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Review article

Lycopene Supplementation for Patients Under Cancer Therapy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials[1]

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ABSTRACT

Introduction: Lycopene supplementation has been considered potentially useful as an adjuvant cancer therapy according to its anticancer properties. The present study aimed to investigate the effects of lycopene supplementation on outcome improvement in patients with cancer therapy. As a secondary aim, we conducted a meta-analysis to investigate the efficacy of lycopene supplementation on circulating lycopene concentration in patients with cancer therapy.

Methods: A systematic and comprehensive search was performed in electronic databases, including PubMed, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS, EMBASE, MedNar, and OpenGrey up to March 2023. The inclusion criteria were randomized controlled trials conducted on patients under cancer therapy (i.e., radiotherapy, chemotherapy, surgery, etc.) supplementing with lycopene. Data extraction and analysis: two different evaluators screened and collected literature independently. Information regarding the study design, participants, intervention, and dependent outcomes was extracted, and the bias of the study was assessed. Additionally, separate random-effect meta-analyses were performed to examine the effects of lycopene supplementation on circulating lycopene concentration in patients under cancer therapy.

Results: The initial search retrieved 7 565 articles of which eight met the inclusion criteria. Lycopene supplementation did not modify cancer hallmarks in these studies. However, despite the heterogeneity between studies, we show that, compared with control, lycopene supplementation had moderate effects on circulating lycopene concentration in patients under cancer therapy (pooled mean difference, 0.1361; 95% CI [0.0574; 0.2148], $P = .0007$).

Conclusions: Our study shows that lycopene supplementation does not modify the main hallmarks of cancer, but it increases circulating lycopene concentration in patients under cancer therapy, which could have a positive impact on potential clinical and molecular outcomes in cancer patients.

Introduction

Tomatoes are well recognized for their contribution to the nutritional value of the diet and their contribution to health-related benefits such as lowering all-cause mortality and improving cardiometabolic risk factors (Burton-Freeman and Sesso, 2014; Cheng et al., 2017; Mazidi et al., 2019). Tomato and tomato-based products (i.e., tomato sauce) are rich in dietary lycopene, one of the most potent antioxidants, the most predominant carotenoid in human plasma, and the most relevant bioactive compound responsible for the health benefits of tomato (Mein et al., 2008). In this sense, the protective effect of the Mediterranean diet against several cancer types may be partly due to the high consumption of tomato and tomato sauce (Capurso and Vendemiale, 2017).

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen; SMD, standardized mean differences; RCT, randomized controlled trial

[1] Trial registration: PROSPERO systematic review registration number: CRD42020183587

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Preliminary evidence has shown a direct relationship between tomato-based products consumption and blood lycopene concentrations (Burton-Freeman and Sesso, 2014) and an inverse relationship between blood lycopene concentrations and cancer risk in humans (Chen et al., 2015; Xu et al., 2016). Indeed, lycopene supplementation has been considered potentially useful as an adjuvant cancer therapy according to its anticancer properties: anti-inflammatory, antioxidant, anti-angiogenesis, inhibition of cell proliferation, pro-apoptotic, and immune modulation, among others (Mein et al., 2008). Based on the relationship between blood lycopene concentration and cancer risk and the potential anticancer mechanisms, clinical studies have been conducted to investigate whether lycopene supplementation during cancer therapy has positive effects (Grainger et al., 2015; Paur et al., 2017). A systematic review and meta-analysis reported that tomato and lycopene supplementation have positive effects on cardiovascular risk factors (Cheng et al., 2017). Since cancer treatment, especially chemotherapy, and radiotherapy, could deteriorate several cardiometabolic risk factors (Meijers and De Boer, 2019) and decrease tissue antioxidant levels, thereby increasing oxidative stress (Datta et al., 2013), it seems plausible that lycopene supplementation may have benefits in the oncology population during cancer treatment. To understand the effects of tomato products or lycopene supplementation in cancer patients with therapy, it is of clinical interest to guide clinical practice in terms of dose, duration, and type of intervention. However, no comprehensive systematic review of randomized controlled trials (**RCTs**) has been published. Thus, the present systematic review aimed to investigate the efficacy of lycopene supplementation on cancer-related outcomes in patients under cancer therapy (i.e., chemotherapy, radiotherapy, or surgery). As a secondary aim, we conducted a meta-analysis to investigate the efficacy of lycopene supplementation on circulating lycopene concentration in patients under cancer therapy.

Methods

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (Page et al., 2021). The protocol was registered with PROSPERO in July 2020 (ID: CRD42020183587) (Appendix).

Search Strategy

PubMed, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS, EMBASE, MedNar, and OpenGrey databases were searched until March 2023. The following MeSH and non-MeSH terms related to lycopene/tomato and chemotherapy/radiotherapy were used: (“radiotherapy” or “chemotherapy” or “chemoradiotherapy” or “hormone therapy” or “antineoplastic therapy” or “cancer” or “neoplasm” or “tumor” or “oncol” or “carcinoma” or “malignant”) and ("lycopene" or "tomato" or “Lycopersicon esculentum” or “Solanum Lycopersicum”).

