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The effect of pomegranate on oxidative stress parameters: A systematic review and meta-analysis

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ABSTRACT

Objective: Pomegranate contains remarkable amounts of phenolic ingredients and it has been related to the antioxidant capacity of this fruit. Several primary studies show that pomegranate intake can improve antioxidant status. The objective of this systematic review and meta-analysis consisted in investigating the effect of pomegranate on oxidative stress (OS) parameters.

Methods: A comprehensive electronic database search in Scopus, Web of science, Embase, Cochrane library and Medline was performed to identify eligible randomized controlled trials (RCTs). A meta-analysis of included studies was performed on selected variables using a random-effects model. Quality assessment was conducted by means of Cochrane risk of bias assessment tool.

Results: Systematic search yielded 575 references. A total of 11 RCTs reporting data from 484 participants included. Meta-analysis of data from 11 included RCTs did not support convincing evidence as to a significant increasing effect of pomegranate intake in TAC (SMD: 0.43 ; 95 %CI: -0.19, 1.06), Gpx (SMD: 0.18, 95 % CI: -0.25, 0.62, p = 0.4) and paraxonase (SMD: 0.36, 95 % CI: -0.50, 1.22, p= 0.41) as well as not significant decrease in Malondialdehyde (MDA) (SMD: -0.81, 95 % CI: -1.79, 0.09, P = 0.08).

Conclusion: Future well-designed clinical trials are needed before definite conclusive claims can be made about the effect of pomegranate on OS parameters.

1. Introduction

All cells under normal physiological conditions in the body are exposed to endogenous and exogenous oxidants.[1] Oxidative stress (OS) defined as an imbalance between the production of reactive oxygen/nitrogen species (ROS/RNS) and the cell's capacity to neutralize them by the anti-oxidative protection systems.[2] Electron transport chain (ETC) in the inner membrane of mitochondria is the main source of ROS, where the energy is produced. Electrons are given from NADPH and $FADH_2$ to oxygen by the help of four membrane complexes.[3] As a natural occurrence, some electrons are leaking from the inner membrane to react with oxygen and form superoxide anions, which can then generates other forms of ROS and also RNS.[2] Increased ROS/RNS generation or impaired ability of anti-oxidant production are the cause of OS emerging, which showed the reduction of endogenous system capacity to fight against oxidative attack.[4] ROS/RNS can damage and modify different types of macromolecules in the cell, like DNA, RNA, proteins and lipids, these process can generate more potent reactive molecules too.[5] It was confirmed that OS is associated with various disorders and diseases.[6–10] On the other hand, OS maybe can be prevented by antioxidant potential manifestation at the proper site. So the pathological consequences or even cell death of reactive species activity will be impaired.[11]

Endogenous antioxidant defense system includes some enzymes (like superoxide dismutase, glutathione peroxidase and catalase) and non-enzymatic compounds such as proteins (ceruloplasmin, ferritin, transferrin, and also albumin), glutathione and some scavengers like coenzyme Q, uric acid and lipoic acid.[12] In addition, exogenous

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antioxidants has a remarkable role respectively. Fruits and vegetables contain antioxidants which can counterpart the activity of the endogenous antioxidant defense.[13] Antioxidant and anti-inflammatory effects of poly phenols have been confirmed previously.[14]Studies have demonstrated that the chemical structure of plant polyphenols is appropriate for reactive species scavenging, and also in vitro studies the effectiveness of poly phenols antioxidant activity is more than ascorbate and tocopherols.[15] Instead of supplements, using naturally occurring phytonutrients for limiting or reducing the OS is cost-effective and also a better way to make healthier behaviors.[16]

Pomegranate is a fruit which is a good source of polyphenols and other compounds such as flavonols, flavonoids, quercetin, gallic acid, ellagic acid, ellagitannins, nitrate.[17,18] Pomegranate also contains anthocyanins like cyanidin, delphanidin and pelargonidin and other tannins like punicalin, pedunculagin and punicalagin.[19,20] Previous studies showed that pomegranate juice (PJ) are potential in lowering the lipid profile parameters and homocysteine.[21] In vitro studies show antimicrobial effect of PJ.[22] Compared to other juices (such as other fruit juices or black tea and green tea), PJ has more and better effects on increasing the body antioxidant capacity and decreasing oxidative damages to biomolecules.[23] In addition, pomegranate economically considered as a health-beneficial food, and it has an abundant place in the international commercial markets.[24] Studies showed that prodelphinidines treatment has an inhibition effects on cyclooxygenase-2 and lipoxygenase activity, prostaglandin E2 production and type 2 collagen synthesis activation in human chondrocytes.[25,26]In overall view, potent mechanisms mediating the antioxidant properties of PJ is still unclear, but its effects has been attributed to increase polyphenol bioavailability in comparison to other foods which are rich in polyphenols.[27] Studies regarding the beneficial effects of PJ on improving OS are controversial. Several studies have shown beneficial effects of PJ on OS markers while no significant changes were seen in others. Therefore, we conducted a systematic review and meta-analysis of the beneficial effects of PJ on controlling OS factors.

