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Review

Effect of propolis supplementation on C-reactive protein levels and other inflammatory factors: A systematic review and meta-analysis of randomized controlled trials

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CRP: c-reactive protein
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IL-1: Interleukin 1
WMD: Weighted mean differences

ABSTRACT

Propolis is a resin-like substance collected by honeybees from certain plants that have been shown to positive effect on inflammatory factors. Therefore, the aim of this study was to systematically review and meta-analyse the effects of Propolis supplementation on CRP, TNF-a, IL-1, and IL-6 in Randomized Controlled Trials (RCTs). A comprehensive systematic search of articles was conducted in PubMed/MEDLINE, Web of sciences, and Scopus to identify the potential titles up to August 2019. PRISMA guidelines were performed for this study. Inclusion was 1-study design was parallel or cross over randomized controlled trial (RCT), 2- consumption of Propolis as intervention, 3- reported sufficient information about inflammatory factors, CRP, IL1, IL6, TNF-a. Six studies were identified by comprehensive search. This meta-analysis study found a significant reduction in IL-6, CRP, and TNF-α following Propolis consumption (Weighted mean differences (WMD): −17.96 pg/ml, 95% CI: −35.53, −0.38, I2 = 98%), (WMD: −1.16 pg/ml, 95% CI: −2.28, −0.03, I2 = 97%), and (WMD: −34.08 pg/ml, 95% CI: −60.25, −7.91, I2 = 97%), respectively. Propolis did not showed any significant effect on IL-1 (WMD: −17.36 pg/ml, 95% CI: −37.60, 2.87, I2 = 97%). In conclusion, the results demonstrated that CRP, TNF-a and IL-6 were significantly reduced following propolis supplementation.

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1. Introduction

Propolis has been a part of human medicine for thousands of years with the Egyptians, Greeks and Romans benefiting from its property's centuries ago. In the middle ages, the popularity of propolis declined only to resurface in the early 1900 s thanks to increasing research on its molecular properties (Kuropatnicki et al., 2013). Propolis is a resin-like substance collected by honeybees from certain plants of which some of the commonest are Eucalyptus citriodora, Baccharis dracunculifolia, and Araucaria angustifolia (Szliszka et al., 2013). This substance is then used by bees to glue together their hives as if it were a type of cement. Propolis remains popular in over the counter medicine for its antioxidant and anti-inflammatory effects. Successful uses of propolis include mouth wash, throat sprays, cough medicine, wound healing in diabetic foot ulcers and topical applications for acne vulgaris (Ali et al., 2015; Henshaw et al., 2014; Khurshid et al., 2017). Currently, China is the world's greatest producer and exporter with strong research showing its anti-inflammatory effects in animal models, however, studies demonstrating its mechanism at a molecular level are still limited (Wang et al., 2013).

With the escalating concerns surrounding anti-microbial resistance there has been a recent move towards reconsidering natural substances and their anti-microbial and anti-inflammatory properties. For example, another substance related to bees, Manuka Honey, is shown to contain high levels of methyl glyoxal (MGO), leptosin and hydrogen peroxide. Manuka honey has been widely tested and studies in vitro have confirmed that it is effective against a range of different bacteria, especially those that often colonize skin wounds (Carter et al., 2016). Similarly, nanocrystalline silver (nAg +) has also been found to be effective in the treatment of chronic wounds due to the electrostatic attraction between nAg + and the negatively charged cell membranes of bacteria. Its anti-inflammatory actions have been observed in vivo, but the underlying molecular pathways are still unclear. Nevertheless, in vitro research has shown it to suppress TNF-a, IL-8, IL-6 and IL-12 (Nadworny et al., 2010; Tsang et al., 2015).

Since the early twentieth century research surrounding the molecular mechanisms of propolis have increased correlated with the advance of molecular chemistry. Today, propolis is known to be high in flavonoid content, a substance originating from plants, which has been found to inhibit the production of nitric oxide (NO), IL-1 & IL-6 (Wang et al., 2013). In vitro studies have also demonstrated the efficacy of flavonoids against over 25 strains of bacteria and 20 strains of fungus that can cause disease in humans (Tsang et al., 2015). Another immunomodulatory substance known to be abundant in propolis is phenolic acids whose molecular activity diminish the quantity of NO, cytokines and neutrophils (Szliszka et al., 2013).

