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The effect of green tea on prostate specific antigen (PSA): A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Prostate cancer is a major malignancy, affecting men, worldwide. The protective effect of green tea consumption on prostate cancer has been reported in several studies; however, the findings are equivocal.
Objective: The aim of this study was to evaluate the effects of green tea on PSA level, by conducting a systematic review and meta-analysis of randomized controlled trials.
Methods: We searched online databases, including PubMed, Scopus, and Web of Science, up to 11 Aug 2020, to obtain relevant publications. The publication search was not limited by language or date.
Results: A total of 2488 records were identified in the systematic search; from these, seven were included in the meta-analysis. The overall analysis showed no significant changes in PSA levels in subjects treated with green tea, (WMD: –0.60 ng/mL; 95 % CI: –1.32, 0.12 ng/mL; P = 0.104, I^2 = 93.80 %, P heterogeneity<0.001). Subgroup analysis based on geographical location showed that green tea significantly reduced PSA level in the USA population (WMD: –1.02 pg/mL, 95 % CI: –1.30, –0.73, P < 0.001) compared to non-USA populations (WMD: –0.22 pg/mL, 95 % CI: –0.95, 0.50, P = 0.539) (P < 0.001).
Conclusion: The results of this review show that green tea has no significant effect on PSA level. However, due to the heterogeneity among studies more consistent clinical trials, with larger sample sizes are required.

1. Introduction

Prostate cancer (PCa) is the major cause of cancer related mortality among men, with a globally high incidence and wide geographical differences.[1] Beside histological assessment, as a diagnostic method, prostate specific antigen (PSA) levels have been considered for screening PCa in early stages. Plasma level of PSA is also used for assessing clinical risks, follow-ups, and risk classifications of patients with PCa.[2,3] Depending on the clinical stage, type of the cancer, serum PSA, and possible side effects, common types of treatments include active surveillance, surgery, chemotherapy and radiation therapy.[4,5] Given the geographical pattern of the PCa, its unfavorable prognosis in high grades and adverse effects of aforementioned treatments on patients' quality of life, preventive strategies, such as lifestyle modifications and the use of chemo-preventive agents, may be a helpful approach to decrease the risk of PCa.[6–8] In this context, green tea-derived polyphenols, and dietary agents with chemo-preventive properties against PCa, have attracted much attention. Indeed, several epidemiological studies have reported that green tea consumption significantly reduces the risk of PCa.[9,10] Green tea, produced from the leaves of Camellia sinensis, is one of the most popular drinks consumed worldwide, particularly in Asian countries. Green tea catechins (GTCs), including epicathechin, epicathechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate, are the main polyphenolic ingredients in green tea, having strong antioxidant activities.[11] In vitro and in vivo studies demonstrated anti carcinogenic effect of green tea catechins via the induction of apoptosis and cell-growth arrest in PCa cells, thereby affecting the progression of PCa.[12] The beneficial effects of green tea catchins on the risk of PCa, and PSA level, as a screening biomarker, have

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also been reported in several trials.[13,14] However, data from other studies are equivocal. [15,16] Previous systematic reviews and meta-analysis, reporting protective effects of green tea on PCa risk, either focused mainly on observational studies[17] or did not perform a quantitative analyses on PSA level.[11] Therefore, the aim of this study was to systematically evaluate the RCTs investigating the effect of green tea/GTCs on PSA levels in subjects with or without PCa.

2. Methods

2.1. Search strategy

A comprehensive literature search was performed to identify relevant studies by using online databases, including PubMed, Scopus, and Web of Science, up to 11 Aug 2020. MeSH (Medical Subject Headings) terms related to green tea and catechins, and in combination with key words related to PSA were searched (Supplementary Table 1). In addition, the first four pages of Google Scholar and the reference list of included studies and recent reviews were checked to determine other, potentially relevant, articles. The publication search was not limited by language and date. This review is reported in accordance with the Preferred Reporting Items In Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] We used a PICOS (population, intervention, comparator, outcomes and setting) strategy to design the present systematic review as follows: Population: men with or without prostate cancer, Intervention: the supplementation of green tea or GTC, Comparator: using a placebo or active control, Outcome: circulating levels of PSA, Setting: randomized controlled trials. The study protocol was registered in the PROSPERO international prospective register of systematic review (CRD42020216149).

