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Review

Effects of supplementation with pomegranate juice on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Pomegranate juice (PJ) has a high content of antioxidants and bioactive polyphenols, being widely used for its antioxidant, anti-inflammatory and chemopreventive effects.
Purpose: The objective of this meta-analysis consisted in investigating the impact of PJ on plasma C-reactive protein (CRP) concentrations.
Methods: The search included SCOPUS, Medline and two Iranian bibliographic databases namely MagIran and Scientific Information Database (from inception to December 09, 2014) to identify prospective trials for investigating the impact of pomegranate preparations on serum concentrations of CRP. Two independent reviewers extracted data on study characteristics, methods and outcomes.
Results: Among 427 participants in the selected studies, 216 were allocated to PJ groups, and 211 to control group. Meta-analysis of data from 5 eligible randomized controlled trials (RCTs) arms did not provide compelling evidence as to a significant CRP-lowering effect of supplementation with pomegranate juice (WMD: −0.22 mg/l, 95% CI: −0.45, 0.01, $p = 0.061$). The impact of pomegranate juice on plasma CRP levels was found to be independent of duration of supplementation (slope: 0.003; 95% CI: −0.005, 0.011; $p = 0.444$).
Conclusion: In conclusion, this meta-analysis of data from 5 prospective trials did not indicate a significant effect of PJ on plasma CRP levels, and this effect was independent of duration of supplementation.

Introduction

Pomegranate (*Punica granatum L.*, Family *Punicaceae*) is an ancient spiritual fruit native to the Middle East, with a high content of antioxidants and bioactive polyphenols. The fruit has antioxidant, anti-inflammatory and chemopreventive effects (Asgary et al. 2013, 2014a; Banihani et al. 2013; Bouroshaki et al. 2010). Today, pomegranate is cultivated in the United States, China, Afghanistan, India, Iran, Japan and many countries located in the Mediterranean basin (Matthaiou et al. 2014). PJ is rich in flavonoids (quercetin, luteolin glycosides and kaempferol), hydrolysable tannins (ellagitannins – punicalagins and gallotannins), condensed tannins (proanthocyanidins), anthocyanins (3.5-glucosides of cyanidin, delphinidin, and pelargonidin and 3-glucosides), polyphenolic acids

Abbreviations: BMI, body mass index; CIMT, carotid intima-media thickness; CI, confidence interval; CMA, Comprehensive Meta-Analysis; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment-insulin resistance; MPO, myeloperoxidase; NF-kB, nuclear transcription factor kappa B; NSAID, nonsteroidal anti-inflammatory drug; NAG-1, NSAID activated gene-1; PGE2, prostaglandin E2; PON-1, paraoxonase 1; PPARs, peroxisome proliferators active receptors; PJ, pomegranate juice; PRISMA, preferred reporting items for systematic reviews and meta-analysis; RCTs, randomized controlled trials; SDs, standard deviations; WMD, weighed mean difference.

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(ellagic acid, gallin acid), sterols, triterpenoids, alkaloids, carbohydrates, fibers and minerals (sodium, potassium, calcium, iron) (Basu et al. 2013; Hamoud et al. 2014; Rojanathammanee et al. 2013). It has been shown that a substantial amount of phenolic compounds present in the rind or husk of pomegranate fruit migrate to the juice during the manufacturing process, thus increasing the quantity of antioxidant compounds in commercial juices (Tezcan et al. 2009). It has been shown that juices used for commercial purposes have a different polyphenolic composition compared with those utilized for research (Syed et al. 2013). The presence of numerous types of polyphenols confers PJ a higher antioxidant activity compared with green tea or red wine (Gil et al. 2000). Punicalagins, hydrolysable tannins, anthocyanins, and ellagic acid are among the most important compounds responsible for the anti-inflammatory and antioxidant activities of PJ (Chen et al. 2012). Several experimental studies have emphasized the beneficial effects of PJ consumption in reducing the risk of cardiovascular disease (Aviram and Rosenblat 2012; Stowe 2011), diabetes mellitus (Banihani et al. 2014; Nekooeian et al. 2014), breast cancer (Jeune et al. 2005; Sturgeon and Ronnenberg 2010), prostate cancer (Bell and Hawthorne 2008; Wang et al. 2012), colon cancer (Jaganathan et al. 2014), acquired immune deficiency syndrome (AIDS) and Alzheimer's disease (Sreekumar et al. 2014; Wang and Martins-Green 2014).