Undoubtedly, the number of studies evaluating the molecular anti-inflammatory properties of propolis has been increasing. However, to the best of our knowledge, no systematic review has attempted to summarize this evidence. Our study will attempt to summarize, critically evaluate and establish the dose response relationship surrounding the effects of propolis on inflammatory factors.

2. Methods

2.1. Literature search

For conducting this systematic review and meta-analysis following Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines was conducted (Moher et al., 2011). Two study authors (G.K and G.R) independently conducted a systematic search of the databases MEDLINE/PubMed, Web of sciences, and Scopus (all years to August 5st 2019). MeSH terms and title and/or abstract keywords used in the search strategy (supplementary Table 1). Reference lists of included studies were searched to avoid missing any relevant article. No language or date restrictions was applied. Any disagreements between the authors are resolved by senior author (QY).

2.2. Study selection

Screening of studies performed in title and/or abstract and full text. The PICOS (patients: public population, intervention: propolis, comparator: Placebo, outcome: CRP, TNF-a IL-1, and IL-6 study design: RCTs) criteria was used to establish study Selection.

2.3. Eligibility criteria

We included studies that have a) the study design was parallel or cross over randomized controlled trial (RCT), b) consumption of Propolis c) reported sufficient information about inflammatory factors, CRP, TNF-a, IL1, and IL6. We excluded animal, in-vitro studies, done on children, studies without placebo-control group or did not report inflammatory factors, CRP, TNFa, IL1, and IL6 at baseline and end of the intervention and non-original papers. Corresponding authors were contacted for any additional details or missing data of selected articles, when required.

2.4. Statistical analyses

Data was analyzed by STATA software version 12 (STATA Corp, College119 station, Texas). Mean change and standard deviation (SD) for CRP, TNFa, IL1, and IL6 were estimated using Weighted mean difference (WMD) of the intervention. If the studies did not

report SD change of the mean differences are calculated using SD2 = [(SD baseline2 + SD final2) − (2 × r × SD baseline × SD final)] formula (Higgins and Green, 2011). The heterogeneity among the studies was assessment by the I-squared (I2) statistics and Q test. Meta-regression based on duration of supplementation conducted to find source of heterogeneity. Publication bias was assessed using funnel plots and Egger's and Begg's tests of weighted regression (Egger et al., 1997). The effect of each study on pooled results evaluated by sensitivity analysis. Quality assessment of randomized control trials were assessed by the Cochrane collaboration's tool (Higgins et al., 2011).

3. Results

In initial search from PubMed, Scopus, and web of sciences and after removing duplicated studies, 814 articles were identified that presented in Fig. 1. In first step, 791 paper removed based on title and abstract screening and 23 articles were retrieved for more evaluation. Finally, six article included in this meta-analysis and 17 article excluded because did not meet inclusion criteria (Afsharpour et al., 2017; Fukuda et al., 2015; Khayyal et al., 2003; Mujica et al., 2017; Zakerkish et al., 2019; Zhu et al., 2018).

3.1. Mine characteristics of studies

Included studies Characteristics are presented in Table 1. Included studies sample size was 63 ranged from 17 to 94, all studies conducted on both genders and mean age of participants was 57 years. Included studies were conducted Iran (Afsharpour et al., 2017; Zakerkish et al., 2019), China (Zhu et al., 2018), Chile (Mujica et al., 2017), Japan (Fukuda et al., 2015), and Egypt (Khayyal et al., 2003). They were published between 2003 and 2019. Cochrane collaboration's tool for quality assessment of randomized controlled trials was used to assess the quality of included studies and most of them had appropriate quality.

3.2. Meta-analysis results

Four studies with 279 participants reported IL-6 as an outcome measure (Fukuda et al., 2015; Khayyal et al., 2003; M. Zakerkish et al., 2019; Zhu et al., 2018) and pooled results showed a significant reduction effect of Propolis on IL-6 (WMD: −17.96 pg/ml, 95% CI: −35.53, −0.38, I2 = %98) (Fig. 2). Meta-regression analysis based on duration of intervention (Supplemental Fig. 1) show an indirect relation between duration of intervention by Propolis and levels of IL-6 (Coef = −0.1054) but this relation was not statistically significant (p = 0.71). While, Propolis did not have any significant reduction effect on IL-1 (WMD: −17.36 pg/ml, 95% CI: −37.60, 2.87, I2 = %97) and because low number of included studies in this outcome we could not run meta-regression analysis on IL-1 (Zakerkish et al., 2019; Zhu et al., 2018).

