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REVIEW

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Propolis supplementation can reduce serum level of interleukin-6, C-reactive protein, and tumor necrosis factor-α: an updated systematic review and dose-response meta-analysis on randomized clinical trials

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Abstract

Background New evidence suggested that propolis might reduce serum levels of inflammatory mediators; therefore, in this study we aimed to prove the potential effect of propolis on serum levels of interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α) through conducting a systematic review and meta-analysis.

Methods Databases including PubMed, ClinicalTrials.gov, Scopus, Cochrane Library, and ISI Web of Science were searched until October 2023. In the present meta-analysis, we detected the overall effect sizes using extracted standard mean differences (SMD) and the standard deviations (SDs) from both study groups through DerSimonian and Laird method. Exploring the statistical heterogeneity was done through Cochran's Q test and I-squared statistic.

Results In total, seventeen and sixteen studies were included in the systematic review and meta-analysis, respectively. The overall estimate indicated that the propolis significantly reduced serum levels of IL-6 (SMD = -3.47, 95% confidence interval (95%CI): -5.1, -1.84; $p < 0.001$), CRP (SMD= -1.73, 95%CI: -2.82, -0.65; $p = 0.002$), and TNF-α (SMD= -1.42, 95%CI= -2.15, -0.68; $p < 0.001$). These results also revealed geographical region and propolis dose were the critical points to get the beneficial effects.

Conclusion According to our result, propolis supplementation can decrease serum levels of IL-6, CRP, and TNF-α; therefore, it might be considered as complementary therapy for the treatment of certain chronic diseases.

Keywords Propolis, Interleukin-6, C-reactive protein, Systematic review, Tumor necrosis factor-alpha, Meta-analysis

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Introduction

Inflammation considers as the main cause of chronic diseases such as type 2 diabetes mellitus (T2DM), insulin resistance, and cardiovascular disease (CVD). Inflammatory factors such as interleukin-1 alpha (IL-1α), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), transforming growth factor-β (TGF-β), and C-reactive protein (CRP) play important roles in lipid disorders, insulin resistance, and increased oxidative stress [1]. Recent documents revealed the beneficial effects of some nutrients with antioxidant and anti-inflammatory features on the management and the prevention of inflammation [2, 3]. Therefore, taking these functional foods with antioxidant or anti-inflammatory properties is increasing.

Honeybees produces a resin-like substance named propolis. Propolis collected from certain plants such as citriodora, Eucalyptus citriodora, Araucaria angustifolia, and Baccharis dracunculifolia. This substance contains different kinds of phytochemical components which mainly belong to phenolic acids, flavonoids, stilbenes, and terpenes and have been identified that directly and indirectly scavenge free radicals [4]. Free radicals increase the inflammatory process through activating nuclear factor of kappa (NF-κB), a transcription factor, which elevates the gene expression of pro-inflammatory cytokines [5]. Therefore, propolis can act as an anti-inflammatory agent through scavenging free radicals.

Recently, propolis considers as complementary medicine for its various beneficial biological properties besides anti-inflammatory and anti-oxidant effects such as anti-tumor, anti-microbial, and immunomodulatory actions [6, 7]. Health-promoting properties of propolis are due to the cumulative and interaction effects of its complex components [6]. The in vivo evidence has shown that propolis can alleviate genes expression especially genes responsible for inflammation and lipid metabolism [8, 9].

Moreover, recent documents suggest that propolis as an anti-inflammatory and antioxidant compound can prevent or reduce the consequence of inflammatory diseases, which makes it the most appropriate candidate for the prevention or improving these disorders [10, 11].

Previous outcomes have showed the beneficial effects of propolis on antioxidant status through decreasing malondialdehyde and increasing glutathione in humans [10, 12, 13]. As well, its therapeutic role in the treatment and prevention of T2DM has been suggested in several clinical trials [11, 14].

Furthermore, many randomized clinical trials (RCTs) assessed propolis supplementation effects on inflammation, but their results are contradictory [15–31]. Two systematic review and meta-analysis articles in year 2021 on a few trials proposed that propolis supplementation had useful effect on serum concentration of CRP, IL-6, and TNF-α [32, 33]. Meanwhile, several new RCTs after their systematic search date have been published.

Since there are twelve RCTs [15, 17–19, 21, 22, 24, 26–28, 30, 31] which were not included in the previous articles, we tried to conduct an update systematic review and performed a meta-analysis to summarize the overall effect of propolis supplementation on serum levels of IL-6, CRP, and TNF-α.

Materials and methods

For the current study, a systematic and comprehensive search was done following PRISMA guidelines. Its protocol was registered in the PROSPERO database (No. CRD42023470555).

Search strategy

The systematic search was performed using the following medical subjects heading (MeSH) terms and non-MeSH terms for intervention ("Bee Bread", "Propolis", "Glue, Bee", "Bee Glue", "Bread, Bee"), outcomes ("CRP", "Protein-C Reactive", "C-Reactive Protein", "Tumor Necrosis Factorα", "Tumor Necrosis Factor-alpha", "TNFα", "Cachectin", "TNF-α", "IL6", "Interleukin-6", "Interleukin6", "IL-6"), and study type ("Clinical Trial", "RCT", Random*, Trial*, Intervent*, "Cross-Over Studies", "Cross Over", "Crossover"). The design of systematic search was done through asterisks, quotation marks, and parentheses; furthermore, designing search strategy was done through Boolean operators (OR and AND). Then databases including PubMed, ClinicalTrials.gov, Scopus, Cochrane Library, and ISI Web of Science were searched until October 2023. All found articles through searching those databases were exported to the EndNote X19. Reading the articles titles and abstracts was done separately by two reviewers (AGh and MH). In addition, the reference of all relevant articles were reviewed to find missed articles. If there was any unclear information, the authors sent emails to the corresponding authors for the clarification.

Eligibility criteria

The eligibility criteria for including articles in this study were as listed below: (1) RCTs with parallel or crossover designs, (2) Studies on adult participants (≥18 years), (3) RCTs used propolis supplements as an intervention, (4) RCTs that reported serum levels of IL-6, CRP, and TNF-α at the beginning and the end of the intervention.

Following criteria were considered as the exclusion criteria: (1) Studies conducted on participants with age < 18 years, (2) Studies without control group or randomization, (3) Using propolis supplements in combination with other nutrients or other interventions, (4) Reporting serum levels of IL-6, CRP, and TNF-α in figures, (5)

Intervention duration less than one week, (6) Non-English RCTs.

Data extraction

Following the title and abstract assessment, all the full texts of potential studies were reviewed closely by two separate reviewers based on inclusion and exclusion criteria to detect the eligible articles. After selecting eligible articles, we extracted the following data: the first author's last name, study publication year, geographical region, participants number, participants' age, gender, and body mass index (BMI), trial design, the dose of propolis, placebo kind, intervention duration. In addition, the mean and standard deviation (SD) of IL-6, CRP, and TNF-α at baseline and after the intervention period were extracted.

Studies with more than one comparison or intervention group or more than one intervention period were considered as separate studies in systematic review and meta-analysis. Two reviewers independently executed data extraction (AGh, MH) and all disagreements resolved through group consultation between the reviewers.

