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# Resveratrol has not been proven its enhancement of the physical activity among users: A systematic review and meta-analysis study

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ABSTRACT

Current evidence of resveratrol on physical activity were summarized using a systematic review and meta-analysis approach. Fourteen randomized controlled trials met the eligibility criteria. All included studies enrolled a few subjects. Five studies with 139 participants measured the same outcome and then were pooled using the meta-analysis program. The mean change between pre- and post-test when compared resveratrol to control on the peak oxygen uptake outcome is 0.30 mL/kg/min (−2.49 to 3.09). This meta-analysis results showed that resveratrol slightly increases a surrogate outcome of physical activity. However, the increment was not achieved minimally clinical significance of at least 2 mL/kg/min. In summary, resveratrol slightly improves one indicator of physical activity, but did not demonstrate statistical and clinical significances. However, these combined results were drawn out from multiple studies with small participants. Therefore, rigorous efficacy trials in large subjects are still warranted to ensure the effect of resveratrol on physical activity.

## 1. Introduction

In general, physical activity refers to movement that enhances health (National Institutes of Health, 2016). Any body movement operated by skeletal muscles requiring energy expenditure is also a definition (World Health Organizition, 2017a). Appropriate intensity of routine physical activity; for example, walking, jogging, swimming, or sport participation has significant health benefits. It can help reduce the risk of chronic diseases, colon cancer, and depression. On the other hand, physical inactivity or lack of physical activity has been estimated as the fourth leading risk factor for global mortality of 3.2 million deaths globally by the World Health Organization (WHO). It is estimated to be the main cause for approximately a quarter of colon cancer cases and one-third of both diabetes and ischemic heart disease cases (World Health Organizition, 2017a). The main cause of physical inactivity is sedentary lifestyle, which is very common in the modern world. Junk food consumption is also a leading cause (World Health Organizition, 2017b). We all know that physical activity is essential for daily living. However, some people such as healthy elderly and the bedridden may have difficulty in performing physical activity (McPhee et al., 2016). Researchers are continually seeking a harmless substance that can help to improve physical activity in those with a sedentary lifestyle (Smoliga, Colombo, & Campen, 2013).

In France, one element may have been found. The incidence rate of cardiovascular disease was substantially lower than in the United States and other countries in Europe because of French people routinely consuming red wine. This is known as the French paradox (Baur & Sinclair, 2006). In 1990, researchers found red wine rich in resveratrol that has a potent antioxidant property. Therefore, resveratrol, discovered in 1939 by a Japanese scientist, has been increasingly used to manage conditions or diseases (Catalgol, Batirel, Taga, & Ozer, 2012). The first isolation of pure resveratrol was from the roots of White Hellebore (*Veratrum album* L.) via enzymatic hydrolysis and fermentation isolation technique in 1940 (Baur & Sinclair, 2006), and subsequently identified in various sources. Recently, this compound has become of increasing interest in medical research. (Feng, Zhou, & Jiang, 2016; Liu, Zhou, Wang, & Mi, 2014; Y. Liu, Ma, Zhang, He, & Huang, 2015; Sahebkar, 2013) Resveratrol is a stilbenoid, a type of natural phenol (i.e., eugenol, capsaicin, or cannabinoids), and a phytoalexin produced by several plants in response to injury or, when the plant is under attack by pathogens such as bacteria (*Xylella fastidiosa*) or fungi (*Guignardia bidwellii*). Sources of resveratrol in plants include the skin of grapes (*Vitis vinifera* L.), blueberries (*Vaccinium* spp.), raspberries (*Rubus* spp.) and mulberries (*Morus* spp.). Presently, it is available as a

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dietary supplement (Kuršvietienė, Stanevičienė, Mongirdienė, & Bernatonienė, 2016).

The mechanism of resveratrol provides a wide range of beneficial effects on physical activity. Resveratrol induces expression of genes for oxidative phosphorylation and mitochondrial biogenesis. This was largely explained by resveratrol-mediated decrease in proliferator-activated receptor γ coactivator-1α (PGC-1α) acetylation and then, the increase in PGC-1α activity resulted in increased energy expenditure (Davinelli, Sapere, Visentin, Zella, & Scapagnini, 2013). It is also known as the activator of the protein deacetylase, sirtuin 1 (silent mating type information regulation 2 homologs) (SIRT1) as a key regulator of energy and metabolic homeostasis. Since it was reported that SIRT1 is required for increasing physical activity (Chen et al., 2005; Markus & Morris, 2008).

Previous systematic review and meta-analysis studies have been conducted in hypertension (Y. Liu et al., 2015), diabetes (K. Liu et al., 2014), lung cancer (Feng et al., 2016), and dyslipidemia (Sahebkar, 2013). However, little is known regarding the efficacy of resveratrol on physical activity in humans. Using systematic review to summarize clinical evidence of intervention of interest has been considered as one tool to get the overall and inside information from relevant clinical trials. Therefore, this study aims to determine the efficacy of resveratrol on physical activity using systematic review with meta-analysis approach.

