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Review

Effect of resveratrol on lipid profile: An updated systematic review and meta-analysis on randomized clinical trials

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ABSTRACT

Background: New studies indicate that resveratrol can significantly reduce plasma lipids, but the result of randomized clinical trials (RCTs) on resveratrol effect and the serum lipid profile are contradictory. Our objective was to conduct a systematic review and meta-analysis on RCTs assessed the effect of resveratrol on lipids.
Material and methods: PubMed, ISI Web of Science, Scopus and Google scholar data bases were searched up to Jun 2017. RCTs which assessed resveratrol effects on lipid profile among adult participants were chosen. Treatment effects were considered as weighted mean difference (WMD) and the corresponding standard error (SE) in concentrations of serum lipids. To estimate the overall summary effect, we used random-effects model. The protocol was registered with PROSPERO (No. CRD42017072365).
Result: This meta-analysis was performed on twenty-one trials. Our results indicated that resveratrol can significantly reduce total cholesterol (TC) (WMD = −0.26 mmol/L, 95% CI: −0.40, −0.12; P < 0.0001, I^2 = 93.4%), but its effects on triacylglycerol (TG) (WMD: −0.02 mmol/l, 95%CI: −0.08, 0.04; P = 0.467, I^2 = 79.4%), low-density lipoprotein (LDL-C) (WMD: 0.01 mmol/l, 95% CI: −0.15, 0.17; P = 0.898, I^2 = 94.6%), and high density lipoprotein (HDL-C) (WMD: 0.00 mmol/l, 95% CI: −0.02, 0.03; P = 0.878, I^2 = 64.2%) were non-significant. In cross-over trials, resveratrol could significantly increase HDL-C. We also found that sex, age, BMI, resveratrol dosage, and intervention duration could not change the results.
Conclusion: Resveratrol might be able to change TC and HDL-C, but for confirming the results, more studies exclusively on dyslipidemia patients and considering the intake of lipid lowering agents as exclusion criteria is necessary.

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1. Introduction

The prevalence of cardiovascular disease (CVD) is increasing all over the world. The enhancement of total cholesterol and low density lipoprotein cholesterol (LDL) are risk factors for CVD [1]. Scientists recommend following a healthy diet instead of taking medicine can reduce CVD risk factors [2–5].

Resveratrol is a natural polyphenolic compound in grapes, nuts, fruits, and vegetables [6]. Food and drug administration (FDA) has approved resveratrol as a dietary supplement, because it has multiple functions and low cytotoxicity [7]. According to the new evidence from non-human studies, resveratrol has health promoting functions such as anti-inflammatory, antioxidant, antitumor activity, and cardio protective effect [8–11]. The results of cell culture and animal studies have indicated that resveratrol can prevent CVD through the reduction of inflammation, oxidative stress, platelet aggregation, the enhancement of vaso-relaxation, and endothelial function [12–15].

Animal studies suggested that resveratrol can significantly reduce the plasma lipid profile by the enhancement of bile acid and neutral sterols excretion from liver to feces or changing in inflammatory mediators [16,17]. Therefore, scientists consider increasing the secretion of lipids out of the body as one of possible mechanisms whereby resveratrol can reduce lipid profile [18].

While resveratrol passed through gut and liver, it can be changed to resveratrol glucuronides [19]. Resveratrol also can efficiently go into the liver and metabolized into resveratrol glucuronides [20–22]. Resveratrol glucuronides can reduce cholesterol synthesis in liver, but little is known about the exact mechanism of resveratrol in liver. One in vitro article revealed that resveratrol increased the expression of cholesterol transporter protein, promoted Apo-A1 production and diminished foam cell formation through PPAR-γ and adenosine 2A receptor pathways [23].

Although there are many randomized clinical trials (RCTs) on resveratrol effects on the serum lipid profile, the results are contradictory. A few articles indicated lowering effect of resveratrol on lipids [24–27], while most of them did not indicate any effect [28–34]. Consistently, a meta-analysis in year 2013 involving seven RCTs indicated no significant effect of resveratrol on any of the lipid parameters [35]. This result might be due to in part that they considered just seven articles with low dose of resveratrol. Meanwhile, several new RCTs are available and used higher dose of resveratrol and longer duration of intervention to find resveratrol effect on lipid parameters. Whether new RCTs changed the result of previous meta-analysis is unknown.

