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Original Article

Effect of pomegranate juice on vascular adhesion factors: A systematic review and meta-analysis

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ABSTRACT

Background: Cardiovascular diseases, obesity, and insulin resistance demonstrate elements of functional impairment of the endothelium. Treatment of endothelial dysfunction with natural products, such as pomegranate, can open new ways in the treatment of cardiovascular diseases.
Purpose: The present meta-analysis provides information in highlighting the role of pomegranate in endothelial dysfunction.
Methods: Various databases, such as PubMed, Scopus, Web of Science, Cochrane, and Google Scholar, were searched up to July 2020 using relevant keywords. We have selected the studies that investigated the effects of pomegranate on vascular adhesion factors, including intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and interleukin-6 (IL-6). MD with 95% CrI with 100,000 iterations by using Markov chain Monte Carlo code were used.
Results: Pooled effect size of articles in human studies indicated that pomegranate juice was not significantly effective on ICAM-1 [MD: −0.42; CrI: (−1.01, 0.17)], VCAM-1 [MD: −0.20; CrI: (−1.95, 1.40)], and E-selectin [MD: −0.21; CrI: (−1.62, 1.21)] compared to the control group. But it can significantly reduce IL-6 [MD: −1.07; CrI: (−1.90, -0.19)].
Conclusion: Generally, present study showed that pomegranate juice has no significant effect on vascular adhesion factors, ICAM-1, VCAM-1, and E-selectin, but can reduce IL-6 significantly. Future prospective randomized clinical trials with longer intervention duration are warranted to obtain a precise conclusion.

Introduction

The vascular lumen is covered by a layer of cells called endothelium (Esper et al., 2006; Sena et al., 2013) . Endothelial cells play an important role in metabolic functions and have important autocrine, paracrine, and endocrine functions in the body (Sena et al., 2013). Endothelium maintains the balance between vasoconstriction and vasodilatation and plays a significant role in the regulation of thrombogenesis and proliferation and migration of smooth muscle cells. Thus, dysfunction can produce disturbances in the body and lead to diseases, such as diabetes, atherosclerosis, and hypertension. Cardiovascular disease, obesity, and insulin resistance demonstrate elements of functional impairment in the endothelium (Sena et al., 2013). Increases in the levels of cholesterol, low-density lipoprotein, triglyceride and a

Abbreviations: CrI, credible intervals; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; MD, mean difference; NF-κB, nuclear factor-κB; NO, nitric oxide; PICOS, participants interventions comparisons outcomes and study design; PRISMA, preferred reporting items for systematic review and meta-analysis; RCTs, randomized controlled trials; SIRT1, Sirtuin 1; VCAM-1, vascular cell adhesion molecule 1

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decrease in high-density lipoprotein, hypertension, hyperinsulinemia, smoking, and hyperglycemia are among the main risk factors that are related to the development of endothelial dysfunction (Sena et al., 2013).

Endothelium plays a very critical role in inflammation. Intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), interleukin-6 (IL-6), and E-selectin are adhesion molecules that are involved in interaction with leukocytes in adhesion and extravasation (Söderquist et al., 1999). It has been observed that serum concentrations of ICAM-1, VCAM-1 and E-selectin (also known as CD62 antigen-like family member E, endothelial-leukocyte adhesion molecule 1, or leukocyte-endothelial cell adhesion molecule 2) are considered independent risk factors for the development of cardiovascular diseases and atherosclerosis (Demerath et al., 2001). ICAM-1 and E-selectin serve as molecular markers for detection of atherosclerosis and coronary heart disease (Hwang et al., 1997). In more recent years, scientists throughout the world are considering herbal medicine for treatment of various diseases and disorders. Therefore, the treatment of endothelial dysfunction with plants and natural products is an area of interest in the treatment of conditions associated with endothelial dysfunction (Suman and Bhatnagar, 2019).

