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Lipid profile changes after pomegranate consumption: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Transport of oxidized low-density lipoprotein across the endothelium into the artery wall is considered a fundamental priming step for the atherosclerotic process. Recent studies reported potential therapeutic effects of micronutrients found in natural products, indicating positive applications for controlling the pathogenesis of chronic cardiovascular disease driven by cardiovascular risk factors and oxidative stress. A particular attention has been recently addressed to pomegranate; however findings of clinical studies have been contrasting.
Purpose: To evaluate the effects of pomegranate consumption on plasma lipid concentrations through a systematic review and meta-analysis of randomized controlled trials (RCTs).
Methods: The study was designed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. Scopus and Medline databases were searched to identify randomized placebo-controlled trials investigating the impact of pomegranate on plasma lipid concentrations. A fixed-effects model and the generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the one-study remove approach. Random-effects meta-regression was performed to assess the impact of potential confounders on the estimated effect sizes.
Results: A total of 545 individuals were recruited from the 12 RCTs. Fixed-effect meta-analysis of data from 12 RCTs (13 treatment arms) did not show any significant effect of pomegranate consumption on plasma lipid concentrations. The results of meta-regression did not suggest any significant association between duration of supplementation and impact of pomegranate on total cholesterol and HDL-C, while an inverse association was found with changes in triglycerides levels (slope: −1.07; 95% CI: −2.03 to −0.11; $p = 0.029$). There was no association between the amount of pomegranate juice consumed per day and respective changes in plasma total cholesterol, LDL-C, HDL-C and triglycerides.
Conclusion: The present meta-analysis of RCTs did not suggest any effect of pomegranate consumption on lipid profile in human.

Introduction

Atherosclerosis is the underlying pathophysiologic factor for the majority of cardiovascular diseases (Grassi et al. 2010, 2011). Endothelial dysfunction has been suggested to be the first step in atherogenesis. In addition, an important initiating event for atherosclerosis may well be the transport of oxidized low-density lipoprotein across the endothelium into the arterial subendothelial space (Grassi et al. 2010, 2011). Indeed, cardiovascular risk factors significantly cause oxidative stress, which contributes to a disruption in the balance between nitric oxide (NO) and reactive oxygen species, with a resulting relative decrease in NO bioavailability. The resulting endothelial dysfunction has been supposed to be the first step of atherosclerosis. Further, the majority of cardiovascular

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized controlled trials; WMD, weighed mean difference.

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diseases follow from complications of atherosclerosis (Grassi et al. 2010, 2011). According with this, among patients with hyperlipidemia, the health and economic burden of cardiovascular events is a major issue of interest. Elevated LDL-cholesterol is associated with increased risk of developing coronary heart disease, one of the most common causes of death worldwide. In line with this, a meta-analysis of 26 clinical trials demonstrated that risk of any cardiovascular event was reduced by 20% and mortality was reduced by 10%, for every 38.7 mg/dl reduction of LDL cholesterol (Delahoy et al. 2009). Therefore, the treatment and prevention of hyperlipidemia and atherosclerotic disease are significant public health focus since many years. It is of critical importance to identify new strategies that would be safe and effective in lowering circulating cholesterol and prevent dyslipidemias and atherosclerosis.Finding new drugs like complementary treatments can be beneficial in this subject.

Diet plays a fundamental role in cardiovascular prevention and in maintaining physiological homeostasis (Grassi et al. 2010). Recent literature emphasizes the potential therapeutic effects of micronutrients found in natural products, indicating positive applications for controlling the pathogenesis of chronic cardiovascular disease driven by cardiovascular risk factors and oxidative stress (Grassi et al. 2010, 2011). Pomegranate (*Punica granatum L*) is an ancient fruit-bearing deciduous shrub member of two species comprising the Punicaceae family (Lansky and Newman 2007). The pomegranate is native from the Himalayas in northern India to Iran but has been cultivated and naturalized since ancient times over the entire Mediterranean region. In addition to its ancient historical uses, pomegranate is used in several systems of medicine for a variety of ailments. In Ayurvedic medicine the pomegranate is considered “a pharmacy unto itself” and is considered able to improve the arterial tone and to treat aphthae, diarrhea, and ulcers also with antimicrobial effects (Naqvi et al. 1991; Saxena and Vikram 2004). Further, pomegranate is also considered a remedy for diabetes in the Unani system of medicine practiced in the Middle East and India (Saxena and Vikram 2004). Moreover, of interest pomegranate was used in combination of Ephedra vulgaris to prepare a holy and medicinal drink (called haoma) in ancient Persia. Also, in medieval age, it was used in Persian medicine as well as in the west (Wohlberg 1990).

