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Effects of ginseng on C-reactive protein level: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Objective: The aim of this meta-analysis was to assess effects of ginseng supplementation on CRP/hs-CRP levels in clinical trial studies.
Design: A systematic literature search was carried out for clinical trials published in ISI web of Science, Scopus, PubMed and Cochrane Library databases from the beginning to 16th February 2018. Of 83 articles found in the first step of the systematic search, seven studies with nine arms included in this meta-analysis.
Results: Results of pooled random-effect size analysis of nine trials showed non-significant decreasing effects of ginseng supplementation on CRP level (WMD: −0.1 mg/l, 95% CI, −0.26, 0.1; P = 0.27) with significant heterogeneity shown within the studies. The subgroup analysis showed that ginseng supplementation could significantly reduce CRP level by 0.51 (95% CI: −0.68, −0.34; P < 0001, test for heterogeneity: P = 0.44, I^2 = 0.0%) in patients with a baseline serum CRP level of greater than 3 mg/dl. Trial duration and dose of ginseng supplementation included no significant effects on CRP level in this meta-analysis.
Conclusion: Results of the current meta-analysis study have shown that ginseng supplementation can decrease significantly serum CRP/hsCRP levels in patients with elevated serum level of this inflammatory marker.

1. Introduction

Red ginseng (RG) is a product of Panax herb which have been used in herbal medicine for a long time to treat various diseases. This type of ginseng can be obtained by steaming the fresh ginseng; also known as white ginseng.[1] With a concept of “all healing”, Panax stemmed from a traditional belief that ginseng could be used for the treatment of all human illnesses.[2] Experimental studies have revealed beneficial effects of ginseng on post-prandial glycemia[3] and treatment of cardiovascular diseases.[4] Ginsenosides are saponin triterpene compounds with more than 20 types which are known as active constituents of ginseng.[5] Anti-hyperlipidemic and antioxidant effects of various ginsenosides of ginseng, including Rb1, Rg1, Rg3 and Rh2, have been proven previously in experimental and human studies.[6–8] Furthermore, it has been shown that the vinegar extract form of Panax ginseng (i.e ginsam) can improve glucose homeostasis in experimental studies in rats.[9] The ginsenosides or their metabolites include the ability to influence inflammatory signaling pathways such as nuclear factor kappa β (NFkB) and activator protein 1 (AP-1) and exert their inflammation suppressing effects.[10]

Belonged to pentraxin family, C-reactive protein (CRP) is an acute phase reactant protein which can be used as predictor in CVDs. Serum level of this marker could increase rapidly up to 1000-fold in initial stages of inflammation which can justifying its clinical use.[11] This biomarker has constant plasma half-life and its level determined solely by synthesis through pathologic conditions stimulating CRP production.[12] Because of this CRP characteristic and its relatively low cost, the protein can be used greatly in identification of patients who are at increased risk of CVDs.[13] High-sensitivity assays of CRP have been developed in current years which can detect minimal levels of CRP at a sensitivity range of 0.01–10 mg/l. High-sensitivity CRP (hs-CRP) levels can help recognizing low grades of inflammation when there are no evident systemic inflammatory or immunologic disorders.[14] Increased levels of hs-CRP are associated to higher mortality rates in various cancers including lung, breast and renal cell carcinoma.[15]

Experimental studies showed that ginsenosides including GRb1 and G-Rg1 could reduce TNF-α production or inhibit inflammation induced through IRAC activation.[16,17] The anti-inflammatory effects of ginseng supplementation on CRP/hs-CRP levels have been studied recently in clinical trial studies. One study in acute myocardial infarction (AMI) patients showed that using red ginseng supplement for eight months

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could significantly reduce IL-6, TNF-α, s-ICAM-1 and s-VCAM-1 while having no beneficial effects on hs-CRP levels, compared to those in placebo group.[18] Another study on menopausal women revealed no significant decreasing effects of red ginseng on hs-CRP levels when consumed daily with doses of 3 gr for 12 weeks. However, Hosseini et al. in a study on type-2 diabetic patients showed that using standardized extract of ginseng (G115) for eight weeks could significantly decrease hs-CRP levels in these patients.[19] Because of these conflicting results, the aim of the current meta-analysis study was to assess effect of ginseng supplementation on CRP levels in clinical trial studies.

