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Potential of Naringin in Reducing Aorta Lesion Atherosclerosis in Hypercholesterolemia: A Systematic Review

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A B S T R A C T

Hypercholesterolemia is a condition that affects cholesterol levels because of the increase of LDL. Hypercholesterolemia is connected to atherosclerosis disease, which causes the blockage of blood flow. Naringin is a flavonoid primarily found in the citrus family and proved to have various benefits, one of which is antiatherogenic. The article searching was done in PubMed, Wiley Online Library, Cochrane, ProQuest, ScienceDirect, and Google Scholar databases. The final three studies about naringin supplementation in animals models are assessed. Naringin had an antiatherogenic effect and decreased the aorta lesion in atherosclerosis by several different mechanisms.

1. Introduction

Hypercholesterolemia is a condition in which high levels of cholesterols, with moderate plasma triglycerides, happen because of the increase of cholesterol and apolipoprotein B lipoprotein, called low-density lipoprotein (LDL). Hypercholesterolemia can be divided into two groups which are primary and secondary. Primary, caused by genetic formation, can be passed down in the family, or some with no known genetic mutation. The member of this group is familial hypercholesterolemia (FH), polygenic hypercholesterolemia (PH), and hyperlipoproteinemia. Secondary, caused by environmental factors or other diseases induce hypercholesterolemia.[1] Atherosclerosis is a disease caused by multifactorial factors. The rise of LDL cholesterol levels is connected to inducing atherosclerotic cardiovascular disease (ASCVD).[2] LDL would be modified oxidatively to induce inflammation and fatty streak form in the tissue. A fibrous plaque evolves to form a mature lesion with plaque rupture culminating in a cardiovascular (CV) event.[3]

Naringin is a glycoside form of naringenin, a constituent flavonoid in the citrus family.[4] Naringin is beneficial because of its activity as an antioxidant and anti-inflammatory based on the test either in vitro or in vivo.[5] Some studies proved the potential of naringin to have antiatherogenic effects in hypercholesterolemic rabbits.[4]

2. Methods

The articles were searched online by December 2021 on PubMed, Wiley Online Library, Cochrane, ProQuest, ScienceDirect, and Google Scholar databases using keywords related to "hypercholesterolemia," "naringin," and "atherosclerosis". The term "naringin" was used in the search for all databases. The relevant papers then get selected based on inclusion and exclusion criteria. This study reviews research articles published between 2000 and 2021 to examine the effect of naringin in lowering plaque in atherosclerosis. The flowchart presents the data acquisition process to select the concordant studies is illustrated in Figure 1.

The inclusion and exclusion of this study were already decided before the search. This study included all research articles using naringin either with or without control groups; the studies have already been collected and then filtered; duplicates are removed. The articles are then studied, and the irrelevant studies get removed.