2.2. Eligibility criteria

One researcher (ESZ) searched the mentioned online databases to retrieve potentially related articles. Titles, abstracts, and full texts of the retrieved studies were screened independently by two authors (ESZ and FHS), according to the following inclusion criteria: 1) all RCTs with men aged $>$ 18 years old, 2) studies assessing the effects of green tea drink or GTCs on PSA level, as an outcome, and 3) publications in which mean $\pm$ standard deviation (SD), mean $\pm$ standard error (SE), or mean (95 % CI) were used to report effect sizes. In studies assessing the effect of multiple doses of green tea/ GTC on PSA, the highest dose was selected for evaluation in the meta-analysis. In addition, for trials evaluating the changes in PSA at multiple time points, only the most recent measurement was included for assessment. In this review, we excluded publications with any design other than RCT, studies in languages other than English, studies in which green tea or catechins were combined with other supplements (e.g. soy isoflavon), reviews, and meta-analyses.

2.3. Data extraction

After reviewing the full text of identified studies, all required data were extracted, by one of the investigators (FHS), based on a predefined screening form which was checked by the two researchers (HA and FS). Extracted information for each included article was as follows: first author's last name, year of publication, country, study design, study population characteristic, mean age of participants, study duration, sample size, dose and type of intervention (green tea drink / GTCs), placebo type, and outcome (mean of PSA). Any disagreement regarding data extraction was resolved by discussion.

2.4. Risk of bias assessment

Quality and risk of bias for eligible studies were evaluated by (ESZ and FHS) using the Cochrane Risk of bias assessment tool.[19] The following domains were considered for each included studies: adequate random sequence generation and allocation concealment (selection bias), blinding of participants and researcher (performance bias), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and any other bias. The quality of studies was scored and identified as poor (low risk for less than four domains), fair (low risk for four domains), and good (low risk for more than four domains), respectively. Any disparity regarding risk of bias was discussed and resolved by consultation with principal author.

2.5. Assessment of the quality of meta-evidence

The quality of meta-evidence for this review was evaluated by using the NutriGrade (Grading of Recommendations Assessment, Development, and Evaluation) scoring system.[20] This system, for a systematic review of RCTs, has a maximum of 10 points and includes: 1) risk of bias, study quality and study limitations, 2) precision, 3) heterogeneity, 4) directness, 5) publication bias, 6) funding bias, and 7) study design. The overall quality of meta-evidence for the outcome was classified as: high ($\geq$8 points), moderate (6–7.99 points), low (4–5.99), or very low (0–3.99).

2.6. Data synthesis and analysis

Mean differences (MD) for PSA, and their corresponding standard deviations between intervention and control groups (SDs) were utilized to calculate the effect size for PSA in each study.

For studies that did not report the MD and their SD values within intervention and control groups, the correlation *r*, based on baseline, post intervention, and change values of PSA ($r = 0.5$), was used to calculate MD and SD. All reported units of PSA were converted to the same unit before inclusion in the meta-analysis. The weighted mean difference (WMD) and its corresponding SD was calculated for PSA and pooled by using the DerSimonian and Laird method,[21] and taking between-study heterogeneity into account. Between-study heterogeneity was assessed by using Cochrane's Q statistic and I-squared statistic,[22] where I^2 value $>$ 50 % was defined as high heterogeneity. Subgroup analyses, according to participant's disease status (diagnosed PCa or increased risk but free of PCa), study duration ($\leq$ 12 week or $>$12 week), type of intervention (green tea drink or catechins supplement), amount of catechins ($\leq$600 mg or $>$ 600 mg), and geographical location (US Vs non US) were conducted to determine heterogeneity between studies. Sensitivity analysis was carried out to evaluate the effect of each study on the results. Publication bias was also evaluated by Begg's and Egger's regression test. All analyses were conducted by using Comprehensive Meta-analysis V2, and a $P < 0{\cdot}05$ representing statistical significance.