Study Criteria Selection

Two researchers (LJF and AMF) independently screened titles and abstracts for relevant studies. The systematic review included only RCTs (blinded or non-blinded) that evaluated the chronic effects of lycopene supplementation in cancer patients during therapy on cancer-related outcomes and circulating lycopene concentration. Interventions with other supplementation or any intervention in the control group were excluded. Studies on healthy populations were excluded.

Where information about the required outcomes was insufficient, corresponding authors were contacted to request the necessary data. Studies whose authors did not reply were excluded from the meta-analysis. Studies reporting the same results were also excluded. Non-English language articles were excluded.

Data Extraction

Two independent researchers (LJF and CRG) extracted data from the selected studies. Data of age, gender, body mass index (**BMI**), cancer location, lycopene or tomato source, lycopene amount, intervention duration, and endpoint measurement of prostate-specific antigen (**PSA**) and lycopene values were extracted. Any differences in extracted data were solved by consultation (LJF and CRG) and, if required, with a third author (AMF) until a consensus was achieved.

Quality Assessment

The risk of bias of RCTs was assessed by two independent researchers (LJF and AMF). The evaluation was conducted with the revised Cochrane risk of bias tool (RoB 2.0) (Sterne et al., 2019). This tool evaluates whether a study has a high, unclear, or low risk of bias. Discrepancies were solved through group consultation (LJF, AMF, and CRG) until an agreement was achieved.

Certainty of Evidence

The grading of recommendations assessment, development, and evaluation (GRADE) approach was used to asses certainly of the evidence from eligible studies (GRADEpro Guideline Development Tool Software, 2022). Based on the bias factors, including imprecision, indirectness, inconsistency, the risk of bias, and other considerations, GRADE classified the evidence into four levels (very low, low, moderate, and high).

Publication Bias

No funnel plot asymmetry analysis was performed since no analysis includes 10 or more studies.

Statistical Analyses

Due to the low number of studies included, and the wide dependent outcomes analyzed in these studies, the meta-analysis was only performed investigating the effects of lycopene supplementation on circulating lycopene concentration. There was a variety in the main outcomes of the studies that did not allow us to meta-analyze the main outcomes of these studies.

A random-effects model (using the DerSimonian-Laird method) and the generic inverse variance method were used to derive pooled estimates across studies. The net changes in SD of measurements were calculated as follows: $\sqrt{[(SDB)^2 + (SDF)^2 - (2 \times R \times SDB \times SDF)]}$, where SDB and SDF are the SD of the measures at baseline and the end of follow-up, respectively, and R is a correlation coefficient of 0.9 (Borenstein et al., 2021). Studies reported median with interquartile ranges (IQRs) or 95% CIs were converted to mean and SD (Wan et al., 2014). The following formula: SD = SEM $\times$ $\sqrt{n}$, (n = number of participants) was used to convert the SEs to SDs. Data were expressed as mean differences (**MDs**) with 95% CIs. Statistical significance was set at a P-value less than .05. MDs between the lycopene supplementation and control groups were computed. Heterogeneity was measured using the I^2 statistic (the percentage of total variability attributed to between-study heterogeneity). High, moderate, and low I^2 values are 75%, 50%, and 25%, respectively. In addition, subgroup analysis according to the type of administration (food or capsules) was addressed to detect potential sources of heterogeneity. A leave-one-out sensitivity analysis was conducted by removing one study at a time iteratively to determine that our results were not due to a single study. All analyses were conducted using R Statistical Software (v4.3.0; R Core Team 2021).