Quality assessment

Two reviewers separately performed the quality assessment for each included RCTs through the Cochran scoring method [34]. This method contains following bias domains to evaluate the risk of bias including: detection bias, selection bias, performance bias, attrition bias, and reporting bias. Then, assigning a judgment of unclear, low, and high risk of material bias for each item was done and trials with ≥3 items with low risk judged as "good quality", trials with at least 2 items with low risk judged as "fair quality" and trials with <2 items with low risk judged as "weak quality".

Meta-analysis

In the present meta-analysis, we detected the overall effect sizes using extracted standard mean differences (SMD) and the SDs from both study groups through Der-Simonian and Laird method [35, 36]. We also used Hozo et al., [37] method to convert 95% confidence intervals (95%CIs), standard errors (SEs), and interquartile ranges (IQRs) to SDs and the median or range to the mean. Cochran's Q test was used to test the between-study heterogeneity and was measured by the I-squared statistic (I^2). The potential sources of heterogeneity were detected through subgroup analyses based on the pre-planned criteria including participants' age, sex, and BMI, intervention duration, sample size, propolis dose, publication year, geographical region, and quality assessment.

Determining the effect of each study on the overall effect was performed through sensitivity analysis. Subsequently, the possibility of publication bias was evaluated via the visually inspected of Begg's funnel plot, and Eggar's weighted regression and Begg's rank correlation test [38, 39]. All statistical analyses were done using stata version 15.0.

We provided all calculated effect sizes with 95% CI. A value≥50% for Cochran's Q test and a p-value≤0.10 for I-squared statistic revealed the heterogeneity between studies.

Results

Study selection

As mentioned in Fig. 1, in the first step of systematic search, 1108 studies were found in the databases. However, 337 articles were deleted due to duplication. Afterward, we assessed the titles and abstracts of remained articles exhaustively and 747 unrelated articles were removed. Furthermore, seven irrelevant studies based on exclusion criteria were removed as either not having control group ($n=1$), not randomization in trail design ($n=1$), using propolis in combination with other nutrients ($n=2$), not reporting the dose of propolis ($n=1$), combining exercise with propolis supplementation ($n=1$), and using propolis as spray form ($n=1$). After all, we included 17 appropriate RCTs with the closest characteristics to the mentioned inclusion criteria in systematic review [15–31]. Since one study did not report the serum levels of mentioned inflammatory mediators at the baseline and after intervention [18], we did not include it in our meta-analysis; therefore, the meta-analysis was conducted on sixteen studies. Since one RCT regarding serum concentration of CRP had a large effect size was removed from the meta-analysis due [29].

Study characteristics

The effect of propolis supplementation on serum levels of IL-6, CRP, and TNF-α was assessed in 10 [18–20, 22–27, 29], 9 [15, 17–19, 21–23, 29, 30], and 11 [16, 19, 20, 23–25, 27–31] RCTs (Table 1). The publication date for included studies was from 2014 until 2023. Sample size differed from 19 to 94 persons. The propolis dose ranged from 226.8 mg/day to 1500 mg/day and the intervention duration was from 1 week to 96 weeks. All trials had parallel design. Various subjects participated in included studies, like women with polycystic ovary syndrome [17], type 2 diabetes patients [20, 23, 29, 30], patients with chronic kidney disease [19], patients undergoing hemodialysis [27], HIV-infected people [24], patients with breast cancer [31], women with rheumatoid arthritis [18, 21], non-alcoholic fatty liver patients [15, 28], patients with primary pneumosepsis [22], healthy men [26], patients with dengue hemorrhagic fever [16], and elderly people living at high altitude [25]. Studies were conducted in Iran [15, 17, 21–23, 26, 28, 30, 31], Japan [18, 25, 29], Brazil [19, 24, 27], China [20] and Indonesia [16]. Three studies were on female [17, 18, 21], one study was on male

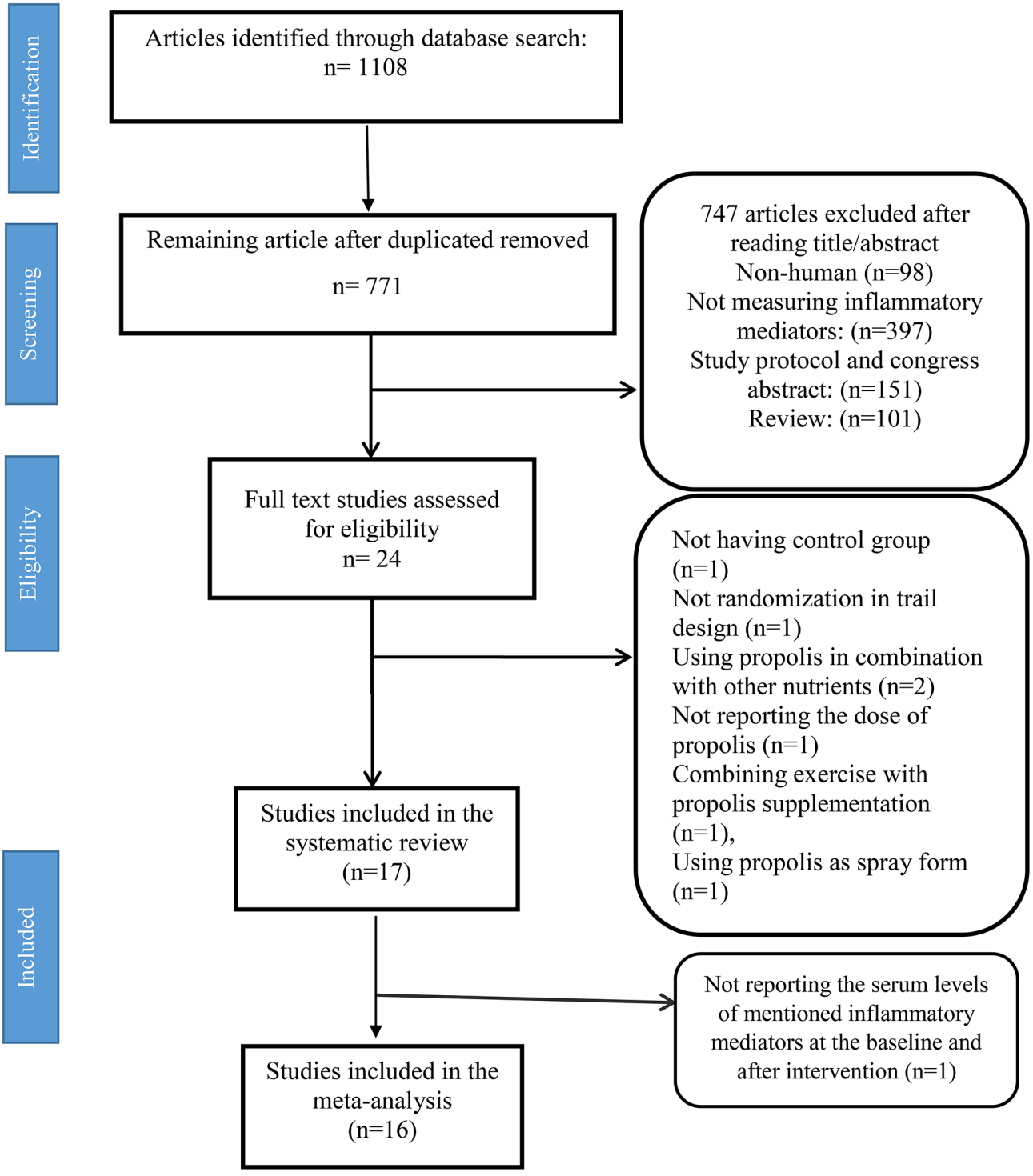

Fig. 1 Flowchart of study selection process

[26], and other studies were on both gender [15, 16, 19, 20, 22–25, 27–31]. In one study the effect of propolis was assessed after 24, 48, and 96 weeks; therefore, we considered it as three separate studies in our systematic review and meta-analysis [25]. More details are presented in Table 1.