2. Methods

This research was conducted according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement.[28] We perform meta-analyses of existing evidence based on the ability of pomegranate to alter OS parameters compared to placebo in either healthy individuals or patients.

2.1. Search strategy

Two separate electronic searches were conducted to identify RCT relating intake of pomegranate to measures or changes of OS parameters. The search was performed in the following databases: Embase, SCOPUS (http://www.scopus.com), Web of Science, Cochrane Library and Medline (http://www.ncbi.nlm.nih.gov/pubmed) up to 15th January 2019. Keywords included the following mesh terms (for Medline) or subject headings (For Web of Science, Embase, Scopus and Cochrane Library): Glutathione Reductase OR Reductase, Glutathione OR Glutathione Peroxidase OR Peroxidase Glutathione OR Superoxide Dismutase OR Dismutase Superoxide OR Oxidative Stress OR Stress Oxidative OR Stress, Oxidative OR Total Antioxidant Capacity OR Total Antioxidant Status OR antioxidant OR Oxidant OR reactive oxygen species OR Catalase OR Oxygen Radical Absorbance OR reactive nitrogen species OR protein carbonyl OR lipid peroxide OR Total Radical Trapping Antioxidant Parameter OR Malondialdehyde OR Nitric oxide OR 8-hydroxydeoxyguanosine OR thiobarbituric acid reactive substances OR nitrotyrosine OR sulfhydryl group OR oxidized LDL lipoprotein OR xanthine oxidase OR paraoxonase-1 AND Pomegranate OR Pomegranate juice OR Pomegranate extract (PE) OR Punicaceae OR Punica granatum. The sequence used is described in Appendix 1. No language limitation was used in the literature search. The search was restricted to studies in human.

2.2. Study selection

Two reviewers independently evaluated titles and abstracts of all identified studies. Abstracts were read to determine and include articles that fulfilled the selection criteria. Disagreements in opinion as to whether articles should be included for full review were firstly discussed and resolved by consensus. If no consensus could be attained, a third reviewer intervened to determine the inclusion or exclusion of the study. Parallel or case-cross-over trial studies were included. Studies assessing the impact of PJ on OS parameters, conducted in a range of age between 18 and 80 years old. Studies should report enough information on beginning and at the end of study in both pomegranate and control groups. Studies were excluded if they are non-clinical studies, uncontrolled trials or administering pomegranate preparations via non-oral routes e.g. mouthrinse or topical application. Additionally, literature reviews, case–control studies, cohort studies, case reports, letter to editors, anthropological studies, in vitro studies or comments were also excluded.

2.3. Data extraction and quality assessments

Data extraction and quality assessment were performed separately by two reviewers (J.H. and M.S.). Information extracted from the articles included: (1) first author's name; (2) time of publication in year; (3) Country where study is done; (4) number of subjects in the pomegranate and control groups; (5) dose of supplementation with pomegranate products; (6) duration of intervention; (7) serum concentrations of TAC, GlutathionePeroxidase (Gpx), Malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), paraoxonase (8) and also age and gender of participants. A systematic assessment of bias in the included articles was carried out independently by two reviewers (J.H. and M.M) using the Cochrane criteria.[29] The criteria's used for the evaluation of each study were included: The assessment included selection bias (method for random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other sources of bias.