Pomegranate is a native plant of India and Iran that numerous phytochemicals have been reported in the fruit, with polyphenols being the most abundant class and are found in various parts of the tree (Lansky and Newman, 2007; Suman and Bhatnagar, 2019). Clinical studies have shown that pomegranate has several beneficial effects on the cardiovascular system, such as improved endothelial function and lowered blood pressure (Basu and Penugonda, 2009; Sahebkar et al., 2017; Stowe, 2011). Pomegranate juice can enhance blood flow to the heart and can decrease the chances of a heart attack (Hwang et al., 1997). A change in vascular reactivity to catecholamines was also shown after the administration of pomegranate juice (Suman and Bhatnagar, 2019). Pomegranate has led to improvements in endothelial dysfunction by modulating the levels of ICAM-1, VCAM-1 and E-selectin in different studies (Asgary et al., 2014; Kelishadi et al., 2011; Sohrab et al., 2018). The present meta-analysis highlights the role of pomegranate in endothelial dysfunction and its effect on related parameters, such as ICAM-1, VCAM-1, E-selectin and IL-6.

Pharmacological mechanisms of natural product-derived extracts and compounds on endothelial dysfunction pathways

Mounting evidence suggests that high intake of medicinal plants and natural phytochemicals are involved in the prevention of endothelial and vascular diseases via regulation of endothelial function. Several plant-derived natural products have the potential to ameliorate endothelial dysfunction. Catechin, resveratrol, epigallocatechin gallate, curcumin, and quercetin are among the well-established natural agents that are able to ameliorate endothelial dysfunction through various pharmacological mechanisms (Vazhappilly et al., 2019). These phytocompounds can reduce the expression of adhesion molecules, including ICAM-1, VCAM-1, and E-selectin, which are involved in interaction with leukocytes during endothelial dysfunction and extravasation. These plant-derived phytochemicals inhibit oxidative stress in endothelial cells by modulating the expression of enzymes which are involve in antioxidant effects, leading to the inhibition of ischemic heart disease, angina pectoris as well as stroke. They can promote vascular endothelium-dependent vascular relaxation through nitric oxide production (Grassi et al., 2010).

Preclinical investigations showed that natural products exert their therapeutic benefits via the regulation of endothelial function through several mechanisms, including, enhancing the level of endothelial nitric oxide synthase as well as the generation of nitric oxide (NO), and elevating the intracellular calcium concentration. In addition, suppression of xanthine oxidase and protein kinase C activities, resulting in the reduced generation of the superoxide radical, inhibition of redox-sensitive gene expression, and also protection of vascular endothelial tissue against oxidation are among mechanisms of natural products in regulating endothelial function (Malekmohammad et al., 2019). Polyphenols which are the most important natural products with pharmacological effects in endothelial dysfunction perform their therapeutic effects through inhibiting pro-angiogenic agents, including vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) (Yamagata, 2019). Animal models of endothelial dysfunction revealed the pivotal role of nuclear and intracellular signaling pathways, with transcription and transduction activity in the disease pathogenesis. The inhibitory potential of natural products on inflammatory reaction, and over expression of pro-inflammatory cytokines is mediated by modulating transcriptional signaling pathway. It has been found that some of the polyphenolic agents suppress the expression of pro-inflammatory mediators, such as ILs and well as tumor necrosis factor-α which are involved in platelet aggregation and disturbance in endothelial function (Wang et al., 2011).

Methods

Search strategy

This meta-analysis was conducted in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines (Moher et al., 2009). The search involved all the studies published up to July 2020. We systematically searched databases, including PubMed, Web of Science, Scopus, Cochrane Library and Google Scholar, for English language articles. The following terms were used: “pomegranate” OR “*Punica granatum*” AND “ICAM-1″ OR “VCAM-1″ OR “E-selectin” OR “interleukin” OR “IL” OR “endothelial adhesion molecules” OR “vascular adhesion molecules” AND “clinical trial”. The information about participants, interventions, comparisons, outcomes, and study design (PICOS) criteria are presented in Table 1.

