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Systematic Review

Nutraceutical and Dietary Interventions to Aid Prostate Cancer Management: A Systematic Review

Haoyue Zhang [1,*,‡], Shaoting Zhang [1,‡], Jonathon Carll [1,2,3] and Nathan Lawrentschuk [1,2,3,4]

[1] Department of Urology, The Royal Melbourne Hospital, Parkville, VIC 3050, Australia
[2] EJ Whitten Centre for Prostate Cancer Research, Epworth Healthcare, East Melbourne, VIC 3002, Australia
[3] Department of Surgery, University of Melbourne, Parkville, VIC 3010, Australia
[4] Division of Cancer Surgery, Peter MacCallum Cancer Centre, Parkville, VIC 3000, Australia
* Correspondence: haoyue.zhang@mh.org.au; Tel.: +61-3-9342-7000
‡ These authors contributed equally to this work and share first authorship.

Abstract

Background/Objectives: Nutraceutical use is common among men with prostate cancer, but its clinical efficacy remains uncertain. We systematically reviewed randomized controlled trials evaluating orally administered nutraceutical and defined dietary interventions after prostate cancer diagnosis. **Methods**: PubMed, MEDLINE, and Embase were searched through September 2026, and risk of bias was assessed using the Cochrane Risk of Bias 2 tool. **Results**: Twenty-six trials involving 2188 randomized participants were included. Four were judged to be at low risk of bias, 15 had some concerns, and seven were at high risk. An exploratory random-effects meta-analysis of three soy trials showed no significant difference in post-intervention serum prostate-specific antigen compared with placebo or control (mean difference: −0.50 ng/mL, 95% confidence interval: −2.14 to 1.14; $p = 0.55$; $I^2 = 0\%$). Across the wider evidence base, effects on prostate-specific antigen kinetics, tissue biomarkers, oxidative stress, and inflammatory markers were inconsistent. The available evidence was insufficient to establish a validated benefit for disease progression, metastasis, cancer-specific survival, or overall survival. **Conclusions**: The current evidence is insufficient to establish a clinically meaningful benefit of nutraceutical or defined dietary interventions in prostate cancer management. Larger, well-designed trials using standardized interventions, clinically meaningful endpoints, and longer follow-up are required.

Keywords: dietary supplements; prostate-specific antigen; prostatic neoplasms; randomized controlled trials as topic; treatment outcome

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1. Introduction

Prostate cancer (PCa) remains a major global health challenge arising from both genetic susceptibility and potentially modifiable environmental exposures [1]. Diet and broader lifestyle patterns continue to be investigated as potential modifiers of PCa risk and progression [2]. Use of complementary and alternative medicine, including dietary supplements, is common among men with PCa; in a large CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) cohort, 56% reported complementary and alternative medicine use, while multivitamins and omega-3 fatty acids were used by 40% and 24% of patients, respectively [3]. This widespread use of nutraceuticals highlights the need to validate their safety and clinical effectiveness as an adjunct to PCa management. However, unlike conventional pharmacotherapies, nutraceutical products are marketed within a less stringent regulatory framework, creating uncertainty regarding product quality, safety, and

clinical efficacy [4]. Early herbal combinations such as PC-SPES demonstrated biological activity but were withdrawn because of contamination, safety concerns, and manufacturing instability [5]. Randomized trials of other individual supplements have not established clinically meaningful benefits. Conversely, polyphenol-rich products and combination formulations have generated interest because of their potential effects on prostate-specific antigen (PSA) kinetics and other biological markers [6].

Randomized trials in this field vary substantially in PCa setting, intervention composition, treatment duration, and outcome selection. Many have focused on short-term PSA kinetics or biological biomarkers rather than validated oncological endpoints, making the clinical significance of reported effects difficult to determine. Recent systematic reviews have examined broader dietary patterns and postdiagnosis diet and lifestyle exposures, but they do not specifically isolate randomized nutraceutical interventions after PCa diagnosis [7–9]. Given the widespread use of nutraceuticals and the absence of standardized clinical guidance, we systematically evaluated randomized controlled trials (RCTs) of oral nutraceuticals and defined dietary interventions administered after PCa diagnosis, with a focus on PSA-related outcomes, tissue and circulating biomarkers, safety, and clinically relevant disease outcomes.

