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The Effect of Soy and Soy Products Consumption on Inflammatory Biomarkers: Protocol for a Systematic Review and Meta-analysis

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ABSTRACT

Background: Inflammation is a process that occurs in early phase of recovery in which immune system recognizes and removes immunological stimuli. Many chronic diseases have inflammation based pathogenesis. Several studies used soy and soy products for reducing inflammatory biomarkers.

Objectives: The purpose of the present systematic review and meta-analysis of randomized clinical trials is to determine the effects of soy and soy products on inflammatory biomarkers.

Methods: The following databases will be investigated for randomized controlled trials published until October 2019 to evaluate the effects of soybean and soy products on the inflammatory biomarkers in healthy subjects and patients with high inflammatory biomarkers: PubMed, Scopus, ISI Web of Science and Google scholar.Two independent investigators (M.R and F.M) will screen the title and the abstract of included articles. Mean and standard deviation (SD) or standard error (SE) for outcomes will be extracted. The quality of studies will be assessed by Cochrane Risk of Bias Tool. STATA software will be used to do a standard statistical analysis. A subgroup analysis will be applied to find out potential sources of inter-study heterogeneity. A Random-effects model will be conducted to calculate pooled effect size. A fixed-effect model will be incorporated to estimate the between-subgroup heterogeneity. Moreover, sensitivity analyses, Egger's regression asymmetry test and Begg's rank-correlation methods will be conducted.

Results: We will try to find a major number of articles about the effectiveness of soy and soy products on inflammatory biomarkers. Tumor necrosis factor α (TNF-α), interleukine 6 (IL-6), interleukine 2 (IL-2), interleukine 1-β (IL-1β), interferon-gamma (IFN-γ) and Interleukine 10 (IL-10) are considered to be the outcome.

Conclusion: The findings of this systematic review and meta-analysis may provide evidence on the effectiveness and safety of soy and soy products for reducing inflammation.

Keywords: Soy, Inflammation, Interleukine, Tumor necrosis factor α, Interferon-gamma, Meta-analysis

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Introduction

Inflammation is considered as a basic component which is critical for immune homeostasis and human health *[1]*. Cell-mediated and humoral responses contribute to inflammation *[2]*. Some chemical compounds are considered as pro-inflammatory or anti-inflammatory markers *[3]*. Furthermore, reactive oxygen species (ROS) are associated with initiation and progression of the inflammatory response *[4]*.

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There are two types of inflammation namely acute and chronic inflammation *[5]*. It can be beneficial as an acute, rapid immune response to detrimental conditions such as traumatic tissue damage or an attacking pathogen. This response also comforts the repair, turnover, and adaptation of many tissues. Chronic inflammation has many properties of acute inflammation but it is usually mild and permanent which finally leads to tissue degeneration *[6]*. Although chronic inflammation is not considered as a disease by itself, several chronic diseases have inflammation based pathogenesis *[5]*. Evidence showed that cardiovascular diseases *[7]*, diabetes *[8]*, cancer *[9]*, rheumatoid arthritis *[10]*, obesity *[11]* and chronic respiratory diseases *[12]* are associated with inflammation.

Appropriate lifestyle including having a healthy diet *[13]*, regular exercise *[14]*, adequate sleep *[15]*, avoiding smoking *[16]*, avoiding alcohol consumption *[17]* and stress management *[18]* can reduce chronic inflammation. Adequate intake of vegetables and legumes is also a part of a healthy diet *[19]*. Soybean is a legume rich in health promoting components such as amino acids, nutrients, and bioactive compounds *[20, 21]*. It is proposed that soybean protein has remarkable antioxidant, anti-inflammatory and anticancer features *[22]*. In addition to fiber, minerals, vitamins and omega-3 fatty acids; soybean is considered to be a major source of phytoestrogens especially isoflavones *[23, 24]*. Genistein, daidzein and glycitein are the main isoflavones found in soybean *[24]*. Genistein has anti-inflammatory properties and is a strong inhibitor of tyrosine kinase enzyme *[25]*. Therefore, soybean intake may be effective in the prevention and treatment of inflammation related chronic diseases *[23]*.

According to clinical trials conducted on the effect of soy and soy products on inflammatory biomarkers, soy consumption might reduce some inflammatory biomarkers *[26, 27]*. In other studies, soy consumption had no effects on inflammation *[28, 29]*. Even in two trials, soy was able to increase some of the inflammatory biomarkers *[30, 31]*. Therefore, to address this inconsistency, a systematic review and meta-analysis is needed to determine the overall effect of soy and its products consumption on the inflammatory biomarkers.

Although previous meta-analysis reported the effect of soy consumption on CRP*[32]*, there is no comprehensive systematic review and meta-analysis of clinical trials regarding the effects of soy and soy products on others inflammatory biomarkers. The aim of this systematic review and meta-analysis is to determine the effects of soy and soy products on the inflammatory biomarkers.