Study selection process

A comprehensive literature search up to July 2020 was carried out. The selection of studies eligible for this work is summarized in Fig 1. At first, two independent researchers (SA and RK) performed the study selection, and a third investigator MHF was involved to resolve any differences or controversies. Overall, by systematic search of the databases, 1567 potentially eligible studies were identified based on the inclusion criteria of this meta-analysis. After excluding duplicates and screening the title and abstracts, we selected 716 full-length articles for further evaluation. 571 studies were excluded because they did not meet the eligibility criteria based on the contents in the titles and abstracts. After reviewing the full texts, only eight articles were selected for meta-analysis initially, but later two article was excluded due to a lack of control group. Finally, six studies were included for this meta-analysis.

Table 1
PICOS criteria for inclusion and exclusion of studies.

Parameter	Criteria
Participants	General population of adults and adolescents aged ≥ 12 years old
Intervention	Pomegranate
Comparison	Δ-changes between treatments (pomegranate/placebo)
Outcomes	Effect of pomegranate juice on ICAM-1, VCAM1, E-selectin, and IL-6.
Study design	Randomized clinical trials

ICAM-1, intercellular adhesion molecule 1; PICOS, participants, interventions, comparisons, outcomes, and study design; VCAM-1, vascular cell adhesion molecule 1; IL-6, interleukin-6.

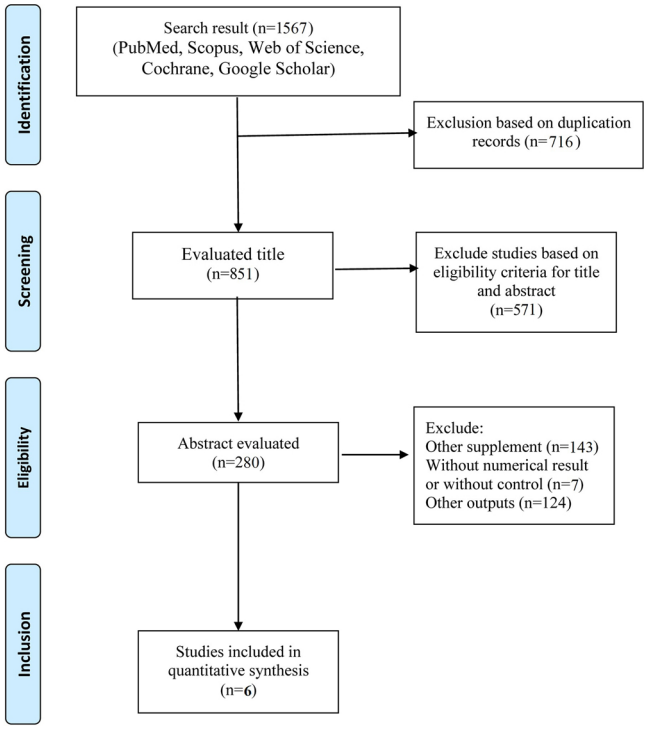

Fig. 1. PRISMA flow diagram showing the process of study selection.

Study eligibility criteria

We included studies that met the following inclusion criteria: (i) randomized controlled trials (RCTs) were published in English on human subjects; (ii) study participants were aged between 12 and 67 years old; (iii) randomized allocation to pomegranate group or placebo; (iv) ICAM-1 or/and VCAM-1 and/or E-selectin and/or IL-6 were out come measures. We excluded clinical trials that lacked a suitable control group and publications that examined the effects of pomegranate supplementation in combination with other interventions.

Bayesian meta-analysis

For each study, we computed the mean Δ-changes from baseline for the pomegranate treatment and control group. Then, the difference of mean Δ-changes between treatments (pomegranate/placebo) was calculated at the endpoint. As our meta-analysis included a small number of studies, we used the Bayesian method in addition to the traditional meta-analysis because the Bayesian approach can provide more accurate estimates for small samples (Higgins et al., 2009; Lee and Lio, 1999; Mila and Ngugi, 2011). In this situation, the prior for estimating between study variance can affect the analysis (Lambert et al., 2005), because it takes into account all sources of variation and reflects these variations in the pooled result (Sutton and Abrams, 2001). In this regard, we defined γ-distribution and half-normal as an informative prior, in addition to using uniform distribution for between studies variance and a normal prior with a large variance N (0.103) for the mean difference of outcome.