Since, they are more than fifteen articles after year 2013 we tried to perform an update systematic review to summarize the data from RCTs exploring the effect of resveratrol on serum lipid profile and if possible to conduct a meta-analysis.

2. Material and method

2.1. Search strategy

In order to find related articles, we searched data bases including: ISI web of science, Ovid, PubMed/Medline, SCOPUS, and Google Scholar up to Jun 2017. We searched those data bases by using following MeSH and non-MeSH terms related to lipid profile and resveratrol: “Lipoproteins, LDL”, “Low Density Lipoprotein Cholesterol”, “Cholesterol LDL”, “LDL triacylglycerol”, “Triglycerides”, “Triacylglycerol”, “Triacylglycerols”, “Triglycerides”, “Lipoproteins, HDL”, “HDL Lipoproteins”, “High-Density Lipoproteins”, “High Density Lipoproteins”, “Lipoproteins, High-Density”, “Lipoproteins, VLDL”, “Cholesterol”, “Cholesterol, VLDL”, “VLDL Cholesterol”, “Very Low Density Lipoprotein Cholesterol”, “VLDL Lipoproteins”, “Very-Low-Density Lipoproteins”, “Lipoproteins, Very-Low-Density”, “Very Low Density Lipoproteins”, “Lipoproteins VLDL”, “VLDL Lipoproteins”, “Lipoproteins, VLDL”, “total cholesterol”, “TC”, “LDL”, “HDL”, “VLDL”, “TG”, “resveratrol”. Moreover, the reference lists of all retrieved RCTs were checked to find further RCTs. MH and FH separately screened titles and abstracts to find potentially relevant studies for reading the full text. We also had group discussion to solve any discrepancies. Quotation marks, parentheses, and asterisks were used to search for the exact terms, locating a group of search terms, and all the words derived from one key word respectively. We also used Boolean operators (AND and OR) for designing our search strategy. We did not restrict our search to publication time and language. The protocol was registered with PROSPERO (No. CRD42017072365).

2.2. Inclusion criteria

Trials with following criteria were considered in our meta-analysis: (i) Original articles; randomized clinical trial; (iii) Using resveratrol as a mono food supplement in intervention group; (iv) Assessed serum lipid profile as an outcome; (v) Not using other food or supplement in intervention or control group.

2.3. Exclusion criteria

After reading the full text of selected articles, we excluded trials if they had following criteria: A) Using any intervention in control group, B) Using red wine instead of resveratrol supplements, C) Using other food supplements with resveratrol, D) Not having control group, E) Having unclear data.

2.4. Data extraction

After reading title, abstract and considering inclusion and exclusion criteria eligible articles were selected. Extracted data includes: the last name of the first author, publication year, Study location, sample size in each group, patients’ characteristics such as gender, age, disease, BMI, resveratrol dose used for intervention, and treatment duration.

2.5. Statistical analysis

Treatment effects were considered as weighted mean difference (WMD) and the corresponding standard error (SE) in concentrations of serum lipids (TC, LDL-C, HDL-C and TG). To estimate the overall summary effect, we used a random-effects model suggested by DerSimonian and Laird which considers both within- and between-study heterogeneity [36]. The statistical heterogeneity was assessed using I^2 test [37], and was considered as significant heterogeneity where it was >50% [38]. To explore the heterogeneity source, subgroup analyses and meta-regression test were run. The heterogeneity between subgroups was tested using fixed effect model. Subgroup analyses were conducted by BMI (normal vs. overweight vs. obese), study design (cross-over vs. parallel), sex (male vs. female vs. both genders), the median of subjects’ age (< or ≥45 yr), the median of study duration (< or ≥8 weeks) and the median of resveratrol dosage (< or ≥275 mg). Sensitivity analysis was performed to find the effect of each specific study on the overall estimation. Publication bias was examined using funnel plots and Egger’s regression asymmetry tests.

When standard deviations (SDs) or SEs were not directly reported in studies, they were calculated using 95% CI. In addition, when studies have reported median and interquartile range, they were converted to mean and SE using available formulas. Statistical analyses were done using Stata, version 11.2 (Stata Corp.,

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