3. Results

3.1. Study characteristics

Fig. 1 presents the detailed process of study selection. A total of 2488 studies were initially identified by the online databases search. Based on title and abstract screening, 150 duplicates and 2316 irrelevant articles were excluded. Of the remaining 22 articles, an additional 15 studies were removed due to the reasons mentioned in Fig. 1. Ultimately, seven RCTs remained for inclusion in the present meta-analysis (Fig. 1).

Table 1details the main characteristics of the eligible studies for this systematic review. The design used in all the studies was parallel RCTs and based on study blinding, there were six double-blind, and one non-blinded studies. The total sample size included in the analyses was 455 participants. The participants of all studies were the elderly (mean age of 60–65 years) with the mean BMI of 26−30. Of the seven included studies, five were conducted on individuals at increased risk of PCa[15,23–26], and two on individuals with a diagnosis of PCa[13,27] (Table 1). Green tea was consumed in the form of GTCs in all studies

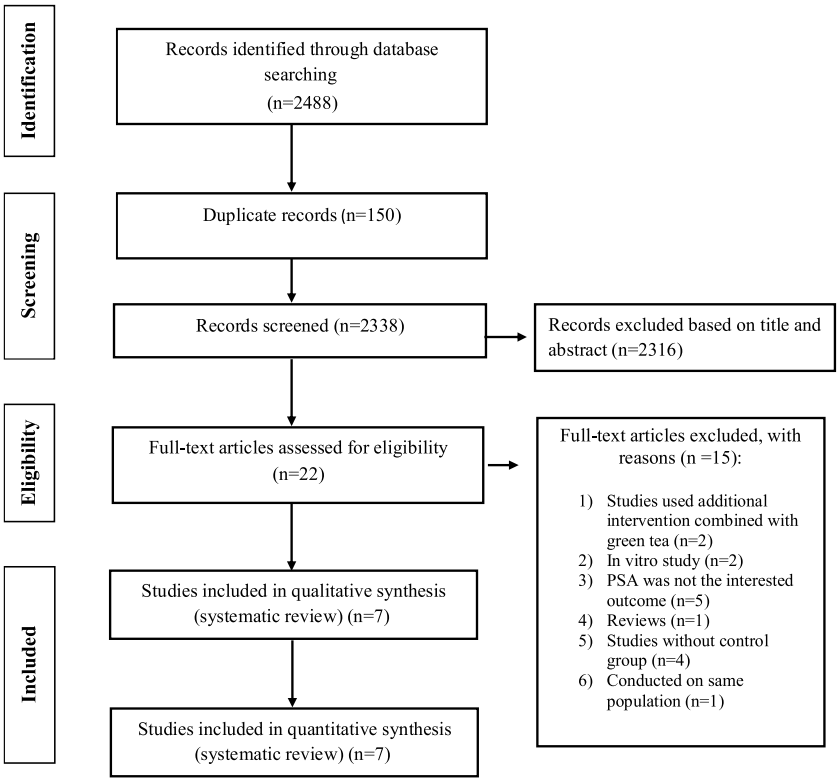

Fig. 1. Flow chart of study selection process.

except the one reported by Henning et al.,[13] where green tea drink was used and another reported by Lane et al. who assessed the effects of both green tea drink and green tea extract.[23] The intakes of GTCs and green tea drinks ranged from 400 to 800 mg/d and 6 cups/d to 600 mL/d, respectively. The duration of green tea supplementation varied between three weeks and 12 months. In a study by Lane et al. there were two intervention groups (green tea drink and green tea extract) and one placebo group; therefore, the result of green tea drink and placebo groups was considered as one study and the result of green tea extract and placebo groups as another.[23] Eligible articles were published between 2006 and 2018 in the USA,[13,24,26,27] UK,[23] and Italy. [15,25]

3.2. Assessment risk of bias

The risk of bias for each individual study is shown in Fig. 2. Based on Cochrane Collaboration's tool, the total quality score of included studies was good for 4 studies, fair for 1 and poor for 2 studies. (Table 1). Six studies for the method of random sequence generation and four studies for the process to conceal the allocation of subjects were considered as low risk of bias, whilst others were unclear or high risk of bias. One study did not blind the participants and researcher, whilst blinding of outcome assessment was not reported for four studies, and one study was graded as low risk. Also no studies had selective reporting and incomplete

Table 1
Overview of the characteristics of the clinical trials included in the study.