2. Materials and methods

2.1. Search strategy and study selection

This systematic review was carried out according to PRISMA guidelines. PubMed, Scopus, ISI Web of Science and Cochrane Library databases were searched from beginning to 16th February 2018 using the following terms in titles, abstracts and keywords: "CRP or C-reactive protein or C reactive protein or high-sensitivity CRP or hs-CRP or HSCRP or high sensitivity CRP" in combination with "ginseng or Panax or quinquefolius or notoginseng" without restriction to language. Furthermore, conference papers and meeting abstracts were searched in Scopus and ISI Web of Science. Associated articles from reference lists of eligible articles were manually searched as well.

2.2. Inclusion and exclusion criteria

Studies with the following criteria were included in the meta-analysis: 1) trials which assessed the effects of ginseng on CRP levels for minimum of one week in adults with any healthy status, 2) trials with placebo or control group and 3) reported mean or median values of CRP in baseline and at the end of intervention in both groups. The exclusion criteria included: 1) combined supplementation of ginseng with other herbal medicine, vitamins and minerals, 2) trials with no control or placebo groups, 3) observational studies, and 4) studies without sufficient data. PICO framework was developed for selecting included studies as Participants: all populations, Intervention: ginseng prescription, Comparison: control group consuming placebo, Outcome: serum CRP level.

2.3. Data extraction and quality assessment

First, duplicated studies removed and then two independent authors (OA, MZ) screened titles and abstracts for relevance to the topic. Full texts of the selected studies were found and assessed for eligibility. Disagreements in any stages of the selection were solved by discussion or help of a third author (EY). Cochrane collaboration modified tool was used for quality assessment of the included trials. This tool assesses risk of biases in the trials based on random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting and other biases.[20] The following characteristics of selected studies were collected using extraction forms, including first author, year of publication, origin of the study country, number of samples in control and intervention groups, types and doses of ginseng, sex, mean age and mean BMI of the participants, baseline and final CRP levels in both groups. The CRP levels were reported as mg/l.

2.4. Data synthesis and statistical analysis

Stata Software v.12.0 (Stata Corporation, College Station, TX, USA) was used for the statistical analysis in this meta-analysis. Mean and standard deviation (SD) of CRP concentrations in baseline and final stage of the interventions in both groups were used for the analysis. The mean change (S.D) for CRP concentration were calculated and used for estimation of the overall effect size of the supplementation. If S.D change was not reported in studies, following formula was used for its calculation: S.D change = square root [(S.D baseline^2 + S.D final^2)-(2 × R × S.D baseline × S.D final)]. A correlation coefficient of 0.8 was considered as R-value of the above-mentioned formula.[21] Reported median with range or confidence intervals were converted to mean and SD using an original method by Hozo et al.[22]. Cochran's Q-test at a $P < 0.05$ significance value and I^2 statistic test were used respectively for testing the heterogeneity and estimating the percentage of heterogeneity between the studies.[23] Sub-group analysis was carried out based on baseline levels of CRP, doses of ginseng supplementation and trial durations to find the possible sources of heterogeneity. Sensitivity analysis was performed to estimate effects of omitting each trial on the pooled effect. For testing the existence of publication bias, funnel plot, Beg test and Egger's regression asymmetry test were used. P-values < 0.05 were considered as significant in all analyses.

3. Results

3.1. Search results and study selection

Of the 83 studies found in the systematic search of literature in PubMed, Scopus, Cochrane's Library and ISI Web of Science databases, 38 were excluded due to duplication and the other 45 studies used for title/abstract screening. Of these studies, 36 studies were excluded due to lack of control groups, combined supplementations and missing the relevant data. Then, full texts of studies were retrieved and checked for eligibility and qualitative control. At the end of selection process, seven studies with nine arms were included in the meta-analysis. All studies were designed in randomized placebo controlled. Flowchart of the study selection process is shown in Fig. 1.

3.2. Study characteristics

Included studies were carried out from 2011 to 2014 in Korea[7,18,24–26] and Iran[19,27] with 210 subjects in intervention and 210 subjects in control groups. Mean BMI of the participants included 22.03–29.7 kg/m^2 and the mean age were between 43.1–61.4 years. Duration of intervention included 4–24.8 weeks with the median of

