Effect of Hesperidin on blood pressure and lipid profile: A systematic review and meta-analysis of randomized controlled trials

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Systematic Review

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Abstract

Background

The cardioprotective activity of hesperidin has been well demonstrated in several clinical studies. Also, there is a meta-analysis published on this topic in 2019. However, considering the recently published clinical studies there is a scope for performing a systematic review and meta-analysis on the cardioprotective effect of hesperidin. This systematic review and meta-analysis were performed to determine the beneficial effect of hesperidin in alleviating alterations in cardiovascular parameters based on available clinical studies.

Methods

The literature search was performed using online databases such as PubMed and Google Scholar. The search was mainly focused on the role of hesperidin in various cardiovascular disorders.

Results

Based on the inclusion and exclusion criteria 9 clinical studies involving 2414 subjects were included. The meta-analysis revealed that the hesperidin has significantly reduced the systolic blood pressure (Inverse variance (I.V): -0.86 (-1.53 to -0.18) at 95% CI, p = 0.01, I2 = 100%) and total triglycerides (IV: -0.21 (-0.40 to -0.02) at 95% CI, p = 0.03, I2 = 12%). However, there were no statistically significant changes in the diastolic blood pressure (IV: 0.52 (-1.78 to 2.83) at 95% CI, p = 0.06, I2 = 100%), HDL (IV: 0.04 (-0.25 to 0.34) at 95% CI, p = 0.78, I2 = 56%), LDL (IV: -0.10 (-0.66 to 0.45) at 95% CI, p = 0.72, I2 = 85%), and total cholesterol (TC) (IV: 0.18 (-0.79 to 0.44) at 95% CI, p = 0.57, I2 = 88%) compared with the placebo/control.

Conclusion

The outcomes of the meta-analysis suggest that hesperidin administration could benefit patients with cardiovascular diseases by reducing systolic blood pressure and total triglycerides.

Introduction

As per the WHO fact sheet, cardiovascular diseases (CVDs) are the major cause of death globally (WHO, 2021). WHO estimated that 17.9 million people died from CVDs in the year 2016, which was 31% of all-cause deaths globally (WHO, 2021). Cardiovascular disorder is a broad term that covers coronary heart disease, rheumatic heart disease, cerebrovascular disease, deep vein thrombosis/pulmonary embolism, congenital heart disease, and peripheral arterial disease. Coronary heart disease is most common among these CVDs, (Prabhakaran et al., 2016). Most CVDs are easily preventable regardless of being a foremost cause of mortality globally (Kinoshita et al., 2017) with dietary control (Clar et al., 2017), high-intensity
workouts, active lifestyle (Lavie et al., 2015), and stress management. CVDs are often due to metabolic imbalance (Zhang et al., 2008). Under such conditions, there is a nutritive disparity between supply and demand, which leads to heart-related disorders such as obesity, atherosclerosis, hypertension, ischemic heart disease, and occasionally heart failure (Brandhorst et al., 2019). These disorders are associated with oxidative stress at the cellular level due to mitochondrial dysfunction (Ferrari et al., 1996).

Hesperidin is a polyphenolic compound found most abundantly in citrus fruits that exerts many medicinal uses. Hesperidin has been found to possess many pharmacological activities like hypolipidemic, anti-diabetic, anti-inflammatory, and anti-hypertensive. Relevant to this study, to date there are thirteen clinical studies are available related to the cardioprotective activity of hesperidin in humans. Also, there is a meta-analysis study has been published so far (Mohammadi et al., 2019). However, the meta-analysis performed by Mohammadi et al. considered the studies on orange juice and hesperidin, the comparisons were not solely between hesperidin vs placebo/control. Further, there are two additional randomized controlled trials, Zahra Yari et al., 2019 and Zahra Yari et al., 2020 have been published on hesperidin related to its cardiovascular benefits after the publication of the above-cited meta-analysis papers. Therefore, there is a scope for performing a systematic review and meta-analysis on hesperidin related to its cardiovascular benefits when compared to placebo/control. With this background, the present study was undertaken to carry out a systematic review and meta-analysis to determine the beneficial role of hesperidin in treating cardiovascular diseases.