Inhibition of inflammation-regulating targets, such as nuclear transcription factor kappa B (NF-kB), peroxisome proliferators active receptors (PPARs), and nonsteroidal anti-inflammatory drug (NSAID) activated gene-1 (NAG-1) are several proposed mechanisms for the anti-inflammatory actions of PJ (Yoon and Baek 2005). Moreover, PJ increases nitric oxide synthase bioactivity (de Nigris et al. 2006) and protects nitric oxide against oxidative damage (Ignarro et al. 2006). Nevertheless, it should be mentioned that the clinical studies on anti-inflammatory and antioxidant effects of PJ are scarce. It has been shown that PJ decreases plasma C-reactive protein (CRP) and interleukin-9 concentrations in patients with type 2 diabetes mellitus (Sohrab et al. 2014). Another study has shown that consumption of PJ increases paraoxonase 1 (PON-1) levels in patients with carotid artery stenosis (Hamoud et al. 2014; Tracy et al. 2014). On the contrary, PJ did not have a significant effect on lipid profile and biomarkers of inflammation (CRP and interleukin-6) in hypertensive and hemodialysis patients (Rivara et al. 2014).

In this meta-analysis, the clinical evidence for the effects of PJ on CRP, a systemic marker of inflammation, was assessed to evaluate the anti-inflammatory effects of PJ. CRP was chosen because it is considered a strong predictor of cardiovascular risk when compared with different inflammatory markers (Koenig et al. 1999; Ridker et al. 2000). In the present study, we focused to systematically review all published trials analyzing the impact of PJ on plasma CRP levels.

Material and methods

Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (Moher et al. 2009). SCOPUS (http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/pubmed) and two Iranian bibliographic databases namely MagIran (www.magiran.com) and Scientific Information Database (www.SID.ir) were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (C-reactive protein OR CRP OR hsCRP OR hs-CRP OR clinical OR randomized OR placebo OR subjects OR patients OR individuals OR subjects OR volunteers OR male OR female OR men OR women) AND (pomegranate OR *Punica*). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature was searched from inception to December 09, 2014. Selected articles were hand searched to identify further relevant studies.

Study selection

Original studies were included if they met the following inclusion criteria: (i) be a randomized clinical case-control or case-cross-over trial, (ii) investigated the impact of pomegranate juice on plasma/serum concentrations of CRP, (iii) presentation of sufficient information on plasma/serum CRP levels at baseline and at the end of study in both pomegranate and control groups, and (iv) administering pomegranate for a period of at least one week. Exclusion criteria were (i) non-clinical studies, (ii) uncontrolled trials, (iii) administering pomegranate preparations via non-oral routes e.g. injection, topical application or mouthrinse, and (iv) lack of sufficient information on baseline or follow-up CRP concentrations. Exclusion of an article for the latter reason was done if no feedback was received after contacting the authors.

Data extraction

Eligible studies were reviewed and the following data were abstracted: (1) first author's name; (2) year of publication; (3) study location; (4) number of participants in the PJ control groups; (5) age, gender and body mass index (BMI) of study participants; (6) circulating concentrations of CRP, total cholesterol, LDL-C, HDL-C, triglycerides and glucose; (7) systolic and diastolic blood pressures; (8) homeostasis model assessment-estimated insulin resistance (HOMA-IR) index; and (9) prevalence of smoking, type 2 diabetes, dyslipidemia, hypertension and chronic heart disease (CHD).

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria (Higgins and Green 2008). The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

Quantitative data synthesis

Meta-analysis was conducted using the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) (Borenstein et al. 2005). Plasma CRP concentrations were collated in mg/l. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. In case of reporting SEM, SD was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at end of follow-up in the control group – measure at baseline in the control group). Selection of fixed-effects and random-effects models was performed in cases