Quality assessment

Our result showed nine studies had good quality [15, 17, 21, 22, 26–29, 31], four studies had fair quality [16, 18, 23, 30], and four studies had low quality [19, 20, 24, 25]. Six and eleven studies had a high risks of bias concerning allocation concealment [20, 24, 25, 27, 29, 30] and

Table 1 Randomized controlled trial studies included in the systematic review and meta-analysis

Code Author (year) (country)	Subjects	Age (mean ± SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
1 Abbasi, E. (2023) (Iran)	Women with polycystic ovary syndrome *N* = 57	31.07 ± 5.01	Randomized, triple-blinded, placebo-controlled clinical trial	500 mg propolis/day	Cellulose	12	CRP	CRP decreased significantly in intervention group, but compared to the control group changes were not significant
2 Afsharpour, F (2022) (Iran)	Patients with Type 2 Diabetes *N* = 60	51.81 ± 6.35	Randomized, double-blinded, placebo-controlled clinical trial	1500 mg propolis/day	Wheat flour	8	TNF-α and CRP	CRP and TNF-α decreased significantly
3 Baptista, B. G (2023) (Brazil)	Patients with chronic kidney disease *N* = 19	53.5 (17.7)$^{\varphi}$	Randomized, double-blinded, placebo-controlled clinical trial	400 mg propolis/day	cellulose	8	CRP, IL-6 and TNF-α	CRP and IL-6 did not change significantly, but TNF-α decreased significantly
4 Chermut, T. R (2023) (Brazil)	Patients undergoing hemodialysis *N* = 41	45.0 (14.0)$^{\varphi}$	Randomized, double-blinded, placebo-controlled clinical trial	400 mg propolis/day	Not mention	8	TNF-α and IL-6	IL-6 did not change significantly, but TNF-α decreased significantly
5 Conte, F. L (2021) (Brazil)	HIV-infected people *N* = 40	41.6 ± 7.24	Randomized, double-blinded, placebo-controlled clinical trial	500 mg propolis/day	Not mention	12	TNF-α and IL-6	TNF-α and IL-6 did not change significantly
6 Darvishi, N. (2020) (Iran)	Patients with breast cancer *N* = 50	49.30 ± 9.43	Randomized, double-blinded, placebo-controlled clinical trial	500 mg propolis/day	Starch	12	TNF-α	TNF-α decreased significantly in intervention group, but compared to the control group changes were not significant
7 Fukuda, T (2015) (Japan)	Patients with type 2 diabetes *N* = 80	63.7 ± 9.3	Randomized, double-blinded, placebo-controlled clinical trial	226.8 mg propolis/day	Safflower oil, wheat germ oil and perilla oil	8	CRP, IL-6, and TNF-α	CRP, TNF-α and IL-6 did not change significantly
8 Maddahi, M (2023) (Iran)	Women with rheumatoid arthritis *N* = 43	46.56 ± 1.98	Randomized, double-blinded, placebo-controlled clinical trial	1000 mg propolis/day	Corn starch	12	CRP	CRP decreased significantly
9 Matsumoto, Y (2021) (Japan)	Women with rheumatoid arthritis *N* = 80	60.0 (55.8, 65.3)$^{\varphi}$	Randomized, double-blinded, placebo-controlled clinical trial	508.5 mg propolis/day	Not mention	24	IL-6 and CRP	CRP and IL-6 did not change significantly
10 Nikbaf-Shandiz, M (2022) (Iran)	Patients with non-alcoholic fatty liver disease *N* = 44	38.52 ± 7.50	Randomized, double-blinded, placebo-controlled clinical trial	1500 mg propolis/day	Corn Starch	8	TNF-α	TNF-α decreased significantly in intervention group, but compared to the control group changes were not significant
11 Pahlavani, N (2022) (Iran)	Patients with Primary Pneumosepsis *N* = 27	58.21 ± 15.76	Randomized, double-blinded, placebo-controlled clinical trial	1000 mg propolis/day	Cellulose	1.4	IL-6 and CRP	CRP and IL-6 did not change significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age (mean ± SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
12 Soleimani, D (2021) (Iran)	Healthy men *N* = 49	24.21 ± 1.98	Randomized, triple-blinded, placebo-controlled clinical trial	900 mg propolis/day	Cellulose	4	IL-6	IL-6 decreased significantly
13 Soleimani, D (2021) (Iran)	Patients with nonalcoholic fatty liver disease *N* = 54	42.56 ± 11.2	Randomized, triple-blinded, placebo-controlled clinical trial	500 mg propolis/day	Cellulose	16	CRP	CRP decreased significantly
14 Soroy, L (2014) (Indonesia)	Patients with dengue hemorrhagic fever *N* = 63	29.04 ± 9.01	Randomized, single-blinded, placebo-controlled clinical trial	1200 mg propolis/day	Not mention	1	TNF-α	TNF-α decreased significantly
15 Zakerkish, M (2019) (Iran)	Patients with type 2 diabetes mellitus *N* = 94	55.40 ± 9.09	Randomized, double-blinded, placebo-controlled clinical trial	1000 mg propolis/day	Not mention	12	IL-6, CRP, and TNF-α	IL-6 did not change significantly, but TNF-α and CRP decreased significantly
16 Zhao, L (2016) (China)	Patients with type 2 diabetes mellitus *N* = 65	59.5 ± 8.0	Randomized, placebo-controlled clinical trial	900 mg propolis/day	Nothing	18	IL-6 and TNF-α	TNF-α decreased significantly, but IL-6 decreased significantly
17.1 Zhu, A (2018) (Japan)	Elderly people living at high altitude *N* = 60	72.28 ± 7.23	Randomized, double-blinded, placebo-controlled clinical trial	830 mg propolis/day	Not mention	24	IL-6 and TNF-α	IL-6 and TNF-α did not change significantly
17.2 Zhu, A (2018) (Japan)	Elderly people living at high altitude *N* = 60	72.28 ± 7.23	Randomized, double-blinded, placebo-controlled clinical trial	830 mg propolis/day	Not mention	48	IL-6 and TNF-α	IL-6 and TNF-α did not change significantly
17.3 Zhu, A (2018) (Japan)	Elderly people living at high altitude *N* = 60	72.28 ± 7.23	Randomized, double-blinded, placebo-controlled clinical trial	830 mg propolis/day	Not mention	96	IL-6 and TNF-α	IL-6 and TNF-α did not change significantly

Abbreviations: IL-6: Interleukin-6; CRP: C-reactive protein; RCT: Randomized controlled trial; TNF-α: Tumor necrosis factor-alpha; mg: Milligram; SD: Standard deviation; N: Number

Φ: Median (IQR)

∗: Mean ± Standard error

blinding of outcome assessment [15, 16, 18–20, 22, 24, 27–30], respectively. Incomplete outcome data was the source of risk of bias in six studies [19, 24–26, 28, 31]. More details regarding quality assessment are mentioned in Table 2.