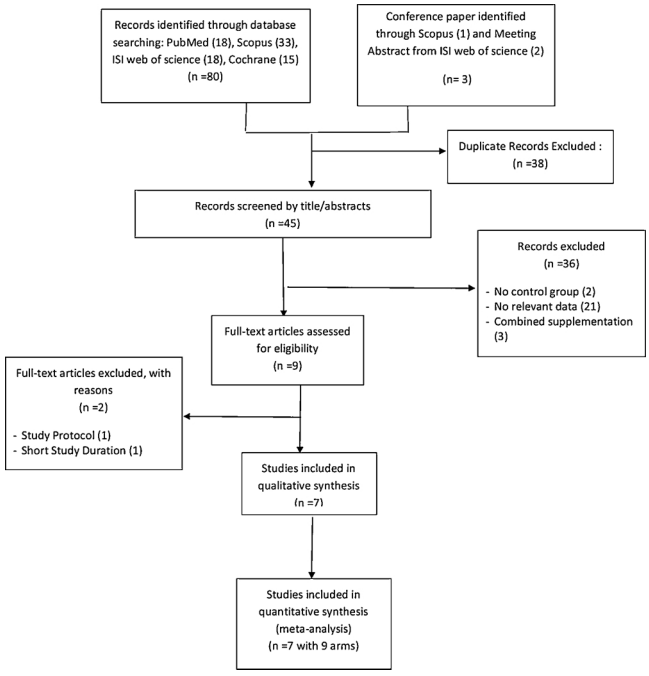

Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

Table 1
Characteristics of included studies in the meta-analysis of ginseng supplementation on CRP level.

Author	Year	Country	Study design	participants	sex	Trial duration(week)	Type and daily dose of ginseng (mg)	Sample size in Intervention/control group	Jadad score
Ahn[18]	2011	Korea	R/PC/DB	Patients with ST-segment elevation MI	M/F	34.28	Red ginseng extract(3000 mg)	25/25	3
Yoon.[24] Three arms	2012	Korea	R/PC/DB	Type 2 diabetic patients	M/F	8/8/8	Vinegar extract from Panax ginseng(1500/2000/3000 mg)	18/18	4
								18/18	
								18/18	
Kim[7]	2012	Korea	R/PC/DB	Healthy postmenopausal women	F	12	Ginseng extracts (3000 mg)	36/36	4
Park[26]	2012	Korea	R/PC/DB	Subjects with metabolic syndrome	M/F	12	Red ginseng (KRG) supplementation(4500 mg)	23/25	4
Delui[27]	2013	Iran	R/PC/DB	Patients with cardiovascular risk factors	M/F	8	Ginseng extracts(500 mg)	20/20	4
Hosseini[19]	2014	Iran	R/PC/DB	Type 2 diabetic patients	M/F	8	Standardized extract of ginseng (G115)(300 mg)	20/20	4
Jung[25]	2014	Korea	R/PC/DB	Men with metabolic syndrome	M	4	Red ginseng(300 mg)	32/30	4

Abbreviations: DBdouble-blinded; PCplacebo-controlled; Rrandomized.

eight weeks. Intervention doses were between 300–4500 mg/day with the median of 2000 mg/day. Baseline serum CRP levels ranged 0.13–4.89 mg/l with a median of 1.2 mg/l in intervention and 0.14–5.11 mg/l with a median of 1.3 mg/l in control groups (Table 1). Table 2 describes risk of bias assessment of included studies in this meta-analysis.

3.3. Meta-analysis and sub-group analysis

Results from meta-analysis of the nine trials showed non-significant effects of ginseng on CRP levels (WMD: −0.1 mg/l, 95% CI, −0.26, 0.1; P = 0.27; Fig. 2) with significant heterogeneity shown in studies (test for heterogeneity: P < 0.001; I^2 = 81.9%). Subgroup analysis was carried out according to the baseline CRP levels, duration weeks of trial and doses of intervention. Results showed that ginseng could reduce the CRP level by 0.51 (95% CI: −0.68, −0.34, P < 0001; test for heterogeneity: P = 0.44, I^2 = 0.0%) only in group with a baseline serum CRP of > 3 mg/dl. However, trial durations and doses of ginseng included no significant effects on the CRP level (Table 3).

3.4. Sensitivity analysis

To test omission of each study effect on pooled effect size, sensitivity analysis was carried out. The range of pooled effect size was between 0.0002 (% CI: −0.09, 0.09) and −0.13 (95% CI: −0.33, 0.06) (Fig. 3).

3.5. Publication bias

The Beg test (P = 0.83) and Egger test (P = 0.72) showed no publication bias. The funnel plot is shown in Fig. 4.