2. Materials and Methods

2.1. Search Strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and was registered prospectively with PROSPERO (CRD420251105463) [10]. The review question and core eligibility criteria were unchanged following PROSPERO registration. PubMed, MEDLINE, and Embase were searched until September 2026 using a structured strategy combining three concepts: prostate cancer, treatment, and nutraceutical or dietary intervention. The completed PRISMA 2020 checklist is provided in Supplementary File S1.

Prostate cancer-related terms were combined with treatment-related terms and with controlled vocabulary terms, including Medical Subject Headings (MeSH) terms where applicable, for dietary supplements, vitamins, minerals, phytochemicals, plant-derived compounds, polyphenols, nutraceuticals, and dietary interventions. Within the intervention concept, individual nutraceutical and dietary terms were also included, such as soy isoflavones, genistein, lycopene, tomato, pomegranate, green tea, curcumin, selenium, vitamin E, vitamin D, cranberry, flaxseed, linseed, fish oil, fat, dietary fat, and low-fat diets.

Searches were limited to human randomized trials published in English. We also checked the reference lists of the included studies and relevant reviews to identify additional eligible trials. The full summary search strategy is provided in Supplementary Table S1.

2.2. Eligibility Criteria

For the purposes of this review, nutraceuticals were operationally defined as food-derived bioactive compounds or nutrients administered orally as discrete products or standardized food-derived preparations with the intention of producing a health- or disease-related effect [4]. These included vitamins, minerals, fatty acids, phytochemicals, plant-derived extracts, isolated bioactive compounds, dietary supplements, and standardized food-derived products. Whole-diet patterns were not classified as nutraceuticals. Defined dietary modifications were considered as a separate intervention category and were eligible only when they were prospectively prescribed after PCa diagnosis and evaluated for a treatment-related biological or clinical effect. Fish-oil supplementation was therefore considered a nutraceutical intervention because it provided a defined orally administered

source of bioactive fatty acids, whereas low-fat dietary modification was classified as a defined dietary intervention rather than a nutraceutical.

Studies were eligible if they enrolled adult men with histologically confirmed PCa; evaluated an eligible intervention after PCa diagnosis; used randomized allocation; and reported at least one treatment-related clinical, biochemical, pathological, tissue, or safety outcome. Eligible comparators included placebo, usual diet or control interventions, alternative randomized nutritional interventions, and randomized dose comparisons. Sequential intervention trials were eligible when allocation to the initial intervention was randomized. Observational studies, nonrandomized interventions, case reports, animal or in vitro studies, primary-prevention trials in men without established PCa, broad multicomponent lifestyle interventions in which the nutritional component could not be evaluated separately, non-English reports, protocols without treatment outcomes, and secondary publications that did not provide an independent randomized comparison were excluded.

The primary outcomes were serum PSA level or change, PSA velocity, PSA doubling time (PSADT), biochemical recurrence, and disease progression. Secondary outcomes included pathological findings, tissue and circulating biomarkers, adverse events, and conversion to conventional treatment. Outcomes were extracted at the time points reported by the individual trials.

2.3. Study Selection and Data Extraction

Search results were imported into Covidence (Veritas Health Innovation, Melbourne, Australia; web-based software, accessed Mar 2026), and duplicates were removed. Two reviewers independently screened titles and abstracts and assessed potentially eligible full-text reports. Disagreements were resolved through discussion and, when required, consultation with a third senior reviewer. Two reviewers independently extracted data using a standardized form. Extracted data included study location, population, disease stage, randomized sample size, intervention, comparator, dose, duration, outcomes, effect estimates, confidence intervals, and p values. Subgroup findings were extracted only when reported by the original trial publications, no de novo subgroup analyses were performed for this review. Subgroup analyses were described as prespecified, post hoc, or exploratory when this was stated in the source publication, and prespecification was not assumed when it could not be established.