## 2. Methods

### 2.1. Data sources and searching strategy

The following databases were systematically searched: Medline, Embase, Google Scholar, and Google search engine. In addition, clinical trial registry (www.clinicaltrial.gov) was used for searching. Databases were searched from the inception until September 21, 2017. For the search strategy, we used the keywords that infer to the substance intervention and outcome of interest as follows: “resveratrol,” “phytoalexin,” “physical activity,” and “exercise.” References that identified full-text articles were examined to identify additional studies that met the selection criteria. This review was signed up and received the registration number of CRD42017076708 in the international prospective register of systematic reviews (PROSPERO) (Centre for Reviews and Dissemination, n.d.).

### 2.2. Study inclusion criteria

The inclusion criteria were studies that: one, randomized controlled clinical trial in human subjects; and two, compared intervention of resveratrol or resveratrol-containing products with placebo or other comparators. There was no language and study design restriction for first round screening on title and abstract. Studies that were not original articles such as comments, letters, reviews, meta-analyses, guideline, case reports, surveys or editorials were excluded. Studies from the same population (duplicate studies), studies not reporting or obtaining effect estimates or with insufficient information to compute effect estimates were also excluded. In the second round, we used strict inclusion criteria for eligible full-text articles as follows: one, study outcomes must have the measurement of physical activity to include walking speed, lower extremity function, exercise capacity, skeletal muscle strength, self-assessed physical function, and skeletal muscle mitochondrial function based on the protocol recommended by the previous study (Layne et al., 2017); two, non-English language was also excluded at this step.

### 2.3. Quality assessment of included study

Screening for eligibility of all retrieved records from searching and decision making on studies or clinical trials to be included were performed by four independent reviewers (Chainarong Srilacorn, Apisada Choosathan, Siriporn Seesuthok, and Somsak Kongna) according to the inclusion and exclusion criteria. Two sets of two authors independently scanned the titles and abstracts to get the eligible randomized controlled trials (RCTs). When abstracts with insufficient information were found, the full text was retrieved and reviewed for eligibility. The discrepancies between two reviewers were consulted for final decision from the third person reviewer (Surachai Kotirum) when necessary. The methodological quality of each included clinical trial were appraised by five reviewers (CS, AC, SS, SO and SK) using a scale score (Jadad et al., 1996) and risk of bias criteria (Higgins et al., 2011). Disagreements in quality of studies were resolved by discussion among the reviewers. Items for methodology evaluation include randomization, blinding, and description of dropouts. We performed this study according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009)

### 2.4. Data extraction and summarizing study results

A data extraction form was constructed based on the PICO (participants, intervention, comparator, and outcome) principle (Moher et al., 2009) to extract data from all eligible full-texts. All authors extracted the relevant characteristics and data related to meta-analysis such as country of study, the health status of participants, and resveratrol regimen. The results from each study on physical activity measurement were extracted into the form of aggregated mean and standard deviation data.

### 2.5. Meta-analysis

Numerical data from all studies that can be pooled in a meta-analysis to determine the overall effect size with 95% confidence interval (95% CI) will be performed using weighted mean difference (WMD). In case of baseline imbalance, the difference of changes from baseline of the outcome variables between intervention and comparator arms were pooled instead. Subgroup analyses will also be used to get more information on the intervention’s effect size. Statistical heterogeneity between studies was assessed using the chi-squared test and $I^2$. A $p$-value of 0.10 or less indicated heterogeneity between studies. $I^2$ values < 50% denoted no or minimal heterogeneity across studies. The random effects model was employed. Meta-analyses were conducted using the computer program entitled Review Manager version 5.3 (Copenhagen, Denmark: The Cochrane Collaboration, 2014). A publication bias was assessed using a funnel plot method; asymmetrical shape indicated an existence of publication bias.

## 3. Results

### 3.1. Study selection

Our search yielded a total of 1,210 potential article while 1,191 studies were excluded because they were not RCT (Fig. 1). Nineteen full-text articles were obtained for further assessment against inclusion criteria and found that five articles were also excluded based on these reasons: one article is in native Arabic language (Malekyian Fini, Shavandi, & Saremi, 2013), one article is the abstract for a conference without full text provided (Avila, Diaz, Coeckelberghs, Vanhees, & Cornelissen, 2004), three articles are not measured physical activity outcome (Macedo, Vieira, Marin, & Otton, 2015; McAnulty et al., 2013; Silva-e-Oliveira, Ferrão, Damasceno, & Furtado, 2016). Finally, we included a total of fourteen studies involving 373 participants in our analysis.