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Effect of Propolis supplementation on serum CRP and TNF- α levels in adults: A systematic review and meta-analysis of clinical trials

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Abstract:

Background: Propolis is a natural Product and the antioxidant properties of Propolis appear to be principally responsible for its therapeutic effects. However, several studies have shown the positive effect of Propolis on the reduction the levels of inflammatory markers; some others have revealed non-significant impacts on them. Hence, the present systematic review and meta-analysis was conducted to investigate the effects of Propolis supplementation on inflammatory markers.

Methods: The systematic search was undertaken in scientific databases that included: PubMed, Embase, Scopus and Web of Science to find studies assessing the effects of Propolis on inflammatory markers up to December 2019. Standardized mean difference (SMD) and 95 % confidence intervals (CI) were pooled using fixed effect model. Potential publication bias was tested using Egger's regression test.

Results: Seven studies comprising 471 participants were included in the meta-analysis. Pooled results of this meta-analysis showed that serum TNF- α levels (SMD = -0.52, 95 % CI = [-0.84, -0.20], $P = 0.001$, $I^2 = 59.5$ %) and CRP (SMD = -0.55, 95 % CI = [-0.86, -0.25], $P < 0.0001$, $I^2 = 41.2$ %) were significantly reduced following Propolis supplementation. No evidence of publication bias was found in the meta-analyses.

Conclusion: The present study concluded in the statistically and clinically improvement of serum CRP and TNF- α levels following Propolis administration.

Keywords: Propolis, Nutrients, Inflammatory markers, Meta-analysis

1. Introduction:

There is substantial evidence that systemic inflammation plays an important role in progression of several chronic diseases [1-3]. Serum CRP and TNF- α are two cytokines that are associated with a number of pro-inflammatory conditions that include: obesity [4, 5], diabetes mellitus [6, 7], fatty liver [8, 9] and metabolic syndrome [10, 11]. Reducing inflammation may be associated with a reduction in the risk of these conditions. Researchers are trying to find ways to prevent and treat inflammatory disturbance using dietary supplements that may have few side effects [12-15]. Studies have been conducted on various supplements, that have potential therapeutic effects through increasing antioxidant defense and inhibition of inflammatory cascades [16-19].

Propolis is a safe natural product that has gained popularity as an alternative medicine in last few years [20] and a sticky resinous substance with a pleasant taste that produce by honeybees after collecting from various plants and combining with its saliva and enzymes. In recent years, studies have demonstrated its ameliorating effects on diabetes [21], atherogenesis [22], cancer [23], oxidative [24], and inflammatory status [25]. The antioxidant properties of Propolis appear to be principally responsible for its therapeutic effects [22, 25]. It enhances the antioxidant defense system and inhibits the production of pro-inflammatory cytokines and the activation of nuclear factor- (NF-) κ B [17, 26, 27].

In a number of studies, the effects of Propolis on TNF- α and CRP levels have been investigated. Some had a shorter duration [23, 28] and some had a longer intervention period [22, 25, 29]. Moreover, some observed positive effects of Propolis in reducing inflammation [22, 23, 29] but other studies have shown no significant effects [25, 28].

Considering the importance of inflammatory disturbance as well as the favorable effects of Propolis on some variable disease related to inflammation [21], and due to the inconsistent results about the effectiveness of Propolis on reduction of TNF- α and CRP, this meta-analysis was conducted to clarify the effects of Propolis supplementation on serum CRP and TNF- α levels in adults.

2. Methods:

The present meta-analysis was conducted based on guidance provided by the *Cochrane Handbook for Systematic Reviews of Interventions* and the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) guidelines [30].

2.1 Literature search

Two independent reviewers systematically searched several scientific databases included: PubMed, Embase, Scopus and Web of Science to detect all available clinical trials examining the efficacy of Propolis supplementation on inflammatory markers up until 10 December 2019, without using any limitation on the language, age, sex or date of publication. While the following pattern was conducted for systematic search, hand-scanning was performed in Google Scholar, Cochrane Library and reference lists of related papers to find additional references: [Key terms for Propolis] AND [Key terms for outcomes] AND [Key terms for study design]. To increase sensitivity of systematic search, term “*” was used in some cases. To avoid including studies, which were performed on the same subjects, but reported some different outcomes, only completes one was selected for eligibility assessment. EndNote V9 was executed to manage detected references and duplicates finding.

2.2 Inclusion and Exclusion criteria

Research articles were considered for the present study if they (1) were clinical trials and (2) reported sufficient and usable data about the effect of Propolis supplementation on inflammatory markers when they have equal or more than 4 effect sizes in adult individuals more than 18 years old. Papers were excluded if they (1) were animal studies, (2) were non-English language, (3) reported data about outcomes was unusable or / and unconvertable and (4) were gray literatures including book chapter, conference abstracts, editorials, patents, dissertations and/or brief reports. Two independent reviewers assessed for inclusion all of the potential references that were detected through a strategy search. Any disagreements were resolved through a discussion with the corresponding author.