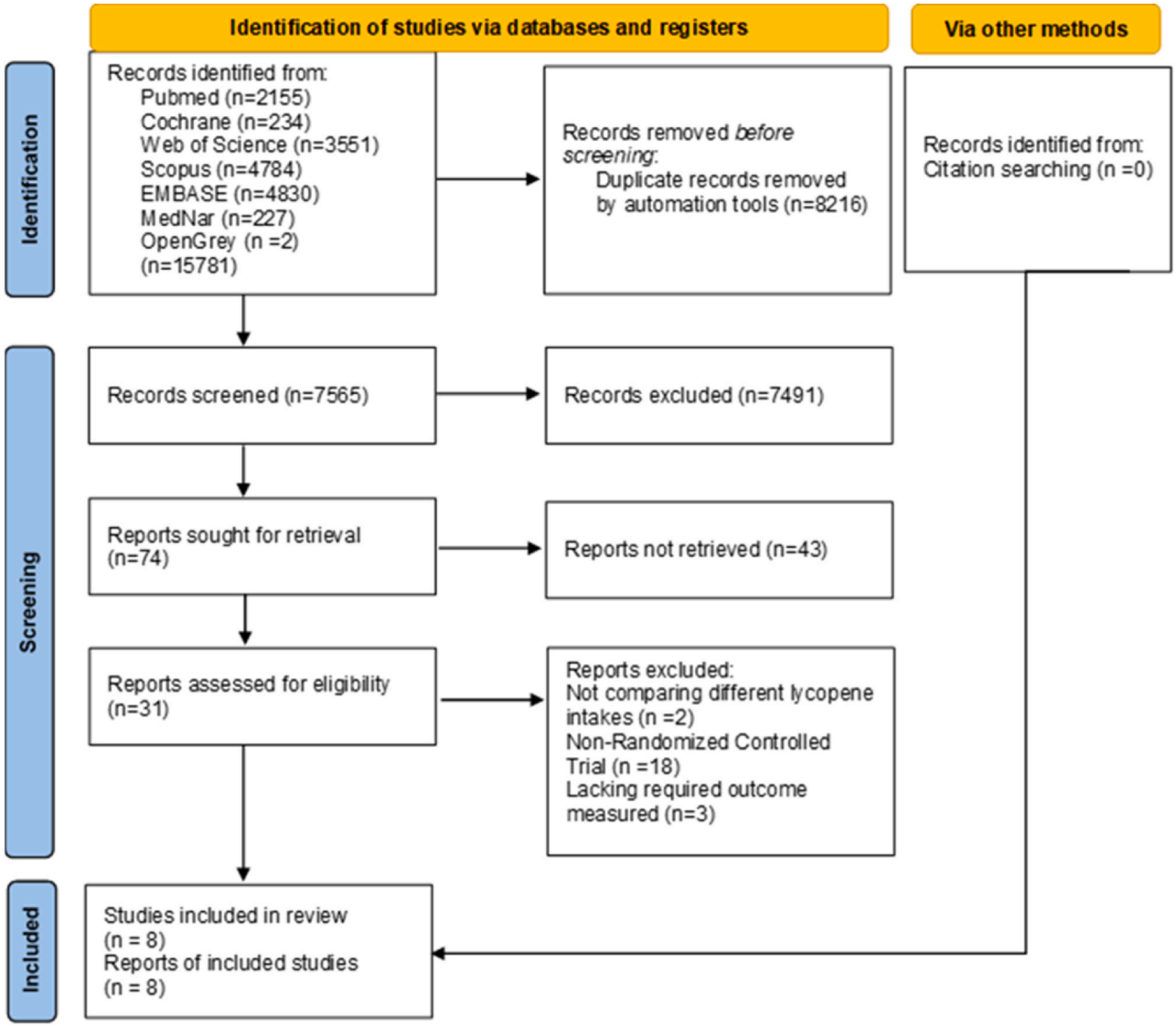

Fig. 1. .Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of studies through the systematic review process.

Results

Flowchart and Characteristics of Included Studies

Figure 1 provides a flowchart of studies in the review process. After eliminating duplicates, 7 565 studies were initially identified by the literature search. Based on review titles and abstracts, 74 potentially relevant articles were selected for full-text assessment. Subsequently, eight eligible randomized controlled studies met the inclusion criteria.

The characteristics of the studies selected in the systematic review, including participant age, BMI, cancer location, cancer treatment, and intervention type, are presented in Table 1. Briefly, studies ranged in sample size from 17 to 120 participants per study, with participants' ages ranging from 38 to 69 years. The cancer location of the studies included prostate (N = 6), high-grade glioma (N = 1), and non-specified cancer locations (N = 1). The cancer therapy of these studies included radiotherapy (N = 1), chemotherapy (N = 1), prostatectomy (N = 4), surgery or radiotherapy (N = 1), and surgery + radiotherapy and chemotherapy (N = 1). Six studies were performed on male participants, whereas two studies were performed on both male and female participants. Three studies did not specify the BMI status of the participants, whereas the BMI range of the other five studies was 26.1–30 kg/m^2.

Lycopene Interventions

Lycopene intervention was based on tomato-based products (three studies) and lycopene capsules (five studies). Sources of tomato-based products included tomato juice (one study), tomato sauce, juice, or soup (one study), and a combination of tomato products (i.e., tomato sauce, juice, and crushed tomatoes) (one study). Per-day supplementary lycopene dose also varied with ranges of 8–24 mg (three studies) and 24–35 mg (five studies). In one study, the lycopene group was compared to a placebo group; in four studies, lycopene groups were compared with a normal diet group; one study was compared with a standard regimen of kidney injury prevention; one study was compared with a controlled lycopene diet ($\leq$5 mg from foods); and one was compared with regular diet and fruit and vegetable recommendations. One possible grade 2 gastrointestinal adverse event was reported in three studies (Grainger et al., 2015; Hackshaw-McGeagh et al., 2019; Kumar et al., 2008); two studies did not find any adverse events (Datta et al., 2013; Kucuk et al., 2001) and there was no available information about adverse events in three studies (Kucuk et al., 2002; Mahmoodnia et al., 2017; Paur et al., 2017; Puri et al., 2010). The intervention duration ranged from 24 to 72 hours until 6 months. However, the intervention of one study was followed until the scheduled surgery date (minimum 14 days), being the intervention duration variable among

Table 1
Characteristics of the eight randomized controlled trials evaluating the effect of supplementation of lycopene for patients in cancer treatment.