2.4. Data analysis

Studies that compared mid-term or long-term interventions of pomegranate content were analyzed. Meta-analyses were performed using Review Manager software (Version 5.2, The Nordic Cochrane Centre, Copenhagen) if two or more articles examined pomegranate with the same outcome measure. Significant heterogeneity was detected ($P < 0.05$, $I^2 > 75$ %); hence, a random-effects model was conducted for the meta-analysis. For continuous outcomes, standardized mean differences (SMD) with 95 % confidence intervals (CIs) were calculated. Statistical analysis for heterogeneity was evaluated using the I^2 statistic to determine total variation across articles attributable to heterogeneity and chi square test for heterogeneity.[29,41] Meta-analysis results are presented as forest plots.

3. Results

3.1. Description of the studies

Fig. 1 shows the study flow diagram. Our systematic search of electronic database yielded 575 references. Reference lists of relevant articles were manually searched and elicited 6 additional studies. After removing duplicates, title and abstract review resulted in 355 original articles. A total of 11 RCTs reporting data from 484 participants were finally fulfilled selection criteria and included in this systematic review

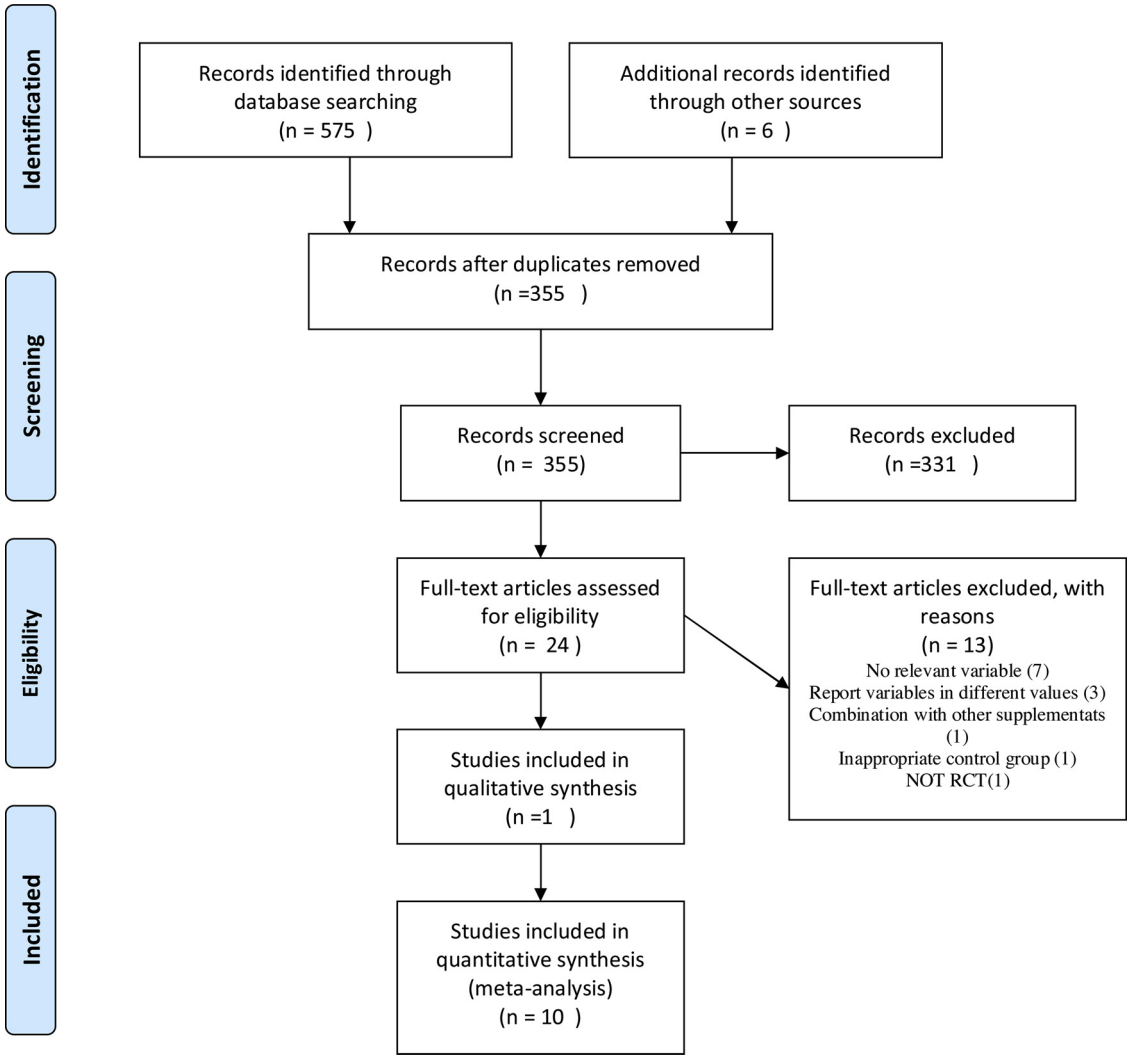

Fig. 1. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:https://doi.org/10.1371/journal.pmed1000097.
For more information, visit www.prisma-statement.org.