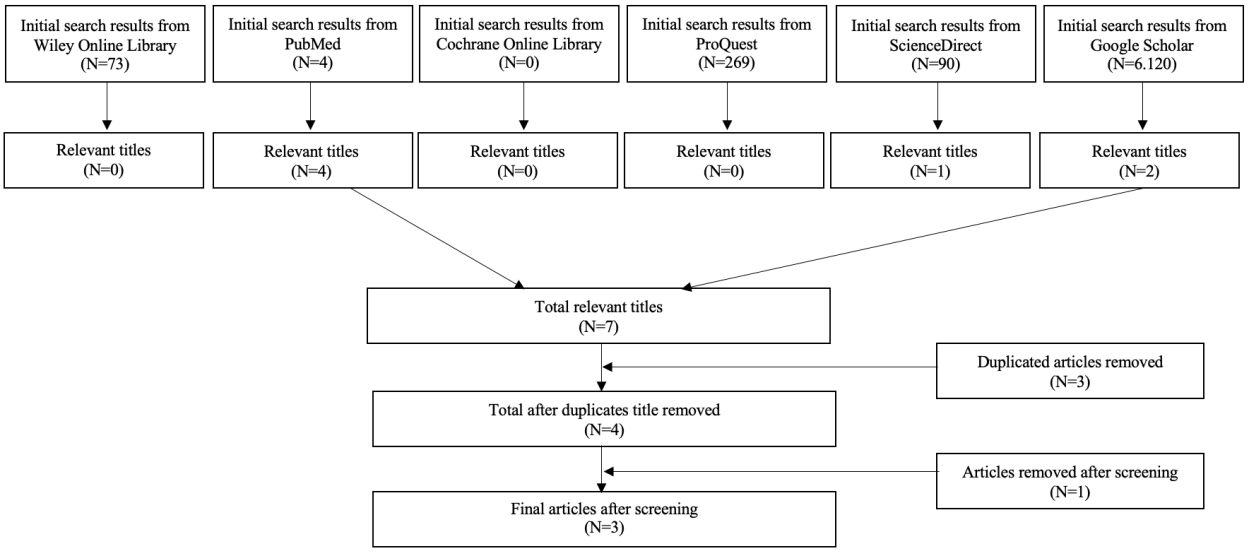

Figure 1. The flow chart in the selection of the article.

This study was written as a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[6] The search tool for this systematic review is PICO or population, intervention, comparison, and outcome.[7] The PICO is population: hyperglycemia model; intervention: the use of naringin; comparison: with or without anti-cholesterol or statin groups and; outcome: reduction of plaque in atherosclerosis.

Statistical analysis

The relevant information from selected articles and then extracted, such as the subject characteristics, interventions, duration, results from the intervention, and methods in data analysis. The main result expected from the selected articles were the potential of naringin in reducing forming plaque in the aorta of atherosclerosis because of hypercholesterolemia subject compared to the available control or standard available.

3. Results and Discussion

Online searching on several sites resulted in 6556 articles from the initial search. However, only seven articles are regarded as relevant from 6 sources: four articles from PubMed, 1 article from Science Direct, and two from Google Scholar, while 6549 articles are excluded because of irrelevant titles. Another three articles were removed from the selection because of duplication. Lastly, 1 article was removed due to its

uneligible criteria for PICO questions.

The final 3 articles selected are from Korea (2001)[8], China (2020)[9], and France (2012)[10]. A total of 92 animal models used in these studies were hypercholesterolemia. Two studies use mice, and one use rabbit. Each study uses a different concentration of naringin; two studies use a high cholesterol diet to induce hypercholesterolemia in their models and, two studies use apo E -/- mice models as their subjects. These studies were conducted at least eight weeks of naringin supplementation to their diet; two studies also use statin groups to compare naringin to statin. One study did not use statin as a comparison but provided control data.

All three articles took pictures of aorta condition after treatment of naringin or statin or control, and then the images were analyzed from the aorta to measure the percentage of lesions forming on the aorta wall using Image-Pro Plus software. Various duration in each study is eight weeks, 16 weeks, and 18 weeks (Table 1), and each subject is sacrificed at the end of the studies. Results from Choe et al.[8] shows the potential of naringin to reduce the fatty streaks accumulated in the aorta significantly by 64% and have the potential in inhibiting neointimal foam cell infiltration by a little over 50% by the end of 8 weeks of continuous supplementation of 0.5% naringin in 5 hypercholesterolemia rabbits.

Wang et al.,[9] reported that naringin is able to significantly reduce atherosclerosis plaque in the aorta surface by 55.92% and reduce lesion area forming in the aorta sinus by almost half of it (48.01%) in 8 ApoE -/- mice with a dose of 100mg/kg/day of naringin for 16 weeks until sacrifice at the end. Chanet et al.,[10] used mice to understand the role of naringin in atherosclerosis on mice fed with high cholesterol high-fat diet and mice with apoE-/-. The two groups were then divided into four random groups to analyze the role of naringin in each group, with two groups given naringin in a diet dose of 0.02%. The result shows apoE -/- mice are forming 10x higher lesions in the aorta than wild-type mice. Naringin could only significantly reduce lesions in wild-type mice by 41%, WT mice also had less atherogenic plasma lipid levels than apoE -/- mice.