2.3 Data selection

After selection of the eligible articles by two independent reviewers, data were separately extracted: last name of first author, publication year, country, study design, mean age of participants, treatment duration, dose of Propolis, net changes ([mean post-treatment] – [mean pre-treatment]) and standard deviation (SD) for changes ($\sqrt{[(SD \text{ pre})^2 + (SD \text{ post})^2] - [2r \times SD \text{ pre} \times SD \text{ post}]}$), with assuming coefficient correlation ($r = 0.5$). Moreover, SD was obtained from standard error (SE) using following formula: ($SD = SE \times \sqrt{n}$). In case of any unclear data about outcomes, an E-mail was sent to the corresponding author. When necessary, E-mail was sent to corresponding author of the eligible trials. Also, any disagreements were clarified through a discussion between named authors or consulting by corresponding author.

2.4 Risk of bias assessment

Two authors performed the quality assessment of trials executing *Cochrane Collaboration risk of bias Tool* [31], which were categorized into the following domains: random sequence generation,

concealment of allocation to conditions, inhibition of awareness of the allocated intervention, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The terms “Low”, “High” and “Unclear” risk of bias were used to show the status of each domain. Also, RevMan V5.3 was used to draw a graph. Furthermore, any doubts were resolved through a consultation with corresponding author.

2.5 Statistical analysis

A random-effects model was used to pool standardized mean difference (SMD) and 95 % confidence intervals (CI). Moreover, I^2 statistic - with values of 25 %, 50 % and 75 % were regarded as low, moderate and high, respectively - and P were considered to detect potential heterogeneity among studies [32]. A random-effects meta-regression was conducted to find the source of heterogeneity between studies. Also, subgroup analyses by participants (diabetic vs. non-diabetic) and treatment duration (> 9 months, < 9 months) were done. Furthermore, sensitivity analysis was planned to find the impact of each individual study on the pooled results. Potential publication bias was tested using Egger’s regression test [33]. A P -value < 0.05 was considered as statistically significant and Stata V13 was used to analyze all data.

3. Results:

3.1 Data selection process:

The details of data selection process are shown in Figure 1. Through initial search in online databases (PubMed, Embase, Scopus and Web of Science), 182 papers were identified in the first step, but 90 of them were excluded as they included duplicate findings. Then, 75 papers were excluded through titles / abstract screening and 17 records were retrieved for further assessment

as full-text. Finally, a total of 7 trials were eligible to enter present meta-analysis [22, 23, 25, 28, 29, 34, 35].

3.2 trials characteristics:

The demographic characteristics of the included studies are described in Table 1. Overall, data were pooled from five included trials which comprised 241 and 230 participants in the treatment and control groups, respectively. The publication date of the included datasets ranged from 2003 to 2019, among which, two studies have been conducted in China [29, 35], two in Iran [22, 23], ones in Chile [25], ones in Japan [28] and ones in Egypt [34]. Participants were aged from 19 to 72.8 years. Only one study did not clearly report a dose for Propolis [25]. A range of treatment duration was between 8 – 104 weeks. Serum CRP and TNF- α were significantly changed in two [22, 23] and four studies [22, 23, 29, 35], respectively. Details of methodological quality assessment are presented in Figure 2.

3.3 Meta-analysis and meta-regression:

The present meta-analysis resulted in a significant reduction of TNF- α (Figure 3A) (SMD = -0.52, 95 % CI = [-0.84, -0.20], $P = 0.001$, $I^2 = 59.5$ %) and CRP (Figure 3B) levels (SMD = -0.55, 95 % CI = [-0.86, -0.25], $P < 0.0001$, $I^2 = 41.2$ %) in compared to the controls.

Random-effects meta-regression find treatment duration as source of heterogeneity between trials and indicated a significant relation between serum TNF- α and treatment duration (Coefficient = -0.009, 95 % CI = [-0.01, -0.0001], $P = 0.04$) (Figure 4).

3.4 Publication bias and sensitivity analysis:

There was no evidence of publication bias in the selected trials investigating the effects of Propolis supplementation on serum CRP ($P = 0.65$) and TNF- α ($P = 0.50$) levels. Moreover, sensitivity analysis showed that pooled results of the present meta-analysis was not substantially modified by omitting a certain study.

4. Discussion:

To the best of our knowledge, this is the first meta-analysis to assess the effect of supplementation with Propolis on serum CRP and TNF- α . The results of the present meta-analysis indicated that Propolis supplementation could significantly reduce serum CRP and TNF- α concentrations. In meta-regression, changes in serum TNF- α following Propolis intake was depended on the treatment duration. Moreover, it should be mentioned that according to the sensitivity analysis, pooled results did not change significantly by omitting any study.