Meta-analysis results

Propolis effect on IL-6

Eleven effect sizes from 9 trials were included to revealed the effect of propolis supplementation on serum levels of IL-6. As showed in Fig. 2A, propolis significantly decreased serum concentration of IL-6 with high heterogeneity (SMD = -3.47, 95%CI: -5.1 to -1.84, $P<0.001$; $I^2=97.9\%$, Cochrane Q test ($P<0.001$)). Subgroup analysis showed propolis supplementation reduced serum levels of IL-6 in RCTs with propolis dose ≥ 830 mg/d (SMD= -5.47, 95%CI= -8.09, -2.85; $P<0.001$) not dose < 830 mg/d (SMD= -0.62, 95%CI= -2.49, 1.25; $P=0.514$), Asian population (SMD= -4.76, 95%CI= -6.79, -2.72; $P<0.001$) not American population (SMD= -0.37, 95%CI= -3.16, 2.42; $P=0.793$) and in RCTs among participants with age < 59 years old (SMD= -2.77, 95%CI= -4.84, -0.71; $P=0.009$) not ≥ 59 years old (SMD= -4.25, 95%CI= -7.27, 1.23; $P=0.006$), BMI < 25 (SMD=-6.70, 95%CI= -11.33, -2.07; $P=0.005$) not BMI ≥ 25 (SMD= -0.44, 95%CI= -2.12, 1.24; $P=0.605$) (Table 3). According to the results of between-group heterogeneity, there was a significant heterogeneity in all subgroups (Table 3).

Table 2 Quality of bias assessment of the included studies according to the Cochrane guidelines

Author name, year of publication, references	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Abbasi, E. 2023	L	U	L	L	L	L	Good
Afsharpour, F. 2022	U	H	U	H	L	L	Fair
Baptista, B. G. 2023	U	L	U	H	H	U	Weak
Chermut, T. R. 2023	L	H	U	H	L	L	Good
Conte, F. L. 2021	L	H	U	H	H	U	Weak
Darvishi, N. 2020	L	L	U	L	H	L	Good
Fukuda, T. 2015	L	H	U	H	L	L	Good
Maddahi, M. 2023	L	L	L	L	L	U	Good
Matsumoto, Y. 2021	L	U	U	H	L	U	Fair
Nikbaf-Shandiz, M. 2022	L	L	L	H	H	U	Good
Pahlavani, N. 2022	L	U	U	H	L	L	Good
Soleimani, D. 2021	L	L	L	L	H	H	Good
Soleimani, D. 2021	L	L	L	H	L	U	Good
Soroy, L. 2014	L	U	U	H	L	U	Fair
Zakerkish, M. 2019	L	U	U	U	L	U	Fair
Zhao, L. 2016	U	H	H	H	L	U	Weak
Zhu, A. 2018	U	H	U	U	H	L	Weak

L, low risk of bias; H, high risk of bias; U, unclear risk of bias

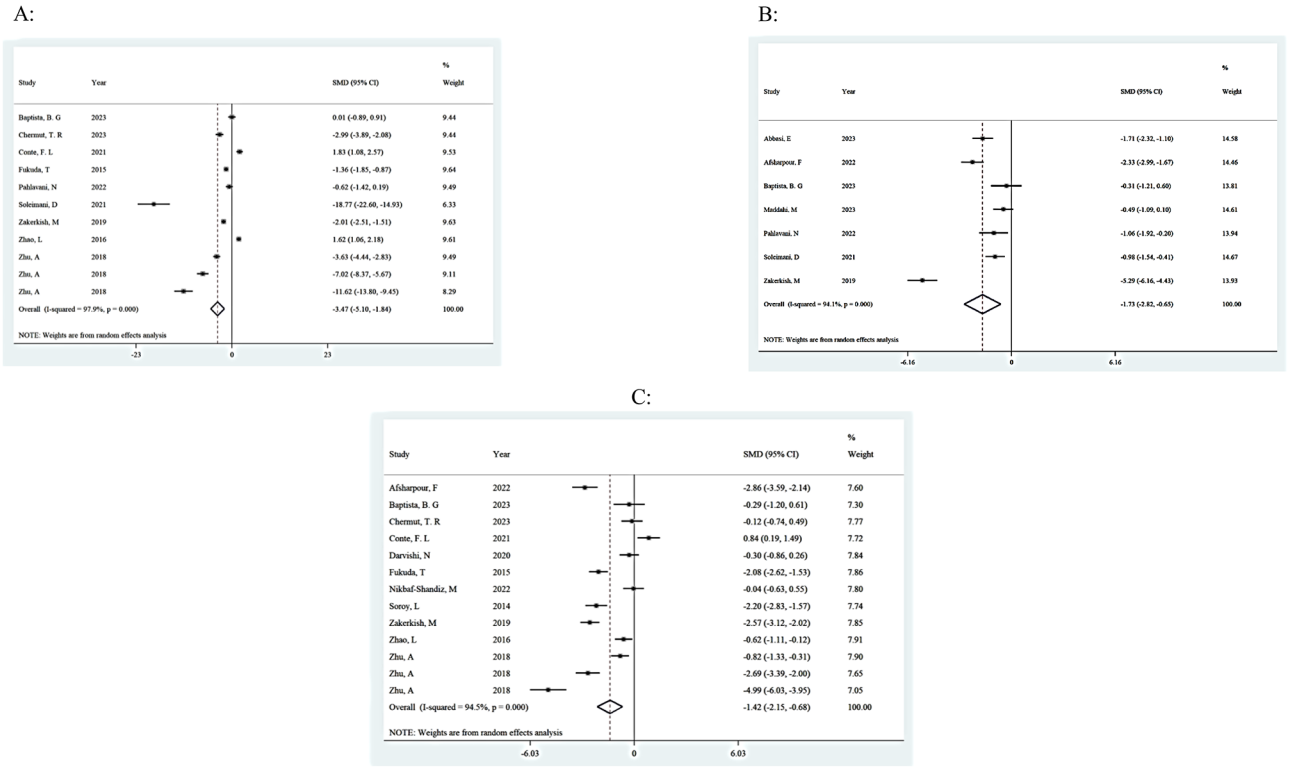

Fig. 2 Forest plot of the effect of propolis supplementation on serum concentrations of inflammatory mediators. **A**: IL-6. **B**: CRP. **C**: TNF-α.

Propolis effect on CRP

The overall effect of propolis supplementation on serum levels of CRP was evaluated with 7 effect sizes from 7 studies. Our results showed propolis supplementation significantly decreased serum levels of CRP in the comparison with control group (SMD=-1.73, 95%CI: -2.82, -0.65; $p=0.002$) with high heterogeneity (Cochrane's Q test, $p<0.001$, $I^2=94.1\%$) (Fig. 2B). Based on subgroup analysis, propolis supplementation reduced serum levels of CRP in studies among Asian

Table 3 Subgroup analyses for studies evaluating the effect of propolis on serum IL-6