Four studies with 301 participants (intervention = 156, control = 145) reported CRP as an outcome measure (Afsharpour et al., 2017; Fukuda et al., 2015; Mujica et al., 2017; Zakerkish et al., 2019) and combined results showed a significant reduction on CRP by propolis consumption (WMD: −1.16 pg/ml, 95% CI: −2.28, −0.03, I2 = %97). Although Meta-regression analysis show reverse relation between propolis supplementation and CRP levels (Coef = -0.1350) but this coefficient was not significant (P = 0.70). Propolis supplementation had significant reduction effect on TNF-a levels (WMD: −34.08 pg/ml, 95% CI: −60.25, −7.91, I2 = %97) (Afsharpour et al., 2017; Khayyal et al., 2003; Zakerkish et al., 2019; Zhu et al., 2018). Meta-regression analysis show reverse relation between propolis supplementation and TNF-a levels (Coef = −0.4600) but was not significant (P = 0.21) (Fig. 3).

3.3. Risk of bias and sensitivity analysis

There is not any asymmetry between included studies (Supplemental Fig. 3). No publication bias was identified in Egger's and begg's tests for IL-6 (p = 0.23, p = 0.09), IL-1 (p=-, p = 0.31), CRP (p = 0.40, p = 0.17), and TNF-a (p = 0.13, p = 0.49), respectively.

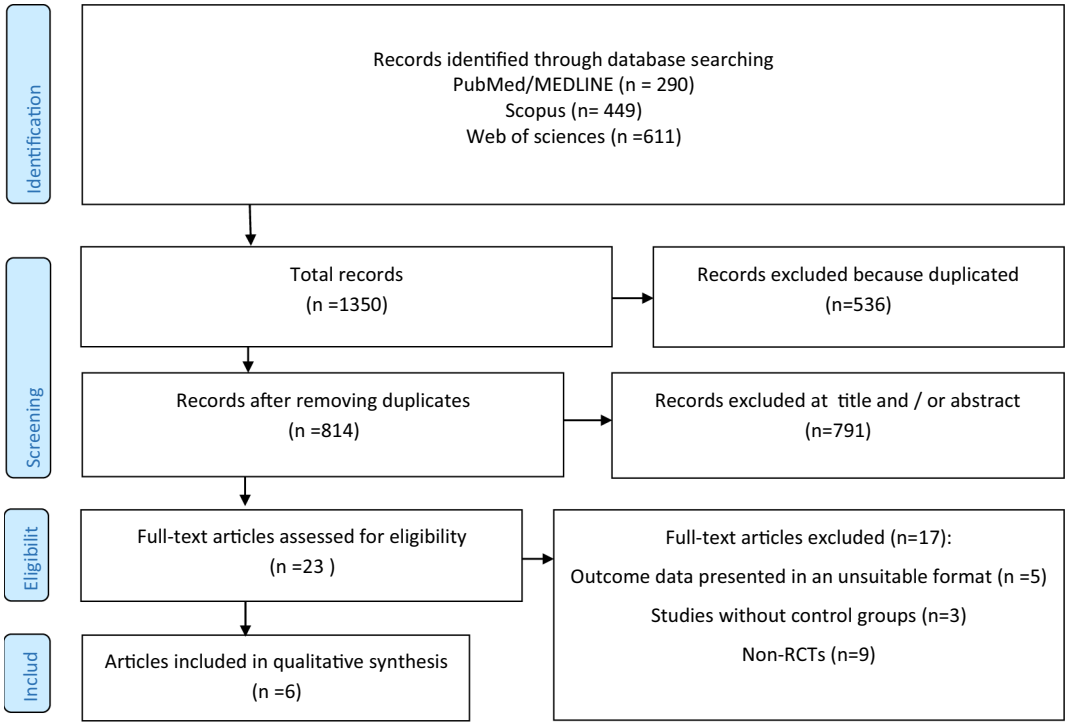


Fig. 1. Flow chart of included studies based on searched database.