Table 1
Main characteristics of included studies.

References	Main outcome[¥]	Pomegranate type	Age (years)		Sample size	Country	Participants	Duration(W)
			Placebo (Mean)	Intervention (Mean)				
[30]	↓MDA, ↑ CAT, ↑ GPx	P J	21.00	21.00	9	Tunisia	Atheletes Elite weightlifters Healthy adults	72
[31]	↑ GPx, ↔MDA	P E	48.40	49.10	55	Iran	Rheumatoid Arthritis patients	8
[32]	↓MDA	P E			42	Iran	Overweight + obese	4
[33]	↓MDA, ↓AOPP	P J	65.90	67.50	101	Israel	Hemodialysis patients	48
[34]	↓MDA, ↑ GPx, ↑ SOD, ↑ TAC	P J	19.07	19.78	28	Iran	Healthy adults, males	2
[35]	↑ GPx, ↑ MMP	P J	56.74	53.84	38	Iran	Knee osteoarthritis	6
[36]	↑ GPx, ↔TAC	P J	46.5	47.5	50	Iran	D M type 2	8
[37]	↓ox-LDL, ↑TAC, ↑PON	P J	54.6	55.3	60	Iran	D M type 2	6
[38]	↑PON-1, ↔Ox-LDL	P J	55.9	52.6	33	USA	Hemodialysis Patients	24
[39]	↑ GPx, ↑ SOD, ↑ TAC, ↑GSH	P J	56.5	49.5	33	Iran	D M type 2, women, menopause	6
[40]	↓TBARS	P J			35	Egypt	healthy adults	3

MDA: malondialdehyde, CAT: catalase, GPx: glutathione peroxidase, AOPP: advanced oxidation protein product, SOD: superoxide dismutase, TAC: total antioxidant capacity, MMP: matrix metalloproteinase, ox-LDL: oxidized LDL, PON: paraoxonase, GSH: glutathione, TBARS: thiobarbituric acid reactive substances.
DM type -2 = Diabetes Mellitus type-2; PE = Pomegranate extract; PJ = Pomegranate juice.
* ↓ This symbol is a sign of decreasing variables in the intervention group, ↑ This symbol is a sign of increasing variables in the intervention group, ↔ This sign indicates that there is no difference between the two groups. NR: not reported.

and are illustrated in detail in Table 1. All identified studies were published after 2012. One study was conducted in the United States,[38] two were from Africa[30,40] and eight were from Asia.[31–37,39] The duration between the pomegranate interventions was wide and ranged from 2 to 72 weeks. All of the studies except one[36] were written in English. The mean age of the participants ranged from 21 to 65 years. The study sample size was always rather small, with the ranging from nine[30] to one hundred and one.[33] The potential effect of PJ were used in nine articles, while PE were used in another two studies. The participants belonged to the elite weightlifters,[30] rheumatoid arthritis patients,[31] overweight and obese individuals,[32] hemodialysis patients,[33,38] patients with kneeosteoarthritis,[35] Type 2 diabetes patient[36,37,39] and healthy participants.[34,40] MDA, TAC, Gpx and paraxonase were fullfiled criteria to be included in quantitative analyses and TBARS reported in qualitative assessment. MDA was assessed in five studies, TAC was assessed in three studies, Gpx and paraxonase were assessed in two studies and TBARS was assessed in one included study.

3.2. Quality assessment

Four of the selected articles did not report enough data about random sequence generation[30,34,35,40] and five of included studies did not report a clear information about allocation concealment.[30,34,36,39,40] Six of included studies not providing information or with enough data about blinding.[30,32,34,36,39,40] Nevertheless, other possible sources of bias were report correctly by most of the included studies. Details on the risk of bias assessment among included studies are summarized in Appendix S2.