Author		n	Age, y	Sex	BMI (kg/m^2)	Cancer location	Cancer therapy	Intervention/Control	Total daily lycopene	Duration	Main outcomes	Included in meta-analysis
(Datta et al., 2013)	Intervention	12	69	M	27.8	Prostate	Radiotherapy	*Food*: Tomato Juice - 118 ml (4 oz) - 237 ml (8 oz) - 355 ml (12 oz)	8 mg/ d16 mg/ d24 mg/d	29–44 d	Increased lycopene levels were observed in the 8 and 12 oz groups from baseline to endpoint	Yes
	Control	5						Normal diet				
(Grainger et al., 2015)	Intervention	22	60	M	30.0	Prostate	Prostatectomy	*Food*: - Spaghetti sauce (Prego, 142–198 g/d) - Vegetable juice (V8, 325–488 ml/d) - Tomato soup (Campbell's Tomato Soup, 473–651 ml/ d)	24–35 mg/ d	Mean duration: 23 [SEM 1.7] days	Tomato soup, sauce, and juice consumption significantly increased both circulating and prostate lycopene levels. PSA concentrations did not differ between the groups	Yes
	Control	11						Controlled lycopene diet (≤5 mg from foods)				
(Hackshaw et al., 2019)	Intervention	28	64	M	26.5	Prostate	Prostatectomy	Lycopene *capsules,* once daily	10 mg/d	24 wk	There was no difference in lycopene between the intervention and the control groups. No other differences were found between the blood biomarkers	Yes
	Control	22						Normal diet				
(Kucuk et al., 2001)	Intervention	15	62	M	N/A	Prostate	Prostatectomy	Lycopene *capsules* (Lyc-O-Mato), twice daily	30 mg/d	3 wk before surgery	Prostatic tissue and circulating lycopene levels were higher in the intervention group. Plasma PSA and IGF-1 levels decreased in the intervention group. No differences in Bcl-2/Bax between groups	Yes
	Control	11						Regular diet and NCI's recommendations to increase daily fruit and vegetable intake until 5 servings/d				
(Kumar et al., 2008)	Intervention	34	60	M	27.3	Prostate	Prostatectomy	Lycopene *capsules* (LycoRed) One, two, or three daily	15 mg/ d30 mg/ d45 mg/d	5 wk	Lycopene levels increased in intervention arms. Serum-free testosterone decreased; no changes in PSA or tissue Ki-67	Yes
	Control	11						Normal diet				

(*continued on next page*)

Table 1 (*continued*)

Author		n	Age, y	Sex	BMI (kg/m^2)	Cancer location	Cancer therapy	Intervention/Control	Total daily lycopene	Duration	Main outcomes	Included in meta-analysis
(Mahmoodnia et al., 2017)	Intervention	60	57	M/F	N/A	N/A	Chemotherapy	Lycopene *capsules* Standard regimen of kidney injury prevention (hydration + magnesium sulfate)	50 mg/d	24 h before to 72 h after cisplatin administration	Lycopene can be effective in decreasing the complications due to cisplatin-induced nephrotoxicity (reducing blood urea nitrogen and creatinine)	No
	Control	60										
(Paur et al., 2017)	Intervention	27	63	M	26.1	Prostate	Surgery or radiotherapy	*Food:* Tomato products (pasta sauces, tomato juice, and crushed tomatoes)	30 mg/d	3 wk	Lycopene in plasma was more than doubled in intervention groups. No changes in PSA	Yes
	Control	27						Normal diet				
(Puri et al., 2010)	Intervention	25	38	M/F	N/A	HGG	Surgery + adjuvant radiotherapy + chemotherapy	Lycopene *capsules* Placebo	8 mg/d	6 mo	Lycopene-supplemented group had significantly higher levels than the placebo group	No
	Control	25										

Abbreviations: y, years; M, male; F, female.N/A, not available; NCI, National Cancer Institute; HGG, High-grade glioma; PSA, prostate-specific antigen.

participants (Grainger et al., 2015). In the study of Datta et al. (2013), the caloric intake of the 8 oz tomato juice group was higher in comparison with the control group, being the sole study that included a dietary assessment to control nutritional differences between groups during the intervention.

Outcome Measures

Cancer Biomarkers

Lycopene supplementation did not change biomarkers in cancerous or benign areas of the prostate (i.e., bcl-2, bax, and Cx43; all $P \geq .13$) and did not change plasma levels of IGF-1 and IGFBF-3 (all $P \geq .49$) (Kucuk et al., 2001). However, in the study by Kumar et al. (2008), lycopene-treated arms showed a greater reduction in the percentage of prostate tissue cells expressing Ki-67 in comparison with the control arm. In the study by Mahmoodnia et al. (2017), lycopene supplementation decreased blood urea nitrogen ($P = .004$), increased glomerular filtration rate in the first 3 days and then decreased partially ($P < .001$), and did not change serum creatinine ($P = .131$) in comparison with the control group as markers of nephrotoxicity after cisplatin treatment. Although without statistical significance, in the study of Puri et al. (2010), a greater number of participants in the lycopene group achieved a complete response after the intervention in comparison with the control group (10 vs 5, respectively; $P = 0.100$). Furthermore, in the same study, the lycopene group showed a higher median follow-up ($P = .05$) and a higher time to progression near-toward significance ($P = .089$) in comparison with the control group (Puri et al., 2010).