To fit the random effect meta-analysis model and get the pooled (overall) estimate, at first 10,000 iterations were burn-in and results were reported as the posterior mean with 95% credible intervals (CrI) based on a further 100,000 iterations by using Markov chain Monte Carlo. In addition, heterogeneity between studies was estimated with I2 statistic and Cochran's Q-statistic by assessing the proportion of variance due to study-to-study heterogeneity (Higgins et al., 2003). Publication bias was estimated by Egger's regression test and the Begg and adjusted rank correlation test (Begg and Mazumdar, 1994; Egger et al., 1997). *P* values below 0.05 were interpreted as statistically significant. Analysis was performed by using R (version 3.6.0, RCore Team, Vienna, Austria) and OpenBUGS (version 3.2.3) software.

Sensitivity analysis

Different prior distributions were used in Bayesian models and their effect on the final outcome of the distribution was investigated by Dvina's statistics to select the appropriate model. The smaller the size of this statistic, the better fit of the model.

Risk of bias

The risk of bias for the included studies was evaluated using the Cochrane quality assessment tool for RCTs (Higgins et al., 2011). The quality of the studies was assessed by checking factors, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding outcome data, incomplete data, and selective reporting and other probable sources of biases. These factors were classified as low risk, high risk, or unclear risk of bias.

Results

Study characteristics

Our literature search identified three randomized clinical trials in humans published between the years 2011 and 2020. The sample size involving 296 patients (pomegranate group: 165 patients and placebo group: 131 patients) investigated the effects of pomegranate on ICAM-1, VCAM-1, E-selectin and IL-6 levels in two groups. Participants were aged between 12 and 67 years old (mean age = 50.27), and the dosage of pomegranate juice ranged from 50 to 250 ml. The duration of RCTs varied from 2 weeks to 48 weeks (Table 2).

ICAM-1

The results of Bayesian hierarchical modeling showed that the mean levels of ICAM-1in the pomegranate group was not significantly different from the placebo group. The Bayesian credible intervals (CrI) were reasonably wider (MD: −0.42, 95% CrI: −1.01 to −0.17) as they accounted for additional variability. The heterogeneity between three studies was not significant (I^2 = 0%, p = 0.866) and the effect size was pooled using the fixed-effect model (Fig. 2).

VCAM-1

As shown in Fig. 3, the result of the combination of the 4 studies) three articles that two articles have been repeated twice because of having two trials) based on random effect Bayesian hierarchical model did not show any significant effect of pomegranate on VCAM-1 (MD: −0.20, 95% CrI: −1.95 to 1.40).The heterogeneity between studies was significant (I^2 = 86.8%, p < 0.001).

E-selectin

Pomegranate consumption had no significant effect on mean of E-selectin level compared to that of control group. As the heterogeneity between studies was significant, random effect Bayesian hierarchical model was used (MD: −0.21, 95% CrI: −1.62to1.21). The result is shown in Fig. 4.

IL-6

The results of Bayesian hierarchical random effect modeling on 7 studies) five articles that two articles have been repeated twice because of having two trials) showed that using pomegranate can significantly

Table 2
Description of the studies included in the meta-analysis.

Authors	Study type	Population	Average age (y)	Mean dose	Duration	Effects of pomegranate juice
(Sohrab et al., 2018)	RCT	Pomegranate = 22 Placebo = 22	55	250 ml	12 weeks	ICAM-1, VCAM-1: no change, ↓E-selectin
(Asgary et al., 2014)	RCT	Pomegranate = 11 Placebo = 10	59	150 ml	2 weeks	ICAM-1: no change ↓VCAM-1 ↑E-selectin ↓ IL-6
(Kelishadi et al., 2011)	RCT	Pomegranate = 15 Placebo = 15	12–15	240 ml	4 weeks	VCAM-1: no change ↓E selectin ↓ICAM-1 ↓ IL-6 (after 4 h) ↑ IL-6 (after a weak)
(Barati Boldaji et al., 2020)	RCT	Pomegranate = 41 Placebo = 40	47.8	100 ml	8 weeks	↓ IL-6
(Shema-Didi et al., 2012)	RCT	Pomegranate = 66 Placebo = 35	66	100 ml	48 weeks	↓ IL-6
(Urbaniak et al., 2018)	RCT	Pomegranate = 10 Placebo = 9	21	50 ml	8 weeks	↓ IL-6 (immediately after exercise) ↓ IL-6 (after 1 day)