Table 1
Characteristics of included studies.

Author	Location	year	Participants (n)	Gender	Age (year)	Dose (mg / day)	Type of Propolis	Duration of study (week)	Population study
Zakerkish	Iran	2019	94	both	55.15	1000	Iranian propolis	12.85	T2DM adults duration < 10 years, not using insulin, no severe renal or hepatic dysfunction or serious cardiovascular/hematological disease, no allergies or pregnancy
Afsharpour	Iran	2019	60	both	50.43	1500	Alamut propolis	8	T2DM, age 33–55, duration < 10 years, not using insulin, without serious disease (e.g., CHD, kidney, hepatic failure, cancer)
Zhu	China	2018	60	both	72.8	66 mg Artepillin C	Brazilian green propolis	104	Elderly people living at altitude without dementia, mental illness, or inflammatory conditions
Mujica	Chile	2017	17	both	46.4	Unstated	Beepolis (from Maule region of Chile)	12.85	One of: altered FBS, altered lipids, altered BP, or T2DM, or CVD, or overweight. Exclusion: alcoholism, serious pathologies.
Fukuda	Japan	2015	80	both	63.31	226.8	Brazilian green propolis	8	T2DM, age 35–80, on non-insulin treatment, without eGFR < 30 mL/min/1.73 m2 or hepatic dysfunction
Khayyal	Egypt	2003	67	both	Unstated	2 mL of 13% aqueous extract of propolis solution (=260 mg if percentage is w/v)	Aqueous decoction of crude Danish, Chinese, Uruguayan and Brazilian propolis, standardized to contain $\geq$ 0.05% aromatic acids	8	Mild-to-moderate asthmatics of duration 2–5 years, aged 19–52. Excluded: adverse effects during treatment, excessive rescue puffer use, corticosteroids in last 2 months, allergy to drugs, acute severe asthma in past 6 months, other comorbidities like diabetes or HTN requiring therapy

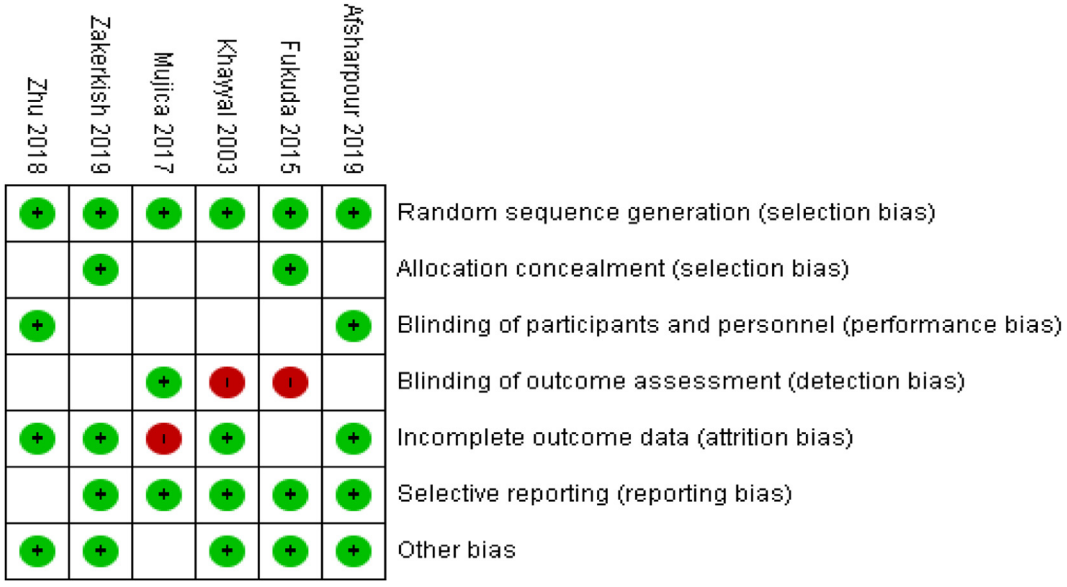


Fig. 2. Cochrane risk of bias assessment of included studies.