Prostate-specific antigen concentration was investigated in three of the eight studies examined. In these studies, plasma PSA levels did not significantly change after lycopene supplementation in comparison with the control group over the study period (Kucuk et al., 2001; Kumar et al., 2008; Paur et al., 2017). However, Paur et al. (2017) reclassified the patients into risk groups (clinical low, intermediate, and high risk) according to PSA, pT-staging, and the Gleason score, and observed that patients reclassified as intermediate-risk patients (n = 17 and 13 in lycopene and control group, respectively) significantly decreased PSA levels after lycopene supplementation in comparison with the control group ($P = .041$) (Paur et al., 2017). No differences were observed in patients reclassified at high risk after the lycopene supplementation (Paur et al., 2017).

Non-lycopene Carotenoids Levels

Two studies determined the effects of lycopene supplementation on non-lycopene carotenoid levels. While lycopene supplementation did not increase non-lycopene carotenoid plasma levels, tomato soup consumption increased plasma β-carotene levels ($P < .05$) (Grainger et al., 2015). These results partially concur with those observed in the study of Paur et al. (2017) who observed that non-lycopene carotenoids did not change after lycopene supplementation (all $P > .05$). Furthermore, the lycopene supplementation did not change the concentration of non-lycopene-carotenoids in human prostate tissue (Grainger et al., 2015).

Lycopene Concentration

Six out of eight studies determined changes in circulating lycopene concentration after the intervention period. One of the studies demonstrated that there was a wide interindividual variation in circulating lycopene concentration after its supplementation (Paur et al., 2017). The study conducted by Puri et al. (2010) was not included in the statistical analyses due to the lack of data to perform the analyses. This study observed that lycopene supplementation increased circulating lycopene concentration in comparison with the control group ($\Delta = 164.431$ vs $\Delta = 5.15$ mg/ml, respectively, no dispersion measures were reported, $P = .009$).

Only one out of six studies evaluated the different circulating lycopene isomers after the supplementation (Grainger et al., 2015).

Tomato soup supplementation increased the percentage of all-*trans*-lycopene and decreased the percentage of total *cis*-lycopene after the intervention duration (Grainger et al., 2015). However, the percentage of all-*trans*-lycopene and total *cis*-lycopene did not significantly change in the tomato sauce and tomato juice groups (Grainger et al., 2015). *Cis*-isomers were the main geometric configuration of lycopene in all prostate tissue samples (79%) (Grainger et al., 2015). In this sense, two studies demonstrated that prostate lycopene concentrations significantly increased after tomato soup supplementation (351%) (Grainger et al., 2015), tomato sauce supplementation (362%) (Grainger et al., 2015), tomato juice supplementation (224%) (Grainger et al., 2015), and after lycopene capsules supplementation (47%) (Kucuk et al., 2001) in comparison with the control group. The prostate concentration of lycopene isomers was not different between tomato soup, sauce, and juice groups after the intervention in the study of Grainger (Grainger et al., 2015).

Synthesis of the Data

We performed meta-analyses including six studies (Datta et al., 2013; Grainger et al., 2015; Hackshaw-McGeagh et al., 2019; Kucuk et al., 2001; Kumar et al., 2008; Paur et al., 2017) to test the effects of lycopene supplementation on circulating lycopene concentration during cancer treatment. Figure 2 depicts the results of the meta-analysis describing the effects of lycopene supplementation on circulating lycopene concentration. In comparison with the control group, lycopene supplementation was effective for increasing circulating lycopene concentration in patients under cancer therapy (pooled MD, 0.1361; 95% CI [0.0574; 0.2148], $P = .0007$). This finding was robust across subgroup analysis when fixed effects models were computed to the food subgroup (pooled MD, 0.27; 95% CI [0.21; 0.32]) and capsules subgroup (pooled MD, 0.01; 95% CI [−0.01; 0.03]). Owing to the small heterogeneity in both subgroups (i.e., I^2 = moderate), post hoc analyses were not needed. These data showed that the effects of the lycopene supplementation were higher when the intervention was food-based.

Risk of Bias Assessment

The risk of bias of RCTs was evaluated with the revised Cochrane risk of bias tool. This tool determined that all studies had some concerns of bias (Fig. 3). We should highlight that seven of eight studies had some concerns about bias in the selection of the reported results. Two out of eight studies had some concerns about the randomization process (Datta et al., 2013; Puri et al., 2010), whereas two studies had some concerns in the deviation from the intended intervention (Paur et al., 2017; Puri et al., 2010). All studies showed a low risk of bias for missing outcome data and the measurement of the outcome.

Certainty of Evidence

The quality of the evidence of the findings following the GRADE approach was low. Among the factors that reduce the quality of evidence, the main responsible in this case is the unclear risk of bias present in all studies.

