



## Review

# Effect of resveratrol on cognitive and memory performance and mood: A meta-analysis of 225 patients



Mohammad Hosein Farzaei<sup>a,b</sup>, Roja Rahimi<sup>c,d</sup>, Shekoufeh Nikfar<sup>d,e</sup>,  
Mohammad Abdollahi<sup>f,g,\*</sup>

<sup>a</sup> Pharmaceutical Sciences Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>b</sup> Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>c</sup> Department of Traditional Pharmacy, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>d</sup> Evidence-Based Medicine Group, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>e</sup> Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

<sup>f</sup> Toxicology and Diseases Group, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>g</sup> Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

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## ABSTRACT

Resveratrol is a natural dietary phenolic compound which is extensively present in many edible fruits, including grape, berries, pomegranates, and peanuts. Resveratrol has a broad spectrum of biological activities including anti-aging, chemopreventive, anti-carcinogenic, anti-inflammatory and antioxidant effects and thus it is effective in related diseases. Particularly, the positive effects of resveratrol in neuropsychological diseases have been proven in in-vitro and in-vivo studies. Some clinical trials have reported that resveratrol possesses preventive and therapeutic effects in cognitive disorders. Therefore, the current systematic review and meta-analysis aimed to assess the effects of resveratrol on cognition and memory performance as well as mood state. Electronic databases including Scopus, PubMed, Science Direct, and Cochrane library were searched with the keywords “Memory”, “Cognitive”, “Cognition” or “Mood” with “Resveratrol” until June 2017. Only clinical studies were included in this review. We have provided the most reliable evidence to date counting results obtained from 226 individuals from four randomized clinical trials evaluating the mentioned specific effects of resveratrol. The results of this meta-analysis showed that resveratrol has no significant effect on memory and cognitive performance assessed by auditory verbal learning tests. Two parameters of Profile of Mood States (POMS) including vigor and fatigue, decreased significantly by resveratrol. However, decrease in other parameters of POMS including tense/anxiety, depression, anger, and confusion by resveratrol was not significant.

The key findings from this meta-analysis are that resveratrol has no significant impact on factors related to memory and cognitive performance, including learning ability, delayed recall, retention, and recognition with all effect sizes non-significant and effectively at zero. However, it has the potential to enhance mood. Further randomized, controlled trials are needed to achieve more conclusive results.

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\* Corresponding author at: Toxicology and Diseases Group, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran. Tel.: +982164122319.

E-mail address: [mohammad@tums.ac.ir](mailto:mohammad@tums.ac.ir) (M. Abdollahi).

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## 1. Introduction

Aging is a natural process that comes with several chronic diseases and disabilities. Most of existing reports address the role of mitochondria in the progression of aging and neurodegenerative illnesses. This process is mediated through production of extra reactive oxygen species that leads to oxidative stress and a progressive apoptosis and cell death [1]. Neurodegeneration is one of the early consequences of aging that reflects itself as brain dysfunctions such as dementia [2]. Despite a wide range of efforts for developing therapeutic approaches, no curative treatment for cognitive decline and dementia currently exists [1]. The increase of life expectancy over the last century is associated with an enhanced number of individuals with cognitive impairment, that results in a massive social and economic burden on healthcare systems as well as society [3]. Statistic shows that approximately 47 million people worldwide suffer from dementia and this number is predictable to become double every 20 reaching about 132 million by 2050 [4].

Phytoalexins are stress-induced metabolites that are produced in response to pathogen attacks and have a specific role in the plant defense. Resveratrol (3,5,4'-trihydroxy-trans-stilbene), is a natural phytoalexin from the stilbenes subgroup [5,6]. Resveratrol oligomers are the largest group of oligomeric stilbenes. In terms of chemical structure, resveratrol comprises a double bond that may undergo *cis* or *trans* isomerization, with two phenolic rings positioned on each end of the double bond [5–8]. Resveratrol is a natural dietary phenolic compound which is extensively present in many edible fruits, including grape skin, blueberries, cranberries, bilberries, lingonberries, partridgeberries, pomegranates, mulberries, peanuts, *Polygonum cuspidatum* (Sieb. & Zucc.) (family, Polygonaceae), and strawberries [5–7]. Among human dietary sources, red wine represents a remarkable amount of resveratrol. The concentration of resveratrol in red wine ranging from 0.4 to 57  $\mu$ M depends on the geographic origin and its type [6,8]. Natural phytoalexin may be helpful in the management of some age and oxidative stress related disorders [9,10]. Generally, polyphenols such as resveratrol have limitations of kinetics if used in human like rapid metabolism and elimination, and thus scientists try to find better formulations for such products. In this regard, some studies have been conducted to improve bioavailability of resveratrol and its products [9,11]. These investigations are commonly according to suppression of cytochrome P450 (CYPs) by means of specific inhibitors, encapsulations, and structure modifications [11,12]. This natural dietary supplement possesses the ability to cross the blood-brain barrier indicating the potential to perform the therapeutic effect on brain tissue [13]. Like other phenolic compounds, resveratrol is frequently recognized for its antioxidant function, and it has been found to alleviate human oxidative damage associated disorders as well as

degenerative diseases [13–15]. In an animal study, chronic injections of trans-resveratrol showed a significant improvement of spatial memory in the Morris water maze test, particularly in animals with streptozotocin (STZ)-induced cognitive impairment. This natural phytoalexin is also able to prevent the pathological condition result in hippocampal neurodegeneration and cognitive impairment in rodent model of neurodegeneration [15,16]. In a primate study, 18 months intake of resveratrol as dietary supplementation could significantly increase cognition and memory performance [17]. Current studies suggest that resveratrol is one of the most promising molecules for treatment of cognitive diseases. In this regard, various neuropharmacological studies revealed several intracellular targets for resveratrol in related diseases [5,13,15,17]. Likewise, some clinical trials have investigated the efficacy of resveratrol in the enhancement of cognitive and memory performance and concluded that resveratrol preparations were effective [18,19]. Contrarily, some investigations reported no efficacy of resveratrol in the improvement of cognition and memory [20,21]. Thus, present review and meta-analysis was conducted to determine the efficacy of resveratrol in cognitive and memory performance as well as mood using data from available clinical trials.

## 2. Methods

### 2.1. Data sources and searches

A literature search was conducted on the electronic databases of Scopus, Pubmed, Science Direct, and Cochrane Central Register of Controlled Trials. The search was carried out without time restriction from 1966 to June 2017 using following search strings in the title/abstract/keywords: "Memory AND Resveratrol, Cognitive AND Resveratrol, Cognition AND Resveratrol, Mood AND Resveratrol". All the relevant papers were included, irrespective of when and where they were conducted and whether they are full text and clinical trials. The reference lists from earlier published review articles and the retrieved papers were manually reviewed for additional applicable studies. The initial search results were recorded for investigating whether they can be included in meta-analysis. An initial assessment was performed by two authors independently, based on the title and abstract of the articles to examine the potential of inclusion in the meta-analysis of each article. The duplicate articles and irrelevant papers were found and excluded. The review articles and the non-human (*in vitro* and animal) studies were also excluded. Studies that examined the effect of resveratrol on the other characteristics of neurological disorders and also those assessing the effect of other therapeutic compounds on the cognitive performance were excluded. Included articles were the randomized controlled clinical trials examining the effect of

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