

Original Article



The Effect of Pycnogenol Supplementation on Plasma C-Reactive Protein Concentration: a Systematic Review and Meta-Analysis

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ABSTRACT

Pycnogenol is a standardized extract from the bark of the French maritime pine. The aim of the present systematic review and meta-analysis was to clarify the effect of Pycnogenol supplementation on C-reactive protein (CRP) concentration. To identify eligible studies in order to find clinical trials which examined the effect of Pycnogenol supplementation on the level of CRP in adult participants, PubMed, Scopus, and Google Scholar were systematically searched until December 2017. Mean of CRP was collected to estimate the effect size of the supplementation. Potential sources of heterogeneity were explored by subgroup analysis. Five trials including 324 participants were included in this meta-analysis. Pooled effect size showed significant effect of Pycnogenol supplementation on CRP (-1.22 mg/dL, 95% confidence interval, -2.43 , -0.003 ; $I^2 = 99\%$, $p_{\text{heterogeneity}} < 0.001$). When the meta-analysis was subgrouped by dose of Pycnogenol, heterogeneity was attenuated in > 150 mg/d category ($I^2 = 0.0\%$, $p = 0.42$). There was significant difference between-subgroup heterogeneity ($p < 0.001$). Furthermore, no evidence of publication bias for CRP ($p = 0.27$, Begg's test and $p = 0.62$, Egger's test) was seen. Present systematic review and meta-analysis suggested Pycnogenol consumption can decrease the level of CRP and have anti-inflammatory effect. So, Pycnogenol as an anti-inflammatory agent might be a priority in interventions. Further studies with large-scale and better design are needed to confirm this result.

Keywords: Pycnogenols; C-reactive protein; Inflammation; Meta-analysis

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Conflict of Interest

The authors declare that they have no competing interests.

INTRODUCTION

Recently there has been growing attention on the use of nutritional supplements, which have become an inseparable part of people's lifestyle worldwide [1]. These supplements are consumed to compensate for nutritional deficiencies or to treat in various diseases [2].

Pycnogenol as a standardized extract from the bark of the French maritime pine (*Pinus pinaster* Aiton subsp. *Atlantica*), is one of the most famous herbal dietary supplements with antioxidant and anti-inflammatory effects [3,4]. In the American and European traditional medicine, the use of the non-standardized extract was common as an anti-inflammatory agent to alleviate the symptoms of scurvy [5,6]. Pycnogenol contains 2 types of flavonoids [4]: polymeric flavonoids (65% ± 75%), such as procyanidins, catechins and epicatechins, and varying change in length and the others with less quantities are monomeric flavonoids, such as gallic acid, caffeic acid, and ferulic acid [4]. The presence of these compounds in the Pycnogenol structure caused the antioxidant and anti-inflammatory effects of this supplement [3]. The antioxidant effects of Pycnogenol include scavenging of free radicals, metal chelation, and activation of lipid peroxidation-preventing enzymes [3,7,8].

Inflammation is a response to conditions such as infection and tissue injury [9]. It causes elevation in the level of inflammatory factors such as C-reactive protein (CRP) [10]. CRP is a positive acute-phase protein, whose plasma concentration increases in response to inflammation, and is related to the risk of serious diseases including cardiovascular events, and myocardial infarction and stroke [11]. The increase in CRP level occurs due to the elevation in proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) [12]. The direct effects of CRP on nuclear factor-kappa B (NF-κB) activation are already determined. In addition, most inflammatory responses depend to NF-κB activation [13].

Some pioneering studies demonstrated that Pycnogenol supplementation can down-regulate the NF-κB pathway and reduce the production of the proinflammatory cytokines TNF-α and IL-1β [14]. Other studies have shown that Pycnogenol extracts have desirable effects in lowering fasting plasma glucose [15], lipids profile [16], and antioxidant levels [17]. It has also been proved that Pycnogenol has inhibitory effects on cyclooxygenases (COX-1 and COX-2) [18]. Controversial results due to Pycnogenol consumption on CRP levels were reported recently [19]. Because of this disagreement, in this meta-analysis, we examined the clinical evidence for the effect of Pycnogenol supplementation on CRP levels among adult subjects of both sexes to evaluate the anti-inflammatory effect of Pycnogenol. CRP was chosen because it's a systematic inflammation indicator and is an important risk factor that associated with chronic disorders [20].