**Methodology**

**Literature search**

The literature search was performed in detail using the search term ‘Hesperidin’ in combination with cardiovascular disease, heart, and clinical trials in online databases such as PubMed and Google Scholar for studies published up to April 2023. Initially, total articles obtained from the above databases were screened with the ‘abstract’ or ‘full-length copy’, and irrespective of the type of experimental model, the articles fitting into the inclusion criteria were considered for the study. Further, cross-references in the articles and reviews were searched wherever additional data was required.

The literature search completely was performed by H Shylaja, GL Viswanatha, and Sunil V; however, after concerning all the co-authors, the final selection of articles for systematic review and meta-analysis was performed with inclusion and exclusion articles.

**Inclusion criteria (Data items)**

The original research articles published until April 2023 involving randomized controlled studies conducted on hesperidin against various cardiovascular disorders including metabolic disorders in healthy/diseased individuals having a comparison to placebo/control were included.

**Exclusion criteria**
1. Studies reporting incomplete data
2. Studies performed without control
3. Studies involving combination formula or other ingredients with hesperidin
4. Duplicates, conference proceedings, book chapters, review articles
5. Only abstracts, non-English papers

Parameters

The meta-analysis was performed for cardiovascular parameters such as blood pressure (both systolic blood pressure (SBP) and diastolic blood pressure (DBP) and lipid profile (LDL, HDL, Total cholesterol (TC), Triglycerides (TG)). The above-listed parameters were compared between the control and hesperidin-treated group.

Risk of Bias (RoB) of included studies

The risk of bias shall be assessed with the Cochrane Collaboration risk assessment tool for RCTs

Data collection and analysis

All the studies were critically scrutinized distinctly as per the inclusion and exclusion criteria by the reviewers. The analysis was done initially at the title and abstract level, and later at the full-text level. Data to be pulled out from the studies included details of experimental conditions, methods used, interventions, and outcome measurements. Wherever necessary, the numerical data from the graphs was extracted using Adobe Acrobat’s XI in-built measuring tool (Adobe Systems Incorporated, San Jose, CA, USA)). Further, in the absence of a standard error of the mean (SEM) or standard deviation (SD), a default value of 10% of the mean was considered as SD for both hesperidin and control groups, instead of assigning zero.

Statistical analysis

The meta-analysis was performed using Review Manager (RevMan, version 5.4; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). For continuous, variables, inverse variance (IV) was estimated using the random-effects model with a standardized mean difference (SMD) as the effect measure. A random-effects model was used to calculate the pooled prevalence with a 95% confidence interval (CI). Heterogeneity was calculated with the $I^2$ statistic. This test evaluated the percentage of the difference between the results of the study that is due to heterogeneity than sampling error. $I^2$ of less than 40% was considered as not significant. On the other hand, the $I^2$ value of more than 40% was regarded as moderate to high heterogeneity.

Results

Selection of articles
During the electronic search, we identified a total of 2905 records across various databases, namely, PubMed/Medline (n = 84) and Google Scholar (n = 2820) based on the pre-defined search criteria. Upon applying the inclusion and exclusion criteria, a total of 9 research articles were selected for systematic review meta-analysis out of 2905 records identified during the preliminary search. The duration of included studies varied from a single day to multiple days. In all the included studies, the pure form of hesperidin was used at different dose levels. The search strategy and descriptions of the studies included in this review have been summarized in Figure 1 and Table 1 respectively.

## Risk of bias in the included studies

The risk of bias assessment for included studies is included in Figure 2.

### Effect of Hesperidin on Blood Pressure

The effect of hesperidin on blood pressure has been evaluated across various studies. Interestingly, hesperidin administration has significantly reduced the systolic blood pressure (SBP) (IV: -0.86 (-1.53 to -0.18) at 95% CI, \(p = 0.01, I^2 = 100\%\)), however, there was no statistically significant difference in the diastolic blood pressure (DBP) (IV: 0.52 (-1.78 to 2.83) at 95% CI, \(p = 0.06, I^2 = 100\%\)) compared with control. The lack of statistical significance in the diastolic blood pressure compared to control is considered due to significant heterogeneity among the included studies. Based on the available evidence, hesperidin administration has shown potential benefit in reducing systolic blood pressure. The results are depicted as forest plots in Figure 3 and Figure 4.