The fruit can be divided into 3 parts: the seeds (3%) and the juice (30%) representing about a third of the fruit weight, and the peels characterized by membranes internal network (Lansky and Newman 2007) which contain different chemical components that have demonstrated beneficial cardiovascular effects, and therefore, this fruit has emerged as an alternative medical management. Pomegranate includes several kinds of phytochemicals such as flavonoids (flavonols, flavanols, and anthocyanins), condensed tannins (proanthocyanidins), and hydrolysable tannins (ellagitannins and gallotannins). Specifically, the pomegranate juice contains anthocyanins, ellagic acid, gallic acid, catechin, epigallocatechingallate, and quercetin; the pomegranate pericarp contains phenolic punicalagins, gallic acid, catechin, epigallocatechingallate, quercetin, rutin, and other flavonols, flavones, flavonones and anthocyanidins; the pomegranate leaves contain tannins (punicalin and punicafolin) and flavone glycosides, including luteolin and apigenin; the pomegranate flower contains the gallic acid; and finally, the pomegranate roots and bark contain ellagitannins, including punicalin and punicalagin (Jurenka 2008).

The polyphenolic fraction of pomegranate appears to be responsible for most of the health benefits owing to the strong antioxidant activity, though exact molecular, cellular, and physiological mechanisms remain unknown (Gil et al. 2000; Kulkarni et al. 2007).

Pomegranate extracts have been used for a long time to treat infection (Naqvi et al. 1991; Caceres et al. 1987). Moreover, pomegranate consumption has been described to decrease blood pressure and positively affect cardiovascular risk factors in several clinical studies (Aviram et al. 2000, 2004; Aviram and Dornfeld 2001; Rosenblat et al. 2006; Davidson et al. 2009). Further, growing evidence is suggesting positive clinical effects of pomegranate preparations as functional foods in people with cardiometabolic diseases e.g. metabolic syndrome (Medjakovic and Jungbauer 2013), obesity (Al-Muammar and Khan 2012) and hypertension (Stowe 2011). Nevertheless, starting from the discordant findings in randomized controlled trials, the panel on Dietetic Products, Nutrition and Allergies of the European Food Safety Authority concluded that no cause-effect relationship may be yet established with certainty between pomegranate consumption and potential beneficial effects (EFSA Panel on Dietetic Products 2010). Hence, attemptig to resolve the inconsistencies focusing on the putative lipid-modifying properties of pomegranate, this study aimed to systematically review and meta-analyze the findings of randomized controlled trials (RCTs) reporting the changes in plasma lipid concentrations following consumption of pomegranate products.

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 (Lansky 2007). SCOPUS (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (“randomized controlled trial” OR randomized OR placebo or cholesterol OR triglyceride or LDL OR LDL-C OR LDL-cholesterol OR HDL OR HDL-C OR HDL-cholesterol OR hyperlipidemia OR hyperlipidemic OR hypolipidemic OR dyslipidemia OR dyslipidemic) 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 01, 2014.

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 preparations (juice, extract, vinegar, paste, etc.) on plasma/serum concentrations of at least one of the main lipid parameters (i.e. total cholesterol, LDL-C, HDL-C or triglycerides), (iii) presentation of sufficient information on plasma/serum lipid 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 7 days. 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 lipid concentrations.

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 pomegranate and control groups; (5) dose and duration of supplementation with pomegranate products; (6) age, gender and body mass index (BMI) of study participants; (7) circulating concentrations of