Sensitivity analysis did not identified significant differences beyond the limits of 95% CI between calculated SESs for metformin intervention studies (Supplemental Fig. 3).

4. Discussion

Propolis is known to possess a high flavonoid content and found to inhibit the production of various inflammatory markers, including Nitric Oxide, IL-1 & IL-6. Although the interest in the molecular anti-inflammatory properties of propolis has increased, with the disease ameliorating and immunomodulatory effects being among the most reported characteristics, to the best of our knowledge, there has been no summative assessment of literature. Therefore, we sought to investigate the effects of propolis supplement on inflammatory factors. In accord with this aim, we found that IL-6, CRP, and TNF-a were reduced following propolis supplementation, whilst no significant effect was manifest in IL-1.

A higher pro-inflammatory cytokines such as TNF-α, IL1, and IL6 and CRP are associated with oxidative stress and chronic

inflammation in the pathogenesis of T2DM (Pradhan et al., 2001; Zhao et al., 2016). Propolis possesses strong anti-inflammatory function (Freires et al., 2016). It can directly influence a decrease in pro-inflammatory cytokines (Al Ghamdi et al., 2015; Silva-Carvalho et al., 2015). Whilst most studies are concordant that propolis elicits a improvment impact on inflammation, and it can decrease TNF levels, its effects on interleukins levels has been inconsistently reported (Orsatti et al., 2010; Silva-Carvalho et al., 2015; Zakerkish et al., 2019). However, in this study, the first summative assessment in the literature, we highlight that IL-6 (WMD: −17.96 pg/ml, 95% CI: −35.53, −0.38, I^2 = 98%), CRP (WMD: −1.16 pg/ml, 95% CI: −2.28, −0.03, I^2 = 97%), and TNF-a levels (WMD: −34.08 pg/ml, 95% CI: −60.25, −7.91, I^2 = 97%) were all significantly reduced following propolis supplementation, yet IL-1