The results of the current meta-analysis was in accordance with the results of other studies emphasizing on the effects of Propolis consumption on decreasing inflammatory markers [23, 24]. Additionally it was reported by some studies that Propolis ingestion can reduce the level of lactate dehydrogenase (LDH) in patients with type 2 diabetes mellitus (T2DM) which is a marker of cell injury [24, 29] and this confirms our results regarding the anti-inflammatory effects of Propolis that can help protecting cells from any damage or injury.

Propolis is a resinous hive matter which is produced by bees from pollen of different plants and it contains various ingredients including flavonoids, trepenes, and many phenolic compounds that possess anti-inflammatory properties [24, 36-40]. An active component of Propolis that can cause anti-inflammatory effect is caffeic acid pohenethyl ester (CAPE) that can inhibit the activation of signaling pathway by nuclear transcription factor-kb (NF-KB), a factor involved in

inflammatory pathways [40]. Moreover, as another mechanism, effects of propolis on diminishing inflammation, cellular damage, and injury might be related to its effects on increasing antioxidants such as GSH, flavonoids, and polyphenols [36].

Further, it is noteworthy to state that propolis may enhance insulin sensitivity through decreasing CRP and TNF- α in diabetic patients and this would be of great importance in this group [23]. On the other hand, it is clear that any increase in inflammatory biomarkers including CRP can elevate the risk of T2DM [41-47] and might increase cardiovascular risk factors [48, 49]. So, it seems that Propolis ingestion might decrease the risk of T2DM complications and prognosis [20].

This systematic review and meta-analysis pooled the results according to the effects of Propolis supplementation on inflammatory markers. However, this meta-analysis has some limitations and further researches are needed to confirm the results of this study. Hence, the results should be interpreted with caution. As a limitation, this study includes a small number of studies, while as a strength, we conducted sub-group analysis to consider the effects of study durations and type of population on changes in inflammatory markers after Propolis ingestion. Moreover, most of the included trials were double-blind and this strengthens the inference for a cause-and-effect relationship.

4.1 Conclusion:

To conclude, in this systematic review and meta-analysis, after assessing all trials to extract a comprehensive result, effect of Propolis supplementation on decreasing inflammation was shown, only in diabetic patients, as it decreased the serum concentrations of CRP and TNF- α . More trials about Propolis supplementation on different groups and various inflammatory markers are

warranted to better elucidate the anti-inflammatory properties and mechanism of action of Propolis. On the other hand, different types of Propolis from various geographical regions might express different properties as the bees might feed from many various plants and this needs further investigation.

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Conflict of interest:

The authors declare no conflict of interest.

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None

Author Contribution:

MJ and ZS contributed in concept and design. MJ, ZM, MM, SPM and RJ contributed in literature search, data collection and analysis. MJ, TR, MM, GF and ZS contributed in drafting the manuscript. All of the authors reviewed and approved the final manuscript.

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Table 1. Demographic characteristics of the included trials

First author (year)	Country	Sample size (T / C)	Mean age of participants (year)	Subjects	Dose (mg/day)	Duration (Week)	Interested outcomes
Zakerkish (2019)	Iran	50 / 44	55.6	Diabetic	1000	12	CRP (↓), TNF-α (↓)
Zhu (2018)	China	30 / 30	72.8	Elderly people	66	104	TNF-α (↓)
Afsharpour (2017)	Iran	30 / 30	50.43	Diabetic	1500	8	CRP (↓), TNF-α (↓)
Mujica (2017)	Chile	35 / 32	46.4	Healthy	NR	12	CRP
Zhao (2016)	China	33 / 32	60.16	Diabetic	900	18	TNF-α (↓)
Fukuda (2015)	Japan	41 / 39	63.31	Diabetic	266.8	8	CRP, TNF-α
Khayyal (2003)	Egypt	22 / 23	19 - 52	Asthmatics	260	8	TNF-α

‡ T (treatment group), C (control group), NR (Not clearly reported), ↓ (significant reduction)

Figure 1. Flow diagram of data selection process

Figure 2. The methodological quality of trials based on authors' judgments

Figure 3. Forest plot detailing SMDs and 95% CIs for the meta-analyses of serum TNF- α (A) CRP and (B) levels

Figure 4. Random-effects meta-regression based on treatment duration for serum TNF- α

Figure legends:

Figure 1. Flow diagram of data selection process

Figure 2. The methodological quality of trials based on authors' judgments

Figure 3. Forest plot detailing SMDs and 95% CIs for the meta-analyses of serum TNF- α (A) CRP and (B) levels