	Subgroup	No. of trial	Change in IL-6 (95% CI)	*P*-value	I^2 (%)	$P_{heterogeneity}$
Total	-	11	-3.47 (-5.10, -1.84)	< 0.001	97.9	< 0.001
Propolis dose (mg/d)	< 830 mg/d	4	-0.62 (-2.49, 1.25)	0.514	96.2	< 0.001
	≥ 830 mg/d	7	-5.47 (-8.09, -2.85)	< 0.001	98.4	< 0.001
Study duration	< 84 day	5	-3.43 (-5.46, -1.40)	0.001	96.1	< 0.001
	≥ 84 day	6	-3.33 (-6.03, -0.62)	0.016	98.6	< 0.001
Sample size	< 60 persons	5	-3.22 (-5.94, -0.49)	0.021	97.4	< 0.001
	≥ 60 persons	6	-3.80 (-6.02, -1.58)	< 0.001	98.3	< 0.001
Geographical region	Americas	3	-0.37 (-3.16, 2.42)	0.793	96.9	< 0.001
	Asia	8	-4.76 (-6.79, -2.72)	< 0.001	98.2	< 0.001
Sex	Male	1	-18.77 (-22.60, -14.93)	< 0.001	-	-
	Both	10	-2.41 (-3.5, -0.87)	0.002	97.7	< 0.001
Age	< 59 year	6	-2.77 (-4.84, -0.71)	0.009	97.2	< 0.001
	≥ 59 year	5	-4.25 (-7.27, 1.23)	0.006	98.6	< 0.001
BMI	< 25	4	-6.70 (-11.33, -2.07)	0.005	97.8	< 0.001
	≥ 25	3	-0.44 (-2.12, 1.24)	0.605	97.0	< 0.001
	Unknown	4	-5.03 (-9.87, -0.20)	0.041	98.9	< 0.001
Quality assessment	Good	4	-4.58 (-7.11, -2.06)	< 0.001	96.8	< 0.001
	Fair	1	-2.01 (-2.51, -1.51)	< 0.001	-	-
	Weak	6	-3.01 (-6.00, -0.02)	0.048	98.5	< 0.001
Publication year of article	< 2019	5	-4.25 (-7.27, -1.23)	0.006	98.6	< 0.001
	≥ 2019	6	-2.77 (-4.84, -0.71)	0.009	97.2	< 0.001

IL-6: Interleukin 6, BMI: Body Mass Index, mg/d: milligram per day, CI: Confidence Interval

Table 4 Subgroup analyses for studies evaluating the effect of propolis on serum CRP

	Subgroup	No. of trial	Change in CRP (95% CI)	*P*-value	I^2 (%)	$P_{heterogeneity}$
Total	-	7	-1.73 (-2.82, -0.65)	0.002	94.1	< 0.001
Propolis dose (mg/d)	< 1000 mg/d	3	-1.06 (-1.79, -0.32)	0.005	71.3	0.031
	≥ 1000 mg/d	4	-2.28 (-4.23, -0.33)	0.022	96.5	< 0.001
Study duration	< 84 day	4	-2.09 (-3.83, -0.35)	0.018	96.6	< 0.001
	≥ 84 day	3	-1.26 (-2.48, -0.05)	0.041	85.4	0.001
Sample size	< 54 persons	3	-0.59 (-1.02, -0.16)	0.007	0.00	0.442
	≥ 54 persons	4	-2.55 (-4.14, -0.96)	0.002	95.7	< 0.001
Geographical region	Americas	1	-0.31 (-1.21, 0.60)	0.506	-	-
	Asia	6	-1.96 (-3.15, -0.77)	0.001	94.7	< 0.001
Sex	Female	2	-1.10 (-2.30, 0.09)	0.071	87.3	0.005
	Both	5	-1.99 (-3.55, -0.43)	0.012	95.4	< 0.001
Age	< 52 year	4	-1.37 (-2.14, -0.60)	0.001	84.6	< 0.001
	≥ 52 year	3	-2.22 (-5.27, 0.82)	0.153	97.2	< 0.001
BMI	< 28	4	-1.06 (-2.02, -0.10)	0.030	85.2	< 0.001
	≥ 28	3	-2.64 (-4.89, -0.38)	0.022	97.1	< 0.001
Quality assessment	Good	4	-1.06 (-1.58, -0.53)	< 0.001	62.5	0.046
	Fair	2	-3.08 (-6.70, -0.90)	0.010	96.5	< 0.001
	Weak	1	-0.31 (-1.21, 0.60)	0.506	-	-
Publication year of article	< 2022	2	-3.12 (-7.35, 1.11)	0.148	98.5	< 0.001
	≥ 2022	5	-1.20 (-1.96, -0.44)	0.002	82.7	< 0.001

CRP: C-reactive protein, BMI: Body Mass Index, mg/d: milligram per day, CI: Confidence Interval

population (SMD= -1.96, 95%CI: -3.15, -0.77; $p=0.001$) not American population (SMD= -0.31, 95%CI: -1.21, 0.60; $p=0.506$), both gender (SMD= -1.99, 95%CI: -3.55, -0.43; $p=0.012$) not female (SMD= -1.10, 95%CI: -2.30, 0.09; $p=0.071$), participants with age < 52 years old (SMD= -1.37, 95%CI= -2.14, -0.60; $p=0.001$) not ≥ 52 years old (SMD= -2.22, 95%CI= -5.27, 0.82; $p=0.153$), and studies with good (SMD= -1.06, 95%CI: -1.58, -0.53; $p<0.001$) and fair quality (SMD= -3.08, 95%CI= -6.70, -0.90; $p=0.010$) not weak quality (SMD= -0.31, 95%CI= -1.21, 0.60; $p=0.506$) (Table 4). The between-group heterogeneity was significant in all subgroups except in

studies with <54 subjects (Cochrane's Q test, $p=0.442$, $I^2=0.00\%$) (Table 4).

Propolis effect on TNF-α

Thirteen effect sizes from eleven studies were used to assess the overall effect of propolis supplementation on serum levels of TNF-α. According to the overall results, the levels of TNF-α significantly reduce following propolis supplementation (SMD= -1.42, 95%CI= -2.15, -0.68; $p<0.001$). There was also significant heterogeneity based on I^2 index (94.50%) and Cochrane Q test (P<0.001). (Fig. 2C). Subgroup analysis indicated propolis supplementation significantly reduced serum levels of TNF-α in trails with propolis dose≥830 mg/d (SMD= -2.06, 95%CI= -2.99, -1.12; $p<0.001$) not <830 mg/d (SMD= -0.40, 95%CI= -1.41, 0.61; $p=0.438$), sample size≥60 subjects (SMD= -2.30, 95%CI= -3.10, -1.50; $p<0.001$) not <60 subjects (SMD=0.03, 95%CI= -0.39, 0.44; $p=0.903$), fair (SMD= -2.52, 95% 95%CI= -2.88, -2.16; $p<0.001$) and weak quality (SMD= -1.39, 95%CI= -2.70, -0.09; $p=0.036$) not good quality (SMD= -0.64, 95%CI= -1.62, 0.34; $p=0.200$), publication year<2019 (SMD= -2.17, 95%CI= -3.17, -1.17; $p<0.001$), not ≥2019 (SMD= -0.76, 95%CI= -1.80, 0.27; $p=0.148$) and trials among both gender (SMD= -1.51, 95%CI= -2.30, -0.73; $p<0.001$) not female (SMD= -0.30, 95%CI= -0.86, 0.26; $p=0.293$), and participants with age≥54 years old (SMD= -1.97, 95%CI= -2.93, -1.02; $p<0.001$) not <54 years old (SMD= -0.77, 95%CI= -1.84, 0.29; $p=0.155$) (Table 5). The between-group heterogeneity was significant in all subgroups except in studies with fair quality (Cochrane's Q test, $p=0.396$, $I^2=0.00\%$) (Table 5).