### Effect of Hesperidin on lipid profile

The lipid profile such as total cholesterol, total triglycerides, LDL, and HDL have a great correlation with cardiovascular health. Particularly, elevated serum levels of LDL, total cholesterol, triglycerides, and decreased HDL levels will distract cardiovascular health and are hence considered potential risk factor/s in the development of cardiovascular diseases. Administration of hesperidin shows a significant reduction in the total glycerides (TG) (IV: -0.21 (-0.40 to -0.02) at 95% CI, \(p = 0.03, I^2 = 12\%\)), however, there is no statistically significant difference in the HDL (IV: 0.04 (-0.25 to 0.34) at 95% CI, \(p = 0.78, I^2 = 56\%\)), LDL (IV: -0.10 (-0.66 to 0.45) at 95% CI, \(p = 0.72, I^2 = 85\%\)), and total cholesterol (TC) (IV: 0.18 (-0.79 to 0.44) at 95% CI, \(p = 0.57, I^2 = 88\%\)).

The results are illustrated as forest plots in Figure 5, 6, 7, and 8.

### Discussion

There are several clinical studies published on the cardiovascular benefits of hesperidin. In addition, there is a meta-analysis published by Mohamaddi et. al., 2019 has reported that hesperidin supplementation does not affect blood pressure and lipid profile (Mohamaddi et. al., 2019). However, Mohammadi et. al. have considered the studies published on both orange juice and hesperidin, and secondly, the comparisons were not solely between hesperidin vs placebo/control. Furthermore, there are two
additional randomized control trials published on hesperidin related to its cardiovascular effects after the publication of the above-cited meta-analysis. The present systematic review and meta-analysis were performed to determine the beneficial effect of hesperidin in alleviating the altered blood pressure and lipid profile among patients with cardiovascular diseases. Considering the clinical studies published up to 2021, having a comparison between hesperidin vs placebo/control.

Worldwide, there are about 1.28 billion people who have hypertension whose age is between 30–79 years. Hypertension is one of the major causes of premature death and cardiovascular disease globally. Hypertension can cause damage to the arteries cells of the inner lining. When fat enters the bloodstream through diet, it can accumulate in these damaged arteries. Eventually, the walls of the arteries become less elastic and limit the flow of blood throughout the body which leads to cerebrovascular diseases like coronary artery diseases (angina, arrhythmia, and heart attack), heart failure, transient ischemic attack, stroke, dementia, and mild cognitive impairment. As per the available literature, treatment for lowering blood pressure significantly reduces the risk of cardiovascular disease and death (WHO; 2023). Reduction of systolic blood pressure by 10 /mm Hg reduces the risk of heart failure by 28%, cardiovascular disease by 20%, stroke by 27%, coronary heart disease by 17%, and all-cause mortality by 13% (Ettehad et.al., 2016). Lifestyle modifications like quitting smoking, and tobacco, being more active, and having a healthier diet may reduce the risk of hypertension. Some patients still need medicines to lower their blood pressure. Medicines that are commonly used to treat hypertension are ACE inhibitors (Ex. enalapril and lisinopril), Calcium channel blockers (Ex. amlodipine and felodipine), Angiotensin-2 receptor blockers (ARBs) (Ex. losartan and telmisartan), and diuretics (Ex. hydrochlorothiazide and chlorthalidone) (WHO 2023). Apart from these allopathic medicines, some herbs and their supplements are also used to treat hypertension. The most commonly used herbs for the treatment of hypertension are garlic (Allium sativum), custard apple (Annona muricate), Tea (Camellia sinensis), Ajwain (Carum coticum), Carrot (Daucus carota), Flaxseed (Linum usitatissimum), Tomato (Lycopersicon esculentum), Basil (Ocimum basilicum), Pomegranate (Punica granatum), Radish (Raphanus sativus), flavonoids, polyphenols, and so on (Tabassum et.al., 2011). Hesperidin reduces blood pressure by decreasing oxidative stress through the renin–angiotensin system cascade suppression (Mas-Capdevila et.al., 2020).

Notably, this meta-analysis revealed that hesperidin administration has significantly reduced the systolic blood pressure, however, there was no statistically significant difference in the diastolic blood pressure compared with control. The lack of statistical significance in the diastolic blood pressure compared to control is considered due to significant heterogenicity among the included studies.