ICAM-1, intercellular adhesion molecule 1; RCT, randomized controlled trials; VCAM 1, vascular cell adhesion molecule 1; IL-6, interleukin-6.

reduce mean of Interleukin-6 (MD: −1.07, 95% CrI: −1.90 to −0.19). The heterogeneity between studies was significant (I^2 = = 87.6%, $p < 0.001$) (Fig. 5).

Publication bias

The results of the publication bias using the Egger test, for ICAM-1 ($p = 0.590$) and interleukin-6 ($p = 0.275$) were not significant, but for VCAM-1 ($p = 0.013$) and E-selectin ($p = 0.043$) were significant. The adjusted trim and fill statistics performed for modify the result but the results were not different.

Discussion

The present meta-analysis is an effort towards evaluating the importance of pomegranate in improving endothelial dysfunction. Pooled effect size of included randomized clinical trials indicated that pomegranate juice was not significantly effective on ICAM-1, VCAM-1, and E-selectin in comparison with the control group. In contrast, the juice significantly reduced the pro-inflammatory cytokine, IL-6. Statistical analysis also revealed that the heterogeneity between the six studies was significant.

Sohrab et al. found that there was a significant decrease in the level of E-selectin in the group given pomegranate juice when comparison was made with that of the placebo group (Sohrab et al., 2018). Asgari et al. (Asgary et al., 2014) found that there was a significant elevation in the levels of E-selectin at the completion of the trial in the group which received pomegranate juice. Kelishadi et al. (Kelishadi et al., 2011) observed that after 1 month of starting the study, the group that was treated with pomegranate juice showed a significant decrease in E-selectin values

The red color of the arils of pomegranate fruit is provided by anthocyanins. Ellagitannins, gallotannins, punicalagin, punicalin are important tannins distributed in various parts of the tree. Sohrab et al. pointed out that the beneficial effect of pomegranate juice with respect to certain parameters could be due to the presence of anthocyanins, such as delphinidin glucosides, or the polyphenols present in it (Sohrab et al., 2018). Another type of anthocyanin found in pomegranate juice is cyanidin glucosides, which lead to a decrease in the level of nuclear factor-κB (NF-κB) (Sohrab et al., 2018). Sohrab et al. showed a decrease in SIRT1 and NF-κB levels. In a study employing the human monocytic cell line (THP-1), it was shown that the decrease in the release of ICAM-1 was produced by peel extract of pomegranate and punicalagin, but no effect was observed by the above on release of VCAM-1 by THP-1 cell line (Sohrab et al., 2018). The study thus focused on the fact that consumption of pomegranate juice can lead to a reduction in inflammation associated with diabetes as shown by the decrease in levels of E-selectin and NF-κB and increase in levels of SIRT-1 (Sohrab et al., 2018). Asgary et al. (Asgary et al., 2014) also pointed that the beneficial effects of pomegranate juice on endothelial function are due to phytochemicals, such as polyphenols, especially anthocyanins, present in pomegranate.

In vitro and in vivo studies have indicated preventive and/or therapeutic effect of pomegranate against cardiovascular disease. To test the effect of pomegranate on cardiac necrosis, isoproterenol-treated rats were received pomegranate juice for 30 consecutive days, and the results indicated that pre-treatment with pomegranate juice reduced infarct size, lipid peroxidation levels, heart weight, levels of Ca^{2+} ATPase, and plasma marker enzymes (Jadeja et al., 2010). Mohan et al. (Mohan et al., 2010) showed that pomegranate Juice (100 or 300 mg/kg) for 4 weeks led to a reduction in the serum angiotensin converting enzyme activity as well as decreased the mean arterial blood pressure in diabetic hypertensive rats. Fuhrman et al. (Fuhrman et al., 2005) have showed that anti-atherogenic properties of pomegranate juice can prevent foam cell progression and cellular cholesterol accumulation in macrophages by suppressing cholesterol biosynthesis and oxidized low-