Publication bias, meta-regression analysis, and sensitivity analysis

The results of dose-response meta-regression revealed there was a non-significant linear association between the dose of propolis supplement and the overall effect size for IL-6, CRP, and TNF-α ($p=0.351$, $p=0.402$, $p=0.351$; Fig. 3A, B, and C, respectively). Visual examination of the funnel plots for IL-6 revealed publication bias which confirmed by the results of Egger's test ($p=0.036$) and Begg's test ($p=0.016$) (Fig. 4A). Funnel plots for CRP and TNF-α revealed nonsymmetrical visual; however, the results of Egger's and Begg's test revealed no evidence of publication bias (Egger's test $p=0.439$, Begg's test $p=0.453$; Egger's test $p=0.223$, Begg's test $p=0.393$, respectively) (Fig. 4B and C). The result of sensitivity analysis showed excluding no trial caused significant changes in the overall effect size of propolis on IL-6, CRP, and TNF-α (Fig. 5A and B, and 5C).

Discussion

This study was an updated systematic review and meta-analysis regarding propolis supplementation effect on serum levels of IL-6, CRP, and TNF-α. Our results suggested that propolis supplementation decreased serum levels of IL-6, CRP, and TNF-α. These results were

Table 5 Subgroup analyses for studies evaluating the effect of propolis on serum TNF-α

	Subgroup	No. of trial	Change in TNF-α (95% CI)	P-value	I^2 (%)	$P_{heterogeneity}$
Total	-	13	-1.42 (-2.15, -0.68)	<0.001	94.5	<0.001
Propolis dose (mg/d)	<830 mg/d	5	-0.40 (-1.41, 0.61)	0.438	92.1	<0.001
	≥830 mg/d	8	-2.06 (-2.99, -1.12)	<0.001	94.5	<0.001
Study duration	<84 day	6	-1.27 (-2.26, -0.28)	0.012	92.8	<0.001
	≥84 day	7	-1.55 (-2.69, -0.42)	0.007	96.0	<0.001
Sample size	<60 persons	5	0.03 (-0.39, 0.44)	0.903	50.8	0.087
	≥60 persons	8	-2.30 (-3.10, -1.50)	<0.001	92.7	<0.001
Geographical region	Americas	3	0.17 (-0.54, 0.88)	0.633	66.5	0.051
	Asia	10	-1.88 (-2.66, -1.09)	<0.001	94.1	<0.001
Sex	Female	1	-0.30 (-0.86, 0.26)	0.293	-	-
	Both	12	-1.51 (-2.30, -0.73)	<0.001	94.7	<0.001
Age	<54 year	6	-0.77 (-1.84, 0.29)	0.155	94.3	<0.001
	≥54 year	7	-1.97 (-2.93, -1.02)	<0.001	93.8	<0.001
BMI	<25.8	4	-1.20 (-2.31, -0.09)	0.035	91.3	<0.001
	≥25.8	5	-1.27 (-2.38, -0.16)	0.025	94.6	<0.001
	Unknown	4	-1.88 (-3.95, 0.18)	0.073	97.3	<0.001
Quality assessment	Good	4	-0.64 (-1.62, 0.34)	0.200	91.3	<0.001
	Fair	3	-2.52 (-2.88, -2.16)	<0.001	0.00	0.396
	Weak	6	-1.39 (-2.70, -0.09)	0.036	95.7	<0.001
Publication year of article	<2019	6	-2.17 (-3.17, -1.17)	<0.001	93.8	<0.001
	≥2019	7	-0.76 (-1.80, 0.27)	0.148	93.8	<0.001

TNF-α: Tumor Necrosis Factor alpha, BMI: Body Mass Index, mg/d: milligram per day, CI: Confidence Interval

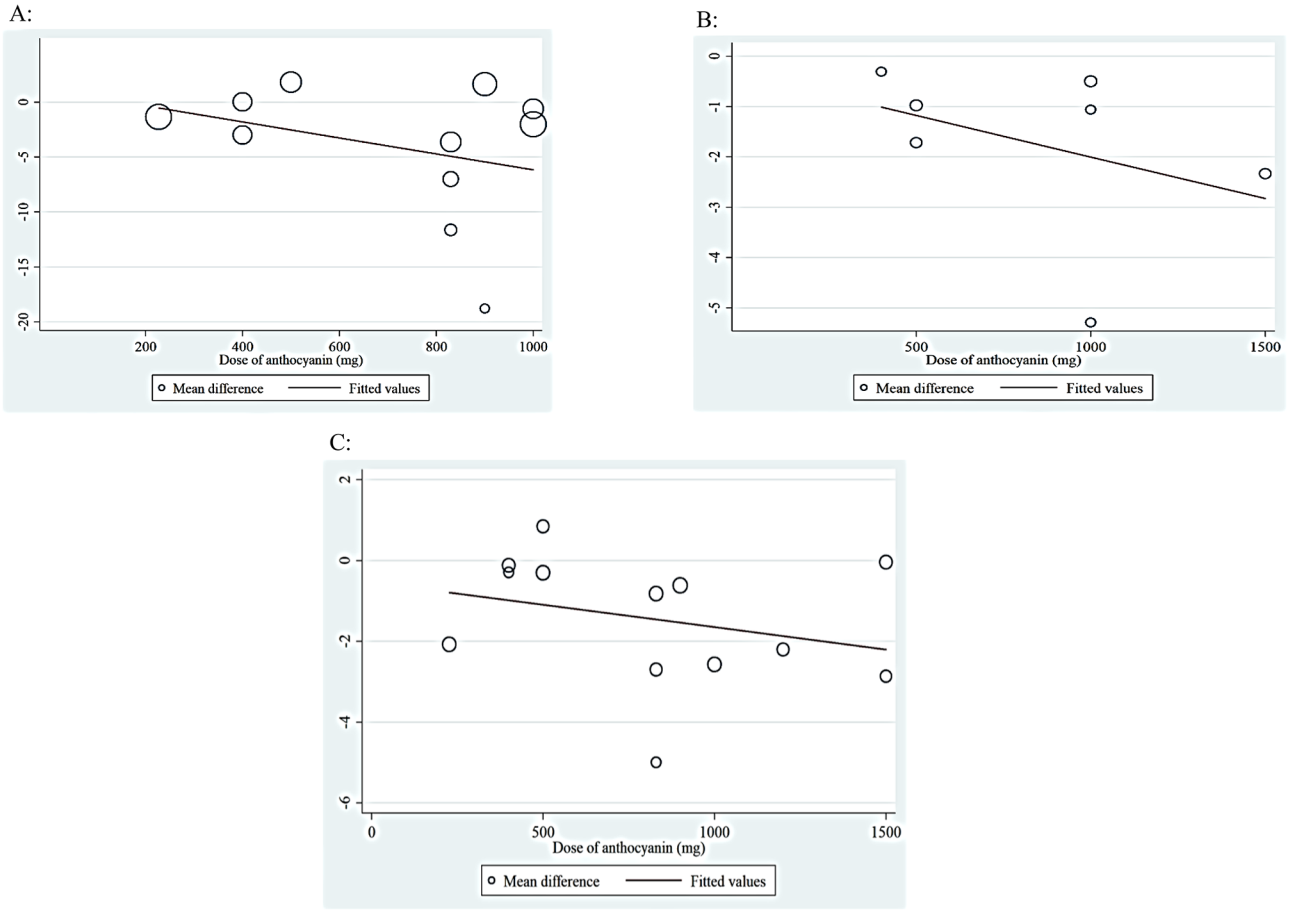

Fig. 3 Meta-regression plot of the effect of propolis supplementation dose on the studied inflammatory mediators. **A**: IL-6; **B**: CRP; **C**: TNF-α.

obtained from 11, 7, and 13 data points from 9, 7, and 11 studies evaluating propolis supplementation effect on IL-6, CRP, and TNF-α, respectively. Our findings are in consistent with the results of previous systematic reviews and meta-analyses [32, 33].