Author/date/ Country	Study design	Study participants	Nutritional intervention			Total quality score
			Groups	Dosage	Duration	
Bettuzzi, et al./ 2006/Italy	Double-blinded, parallel, RCT	60 patients with high-grade prostate intraepithelial neoplasia, aged 64.7 y	Green tea catechins Vs Placebo	600 mg/d	12 months	5
Nguyen, et al./ 2011/USA	Double-blinded, parallel, RCT	48 patients with prostate cancer, aged 62.3 y, mean BMI 27.5 kg/m^2	Polyphenon E Vs Placebo	800 mg/d	3 to 6 weeks	3
Henning, et al./ 2015/USA	Open label, parallel RCT	67 patients with prostate cancer, aged 62.4 y, mean BMI 27.3 kg/m^2	Green tea Vs Black tea Vs Water	6 cups/d (1010 mg catechins)	3 to 8 weeks	3
Kumar, et al./ 2015 /USA	Double-blinded, parallel, RCT	97 men with a diagnosis of HGPIN and/or ASAP, aged 63 y, mean BMI 29.7 kg/m^2	Polyphenon E Vs Placebo	400 mg/d	12 months	4
Zhang, et al./ 2016/USA	Double-blinded, parallel, RCT	86 men at increased risk of prostate cancer, aged 62.7 y, mean BMI 28.8 kg/m^2	green tea catechins Vs Placebo	600 mg/d	12 weeks	5
Micali, et al./ 2017/ Italy	Double-blinded, parallel, RCT	44 patients with high-grade prostate intraepithelial neoplasia, aged 64.3 y, mean body weight 82.7 kg	Green tea catechins Vs Placebo	600 mg/d	12 months	5
Lane, et al./ 2018/UK	Double-blinded, parallel, RCT and unblinded, parallel, RCT	133 men at increased risk of prostate cancer, aged 63.5 y, mean BMI 26.7 kg/m^2	Green tea drink Vs green tea leaf-derived extract Vs Placebo	600 mL/d drink or 600 mg/d extract	6 months	6

Abbreviations: RCT, Randomized controlled trial; BMI, Body mass index; HGPIN, high-grade prostate intraepithelial neoplasia ; ASAP, atypical small acinar proliferation; y, year.

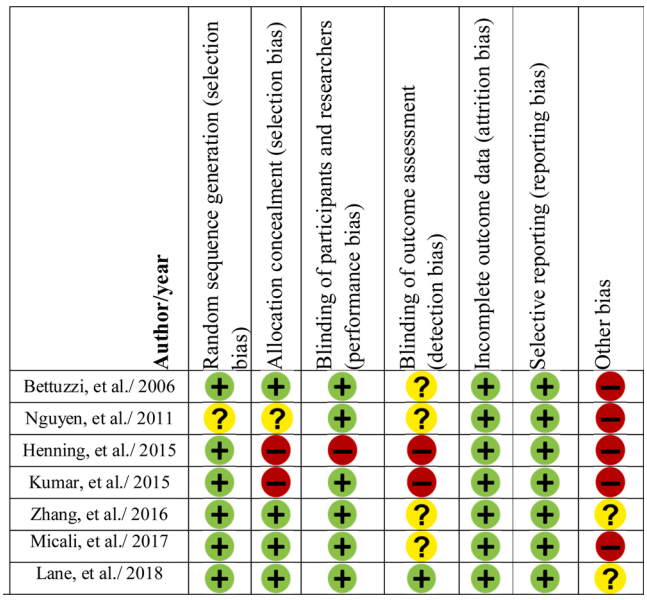

Fig. 2. Risk of bias of the included studies. + shows a low risk, - shows a high risk and? shows unclear risk of bias.

outcome bias. Regarding the last criterion, five studies were defined as high risk of bias due to not considering the baseline values for body mass index (BMI) /weight, dietary habits or any change in weight and/or dietary habits in statistical analysis and two studies were unclear risk of bias.