4. Discussion

The purpose of the current meta-analysis was assessing the effects of ginseng supplementation on serum CRP levels. Results showed that ginseng supplementation included no significant decreasing effects on serum CRP level. However, when patients were divided based on the baseline serum CRP level, sub-group analysis showed that ginseng supplementation could significantly decrease serum CRP levels when the CRP baseline level was greater than 3 mg/dl. It seems that CRP levels respond well to supplements with confirmed anti-inflammatory properties when patients having greater risk of CVD[28] as earlier meta-analysis studies concluded significant decreasing effects of vitamin E and alpha-lipoic acid supplementations only in patients with baseline serum CRP of > 3 mg/dl.[29,30] Sub-group analysis based on trial duration or doses of supplements in the current study did not show any significant differences in response to supplementation in sub-divided study groups.

One possible mechanism explaining anti-inflammatory action of ginseng is that this herb could down-regulate the gene expression of inducible nitric oxide synthase (iNOS), cyclo-oxygenase 2 (COX-2) and TNF-α by blocking the activities of nuclear factor kappa B (NFkB) through reducing the phosphorylation and degradation of inhibitory kappa B (IkB). Fermented ginseng (FG) could inhibit the binding of P65 subunit of NFkB to DNA in a dose-dependent manner.[31] These properties of ginseng could be attributable to the one bacterial metabolite of G-Rb, compound K (CK), which can also suppress the expression of pro-inflammatory cytokines through the down-regulation of IRAK-1, MAPKs, IKK-α and NF-κB.[16] Another mechanism is that FG could inhibit NFkB activation via down-regulation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) and c-Jun N-terminal kinases (JNK) phosphorylation[31] (Fig. 5).

Ginsenosides are active components of various ginsengs responsible for several pharmacological properties of these medicinal herbs, including anti-oxidative and anti-inflammatory effects.[32,33] Studies have shown that G-Rb1 can inhibit the production of TNF-α in

Table 2
Risk of bias assessment of studies included to meta-analysis.

Author	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data (Attrition bias)	Reporting bias	Other sources of bias
Ahn[18]	L	U	U	U	L	U	L
Yoon[24]	L	U	U	U	L	U	L
Kim[7]	L	L	L	U	L	U	L
Park[26]	L	L	U	U	L	U	L
Delui[27]	U	U	U	U	L	U	L
Hosseini[19]	L	U	U	U	L	U	L
Jung[25]	L	U	U	U	U	U	L

