*Review*

# Effect of Resveratrol Supplementation on Inflammatory Markers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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## ABSTRACT

**Purpose:** The evidence has suggested that resveratrol has anti-inflammatory effect; however, the results are inconsistent and inconclusive. The aim of this study was to assess the effect of resveratrol supplementation on the levels of inflammatory markers through a systematic review and meta-analysis of available randomized controlled trials (RCTs).

**Methods:** A search strategy was completed using Medline, ISI Web of Science, Directory of Open Access Journal, SID, ProQuest, Cochrane Library, Scopus, and EMBASE up to May 2017, to identify placebo-controlled RCTs that assessed resveratrol effects on circulating (serum and plasma) inflammatory markers (interleukin [IL]-6, tumor necrosis factor−α [TNF-α], and high-sensitivity C-reactive protein [hs-CRP]) among adult participants aged 17 years and older in 17 RCTs with a total of 736 subjects. The evaluation of study quality was performed using the Jadad scale. Weighted mean difference (WMD) was calculated for evaluating the changes in the inflammatory markers using fixed-effects or random-effects models. We performed subgroup and sensitivity analyses to evaluate the heterogeneity of the studies.

**Findings:** Seventeen RCTs, including 736 subjects, fulfilled the eligibility criteria and were selected for analyses. The results of meta-analysis found significant reductions in the level of TNF-α (WMD, −0.44; 95% CI, −0.71 to −0.164; $P = 0.002$; Q statistic = 21.60; $I^2 = 49.1\%$; $P = 0.02$) and hs-CRP (WMD, −0.27; 95% CI, −0.5 to −0.02; $P = 0.033$; Q statistic = 26.95; $I^2 = 51.8\%$; $P = 0.013$) after supplementation with resveratrol. Resveratrol supplementation had no significant effect on the level of IL-6 (WMD, −0.16; 95% CI, −0.53 to 0.20; $P = 0.38$; Q statistic = 36.0; $I^2 = 72.3\%$; $P = 0.001$). Statistically significant heterogeneity was observed for the type of sample in IL-6 and study duration in inflammatory markers IL-6, TNF-α, and hs-CRP.

**Implications:** Available evidence from RCTs suggests that resveratrol supplementation significantly reduced TNF-α and hs-CRP levels. Significant improvement in inflammatory markers support resveratrol as an adjunct to pharmacologic management of metabolic diseases. (*Clin Ther*. 2018;■:1−18) © 2018 Elsevier Inc. All rights reserved.

**Key words:** hs-CRP, inflammation, meta-analysis, resveratrol, systematic review, TNF-α.

## INTRODUCTION

Inflammation is a series of cellular and molecular events that help to defend the body from infection.[1] The long-term consequence of a prolonged inflammation has detrimental effects and it is now well understood that its dysregulation has as major role in the pathogenesis of several diseases such as type 2 diabetes (T2D), rheumatoid arthritis, atherosclerosis, asthma and other autoimmune diseases.[1] The chronic low-grade inflammation is usually characterized by an increased abundance and activation of innate and adaptive immunity cells in tissues along with an enhanced release of inflammatory factors and chemokines locally and systemically.[2] Among various factors, tumor necrosis factor α (TNF-α) and interleukin 6

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(IL-6) are two cytokines released in large amount during inflammation and are important mediators in T2D and cardiovascular diseases.[3] These cytokines are potent inducers of C-reactive protein (CRP), an acute phase reactant mainly synthesized in the liver, which has been shown to be a strong risk factor for metabolic diseases.[4,5] According to the literature, strategies to restrain chronic inflammation may be effective in treating chronic diseases.[6] In this context, natural products have been documented to reduce systemic low-grade inflammation and are acknowledged as anti-inflammatory interventions.

Resveratrol (3,5,4′-trihydroxy-trans-stilbene), a natural polyphenol with potential health benefits, is generally contained in grapes, peanuts, berries and polygonum cuspidatum.[7] Resveratrol was shown to exert anti-aging activity mimicking some of the molecular and functional effects of caloric restriction.[8] Resveratrol was demonstrated to prevent and treat chronic conditions including cardiovascular disease (CVD), T2D and neurodegenerative disorders.[9,10] The evidence demonstrate that the beneficial effect of resveratrol on health is mediated through its antioxidant, anti-inflammatory, cardioprotective, and neuroprotective activities.[9] Studies using cultured cells, and laboratory animals have also suggested that resveratrol has an anti-inflammatory property.[8] Resveratrol downregulates inflammatory reactions via inhibition of the synthesis of pro-inflammatory mediators, and modification of immune cells through the inhibitory effect on activator protein-1 (AP-1) and NF-$\kappa$B and regulation of mitogen-activated protein kinases/hemeoxygenase-1 pathway, and the mediation of pro-inflammatory cytokines and reactive oxygen species formation.[7,11] In addition to in vitro and animal studies, randomized clinical trial (RCT) studies have also provided the evidence that resveratrol might reduce inflammatory markers in different clinical conditions.[12,13] However, the evidence for the effects of resveratrol on the levels of inflammatory markers is inconsistent and inconclusive. Therefore, here we performed a systematic review and meta-analysis study to assess the effectiveness of resveratrol consumption on the levels of inflammatory markers (hsCRP, TNF-$\alpha$, and IL-6) by searching different bibliographic databases for published RCTs. The meta-analysis was conducted in accordance with the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[14]

## MATERIAL AND METHODS

### Search strategy

We searched PubMed-Medline, Scopus, ScienceDirect, ISI, google scholar, DOAJ (Directory of Open Access Journal), SID ProQuest, Cochrane Library, and EMBASE up to May 2017. We used Mesh databases and the following search queries: ((resveratrol [supplementary concept] OR resveratrol [Title/Abstract]) AND (inflammatory markers [Mesh terms] OR inflammation [Title/Abstract] OR cytokines [Title/abstract].

### Study selection: Inclusion/Exclusion criteria

Original studies were included if they met the following criteria:1) randomized clinical trials with or without concurrent medications, 2) English language, 3) represented the relationship between the consumption of purified resveratrol or resveratrol-enriched extracts with changes of the circulating inflammatory markers, 4) presented sufficient information [standard deviations (SDs), standard error (SE), or 95% CIs] on inflammatory marker levels at the baseline and at the end of the study in both resveratrol and control groups, 5) randomized clinical trials (parallel or cross-over), 6) the studies with an appropriate controlled design, 7) subjected ingested resveratrol supplementation for at least one month and maximum 12 months and 8) participants with the age $\geq$17 years. The following studies were excluded: 1) non-clinical studies, 2) studies without control or placebo groups, 3) lack of sufficient information on inflammatory markers concentrations at the baseline or at the end of the follow-up, and 4) inability to obtain the adequate details of study methodology.

### Data extraction

Two authors extracted the data independently using a standardized electronic form. The extracted data included the following: 1) first author's name; 2) origin country; 3) year of publication; 4) study population; 5) study design; 6) dose of resveratrol; 7) treatment duration; 8) age $\geq$17 and gender (male/female) of the participants; 9) type of resveratrol; 10) total number of subjects in intervention and placebo groups; 11) mean and standard deviation of circulating (serum/plasma) inflammatory markers (IL-6, TNF-$\alpha$ and hsCRP) in both the intervention and placebo groups at the baseline and at end of study (**Tables I and II**). The rationale for selecting IL-6, TNF-$\alpha$ and hsCRP as the inflammatory markers in this study is based on considerable