Discussion

To the best of our knowledge, this is the first systematic review investigating the effects of lycopene supplementation in patients under cancer therapy. In the current study, we found that, compared with the control group, lycopene supplementation in patients under cancer therapy increases circulating lycopene concentration. We also observed that lycopene supplementation does not modify different cancer hallmarks. Taken together, lycopene supplementation may have an influence on clinical and molecular outcomes in patients under cancer

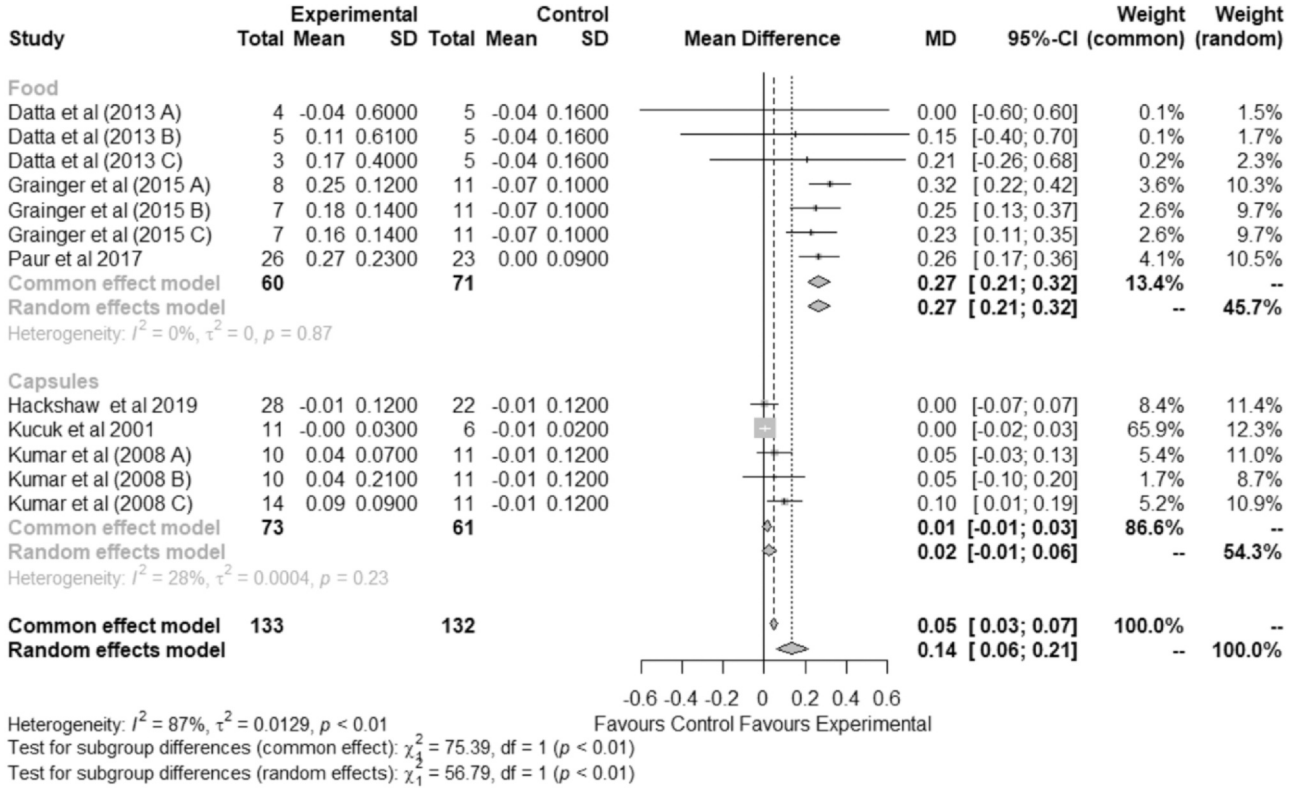

Fig. 2. .Pooled effects of randomized controlled trials analyzing the effect of lycopene supplementation on circulating lycopene concentration in patients under cancer therapy. A random-effects model (using the DerSimonian-Laird method) and the generic inverse variance method were used to derive pooled estimates across studies.

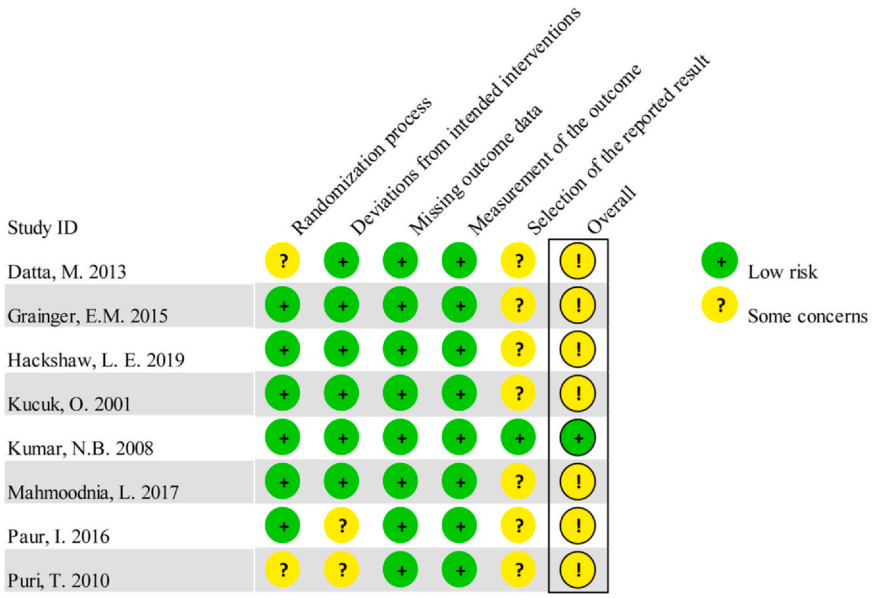

Fig. 3. .Risk of bias assessment of included studies based on Cochrane risk of bias tool.

therapy, mainly explained by the increase in circulating lycopene concentration.