MATERIALS AND METHODS

Search strategy

This study designed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. Four following databases were systematically searched from their earliest online available date up November 30, 2017: MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed>), Scopus (<http://www.scopus.com>), Google Scholar (<http://scholar.google.com>), and Web of Science (<http://www.webofscience.com>). The one-handed

search methodology was performed to achieve all potential studies based on pre-defined search keywords (Pine bark extract or PBE or Pycnogenol or French maritime) without any restrictions for language and time. In order to increase the search accuracy, the wild-card term “*” was applied. In addition, to collect further relevant papers we searched trials registers platform, specifically ClinicalTrials.gov website, and hand-scanned the reference lists of all selected articles or any identified review studies.

Study selection

After the exclusion of duplicate publications in the first screening, 2 investigators (MP and ON) separately appraised the titles and abstracts of all records to identify eligible studies. In cases where the abstract of an article was not sufficient for the investigators to decide its relevance, the full texts of the selected papers were carefully reviewed to determine eligible manuscripts. Any disagreement on the selection was settled by face-to-face discussion between the 2 investigators until a consensus was reached. Finally, all trials that investigated the efficacy of Pycnogenol supplements on CRP level were included in this systematic review and meta-analysis. Exclusion criteria were as follows: 1) studies that investigated only a specific content of Pycnogenol instead of the whole substance; 2) Pycnogenol was part of a multi-herbal treatment; 3) studies which lacked a suitable control group; 4) trials involving subjects aged less than 18 years; and 5) publications with no available full-text and no response from the corresponding author.

Data extraction and assessment of quality

The full text of eligible studies were scrutinized by 2 independent authors (MP and ON) and the following information was extracted using a pre-designed data collection form: 1) the first author's last name, country, and year of publication; 2) number, sex, and mean age of the study participants; 3) study design; 4) duration of treatment; 5) method of administration in the comparison arm; 6) type of intervention in the active arm; 7) doses of Pycnogenol administered; 8) note about subjects; and 9) main outcomes.

The methodological quality of included publications in this systematic review was ascertained by using the quantitative 5-point Jadad scale [22]. This validated checklist incorporates the following 3 major parts: randomization concealment (0–2 points), blinding (0–2 points), and dropout rate (0–1 point). Based on the responses to these items, studies with Jadad score equal or greater than 3 were regarded as high quality. Otherwise, the paper was considered low quality. There was little disagreement between the 2 assessors over data extraction and quality assessment, which these discrepancies were resolved by a senior author (HM).

Statistical analysis

Effect size was assessed by the following formula:

$$\begin{aligned} \text{Effect size} = & [(\text{post-intervention value in the treatment group} \\ & - (\text{pre-intervention value in the treatment group})] \\ & - [(\text{post-intervention value in the control group}) \\ & - (\text{pre-intervention value in the control group})] \end{aligned}$$

To calculate pooled effect size for CRP, we used random effects model. Between-study heterogeneity was evaluated using I-square (I^2) test. A significance level of $I^2 > 40\%$ was considered as clinically important heterogeneity [23]. To find the potential sources of between-study heterogeneity, we carried out a pre-planned subgroup analysis based on

dose of Pycnogenol, mean age of participants, study duration and participants' condition. Heterogeneity between subgroups was evaluated using fixed-effect model. We used Begg's rank correlation test and Egger's regression asymmetry test to evaluate publication bias. Statistical analysis was performed using STATA 11.2 software (StataCorp, College Station, TX, USA). The p values < 0.05 were considered statistically significant.