3.3. NutriGrade

The quality of meta-evidence for the effect of green tea/ GTCs supplementation on the PSA level was rated as "moderate" (Table 2).

3.4. Meta-analysis

A total of 8 WMD from7 RCTs, including 455 participants reported the effects of green tea/ GTCs on PSA level. The overall analysis showed no significant changes in PSA levels in subjects treated with green tea/ GTCs, (WMD: –0.60 ng/mL; 95 % CI: –1.32, 0.12 ng/mL; P = 0.104), and the heterogeneity was high (I^2 = 93.80 %, P < 0.001) (Fig. 3). To explore the causes of high heterogeneity, subgroup analysis was conducted and no detectable effects were obtained across subgroups based on dosage, intervention duration, type of supplement, and diagnosed prostate cancer (P > 0.05). However, subgroup analysis based on geographical location showed that green tea/GTCs significantly reduced PSA level in US population (WMD: –1.02 pg/mL, 95 % CI: –1.30, –0.73, P < 0.001) compared to non-US (WMD: –0.22 pg/mL, 95 % CI: –0.95, 0.50, P = 0.539) populations (P < 0.001) (Table 3). Egger's test (P = 0.28) revealed no evidence for publication bias in the selected studies.

3.5. Sensitivity analysis

We sequentially removed each trial from the analysis in order to perform sensitivity analysis and found that the effect of the green tea/ GTCs on PSA level largely depended on the study performed by Lane et al.; after exclusion of the effect size related to green tea drink used in Lane et al. study, the pooled WMD was shifted to the significance (WMD: −0.96 pg/mL, 95 % CI: –1.85 to –0.0.6, P = 0.036) compared with that from the main analysis.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis assessing the quantitative effect of green tea/GTC on PSA level. The results of this study do not support the effect of green tea/GTCs supplementation on PSA level as compared to control groups. Subgroup analysis, based on the type of intervention, showed a significant reduction of PAS level in subjects receiving pure GTC, but not green tea drink; however, between-group difference was not significant. In addition, our sensitivity analysis showed that the exclusion of the effect size related to the green tea drink used in Lane et al. study changed the overall results to be significant. Therefore, it could be assumed that GTC consumption has more beneficial effects on PSA level compared to green tea drink, potentially due to the higher plasma antioxidant activity of pure green tea supplements (in the form of green tea extract or its total catechin) compared to green tea drink.[28] Moreover, lower serum level of PSA observed in Lane et al. study, compared to other included studies, could be considered as another reason for the non-significant effect of green tea drink on PSA level. Considering geographical location, our subgroup analysis revealed a significant reduction effect of green tea/ GTC on PSA level in American male subjects compared to non-Americans. A possible explanation for the most pronounced effects in American compared to non-American males is the higher baseline level of PSA in American male subjects than non-Americans, suggesting that the baseline serum level of PSA is possibly involved in response to green tea supplementation. However, due to the small number of studies included in each subgroup, these findings should be interpreted with caution.

The results of the present study is consistent with the findings of the previous systematic review conducted on four trials to assess the treatment effects of green tea on PSA.[11] Although, the quantitative effect of green tea on PSA level was not assessed in that systematic review. Indeed, in the present review, the small number of eligible studies and high heterogeneity between studies limited our study for detecting significant results. In addition, other contributing factors including baseline dietary intake, body weight, and changes in dietary habits or body weight during interventions were not taken into account in most of the studies reviewed; however, the role of diet and BMI on PCa progression and PSA level has been well addressed.[29] In fact, an inverse relationship between obesity and PSA, primarily due to hemodilution of serum PSA caused by increased blood plasma volume has been previously reported.[30–32] As the PSA level is proportional to the prostate tumor volume, a reduction in PSA level may represent lower numbers of prostate cancer cells and tumor regression.[33] In the study by Kumar et al., consumption of 400 mg/d GTC was associated with lower rate of PCa plus atypical small acinar proliferation in subjects with high grade prostatic intraepithelial neoplasia (HGIPN). A significantly greater reduction in PSA levels was also observed in GTC arm compared to the control.[24] However, Bettuzzi et al. in the study conducted on patients with HGPIN reported that administration of 600 mg/d GTCs had no significant effect on serum total PSA, despite treating premalignant lesions before progression of PCa.[15] The minimal differences in baseline PSA values between GTCs treated arm and the control group may explain the lack of GTCs effects on PSA. In a phase II trial on patients

Table 2
Meta-evidence judgment based on the NutriGrade[1].