Numerous studies show that the increase in the levels of triglyceride (TG) and total cholesterol (TC) might affect the contraction of blood vessels in the heart, which is significantly associated with the risk of cardiovascular disease. Furthermore, increases in the level of LDL could induce arteriosclerosis due to the buildup of LDL in the intima-media of the arteries, which in turn leads to thrombocytopoiesis. As per available scientific data, HDL is inversely proportional to cardiovascular disease. Higher the HDL level, the lesser the risk of emerging cardiovascular disease. It is also believed that HDL acts by reverse cholesterol transport where HDL interacts with cells in systemic vasculature by a series of reactions and disposes of
excess cholesterol as bile salts by transferring it to the liver (Filippatos et al.). Medicines that are used to lower the lipid profile are of two types namely statins (Ex. lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, etc.) and fibrates (Ex. ciprofibrate, clofibrate, fenofibrate, etc.). Based on the available literature some of the herbs and herbal supplements can also be used for lowering lipid profile. Some of the herbs containing hypolipidemic agents are basil, ginger, dill oil, tea, grapes, and so on.

This systematic review and meta-analysis revealed that the administration of hesperidin has alleviated the triglycerides levels compared to placebo/control in the subjects with cardiovascular diseases compared. However, hesperidin administration has not elicited a beneficial effect on LDL, HDL, and total cholesterol compared to the placebo/control.

In summary, this systematic review and meta-analysis revealed that the administration of hesperidin has alleviated systolic blood pressure and triglycerides in subjects with cardiovascular diseases. However, there is no better beneficial effect of the administration of hesperidin on diastolic blood pressure, LDL, HDL, and total cholesterol compared with the placebo/control. However, the heterogenicity between the studies is considered one of the concerns for all the parameters evaluated except triglycerides. The outcome of this meta-analysis is slightly in contrast to the findings of Mohammadi et al., related to systolic blood pressure and triglycerides. The possible reasons may be firstly Mohammadi et al., have considered the studies published on both orange juice and hesperidin; secondly, in Mohammadi et al., the comparisons were not solely between hesperidin vs placebo/control, and lastly, in this meta-analysis there are two additional randomized controlled trials published on hesperidin have been included.

**Limitations**

Though there are several clinical studies published on hesperidin related to its cardiovascular benefits. In this meta-analysis, we found hesperidin is beneficial in alleviating only elevated systolic blood pressure and serum triglycerides. However, the trend shows that hesperidin has also got the potential to alleviate diastolic blood pressure and other lipid parameters, while these changes are not reflected in the summary because of the significant heterogeneity between the available studies. The possible reasons may be differences in the population included (both diseases and healthy individuals), and the available studies are conducted at different locations by different study groups with different study characteristics. There is further scope for conducting multicentric, double-blind placebo-controlled trials involving patients/subjects with underlying cardiovascular conditions.

**Conclusion**

Based on the available evidence, the present systematic review and meta-analysis suggest that hesperidin supplementation could be an adjuvant in alleviating elevated systolic blood pressure and triglycerides in patients suffering from cardiovascular diseases.

**Abbreviations**
Declarations

Conflict of interest:

Authors declare that they have no conflicts of interest.

References


Figures
Figure 1. PRISMA flow diagram

Records identified using search terms hesperidin AND cardiovascular disease OR heart AND clinical trial

PubMed (n=84), Google Scholar (n=2820)

Total articles Identified N=2905

Additional records identified through other sources (n = 1)

Duplicate records excluded (n=92)

Records after duplicates removed (n = 2813)

Number of Records screened (n = 2813)

Records excluded (N=2800) (not related to the topic=2764, Only abstracts =26, reviews =9, meta-analysis =1)

Full-text articles assessed for eligibility (n = 13)

Full-text articles excluded, with reasons (n = 4)

Studies included in quantitative synthesis (meta-analysis) (n = 9)