Methods

This protocol has been written according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P)*[33]*. Also, the protocol for the presend systematic review is submitted to international prospective register of systematic reviews (PROSPERO) and will receive the registration code.

Search strategy

Electronic search strategy will include the following databases: PubMed, Scopus, ISI Web of Science and Google scholar. Title, abstract and keywords of the articles will be searched using the following search strategy: ("soya" or "soy foods" or "soy milk" or "soybeans" or "soybean protein" or " soy" or "isoflavones" or "phytoestrogens" or "genistein" or "genestein" or "glycitein" or "daidzein" or "isolated soy protein" or "textured soy protein") and ("interleukin-6 " or "IL-6" or "tumour necrosis factor-α" or "TNF-α" or "interleukin"or "interleukin-8" or "inflammation"or "cytokine"or "IL-1β"or "IL-2"or " IL-4"or "IL-8"or "IL-10"or "IFN-γ"or "inflammatory"). The references of the retrieved articles will be also searched manually.

Eligibility criteria

Title, abstract and full text of the included articles will be scanned by two independent investigators

(M.R and F.M). All interventions that evaluated the effects of soybean and soy products on inflammatory biomarkers in healthy adults and patients with high inflammatory biomarkers will be included. Articles will be excluded if they: **1**- are *in vitro*, *in vivo* or animal studies; **2**- are editorials, letters, review articles or meeting abstracts; **3**- do not have a control group or a proper control group (see **Table 1**); **4**- are short-term (<1 week); **5**- use soy in combination with other foods or adjunct interventions; **6**- do not report dose of soy or isoflavone in the intervention group; **7**- report post-exercise inflammation; **8**- have insufficient data and **9**- include pregnant women or children.

Data extraction

Following information will be extracted from each eligible article: **1**- first author's name and year of publication; **2**- sample size; **3**- age of the participants; **4**- the design of clinical trial and its duration; **5**-dosage and type of soy or soy product used in the intervention group; **6**- details regarding intervention in the control group, and **7**- characteristics of the study participants. "IL-6,TNF-α,IFN-γ,IL-2, IL-10 & IL-1β" will be considered as the main outcomes. Mean and standard deviation (SD) or standard error (SE) for outcomes will be extracted. C-reactive protein (CRP) is not included in the present study because previous meta-analysis reported the effect of soy consumption on CRP *[32]*. Population, intervention, comparator and outcome are presented in **Table 1**.

Assessment of quality

The quality of studies will be evaluated by Cochrane Risk of Bias Tool *[34]*. The method includes the followings: random sequence generation, allocation concealmentthan, selective reporting, incomplete outcome data, blinding (participants, personnel and outcome assessment) and other sources of bias. Each item is graded as a highrisk, low risk and uncertain risk of bias in accordance with above seven sections. The blinding domain will not be considered as a key domain; because blinding is not possible in dietary interventions. If each study was "low risk of bias" for all domains, it will be considered as low risk of bias. Studies with at least one domain with unknown risk of bias will ebe categorized as unknown risk. The studies with at least one high risk domain will be considered as high risk.

Statistical analysis

This meta-analysis will be done by using STATA software (version 11.0؛statacorporation). Net changes in the intervention and control groups will be used to estimate the effect size. When net changes are not reported in soy and control groups, effect size will be calculated using baseline and endpoint mean±SD/SE. To compute overall effect, SE to SD are converted. A Random-effects model will be conducted to calculate pooled effect size for each main outcome. I-square (I^2) statistic will be calculated to evaluate inter-study heterogeneity. To understand possible sources of inter-study heterogeneity, subgroup analyses will be runned.

Between-subgroup heterogeneity will be estimated through a fixed-effect model. The stability of the results is controlled using sensitivity analyses to evaluate the possible influence of each study on pooled effect size.

Eventually, Egger's regression asymmetry test and Begg's rank-correlation methods will be conducted to assess the publication bias. P-value <0.05 was considered to be statistically significant.

Table 1. Description of population, intervention, comparator and outcome (PICO)

Population	Healthy subjects and patients with high inflammatory biomarkers
Intervention	Soy protein or soy nut or soymilk or soy isoflavone supplementation
Comparison	Milk protein or match diet or cow milk or placebo
Outcome	IL-6, TNF-α, IFN-γ, IL-2, IL-10 & IL-1β

IL: Interleukin ; TNF-α: Tumor necrosis factor α ; IFN-γ:Interferon γ

Study selection process

The articles will be imported to Endnote referencing software (version 9) and duplicate studies will be excluded. Two independent authors will be reading the titles and the abstracts to exclude the trials that do not meet inclusion criteria. If any summary is not provided using the search strategy above, the full text of the literature will be evaluated. In case of disagreements, they may be resolved by a third author. The process of study selection is presented in a preferred reporting items for systematic review and meta-analysis flow diagram **(Figure 1).**