RESULTS

Included studies

Of 1,306 articles identified from PubMed and EMBASE, 1,277 papers were excluded because of duplication, obvious irrelevance, and the inconsistency in the inclusion criteria. Twenty-four articles were excluded after full-text evaluation (no implied outcome [n = 13], uncontrolled design [n = 2], use of a mixture of Pycnogenol with other substances [n = 7], and animal studies [n = 2]). Finally, 5 randomized controlled trials (RCTs) [16,17,24-27] met all the inclusion and exclusion criteria. The study identification and selection process are illustrated in **Figure 1**.

Study characteristics

Characteristics of the eligible studies are summarized in **Table 1**. A total of 324 subjects were included in the analysis. Publication dates of articles ranged from 2008 to 2017. The trial designs were parallel in 4 studies [16,17,24,25] and was cross-over in 1 [19]. The follow-

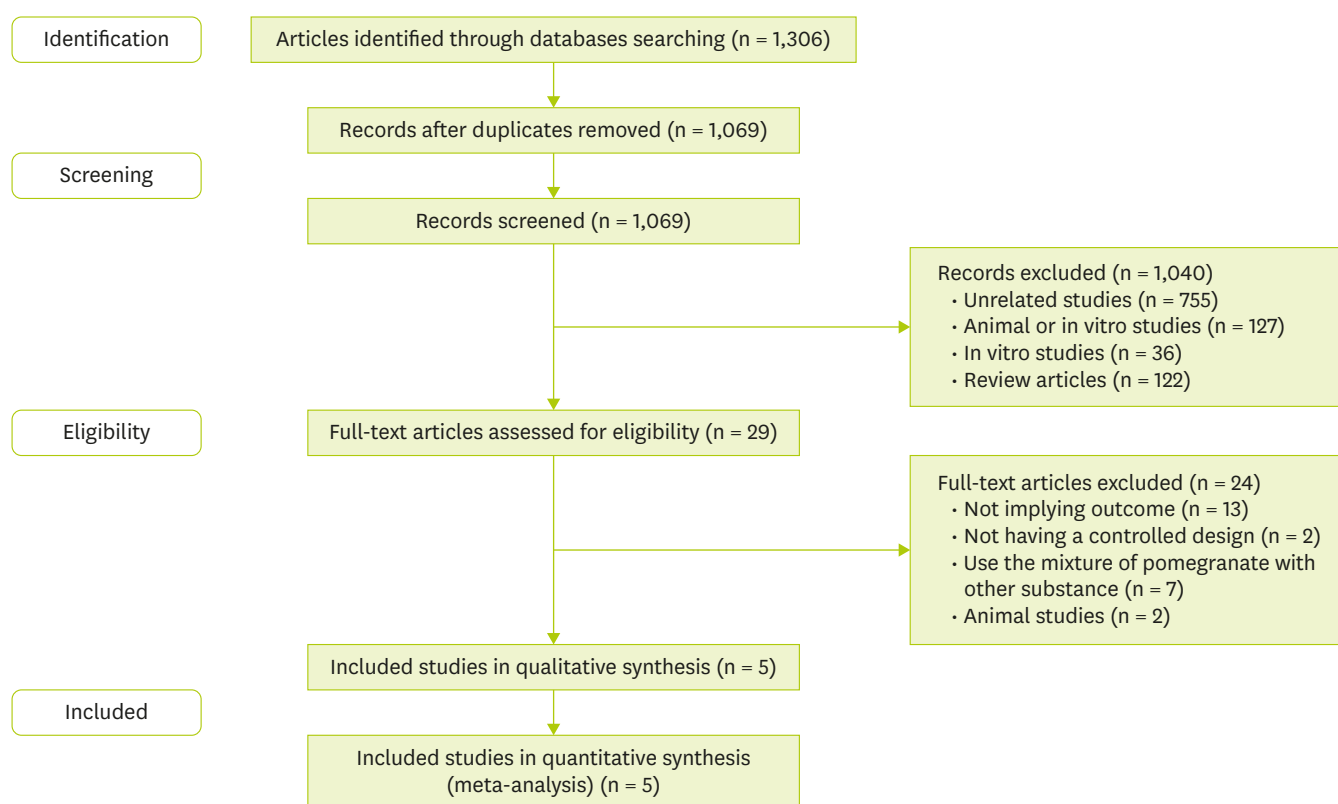


Figure 1. PRISMA flow diagram of study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Data extraction of selected studies