Lycopene Supplementation Does Not Modify Cancer Hallmarks

In our qualitative synthesis of the results, we have observed a wide range of dependent outcomes in the RCTs evaluating the effects of lycopene on cancer-related outcomes. In this sense, lycopene supplementation has been shown to slightly modify different cancer hallmarks in these studies. Lycopene supplementation improved PSA levels in patients with an intermediate risk of cancer according to several clinical parameters (Paur et al., 2017). However, no effect was observed in PSA levels in all participants of the two studies that evaluated the effects of lycopene on this parameter (Kucuk et al., 2001; Paur et al., 2017). This finding partially concurs with the previous Cochrane review, which showed that lycopene does not affect PSA in healthy men without cancer (Ilic et al., 2011). On the other hand, lycopene supplementation did not modify cancer biomarkers in both benign prostate tissue and circulating levels (Kucuk et al., 2001). In contrast, lycopene supplementation induced a complete response after radiotherapy and a higher follow-up after this treatment (Puri et al., 2010). Surprisingly, lycopene has been shown to improve renal makers of nephrotoxicity after cisplatin treatment (Mahmoodnia et al., 2017). This side effect is the main limitation of cisplatin chemotherapy, which is associated with complications and a low survival rate (Mahmoodnia et al., 2017). The main mechanism of this lowering in nephrotoxicity might be through the antioxidant capacity of the lycopene (Mahmoodnia et al., 2017). Regarding the latter, lycopene supplementation through tomato soup has been demonstrated to increase plasma β-carotene levels and not change other carotenoids (Grainger et al., 2015). β-Carotene is another potent antioxidant present in tomatoes that could prevent cancer development (Black et al., 2020).

Lycopene Supplementation Increases Circulating Lycopene Concentration in Patients Under Cancer Therapy

The present meta-analysis demonstrated that lycopene supplementation increases circulating lycopene concentration in patients under cancer therapy. This finding was observed in the study, which was not included in the meta-analyses (Puri et al., 2010), and also demonstrated through the quantitative synthesis of the data. Evidence has shown an inverse relationship between circulating lycopene concentration and cancer risk in humans (Chen et al., 2015; Xu et al., 2016). Previous systematic reviews and meta-analyses of RCTs have demonstrated that lycopene supplementation improves cardiometabolic risk factors (Cheng et al., 2017) and oxidative stress (Chen et al., 2013). However, no comprehensive systematic review and meta-analysis was carried out to assess the influence of lycopene supplementation during cancer treatment. Our results showed a significant increase in circulating lycopene concentration after lycopene supplementation, which may have potential clinical implications.

Clinical Implications

The findings of the present study provide evidence indicating that lycopene supplementation is effective for increasing circulating lycopene concentration in patients under cancer therapy. It is well known that conventional cancer therapy induces a decrease in different antioxidant systems of the organism due to the high production of reactive oxygen species (Singh et al., 2018). A higher reduction in the levels of different antioxidants is related to poor prognostic and less success in cancer therapy (Leone et al., 2017). Lycopene is one of the antioxidants present in the diet, which has widely been demonstrated to have different biological functions that improve human health (Wang, 2012). In this sense, lycopene supplementation may have a positive influence on different potential clinical and molecular outcomes in cancer patients through the restoration of the lycopene concentration in blood (Fig. 4). This restoration into adequate levels of lycopene has demonstrated to improve different cancer-related molecular pathways (Mein et al., 2008; Wang, 2012), to increase immune function , to have cardiometabolic improvements (Cheng et al., 2017; Senkus et al., 2019), to decrease DNA damage (Nakamura et al., 2017), to decrease the oxidative stress due to its antioxidant properties (Chen et al., 2013; Leh et al., 2021), to reduce low-grade inflammation (van Steenwijk et al., 2020), and to decrease tumor cell, invasion, and migration (Yang et al., 2012) (Figure 4).

Taking all these plausible mechanisms together, an emerging finding for clinical care providers has emerged from our review to try to restore lycopene levels in patients under cancer therapy through its supplementation or through the dietary recommendation to increase tomato-based products. However, some previous evidence has suggested a preference in the selection of tomato products rather than lycopene supplementation mainly due to the presence of other phytonutrients, and the benefits of the food matrix (van Steenwijk et al.,