Abbreviations: H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

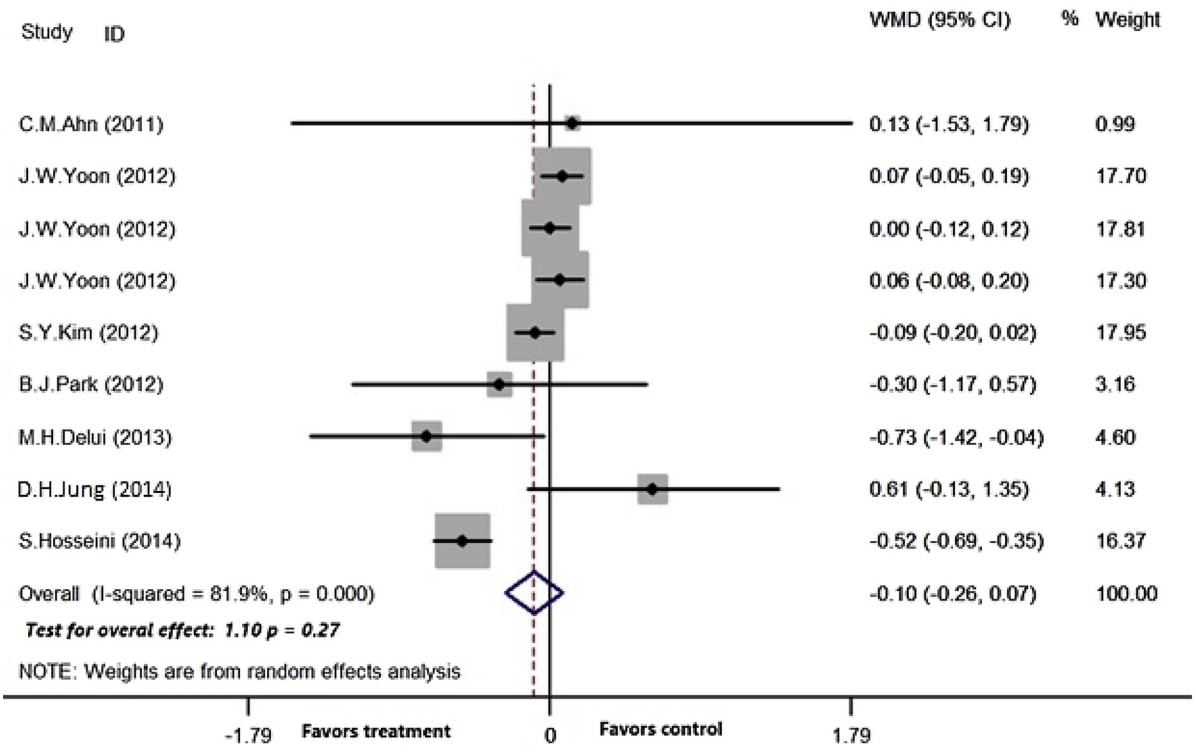

Fig. 2. Pooled effect size of ginseng supplementation on C-reactive protein (mg/l). WMD, weighted mean difference.

Table 3
Subgroup analyses of the effect of ginseng supplementation on CRP levels.

	NO	WMD (95% CI)	P within group	P heterogeneity	I^2
Dosage					
≤1500 mg	4	−0.17 (−0.63, 0.28)	0.45	< 0001	91.2 %
> 1500 mg	5	−0.01 (−0.08, 0.05)	0.71	0.4	0.5 %
Trial duration					
≤8 weeks	6	−0.09 (−0.32, 0.13)	0.42	< 0001	88.5%
> 8 weeks	4	−0.09 (−0.20, 0.01)	0.1	0.86	0.0%
Baseline level of CRP					
0–1 mg/dl	4	0.005 (−0.06, 0.07)	0.89	0.22	31.9%
1-3 mg/dl	3	−0.14 (−0.96, 0.67)	0.73	0.03	70.8%
> 3 mg/dl	2	−0.51 (−0.68, −0.34)	< **0001**	0.44	0.0%

Abbreviations: CI, confidence interval; CRP, C-reactive protein; WMD, Weighted mean differences.

lipopolysaccharide stimulated RAW264.7 macrophages.[17] Another study has shown that G-Rg1 could inhibit IRAK activation mediated inflammation and exhibit its anti-inflammatory properties in experimental studies.[16] This ginsenoside shows protective effects against cerebral ischemia/reperfusion injury through activation of p38 MAPK.[34] Moreover, ginseng can inhibit the development of inflammation to cancer through affecting mediators such as matrix metalloproteases, peroxisome proliferator-activated receptor-γ (PPAR-γ) and transforming growth factor-β1 (TGF-β1) pathways.[35–37] Experimental studies showed beneficial effects of ginseng treatment in protection from bacterial septic responses and cerebral ischemia through modulation of CNS inflammation.[38,39] Moreover, clinical trial studies showed that Korean red ginseng could decrease the frequencies of acute respiratory illness (ARI) through enhancing T-cell mediated

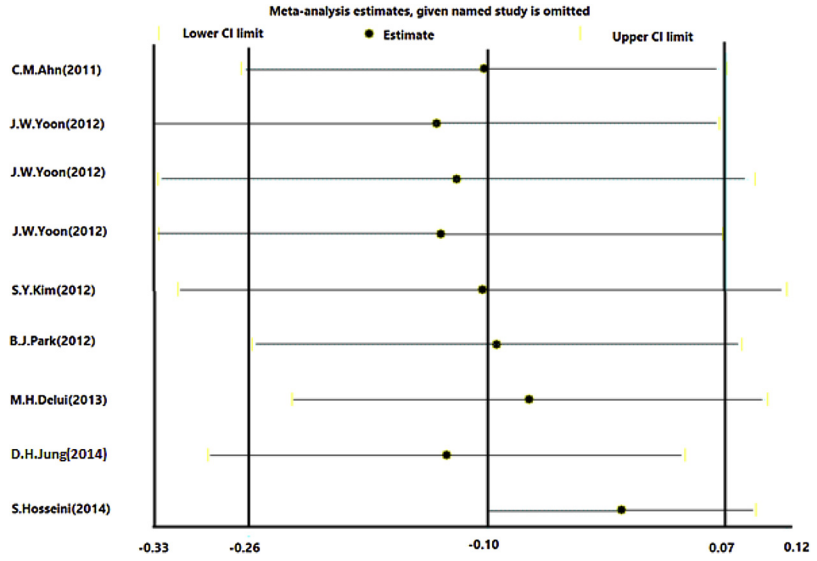

Fig. 3. Sensitivity analysis of ginseng supplementation on CRP level (mg/l).