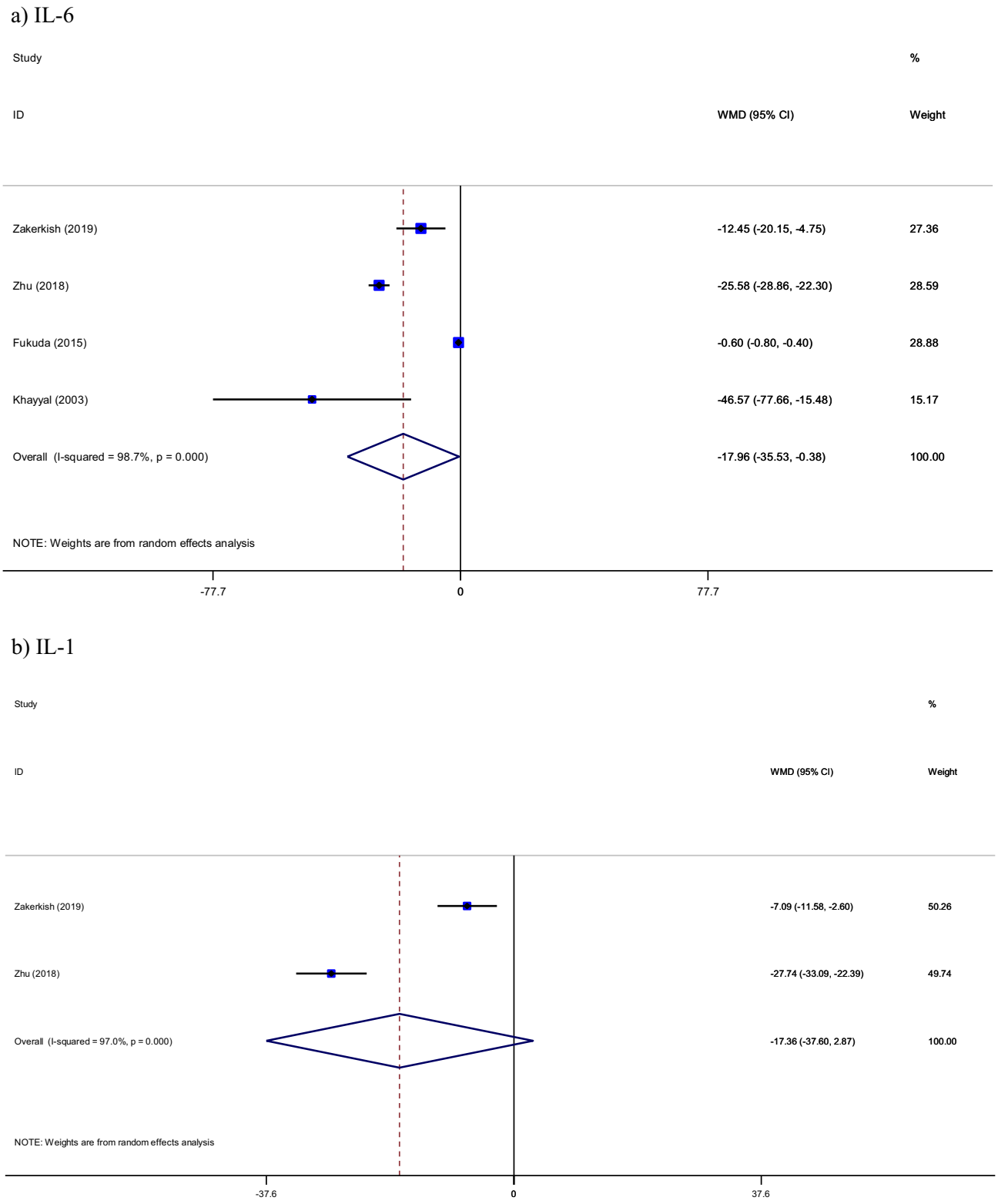
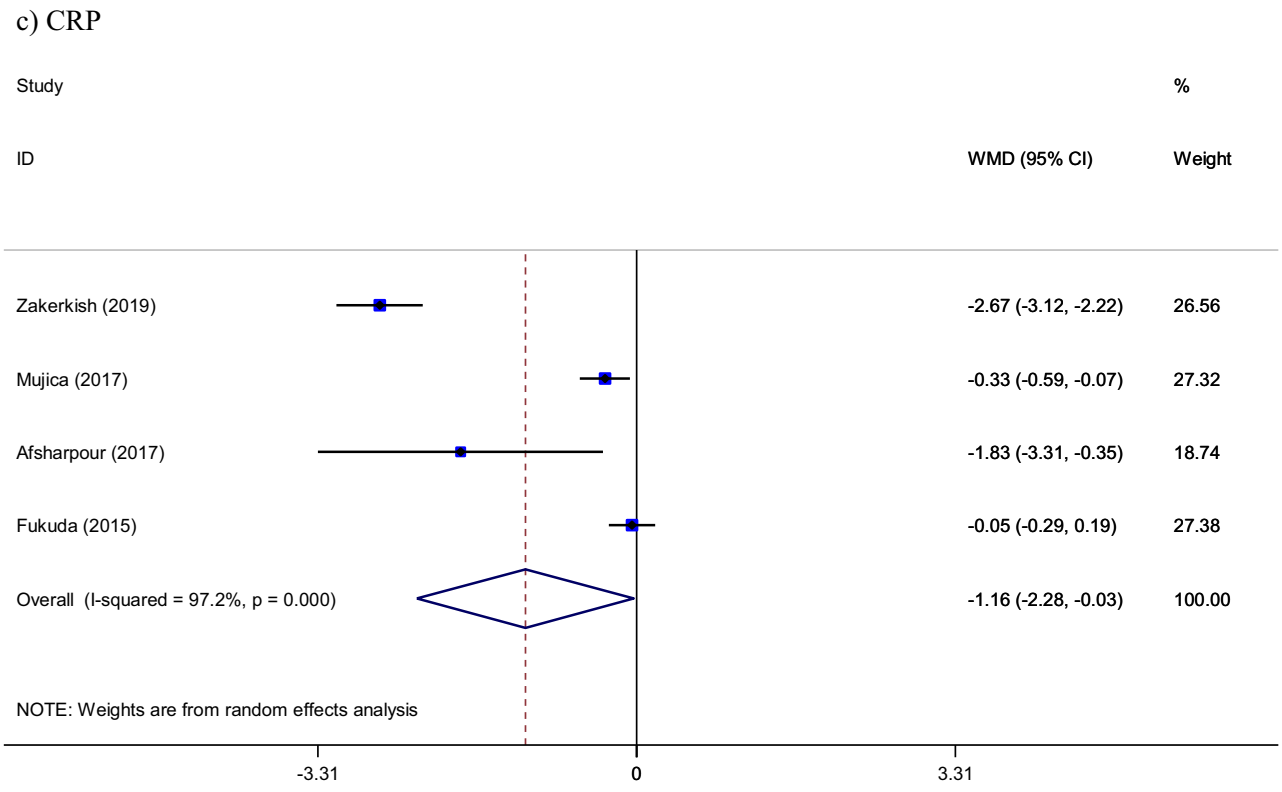