Figure 1

PRISMA flow diagram
Figure 2

Risk of Bias (RoB) of included studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hesperidin Mean</th>
<th>Hesperidin SD</th>
<th>Hesperidin Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haidari et al. (2015)</td>
<td>1.7</td>
<td>0.1</td>
<td>38</td>
<td>-1.5</td>
<td>0.1</td>
<td>37</td>
<td>15.0%</td>
<td>3.20 [3.15, 3.25]</td>
</tr>
<tr>
<td>Homayouni et al. (2018)</td>
<td>-2.1</td>
<td>5.7</td>
<td>31</td>
<td>0.9</td>
<td>9.3</td>
<td>29</td>
<td>10.4%</td>
<td>-3.00 [-6.93, 0.93]</td>
</tr>
<tr>
<td>Morand et al. (2011)</td>
<td>5.8</td>
<td>0.5</td>
<td>23</td>
<td>2.6</td>
<td>0.2</td>
<td>23</td>
<td>14.9%</td>
<td>3.20 [2.88, 3.42]</td>
</tr>
<tr>
<td>Rizza et al. (2011)</td>
<td>-1</td>
<td>0.1</td>
<td>24</td>
<td>-1.1</td>
<td>0.1</td>
<td>24</td>
<td>15.0%</td>
<td>0.00 [-0.66, 0.06]</td>
</tr>
<tr>
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<td>0.5</td>
<td>33</td>
<td>-2</td>
<td>0.2</td>
<td>32</td>
<td>14.9%</td>
<td>-3.00 [-3.18, -2.82]</td>
</tr>
<tr>
<td>Zahra Yari et al. (2019)</td>
<td>-1.86</td>
<td>0.1</td>
<td>25</td>
<td>0.62</td>
<td>0.06</td>
<td>24</td>
<td>15.0%</td>
<td>-2.48 [-2.53, -2.43]</td>
</tr>
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<td>-5.5</td>
<td>0.5</td>
<td>22</td>
<td>-10.2</td>
<td>1</td>
<td>22</td>
<td>14.9%</td>
<td>4.70 [4.23, 5.17]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>196</td>
<td>191</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>0.52 [-1.78, 2.83]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 9.24; Chi² = 32169.51, df = 6 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.45 (P = 0.66)

Figure 3

Effect of Hesperidin on diastolic blood pressure
Figure 4

Effect of Hesperidin on systolic blood pressure

![Graph showing the effect of Hesperidin on systolic blood pressure with study data and statistical analysis.](image)

Test for overall effect: Z = 2.49 (P = 0.01)

Figure 5

Effect of Hesperidin on low density lipoprotein

![Graph showing the effect of Hesperidin on LDL with study data and statistical analysis.](image)

Test for overall effect: Z = 0.36 (P = 0.72)

Figure 6

Effect of Hesperidin on high density lipoprotein

![Graph showing the effect of Hesperidin on HDL with study data and statistical analysis.](image)

Test for overall effect: Z = 0.28 (P = 0.78)
Figure 7

Effect of Hesperidin on total glycerides

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hesperidin</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
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<td>1.24</td>
<td>0.04</td>
<td>59</td>
</tr>
<tr>
<td>Haidari et al. (2015)</td>
<td>139.9</td>
<td>31.7</td>
<td>38</td>
</tr>
<tr>
<td>Morand et al. (2011)</td>
<td>1.3</td>
<td>0.1</td>
<td>23</td>
</tr>
<tr>
<td>Ohara et al. (2016)</td>
<td>153</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>Salden et al. (2016)</td>
<td>1.3</td>
<td>0.1</td>
<td>33</td>
</tr>
<tr>
<td>Zahra Yari et al. (2019)</td>
<td>136.41</td>
<td>72.86</td>
<td>25</td>
</tr>
<tr>
<td>Zahra Yari et al. (2020)</td>
<td>142.06</td>
<td>82</td>
<td>22</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>215</td>
<td>217</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 8.83$, df = 6 ($P = 0.34$); $I^2 = 12%$
Test for overall effect: $Z = 2.12$ ($P = 0.03$)

Figure 8

Effect of Hesperidin on total cholesterol

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hesperidin</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Demonty et al. (2010)</td>
<td>6.19</td>
<td>0.05</td>
<td>59</td>
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<td>Haidari et al. (2015)</td>
<td>186.3</td>
<td>51.3</td>
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<td>Morand et al. (2011)</td>
<td>5.8</td>
<td>0.2</td>
<td>23</td>
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<td>Ohara et al. (2016)</td>
<td>222</td>
<td>28</td>
<td>15</td>
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<td>Salden et al. (2016)</td>
<td>5.4</td>
<td>0.2</td>
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<td>Zahra Yari et al. (2019)</td>
<td>183.86</td>
<td>40.21</td>
<td>25</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>193</td>
<td>195</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 40.87$, df = 5 ($P < 0.00001$); $I^2 = 88%$
Test for overall effect: $Z = 0.56$ ($P = 0.57$)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAChecklist.doc
- Annexure1.SearchStrategyPUBMED.docx
- Annexure2.ListofExcludedstudiesbasedonfulltextscreening.doc