3.3. The effect of pomegranate on serum levels of MDA

Fig. 2 shows a forest plot of the pooled effect of pomegranate on serum MDA concentrations. MDA levels in various samples were reported in a total of five studies conducted in 244 participants. Four of these RCTs shows a significant reduction in MDA concentration after pomegranate intake compare to placebo, while one of these shows no significant change of MDA. Meta-analysis of data from five studies revealed no significant change in serum MDA following treatment with pomegranate (SMD: -0.81, 95 % CI: -1.79, 0.09, P = 0.08). This effect also has a large heterogeneity (Q = 39.24, P < 0.0001; I^2 = 90 %).

3.4. The effect of pomegranate on serum levels of TAC

The pooled SMD of three RCTs showed a non-significant increase in TAC in the pomegranate group compared with the placebo group (0.43 ; 95 %CI: -0.19, 1.06) (Fig. 3). The heterogenicity of this effect was I^2 = 49 %. In Mazani et al[34] and Yarmohammadi et al[39] pomegranate effectively increased the TAC levels, However, in the other study no significant result was reported.[36]

3.5. The effect of pomegranate on serum levels of GPx

In six studies, the effect of pomegranate consumption on Gpx levels was evaluated, but due to differences in measurement units, only two studies found the ability to enter the meta-analysis model. Meta-analysis of data from two trials indicated a non-significant elevation of serum Gpx following pomegranate intake (SMD: 0.18, 95 % CI: -0.25, 0.62, p = 0.4) (Fig. 4), this effect had no heterogenisity (I^2:0 %; p = 0.91).

3.6. The effect of pomegranate on serum levels of paraoxonase

Two studies have examined the effect of pomegranate consumption on serum paraoxonase levels, and Meta-analysis of these studies results are presented in Fig. 5. Meta-analysis represented a non-significant change of serum paraoxonase following pomegranate intake (SMD: 0.36, 95 % CI: -0.50, 1.22, p = 0.41) (Fig. 5), this effect has dramatically high heterogenisity (I^2 = 72 %; p = 0.91).

3.7. The effect of pomegranate on TBARS

Only one study which measuring urinary TBARS levels have fulfilled the criterias to entering this systematic review. Gouda et al. [40]showed that pomegranate consumption reduced the amount of Urinary TBARS.

4. Discussion

Pomegranate has been represented as a polyphenol-rich fruit with expanded health valuable good effects due to its high antioxidative potential.[42] In the present systematic review and meta-analysis of RCTs, pomegranate was not associated with a statistically significant alteration in OS parameters (MDA, TAC, Gpx, and paraoxonase). Although small number of articles were included in this systematic review, all the included studies found a significant improvement on various serum OS parameters. All the included articles were RCTs which increased the power of their study. Nonetheless, due to differences such as duration of intervention, number of subjects, pomegranate dosage, different variables and values and also variable inconsistency made it hard to reach a certain conclusion in this field of study.

To the best of our knowledge, this is the first pooled estimate of the effects of PJ on OS parameters. Our study showed that the consumption of pomegranate causes an insignificant decrease in MDA levels. Although this relationship has a very high heterogeneity, this indicates a very high difference between the studies. Therefore, if more homogeneous studies were available in this field, maybe a more resolute conclusion could be made in this regard. The lack of knowledge about the possible mechanism of pomegranate could be described by the diversity of fruit ingredients.[43,44] The antioxidant power of compounds found in pomegranate is proven in extensive in vitro and animal studies.[45] Tannins and polyphenols present in pomegranate considered as factors affecting the antioxidant properties of pomegranate. Pomegranate may have anti lipid peroxidation effects due to reduction of platelet aggregation, LDL oxidation and macrophage oxidative status.[46,47]

In our study, the results of meta-analysis showed that pomegranate did not have a significant effect on glutathione peroxidase levels. GSH-Pxis the one of the main abundant antioxidant markers in serum and have an important role in ROS scavenging based on in vitro studies.[48] Although previous studies have shown that PJ increases the antioxidant defense.[31,35] However, the antioxidant effects of the wide range of

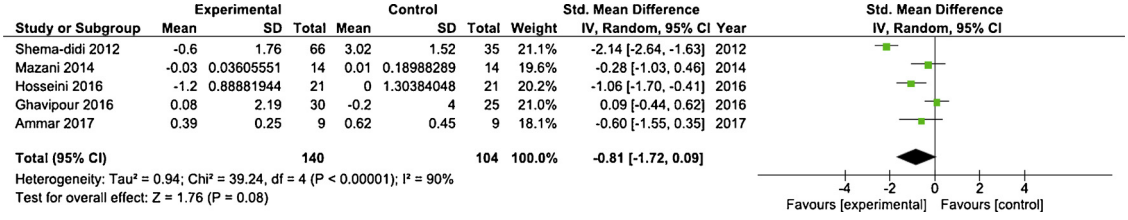

Fig. 2. Forest plot of pomegranate on serum MDA levels.