Subgroup analysis showed following propolis supplementation IL-6 significantly reduced in studies with propolis dose ≥ 830 mg/d not dose < 830 mg/d, participants age < 59 years old not ≥ 59 years old, BMI < 25 not ≥ 25, and Asian participants not American. Subgroup analysis results also revealed that propolis significantly reduced TNF-α in studies with propolis dose ≥ 830 mg/d not propolis dose < 830 mg/d, sample size ≥ 60 subjects not < 60 subjects, Asian population not American, participants age ≥ 54 years old not < 54 years old. The results of subgroup analysis regarding CRP showed that there was a significant effect of propolis supplementation on CRP levels in subgroups with more than 2 effect sizes. Moreover, dose-response analysis results showed a non-significant effect of propolis supplementation dose on serum levels of IL-6, CRP, and TNF-α.

High serum levels of inflammatory mediators such as IL-6, CRP, and TNF-α are associated with oxidative stress and chronic inflammation that causes different diseases such as T2DM [20, 40]. According to the results of in vivo and in vitro studies, propolis have strong anti-inflammatory effects and directly decreased inflammatory mediators [41, 42]. Although, its effects on inflammatory mediators among humans have been inconsistently reported, in this study we highlight that serum levels of IL-6, CRP, and TNF-α were all significantly reduced following propolis supplementation.

The main mechanisms involved in propolis anti-inflammatory action include free radical scavenging, the inhibition of prostaglandin and cyclooxygenase biosynthesis and nitric oxide synthesis, and the reduction of inflammatory cytokines secretion [43]. Propolis has different ingredients such as steroids, phenols, aldehydes, propolins, phenolic acids, amino acids, flavonoids, terpenes, and ketones [43, 44]. Moreover, propolis contains chlorogenic acid and caffeic acid which provide the molecular basis for its anti-inflammatory role [45]. Caffeic acid phenethyl ester (CAPE) is an inhibitor of NF-κB activation and reduces gene expression of inflammatory mediators [46]. Furthermore, the antioxidant activity of flavonoids, a component of propolis, is attributed to their

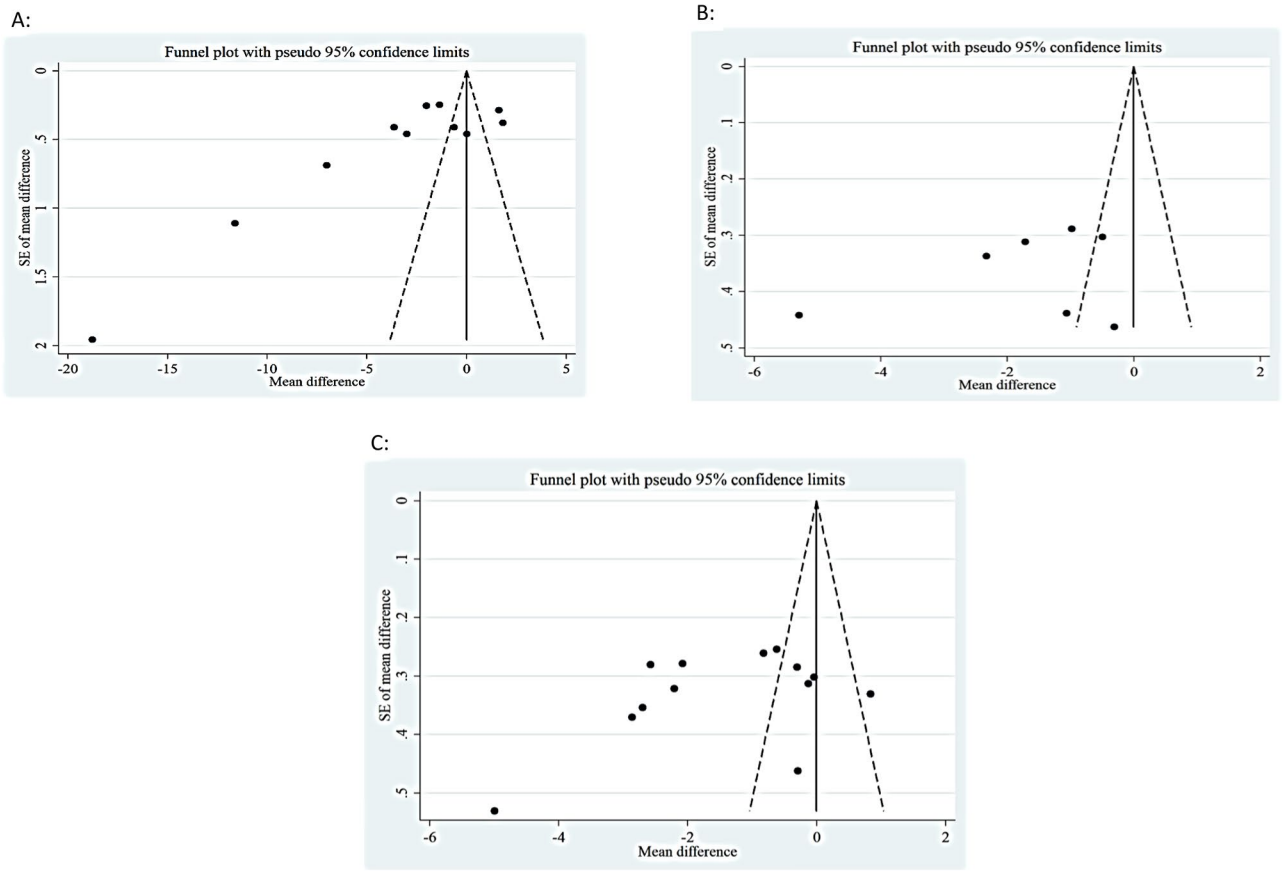

Fig. 4 Funnel plots for the studies of the effects of propolis supplementation on serum concentration of studied inflammatory mediators. **A**: IL-6; **B**: CRP; **C**: TNF-α.

ability to reduce free radical formation and anti-oxidant activity [47]. Since the reduction of oxidative stress can reduce inflammation; therefore, propolis also through anti-oxidative activity can execute inflammation reduction. Evidence also proposed that propolis supplementation might reduce inflammation by downregulating cyclooxygenase 2 and c-Jun-N-terminal kinase expression [41].

According to our subgroup analysis results, geographical region was the critical point to get the beneficial effect. Our results revealed in studies among Asian population propolis can significantly reduce serum levels of IL-6 and TNF-α, but this effect did not indicate in American population. These results might be due to different kind of propolis which used in Asian population (Asian propolis) and American population (Brazilian propolis). Unfortunately, despite extensive research on propolis, scientific evidence comparing propolis benefits from different geographical regions are not enough. In one study, bioactivity and metabolite profile of Chinese propolis and Brazilian propolis were compared and the scientists suggested although Chinese propolis and Brazilian propolis have similar anti-inflammatory potential, but they contained very different levels of total flavonoids, ethanol extract, and total phenolic acids [48].