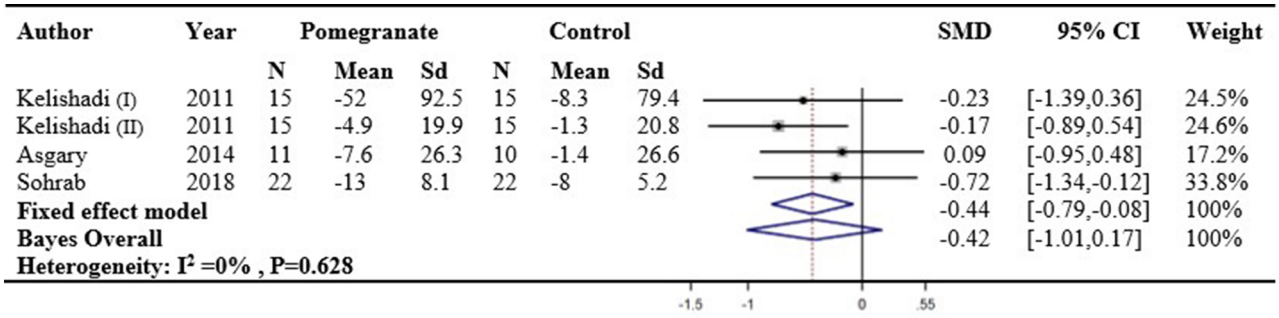

Fig. 2. Forest plot of pooled mean difference of ICAM-1 between pomegranate and placebo groups. I: 4 h; II: 4 week.

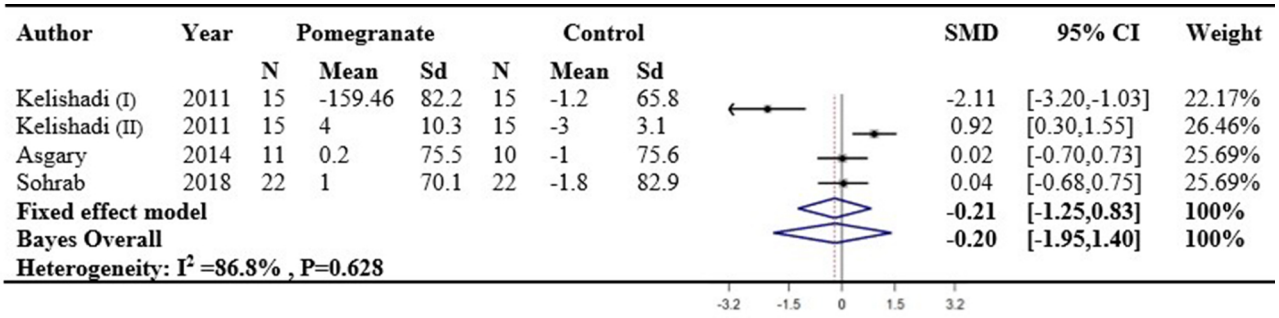

Fig. 3. Forest plot of pooled mean difference of VCAM-1 between pomegranate and placebo groups. I: 4 h; II: 4 week.