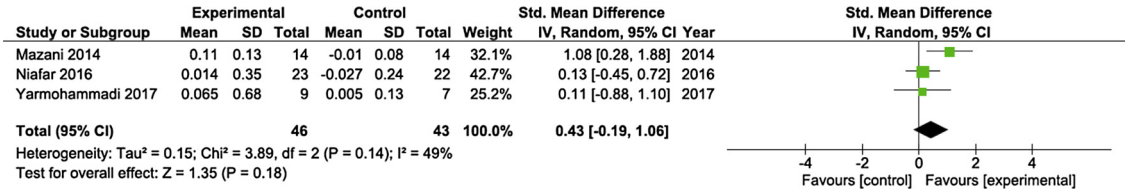

Fig. 3. Forest plot of pomegranate on serum TAC levels.

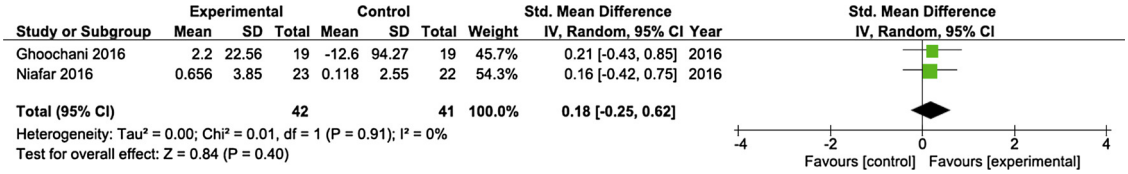

Fig. 4. Forest plot of pomegranate on serum Gpx levels.

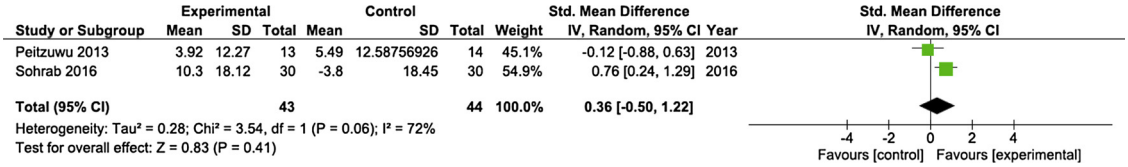

Fig. 5. Forest plot of pomegranate on serum paraxonase levels.

polyphenols present in pomegranate can reduce ROS levels in the body, therefore the body also needs to produce less glutathione to antioxidant defense.[45] Our study also showed that pomegranate causes a non-significant increase in TAC levels, which according to previous studies about the antioxidant properties of pomegranates, if there were more studies in this field that entered into the meta-analytical model, maybe the results would be significant. The results of this meta-analysis showed that pomegranate causes an insignificant increase in paraoxonase levels. Increased paraoxonase after pomegranate intake confirm antioxidative properties of pomegranate polyphenols including ellagic acid, anthocyanin,tannins, and punicalagin which are powerful ROS scavengers.[49,50] Effect of Pomegranate intake on urinary TBARS was also investigated in early studies[40] and positive effects of pomegranate have been observed in reducing this oxidant index. This study has some limitations. The limited number of studies for each of the OS variables made it impossible to conclude certainly about the effect of pomegranate on the OS parameters. In addition dramatically high heterogeneity of the primary studies, included in this systematic review also did not reveal a clear picture of the pomegranate antioxidant effects.

5. Conclusion

Eventually, according to the results of the present systematic review, pomegranate has positive effects on OS parameters. However, based on the Meta-Analysis, because of not enough clinical trials and variable inconsistency no resolute conclusion could be made on the effect of pomegranate on OS parameters. Future clinical trials with large sample size and well design to remove the limitations in the existing literature are necessary before definite claims can be made about the impact of pomegranate on OS parameters.

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Disclosure statement

The authors have nothing to disclose.

Declaration of Competing Interest

The authors declare that they have no conflict of interests to declare

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.102252.

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