Another finding of present study based on subgroup analysis results is that high dose of propolis is more beneficial (≥830 mg/d). In another meta-analysis also showed a stronger effect of propolis in dosage>1000 mg/d on oxidative stress parameters [49] which seems to be due to the high levels of polyphenols and flavonoids in high dosages. However, in this study there was a non-significant linear association between the dose of propolis and overall effect size for all studied inflammatory mediators. Our subgroup analysis results also revealed participants' BMI and age and sample size might be another critical points to get the beneficial effect.

Since the heterogeneity was significant regarding all inflammatory mediators even in most subgroups, the results of our study should be interpreted with caution. We suggest following reasons for the heterogeneity of present study: (1) Included trails had different blinding types for example one trial was not blind [20], one trial was single blind [16], two trials were triple blind [15, 26], other trials were double blind, and in one trial control group was given nothing [20]; (2) The range of

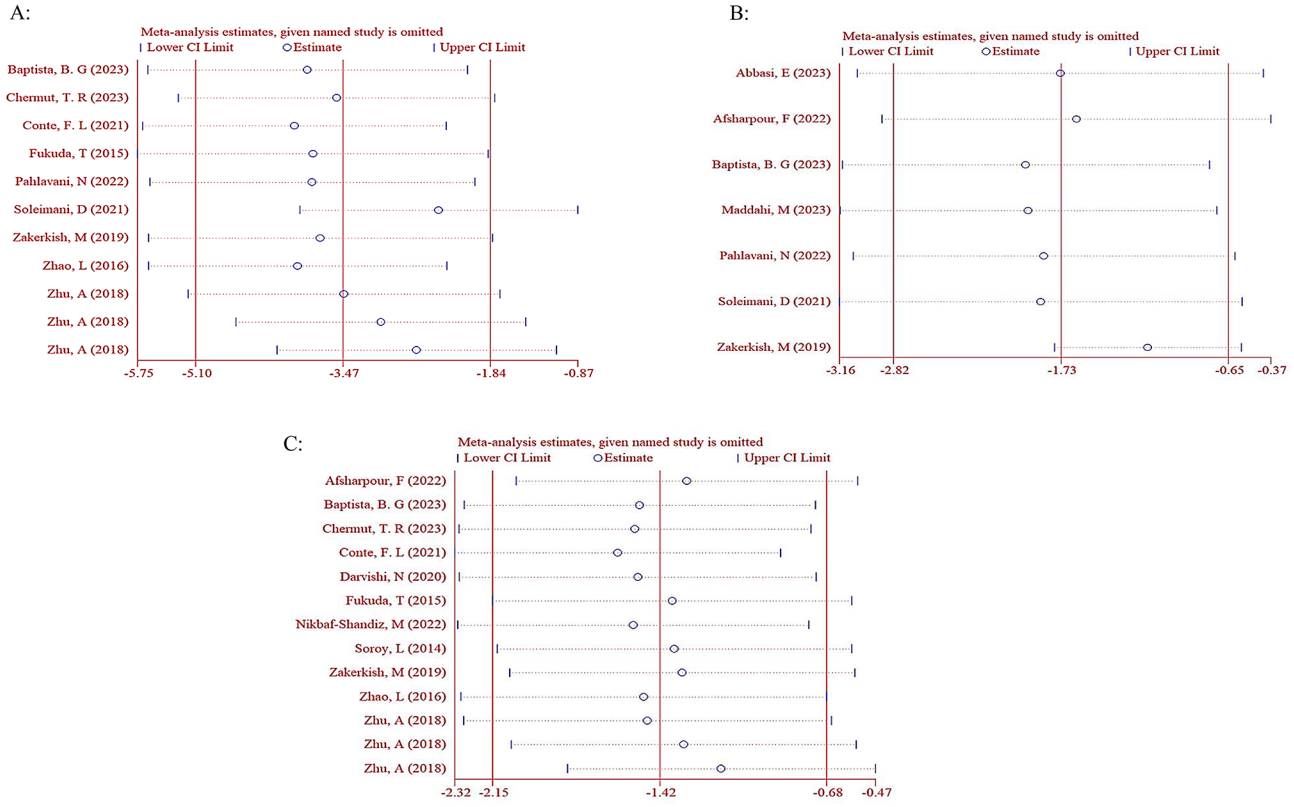

Fig. 5 Sensitivity analysis for the studied inflammatory mediators. **A**: IL-6. **B**: CRP. **C**: TNF-α.

intervention duration and propolis dose was very wide; (3) Trials were conducted on participants with different diseases which affect baseline serum levels of inflammatory mediators; (4) Due to different levels of total flavonoids, ethanol extract, and total phenolic acids in different kinds of propolis using varied propolis in trails might be another reason for heterogeneity.

Our results also revealed a significant publication bias for IL-6 which might be due to the rejection by reviewers or editors, conflict of interest, not revising the manuscript, lack of motivation to write the results in spite of conducting the study.

The present study has some strengths and limitations. We should note that systematic review and meta-analysis is at the top of the hierarchy of clinical evidence; moreover, finding all trials that assessed the effect of propolis supplementation was performed through designing a comprehensive search strategy and searching 5 databases. Our systematic search also was done without any limitation on publication time. We removed all trials that used other interventions besides propolis; therefore, their confounding effects were limited. Furthermore, we performed certain subgroup analyses to achieve more complete results.

Our study had some limitations beside its strengths. First of all, we found significant heterogeneity which did not reduce through subgroup analysis. Secondly, studies have used different types of propolis, and differences in their biological functions were unclear. Thirdly, participants' clinical condition was not similar. Fourthly, the number of included studies especially in subgroup analysis were low; therefore, our findings might be biased. Fifthly, the numbers of participants in the most studies were few and intervention duration was short in most of them. Sixthly, due to lack of enough studies separately on men and women the effect of propolis supplementation separately on men and women remained unclear. Sixthly, all included studies were conducted in American and Asian countries; therefore, the effect of geographical region on propolis supplementation effect remained unclear. Finally, one study regarding serum levels of CRP did not included in our meta-analysis; however, exclusion of that study did not change our overall results [29].

Conclusion

According to our result, propolis reduced serum levels of IL-6, CRP, and TNF-α; therefore, it might be considered as complementary therapy for the treatment of certain chronic diseases. Our result also revealed higher dose and Asian type of propolis might be more efficient to improving inflammatory mediators. However, due to significant heterogeneity more high-quality trials with

broad dosage ranges, larger sample sizes, conducted in different countries and using various type of propolis are warranted to firmly establish the clinical efficacy of propolis.

Abbreviations

BMI	Body mass index
CAPE	Caffeic acid phenethyl ester
CRP	C-reactive protein
CIs	Confidence intervals
CVD	Cardiovascular disease
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IQRs	Interquartile ranges
MeSH	Medical subjects heading
NF-κB	Nuclear factor of kappa
RCTs	Randomized clinical trials
SD	Standard deviation
SMD	Standard mean differences
SEs	Standard errors
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-alpha
TGF-β	Transforming growth factor-β

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Author contributions
The design of search strategy was done by AGh. MH and AGh performed the systematic search and finding relevant RCTs. Data extraction was performed by MH and ND. AGh performed statistical analysis. The manuscript was written by All authors. All discrepancies in every stage were solved through group discussions.

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Data availability
The data presented in this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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