Comparison outcome reference	Risk of bias[2]	Precision	Heterogeneity	Directness	Publication bias	Funding bias	Study design	NutriGrade	Meta-evidence judgment
PSA	2.25	0	0.5	1	0.5	1	2	7.75	Moderate

[1] GRADE, Grading of Recommendations Assessment, Development and Evaluation. [2] Including study quality, and study limitation.

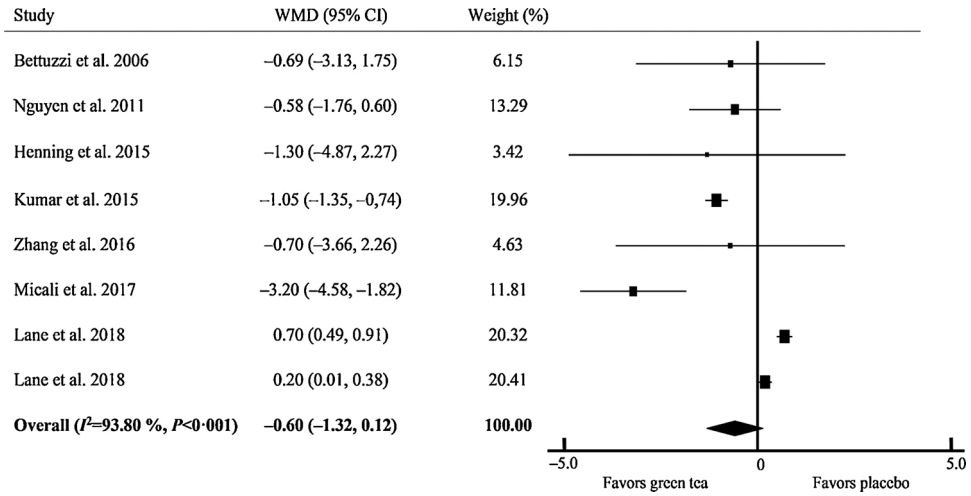

Fig. 3. Forest plot of the effect of green tea on plasma level of prostate-specific antigen.

with androgen independent prostate carcinoma consumption of 6 g/d green tea led to a decline in serum PSA in only one patient and this effect was not sustained after 2 months.[16] The lack of appropriate control group and disease status of the patients make these findings difficult to interpret. Guo et al, in a meta-analysis of cohort or case–control studies and RCTs, showed that a higher intake of green tea (more than 7 cups/day) significantly reduced PCa risk.[17] However, such results have not been reported in the meta-analysis conducted by Lin et al[34] Another meta-analysis of observational studies reported that green tea consumption was associated with reduced risk of PCa by 38 % in Asian population.[35] Although the lower risk of PCa in Asian countries might be related to the inadequate PSA testing in those countries, the role of dietary factors such as green tea consumption cannot be ignored. In vitro and in vivo studies demonstrated a strong and dose-dependent antioxidant activity of epigallocatechin gallate (EGCG) against DNA damage and tumor growth of PC cells.[36,37] Moreover, Henning et al. showed that green tea intake (6 cup/d) led to accumulation of tea polyphenols in the prostate gland, a significant reduction in nuclear factor kappa B (NFκB) which may decrease inflammatory processes contributing to prostate carcinogenesis. In addition, a significant reduction in the systemic antioxidant activity assessed by urinary 8-hydroxydeoxyguanosine (8OHdG) and a decrease in PSA level were observed.[13] Therefore, the decreasing effect of GTC on PSA level might be related to its anti-inflammatory effect. Considering that there are differences in doses and types of administrated green tea, and intervention lengths as well as other limitations that will be discussed later, caution should be taken while interpreting the findings. This is also the case for other dietary antioxidants, where the lack of high quality studies involving optimal dosages lead to inconclusive results.[38] It is important to note that green tea, especially in high doses can potentially be toxic mainly because of its caffeine content.[16] Therefore, green tea should be consumed with caution specially in subjects with compromised health status, including those with cardiovascular diseases and patients with renal failure. Green tea also has diuretic and antioxidant effects leading to its interaction with other drugs, especially chemotherapeutic drugs.[39,40] Given that patients with PCa are mostly on multiple medications, proper instruction should be provided to avoid potential drug interactions in PCa. The current meta-analysis has some strengths, the first of which is the inclusion of four additional RCTs assessing the role of green tea supplementation on PSA level, compared to the previous systematic review.[11] Adopting a comprehensive and robust methodology to identify available studies assessing the effect of green tea on PSA, conducting sensitivity and subgroup analysis to determine the source of heterogeneity, and evaluating the effects of a single study on the overall results represent additional strengths. However, some limitations should be considered when interpreting our results. First, a less stringent inclusion criteria including baseline BMI, baseline serum PSA, patients' health status and PCa stages, in the available RCTs led to heterogeneity among studies, thereby making it difficult to draw a clear conclusion. The overall quality of the available studies was moderate, whilst two of the seven