Fig. 3. Random effect model of *meta*-analysis of effect of propolis supplementation on: a) IL-6, b) IL-1, c) CRP, d) TNF-a.



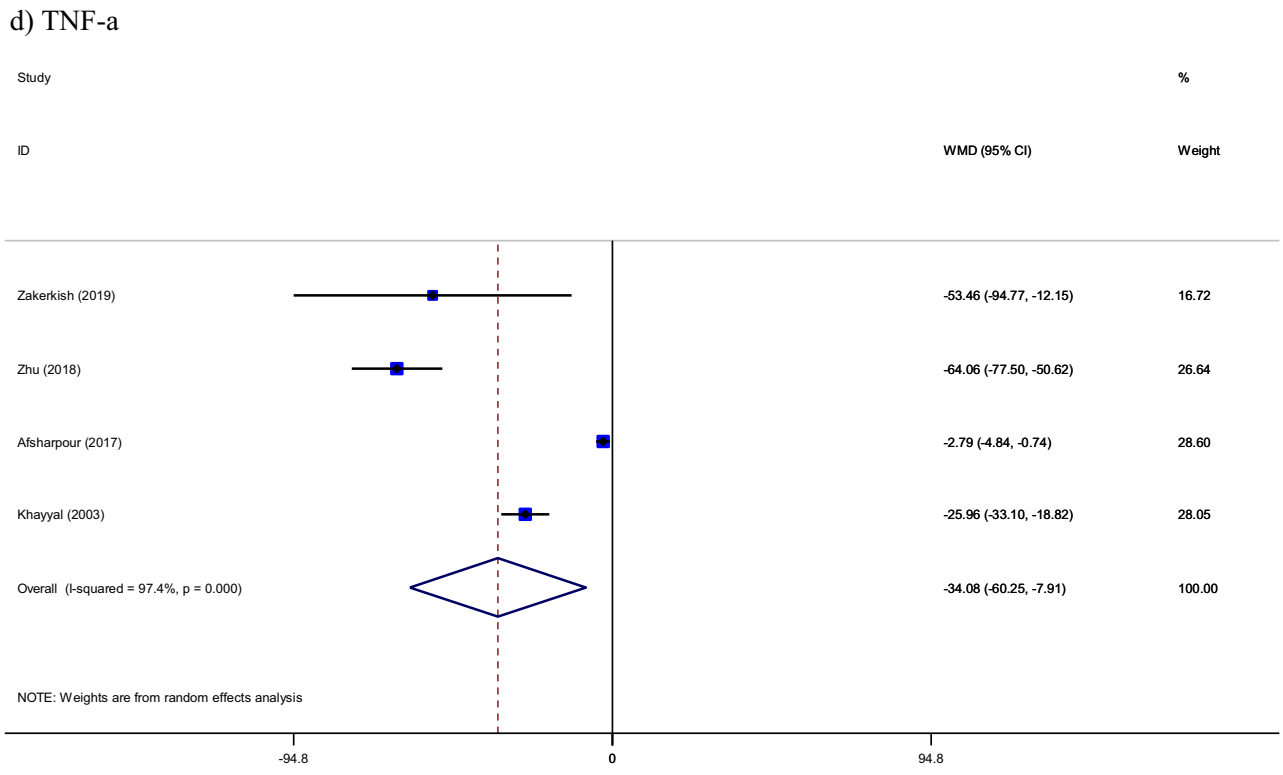


Fig. 3 (*continued*)

was not. In Zakerkish et al. study, by propolis supplementation in T2DM patients, the level of CRP and TNF were decreased (Zakerkish et al., 2019). However, no difference in serum IL-1 and IL-6 levels were noticed. Intervention with Brazilian propolis showed a reduction in serum TNF-a levels, however, IL-1 and IL-6 serum levels were increased in Zhao et al. study. It is suggested that the IL-1 production pro-inflammatory effects may conceivably have been be prevented by the anti-inflammatory effects of IL6. Thus, propolis supplementation have positive effects on chronic inflammation (Zhao et al., 2016).