Table 1. Summary of data description from the included studies

Study	Subject criteria	Intervention	Length of follow up	Outcome
Choe et al. 2001 (Korea)				
	14 male New Zealand rabbits fed with a diet containing 0,25% cholesterol for 2 weeks	The rabbits are divided into three groups, untreated (n=4), 0.5% naringin treated (n=5) and 0.02% lovastatin treated group (n=5)	8 weeks, sacrificed at the end	Naringin reduces fatty streaks in the aorta by 64% and significantly inhibit neointimal foam cell infiltration by 51% ($p<0.05$)
Wang et al. 2020 (China)				
	24 ApoE$^{-/-}$ female mice (7 weeks old) fed with a high-fat diet, eat and drink ad libitum	The mice were divided into three groups, 100mg/ kg/ day naringin (n=8), 10 mg/ kg/ day atorvastatin (n=8) and, control (n=8).	16 weeks, sacrificed at the end	Naringin significantly reduces 55.92% of atherosclerosis plaque forming in the aorta surface and reduce 48.01% of lesion area forming in the aorta sinus ($p<0.05$)
Chanet et al. 2012 (France)				
	Two dyslipidemic male mouse models of atherosclerosis: Wild type (WT) (n=30) mice on a high-fat high cholesterol diet (HF-HC) and apoE -/- mice (n=24) **Study design**: random without a control group	The mice were divided into two groups fed ad libitum, either an HF-HC diet or a standard semipurified diet, both supplemented or not with 0.02% Naringin (NAR)	18 weeks, sacrificed at the end	ApoE-/- mice have 10x higher atherosclerosis lesion than WT mica fed HF-HC diet. NAR only reduces the lesion on WT mice (-41%). WT mice have less atherogenic plasma lipid profile than apoE -/- mice ($p<0.05$)

All three studies focus on the role of naringin as an alternative to the current medication to treat cholesterol, in this case, the statin family medication. The use of naringin is compared to a statin in reducing the lesion forming in the surface of the aorta from hypercholesterolemia models. Most of these studies provided evidence of naringin potential in reducing the lesion in the aorta significantly.[8-10] These findings are also supported by studies by Pu et al., who found that supplementation of naringin to rats fed with a high-fat diet can decrease the elevated plasma lipid concentrations.[11]

Atherosclerosis is a condition in which the fatty deposits form an atheromatous plaque in the inner layer of arteries. The formation started by forming tiny cholesterol crystals on smooth muscle, and the plaques would grow and proliferate the tissue and surrounding muscle and form a bulge that would block blood circulation.[12] WHO stated that cardiovascular disease (CVDs), one of which is atherosclerosis, is a leading cause of death worldwide resulting in almost 17.9 million lives per year.[13] Research shows the connection between cholesterol levels to atherosclerosis development and regression.[2,14] Artherosclerosis establish in the case of low LDL with a combination of comorbid and genetic diseases.[14-16]

Choe et al., stated that naringin had an antiatherosclerotic effect by inhibiting ICAM-1 expression, which affects the growth of an atheromatous fatty streak.[8] Wang et al., reported that naringin could suppress alleviated atherosclerosis in ApoE -/- mice in regulating cholesterol metabolism by remodeling gut microbiota by the modulation of *bacteroides, bifidobacterium, clostridium,* and *eubacterium.*[9] Chanet et al., reported the antiatherogenic of naringin in wild-type mice fed HF-HC diet by improving dyslipidemia and biomarkers of endothelial dysfunction and changing gene expression to preserve the vascular wall.[10] Naringin also affected molecular mechanisms in endothelial cells (ECs) and smooth muscle cells (SMCs).

Although Choe et al., proved the antiatherogenic effect of naringin and proved that naringin had the hepatoprotective effect, the exact mechanism of the latter is still unknown and needs studying further.[8] Wang et al., presented results of the antiatherogenic effect of naringin in ApoE -/- mice; however, the difference in methods and animal models may result in different results to other studies; thus more depth studies are needed to provide evidence of this findings.[9] Chanet et al., also suggested further studies to understand further about lasting effect post supplementation and naringin effect in regression of existing atherosclerosis lesion.[10] This study's limitation is the low number of existing research about the effect of naringin on hypercholesterolemia in reducing aorta lesions in atherosclerosis, with only three relevant articles to inclusion and exclusion criteria.

4. Conclusion

Naringin proved to have an antiatherogenic effect towards hypercholesterolemia models while inhibiting ICAM 1 expression, modulating gut biota, improving dyslipidemia, and affecting molecular mechanisms of ECs and SMCs. Therefore, naringin supplementation may replace the current medication for hypercholesterolemia patients.

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