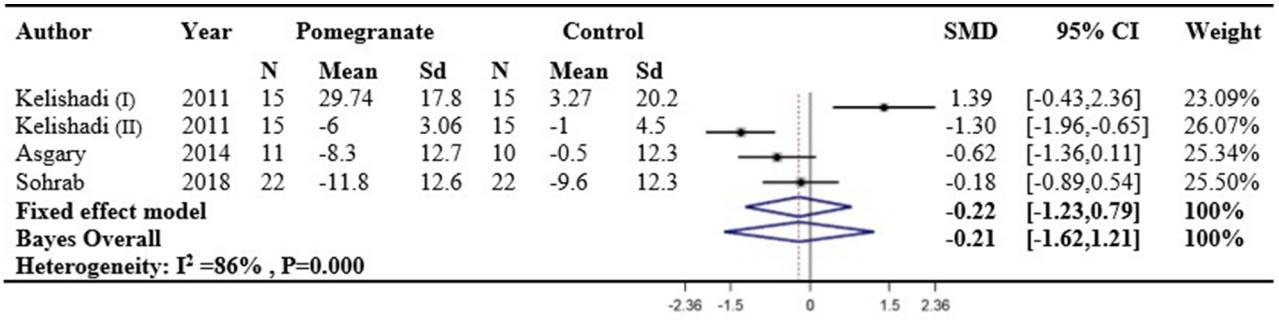

Fig. 4. Forest plot of pooled mean difference of E-Selectin between pomegranate and placebo groups. I: 4 h; II: 4 week.

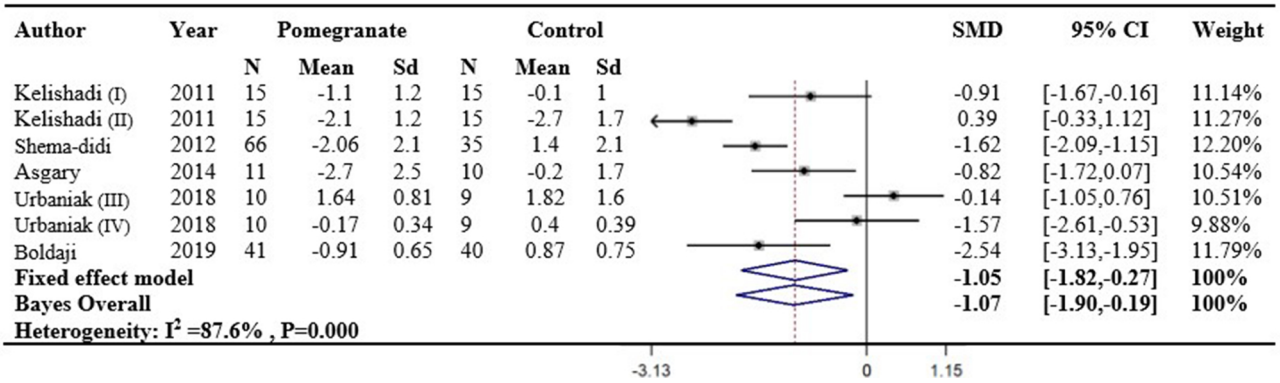

Fig. 5. Forest plot of pooled mean difference of Interleukin-6 between pomegranate and placebo groups. I: 4 h; II: 4 week; III: immediately after the exercise; IV: after a 1-day recovery.

density lipoprotein degradation. Researchers documented that pomegranate pretreatment led to attenuate the cardiac damage through reducing lipid peroxidation, antioxidant activity, anti-inflammatory effect in daunorubicin-induced cardiotoxicity in rats. There was a significant decrease in cardiac biomarkers, such as cardiac troponin I, malondialdehyde, and IL-17, in pomegranate pretreated rats (Al-Kuraishy and Al-Gareeb, 2016).

It has been shown in previous studies that ellagic acid and urothilin are responsible for the anti-inflammatory activity of pomegranate juice. Kelishadi et al. have mentioned that pomegranate juice acts as a potent antioxidant (Kelishadi et al., 2011). Its antioxidant power is three times higher than antioxidant power of red wine (Gil et al., 2000).