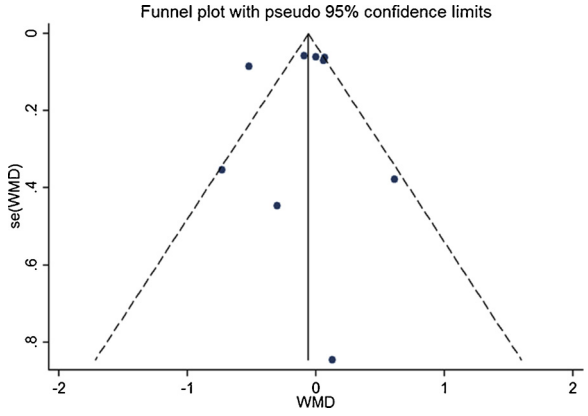

Fig. 4. Funnel plot of included studies detailing publication bias. WMD = Weighted Mean Difference, SE = standard error.

immune responses.[40] Since sub-group analysis in the current study revealed no differences in responding to ginseng supplementation based on the doses; therefore, ginseng doses of ≤1500 mg/day are prudently advisable to prevent the possible side effects of the medicine, including urticaria, rash and diarrhea reported in some studies.[41] Yoon et al. in a clinical trial study on type-2 diabetic patients have demonstrated that a threshold of 1500 mg/day of ginsam can influence glucose homeostasis most effectively.[24] One limitation of the present study was the lack of enough information about ginseng characteristics used in associated clinical trials, including their age and species as well as preparation methods of ginseng which can affect the concentration of active gradients in this herb.[42] Another limitations were different study populations included in the meta-analysis as well as possible missing out of the papers had been published in native languages which did not retrieve in search engines had been used in our search strategy.

5. Conclusion

In conclusion, results of the current systematic review and meta-analysis have shown that ginseng supplementation can beneficially affect CRP/hs-CRP levels only when the serum level of this inflammatory factor in patients was greater than 3 mg/l. Therefore, use of this medicinal herb seems a possible strategy for the control of inflammation in patients suffering from this condition.

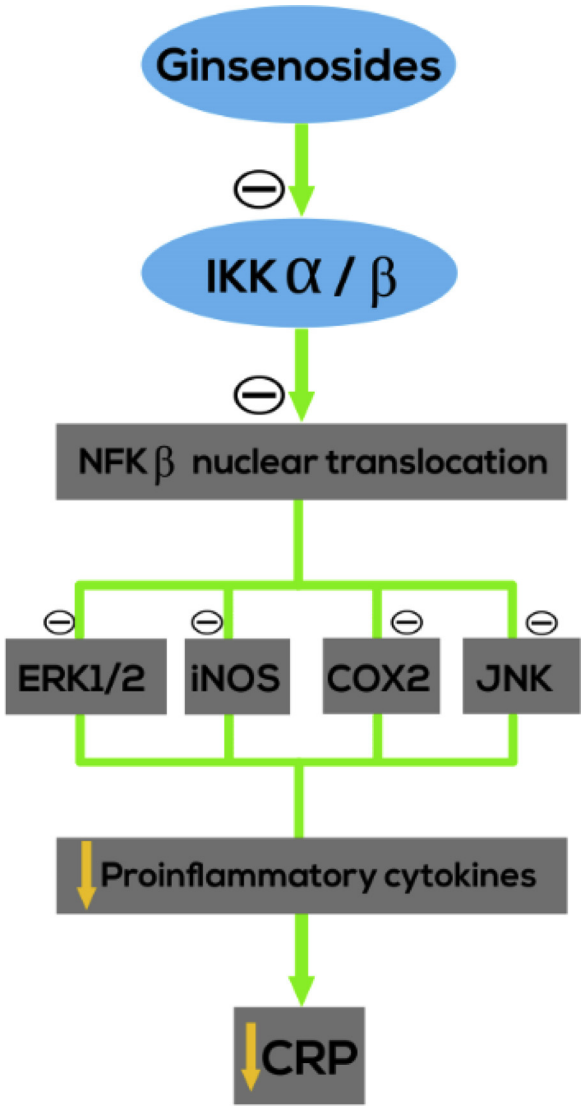

Fig. 5. Schematic diagram of the anti-inflammatory effects of Ginsenosides on CRP level via modulating NF-κB, COX2, ERK1/2 and JNK pathway.

Author contributions

SS and EY designed and searched systematically for the study. OA and MZ reviewed and selected the articles and extracted data from articles under the supervision of EY. SS performed data analysis and interpretation. EY and SS drafted the manuscript. EF revised the article for important intellectual content.

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Conflict of interest

The authors declared that there is no conflict of interest with respect to this manuscript.

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