (SOD) are the main enzymes responsible for regulating ROS production. Naringenin decreased NADPH oxidase activity and increased SOD activity, resulting in a significant decrease in the level of ROS production induced by angiotensin II.37

**Dosage and toxicity**

A study showed that consuming 250 mL of sweet orange juice daily for three months did not increase dietary sugar intake in obese men. Interestingly, regular intake of sweet orange supplements of 0.5-1 g per day in humans has been shown to reduce fat mass and increase lean mass.49–51 The typical intake of hesperidin in Western countries ranges from 193-562 mg, or the equivalent of 2.8-8 mg/kg BW for humans weighing 70 kg. Hesperidin is also available in dietary supplements with a daily dose of 500-2000 mg, or the equivalent of 7-29 mg/kg BW for humans weighing 70 kg. Notably, there are no reported cases of toxicity or side effects following hesperidin administration.14,52,53

**CONCLUSION**

The consumption of sweet oranges and their compounds, such as hesperidin and naringenin, have been shown to provide cardioprotective effects through various mechanisms. These include reducing hyperlipidemia, improving endothelial function, reducing blood pressure, inhibiting blood coagulation, and reducing oxidative stress and inflammation. Furthermore, the intake of hesperidin has been previously reported to be safe, with no reported toxicity or side effects. However, further study is still needed to investigate the benefits of other types of oranges in cardiovascular health, and clinical trials are needed to establish the efficacy of these compounds in humans.

**CONFLICT OF INTEREST**

There is no conflict of interest.

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