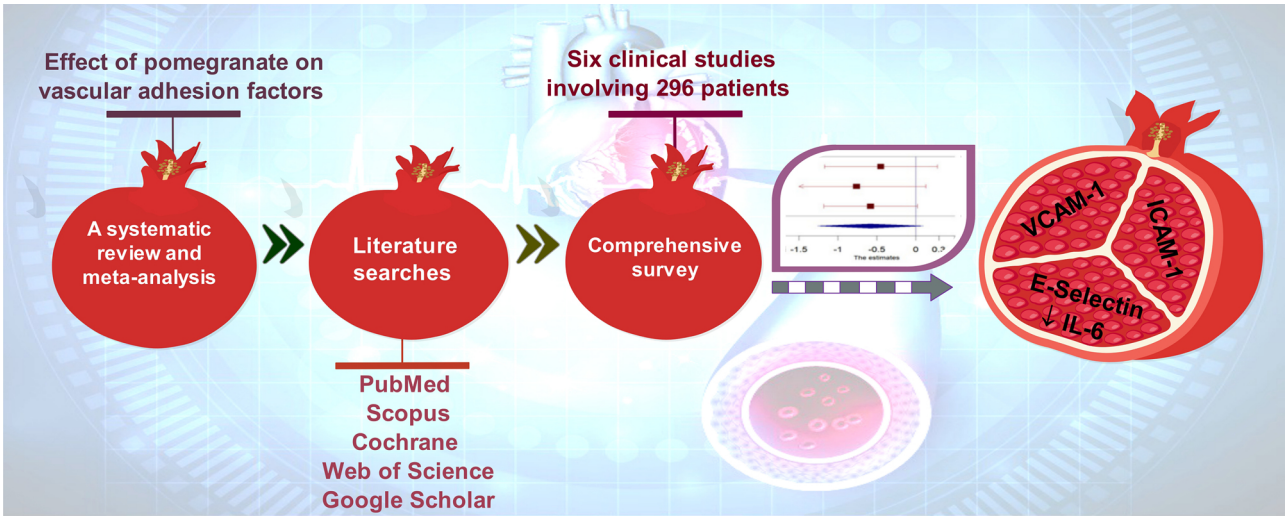

Fig. 6. Schematic diagram of meta-analysis of pomegranate juice role on adhesion factors.

Antiantioxidant properties of pomegranate juice on rat aortic smooth muscle cells have been reported under in vitro conditions, and the results indicated that pomegranate juice promoted the biological actions of NO and protected against oxidative damage inflicted by reactive oxygen species. Activation of NO led to inhibition of vascular smooth muscle cell proliferation and progression of atherosclerosis (Ignarro et al., 2006). However, this meta-analysis found that there was no significant effect of pomegranate juice on the endothelial parameters, such as ICAM-1, VCAM1 and E-selectin. Heterogeneity in the three studies was found to be non-significant with respect to ICAM-1 values but significant with respect to VCAM-1 and E-selectin values. The individual studies also employed various other parameters other than ICAM-1, VCAM-1 and E-selectin.

The main limitations of this systematic review and meta-analysis include a limited number of studies, small sample size, and study duration. Also, significant statistical heterogeneity was observed among the studies. Accordingly, the findings should be interpreted with caution. Regarding the aforementioned limitations, more investigations must be conducted to have a better understanding of the precise effect of pomegranate on endothelial function.

Conclusions

The present meta-analysis focused on analysis of combination of six clinical studies to evaluate the effect of pomegranate juice on endothelial dysfunction by monitoring three vascular adhesion factors, such as ICAM-1, VCAM-1, E-selectin and IL-6 (Fig. 6). This meta-analysis analyzed the three studies in a combined manner and the outcomes were somewhat different than the results of the individual studies. This systematic review focused on a different point of view regarding the effect of pomegranate on endothelial dysfunction. By changing the manner in which the results of a particular study are analyzed and interpreted, newer information can be obtained regarding the efficacy or inefficacy of a particular plant in the treatment of endothelial dysfunction. Generally, present study showed that pomegranate juice has no significant effect on vascular adhesion factors, ICAM-1, VCAM-1, and E-selectin, but can reduce IL-6 significantly. Future prospective randomized clinical trials with longer intervention duration are warranted to obtain a precise conclusion.

Credit author statements

MHF - Conceptualization; SA, RK, TJ, SM, ZS, and EM - Data curation; SA - Formal analysis; SA and RK - Investigation; SA, RK, TJ and SM - Methodology; MHF - Project administration; MHF - Supervision; SA, RK, TJ, SM, ZS, and EM - Roles/Writing - original draft; AB and KLK - Writing - review & editing.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interests.

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