First author (publication year)	Country	Number and gender (male/female)	Mean age, yr	Clinical Trial design/ randomized/ blinding	Duration	Comparison group	Intervention group	Pycnogenol dosage, mg/day	Jadad score	Notes about participants	Results
Luzzi (2017) [16]	Italy	70 (female)	44.0	Parallel/ns/ns	6 mon	Menopausal best management	Menopausal best management + Pycnogenol	100	1	Healthy peri-menopausal women	CRP ↓
Belcaro (2008) [17]	Germany	55 (both gender)	51.7	Parallel/randomized/ doubled blinded	3 mon	placebo	Pycnogenol tablets	100	5	Osteoarthritis	CRP ↓
Enseleit (2012) [19]	Switzerland	23 (both gender)	63.1	cross-over/ randomized/double blinded	8 wk	Placebo or vice versa	Pycnogenol	200	5	Coronary artery disease	CRP ↔
Drieling (2010) [25]	USA	121 (both gender)	55.4	Parallel/randomized/ double blind	12 wk	Placebo	Pycnogenol	200	5	Individuals with increased CVD risk	CRP ↔
Cesarone (2010) [24]	Italy	55 (both gender)	53.5	Parallel/ns/ns	6 mon	10 mg ramipril	Ramipril plus Pycnogenol	150	1	Hypertensive participants, symptomatic for CVD	CRP ↓

ns, not significant; CVD, cardiovascular disease; CRP, C-reactive protein.

Table 2. Risk of bias assessment of included studies

Author (Year)	Randomization	Methodology of randomization	Blinding	Methodology of blinding	Withdrawal of participants	Overall score
Luzzi (2017)	-	-	-	-	-	1
Belcaro (2008)	*	*	*	*	*	5
Enseleit (2012)	*	*	*	*	*	5
Drieling (2010)	*	*	*	*	*	5
Cesarone (2010)	-	-	-	-	*	1

up ranged from 8 weeks to 6 months. Selected studies were conducted in perimenopausal women [16], subjects with hypertension [24], osteoarthritis [17], coronary artery disease [19], and individuals with increased cardiovascular disease (CVD) risk [25]. The summary of the quality assessment of each study is presented in **Table 2**. The control groups of 3 were randomized by a blinding method. Two studies did not used a randomized controlled design. Most of the studies had a few dropouts. Therefore, 3 trials earned a scores of 5 and were considered of as a high quality, whereas 2 studies received a score of 1 and were considered to be of low quality. Two studies investigated Pycnogenol at a dose of 100 mg/d, one study investigated Pycnogenol at a dose of 150 mg/d, and 2 studies investigated Pycnogenol at a dose of 200 mg/d. In 4 studies administered Pycnogenol tablets at a dose of 50 mg to achieve the final dose, whereas in one study, Pycnogenol was administered as a single dose of 300 mg and repeated doses of 200 mg [19].