Of interest, is the fact that, in the present meta-analysis, the propolis administered to participants consisted of varying progeny.

For instance, Brazilian, Iranian, Alamut and Chilean varieties were identified. Propolis is largely comprised of phenols, terpenes, vitamins, amino acids, sugars, and elements (Bankova et al., 2014), and is known to possess a complex chemical composition (Mercuri et al., 2000; Silva-Carvalho et al., 2015). In the present study we were unable to investigate the differing sources of propolis in sub-group analyses, due to a lack of eligible studies. However, we assert that varying species of propolis must be investigated more acutely in future studies.

5. Putative mechanisms

Propolis contains propolins, steroids, phenols, aldehydes, terpenes, phenolic acids, amino acids, flavonoids, and ketones (Trusheva et al., 2010; Xuan et al., 2014). Moreover, the presence of caffeic acid and chlorogenic acid in propolis helps to prevent LDL-C oxidation (Bueno-Silva et al., 2015). DNA oxidative damage inhibit in presence of chlorogenic acid by peroxynitrite scavenging and reduces in the release of myeloperoxidase (Hu et al., 2005). Caffeoylquinic acid derivatives and artepillin C are considered for propolis neuroprotective effects (Franchin et al., 2018), where propolis inhibit of the activities of cyclooxygenases (COX-1 and COX-2), impeding the gene expression of inducible nitric oxide synthase (iNOS), and blocking TNF-α-mediated NF-κB activation (Banskota et al., 2001; Woo et al., 2005). Caffeic acid phenethyl ester (CAPE) inhibitor the NF-κB activation, which provide the molecular basis for its anti-inflammatory activity (Tahira Farooqui and Farooqui, 2010).

The antioxidant activity of flavonoids, a constituent of propolis, is attributed to their ability to reduce formation of free radical (Ahn et al., 2009; Kumazawa et al., 2004). The propolis flavonoids in possess Fe^{2+} chelating can decrease peroxidation lipids (Van Acker et al., 1996). Kumazawa et al (2007) showed that anti-oxidant activity of flavonoid related to the geranyl or prenyl group position in the flavonoid skeleton (Kumazawa et al., 2007). Furthermore, propolis flavonoids exhibit antioxidant activity (Tahira Farooqui and Farooqui, 2010). However, as asserted in Farooqui (Farooqui and Farooqui, 2012), although propolis seems to elicit beneficial effects on human health, the complex structure makes it difficult to ascertain a true causal mechanism; in addition, Sforcin (2016). suggested that the effects of propolis may be the result of several components and not one specific compound.

6. Strengths and limitations

Main strength of this study was that this is the first meta-analysis to assess the impact of propolis supplementation on inflammatory markers. Through this investigation, we demonstrated that there is sufficient evidence for propolis supplementation showed potential and positive effects on IL-6, CRP, and TNF-α.

The current study has some limitations to consider. The analyses were not restricted to solitarily include patients of one type or age; Furthermore, we could not find source of heterogeneity between some results.

Furthermore, this is the first meta-analysis to assess the impact of propolis supplementation on inflammatory markers, which permits more nuanced guidance for further study.

7. Conclusion

Propolis has a several and useful chemical composition with wide phytogeographic characteristics and is asserted to elicit numerous positive biologic effects in humans. Prior to this work, there was no summative assessment of the effect of propolis on inflammatory markers; accordingly, we found that IL-6, CRP, and TNF-α were significantly reduced following propolis supplementation. Given that elevated inflammatory markers are associated with a plethora of non-communicable diseases, propolis may represent a viable adjunct therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jksus.2020.01.003.

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