Table 3
Meta-analysis showing the effect of green tea on PSA level.

Meta-analysis					Heterogeneity	
Study group	Number of effect sizes	WMD[1] (95%CI)	P within group	P between group	I^2 (%)	P heterogeneity
Overall	8	−0.60 (−1.32, 0.12)	0.104		93.80	<0.001
PCa						
Diagnosed PCa	2	−0.65 (−1.77, 0.47)	0.257	0.07	0.0	0.70
High risk for PCa	6	−0.58 (−1.38, 0.22)	0.156		95.50	<0.001
Duration						
≤ 12 wk	3	−0.68 (−1.71, 0.39)	0.221	0.068	0.0	0.932
>12 wk	5	−0.57 (−1.40, 0.25)	0.175		96.39	<0.001
Type of supplement						
Catechins	6	−0.94 (−1.87, −0.01)	**0.046**	0.363	92.64	<0·001
Green tea drink	2	0.53 (−0.56, 1.62)	0.342		16.44	0.274
Dose of catechin						
≤600mg	6	−0.58 (−1.38, 0.22)	0.156	0.07	95.50	<0.001
> 600 mg	2	−0.65 (−1.77, 0.47)	0.257		0.0	0.708
US Vs non US						
US	4	−1.02 (−1.30, −0.73)	**<0.001**	**<0.001**	0.0	0.888
Non US	4	−0.22 (−0.95, 0.50)	0.539		92.36	<0.001

PCa, prostate cancer; US, United States.

included studies had a poor quality, which may be considered as a contributing factor to heterogeneous finding in subgroup analyses. Small number of the available RCTs, differences in doses and type of green tea, with some studies administrated GTCs[6,24–27] and some used green tea drink,[13,23] different intervention lengths, ranged from three weeks to 12 months, patients with different disease status, some studies including patients with PCa while others included patients with HGIPN or increased risk for PCa, and not considering changes in BMI and dietary intakes are other sources of heterogenty contributing to the null results of the present review.

5. Conclusion

The results of this review show that green tea supplementation has no significant effect on PSA level. However, due to the limited number of available studies, heterogeneity in participant's health status, baseline PSA, dietary intake and dose and type of green tea, caution should be taken when interpreting the current results. More consistent clinical trials, with a larger sample size, addressing the aforementioned confounding variables, are required to better discern the actual effect of green tea supplementation on PSA level.

Consent for publication

All authors of this study declared their consent for publication.

Author contributions

ESZ, FHS and HA: Contributed to the study design and data collection, and interpretation and drafting the manuscript. FS, HA and AD: Participated in the revising the paper critically and approving the version of the manuscript being submitted. All authors read the final content of the manuscript before submission.

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Ethics approval and consent to participate

Not applicable

Availability of data and materials

The dataset applied and analyzed for the present study is available from the corresponding author on a reasonable request.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Not applicable.

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.2020.102659.

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