Effect of Pycnogenol supplementation on CRP

Pooled effect size showed significant effects of Pycnogenol supplements on CRP (-1.22 mg/dL, 95% confidence interval [CI], -2.43, -0.003) (**Figure 2**). Due to a significant heterogeneity between studies ($I^2 = 99\%$, $p < 0.001$), subgroup analyses were performed based on the dose of Pycnogenol (> 150 mg/d vs. ≤ 150 mg/d), mean age of participants (> 55 years vs. ≤ 55 years), study duration (> 12 weeks vs. ≤ 12 weeks), and participants' condition (with CVD vs. without CVD; **Table 3**). When the meta-analysis was subgrouped by the dose of Pycnogenol (**Figure 2**), heterogeneity was attenuated in the > 150 mg/d category (-0.094 mg/dL, 95% CI, -0.19, 0.009; $I^2 = 0.0\%$, $p = 0.42$). There was significant heterogeneity between the subgroups ($p < 0.001$) and no evidence of publication bias among the studies examining the effect of Pycnogenol on CRP ($p = 0.27$, Begg's test and $p = 0.62$, Egger's test).

Table 3. Subgroup analysis to assess the effect of Pycnogenol consumption on serum hs-CRP

Categories	Subgroups (number of effect size in each subgroup)	Effect size*	95% CI	I-squared (%)	p for heterogeneity	p for between subgroup heterogeneity
Dose, mg/d	> 150 (2)	-0.094	-0.198, 0.009	0.0	0.424	< 0.001
	≤ 150 (3)	-1.816	-2.809, -0.824	96.8	< 0.001	< 0.001
Duration, wk	> 12 (2)	-1.419	-2.624, -0.214	96.1	< 0.001	< 0.001
	≤ 12 (3)	-1.076	-3.041, 0.888	99.3	< 0.001	< 0.001
Age, yr	> 55 (2)	-0.094	-0.198, 0.009	0.0	0.424	< 0.001
	≤ 55 (3)	-1.816	-2.809, -0.824	96.8	< 0.001	< 0.001
Participants' condition	With CVD (3)	-0.435	-1.013, 0.144	85.8	0.001	< 0.001
	Without CVD (2)	-2.321	-2.879, -1.762	86.9	0.006	< 0.001

CVD, cardiovascular disease; CI, confidence interval; hs-CRP, high sensitivity C-reactive protein.

*Calculated by random effects model.

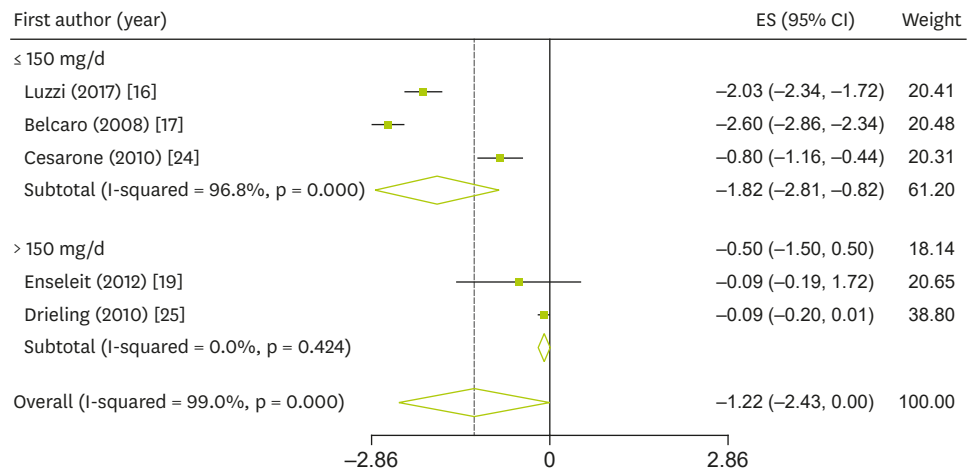


Figure 2. Forest plot of the effect of Pycnogenol supplementation on C-reactive protein. ES, effect size; CI, confidence interval.

DISCUSSION

To our knowledge, the present meta-analysis is the first to assess the effect of Pycnogenol on CRP concentration. Results obtained from RCTs in this meta-analysis showed that Pycnogenol had a significant effect on lowering CRP concentration. However, due to high heterogeneity, these results should be interpreted with caution. The subgroup analysis also revealed that the heterogeneity was attenuated in the > 150 mg/d and > 55 years subgroups.