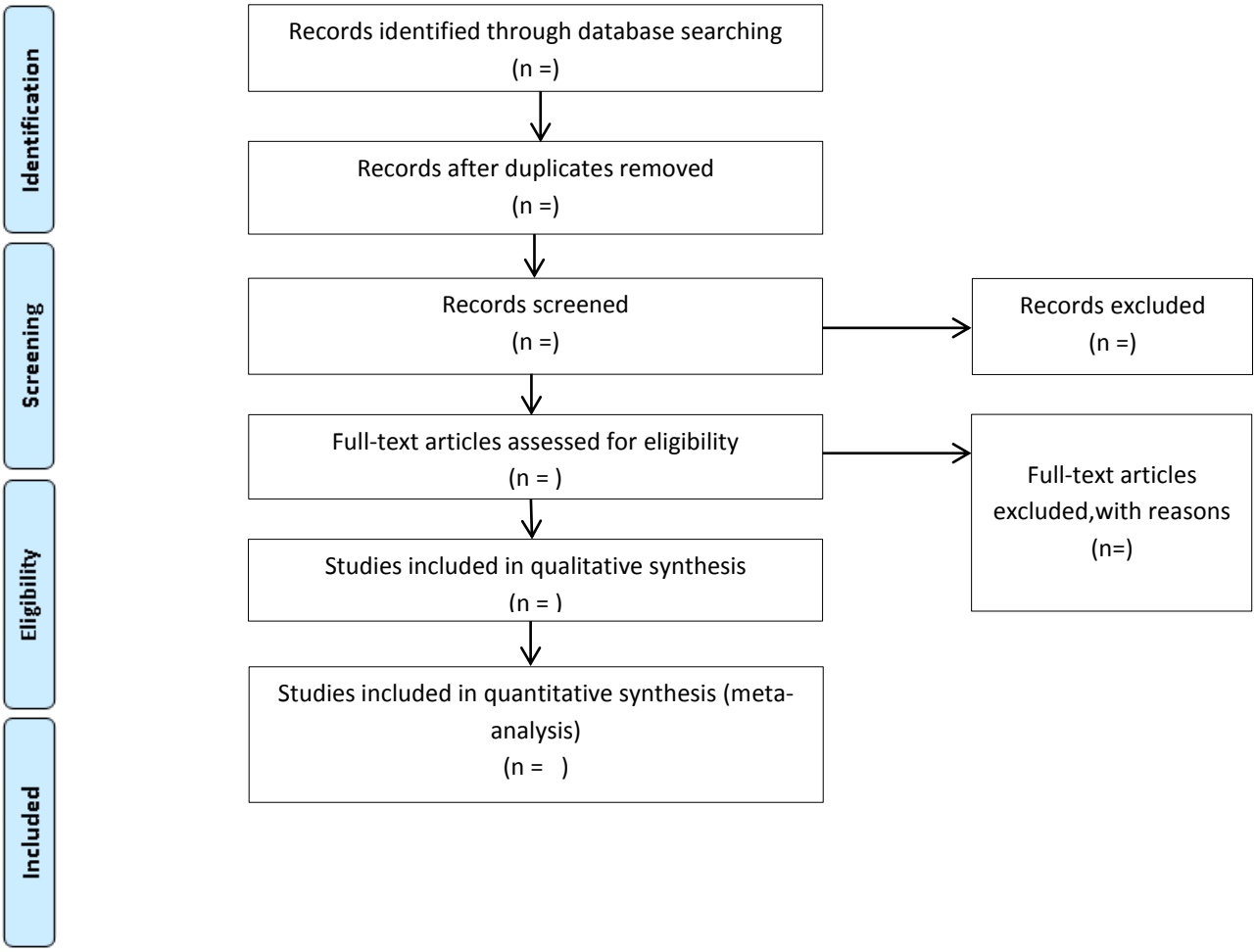

Figure 1. Preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart

Discussion

When inflammation becomes chronic, it acts as a strong disease-promoting factor in a variety of disorders including arteriosclerosis, obesity, and cancer. Hence, chronic inflammation is called the "silent killer" *[35]*. Clinical researches found that soy and soy product can affect the inflammation, but there is no systematic review and meta-analysis (except for circulating CRP levels) regarding its efficacy and safety so far. Therefore, the systematic review and meta-analysis will be carried out with the goal of providing a proof of effectiveness and safety of soy and soy products on inflammatory biomarkers. However, there may be some limitations in this systematic review.

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None

Authors' contributions

M.R conceived the idea of the study and searched databases. M.R and F.M have scanned the articles. M.R, F.M and M.H.R extracted the data. M.R and F.M wrote the manuscript. M.H.R performed statistical analysis and revised the manuscript.

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Conflict of Interest

The authors state that there is no conflict of interests in this study.

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