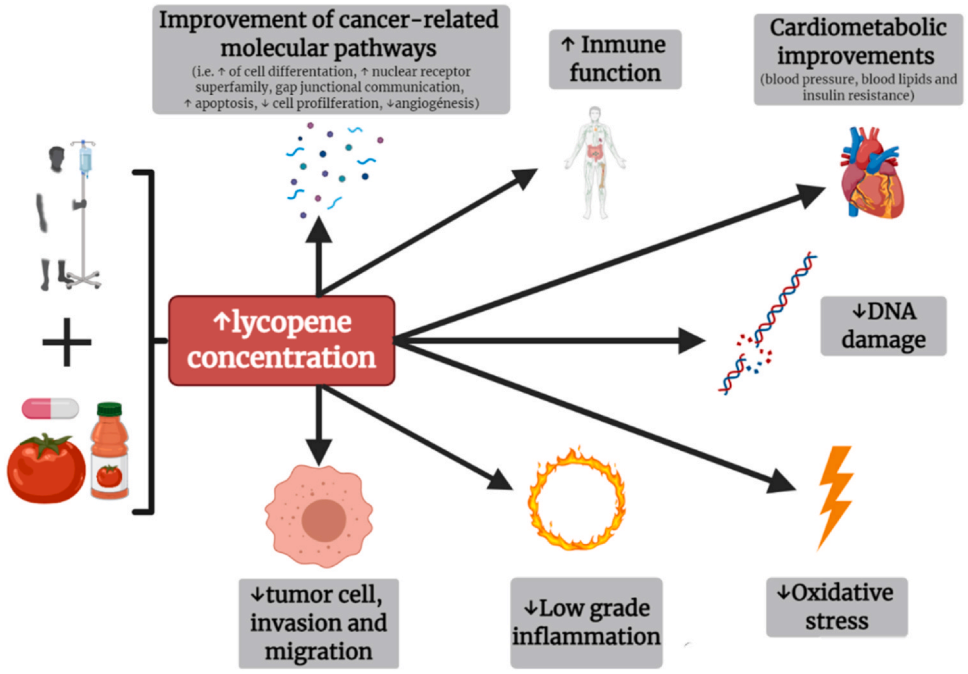

Fig. 4. .Potential clinical and molecular influences of increased circulating lycopene concentration after its supplementation in patients under cancer therapy (picture created with biorender.com).

2020). The results of our meta-analysis show that, when the intervention was performed with lycopene-rich foods, the bioavailability was higher than when lycopene was administered in capsule form. This could be since, like other carotenoids, once it is extracted from its food matrix, its availability is poor. Therefore, lycopene delivery vehicles should be based on lipid-based nano-formulations and biopolymer nano-structures, which enhance its bioavailability and improve its stability in the gastrointestinal tract (Amorim et al., 2022). Furthermore, the dietary recommendations to maximize circulating lycopene concentration during therapy could be easily achieved through the inclusion of tomato products in the daily diet of the patients. This inclusion of tomato products could be reinforced by the fact of preparing Mediterranean tomato-based "*sofrito*" or tomato sauces where the tomatoes are cooked with extra-virgin olive oil, increasing the lycopene bioavailability and maximizing its benefits (Fielding et al., 2005).

Limitations

The present study has several potential limitations. A moderate risk of bias and a low certainty of the evidence were observed in all studies; therefore, the quality of the evidence in the present review is moderate for the outcomes assessed, but the effect size of the meta-analysis is moderate. Somehow, nutritional interventions could be confounded with the effects of primary therapies. Moreover, studies do not provide clinical outcomes (i.e., tumor response to cancer treatment), do not use uniform outcome measures or cancer biomarkers, and do not include an exhaustive dietary assessment to control possible dietary confounders. Note that our review was limited by the small number of available studies. Based on our systematic review, it is apparent that additional studies are needed. It is important to highlight that future studies should include good-quality RCTs that supplement lycopene with active cancer treatment to establish recommendations.

Conclusions

This systematic review shows that lycopene supplementation in patients undergoing cancer therapy does not modify the main hallmarks of cancer. However, the meta-analysis on the effect on circulating lycopene levels shows that lycopene levels increase in the intervention group and are even higher when supplementation is based on lycopene-rich foods. However, due to the low number of studies, the lack of results concerning patient prognosis, the moderate risk of bias, and the low degree of certainty of the included studies, the impact of lycopene supplementation on clinical and molecular outcomes in cancer patients remains unclear. Further RCTs are needed to well-establish the effect of lycopene supplementation on different cancer-related outcomes.

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Author contributions

Conception and design of research: LJF, AMF, and CRG. Performed the searches: LJF, AMF, and CRG. All authors interpreted the results. Data analyses: LJF, LJF, and CRG prepared the figures and drafted the manuscript; all authors critically revised the manuscript and approved the final version.

Declaration of Competing Interest

The authors declared no conflicts of interest.

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Appendix

Disclosure of protocol discrepancies.

The registered protocol in Prospero in July 2020 (ID: CRD42020183587) indicates that the main outcome of the study was:

"Improvement in cancer therapy outcomes associated with lycopene or tomato-based supplementation." However, during data extraction from the studies included in the systematic review, we observed that, despite being randomized clinical trials evaluating the efficacy of lycopene supplementation in cancer therapy patients, they did not report results on major cancer outcomes such as disease-free survival, complete or partial tumor response, or modification in cancer biomarkers. However, the vast majority of the studies reported data on the modification of lycopene levels, so it was included as a secondary outcome, and a meta-analysis was conducted.

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