CRP is known as a valuable marker for the identification and evaluation of disease progression or the efficacy of treatment among clinicians. The mechanism underlying Pycnogenol effect for management of CRP levels is unknown. It seems to be related with the modulation of other proinflammatory factors and proinflammatory cytokines.

Activation of the transcription factor NF- κ B significantly increased the production and release of proinflammatory cytokines including IL-1 β , IL-6, and TNF- α . Particularly, it can be said that the most proinflammatory genes expression are dependent on NF- κ B activation [26]. The active form of NF- κ B are nuclear homo- or heterodimeric complexes. Most of the dimers are formed of P50 and P65 subunits and p65 is their main transcriptional activator [27].

CRP as one of the most important evaluating inflammatory markers of atherosclerosis predominantly synthesized in the liver in response to proinflammatory cytokines, especially IL-6, IL-1 β , and TNF- α [28]. This acute-phase reactant directly increases the degradation of several NF- κ B inhibitor proteins and subsequently activates the NF- κ B pathway. Furthermore, in a 2-way communication, the NF- κ B heterodimeric p50/p65 can cause CRP mRNA accumulation. Additionally, it can stimulate endogenous synthesis of CRP and can have synergistic effect with IL-1 β and IL-6 on CRP production signaling. Therefore, the suppression of NF- κ B pathway is a crucial target to alleviate inflammation via inhibition of CRP production [29].

According to the result of previous studies, Pycnogenol has multiple roles in decreasing CRP level and are related to the suppression of NF- κ B gene expression [14]. It has been proved that Pycnogenol has a significant NF- κ B production-lowering effect in peripheral blood monocytes and to play a role in the reduction of TNF- α [4]. In a recent study, researchers have found that Pycnogenol has a significant repression effect on receptor activator of NF- κ B ligand (RANKL) expression. However, it is important that Pycnogenol doesn't have any effect on RANKL-induced NF- κ B [30]. Due to Pycnogenol's anti-oxidative characteristics and abilities to scavenge free radicals by neutralizing reactive oxygen, it may prevent from activating of NF- κ B and play an anti-inflammatory effect [31]. In one study Pycnogenol could significantly attenuate IL-6, IL-1 β , and TNF levels and then reduce synthesis of CRP in liver and decrease plasma level [32].

Based on reported evidence, no toxicity or mutagenic effects were detected after oral administration of Pycnogenol and it was considered as a safe dietary supplement in the USA [33]. A safety assessment of Pycnogenol supplementation based on 104 clinical studies suggested that the rate of adverse effects in subjects who consumed Pycnogenol was 1.66% [33]. Some of the most common side effects were mild and transient gastrointestinal troubles, dizziness, nausea, headache, and skin sensation [4]. Gastrointestinal discomfort was minimized when Pycnogenol was taken with breakfast [4].

This meta-analysis had the following several limitations: limited eligible clinical trials for assessing the effects of Pycnogenol on CRP; different doses of Pycnogenol and different duration of treatment periods; some of the included trials were not randomized or blinded; and the supplementation was conducted on different diseases. Unavailability of adjustment for potential confounders in some of the study analyse and no investigation for dietary intake in participants during follow-up could have potentially affected the findings of the included studies. Moreover, high heterogeneity of the results can be attributed to duration of intervention, study design, dosage of supplement, type of CRP marker, and participant's conditions in various studies. In order to recognize the source of heterogeneity, we performed various subgroup analysis. The results of subgroup analysis revealed that the heterogeneity was attenuated in dosage and age above 150 mg/d and 55 years, respectively. However, due to the high heterogeneity of our results, interpretation of these results should be cautiously under taken.

Present meta-analysis pooled results from 5 randomized clinical trials about the effect of Pycnogenol supplementation on CRP level. The results showed Pycnogenol consumption can decrease the level of CRP and has anti-inflammatory effect. Larger randomize clinical trial with long duration of treatment are needed to confirm the anti-inflammatory effect of Pycnogenol.

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