2.4. Risk-of-Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for the primary outcome of each trial. When no primary outcome was explicitly identified, the principal efficacy outcome most relevant to this review was selected by consensus between the reviewers [11]. The five domains were the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall judgments were categorized as low risk, some concerns, or high risk. Two reviewers independently performed risk-of-bias assessment. Disagreements were resolved through discussion and, when required, consultation with a third reviewer.

2.5. Statistical Analysis

Quantitative synthesis was undertaken only when trials evaluated interventions within the same broad nutraceutical class, involved comparable PCa settings, reported the same outcome using the same measurement scale at a similar treatment time point, and provided sufficient numerical data for calculation of a common effect measure. Three soy-based trials met these criteria: they enrolled men with localized PCa in the presurgical setting, evaluated short-term soy-based interventions, and reported extractable post-intervention serum PSA values as means and standard deviations in ng/mL after approx-

imately 2–5 weeks [12–14]. The pooled outcome therefore represented post-intervention serum PSA rather than change from baseline. Because this analysis pooled post-intervention values rather than change-from-baseline or baseline-adjusted treatment effects, the estimate may be influenced by chance baseline imbalances between groups, particularly given the small sample sizes, and should therefore be interpreted as exploratory.

Because all studies used the same measurement scale, mean differences with 95% confidence intervals were pooled using inverse-variance random-effects analysis with restricted maximum-likelihood estimation and Wald-type confidence intervals in Review Manager (RevMan) version 7.2.0. Statistical heterogeneity was assessed using the χ^2 test, τ^2, and I^2. A leave-one-out sensitivity analysis was performed by sequentially excluding each trial to assess whether the pooled estimate was disproportionately influenced by an individual study. Because only three studies contributed to the meta-analysis, funnel-plot assessment and statistical tests for small-study effects were not performed because these methods have limited interpretability with fewer than 10 studies.

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework across intervention groups, using the most clinically relevant efficacy outcome available for each intervention. Randomized evidence started at high certainty and was downgraded where appropriate for risk of bias, inconsistency, indirectness, imprecision, and publication bias. During the preparation of this manuscript, the authors used ChatGPT, version 5.5, for grammar and formatting assistance. The authors have reviewed and edited all the outputs and take full responsibility for the content of this publication.

3. Results

3.1. Study Selection and Characteristics

The combined database searches of PubMed, MEDLINE, and Embase from inception through September 2026 identified 6080 records (PubMed, n = 4637; MEDLINE, n = 1303; Embase, n = 140). After removing 903 duplicate records and 3740 records with incorrect study types, 1437 unique records underwent title and abstract screening. Of these, 1385 were excluded, leaving 52 full-text reports for eligibility assessment. Twenty-six full-text reports were excluded: 23 because they did not meet the eligible randomized design or comparator criteria, one because the intervention was assigned before PCa diagnosis, one because it was a secondary analysis of an included randomized trial, and one because it was a protocol or baseline report without treatment outcomes. Twenty-six randomized controlled trials involving 2188 randomized participants were included in the review (Figure 1). The characteristics and principal findings of the included trials are summarized in Table S2.

Clinical settings included presurgical window-of-opportunity studies, active surveillance or localized disease without immediate definitive treatment, biochemical recurrence after local treatment, radiotherapy, and recurrent or hormonally treated disease (Figure 2).

Interventions included soy or isoflavones, pomegranate, lycopene or tomato products, selenium, vitamin E, flaxseed, dietary-fat modification, green tea, curcumin, cranberry, muscadine grape skin, and a multi-ingredient polyphenol formulation.

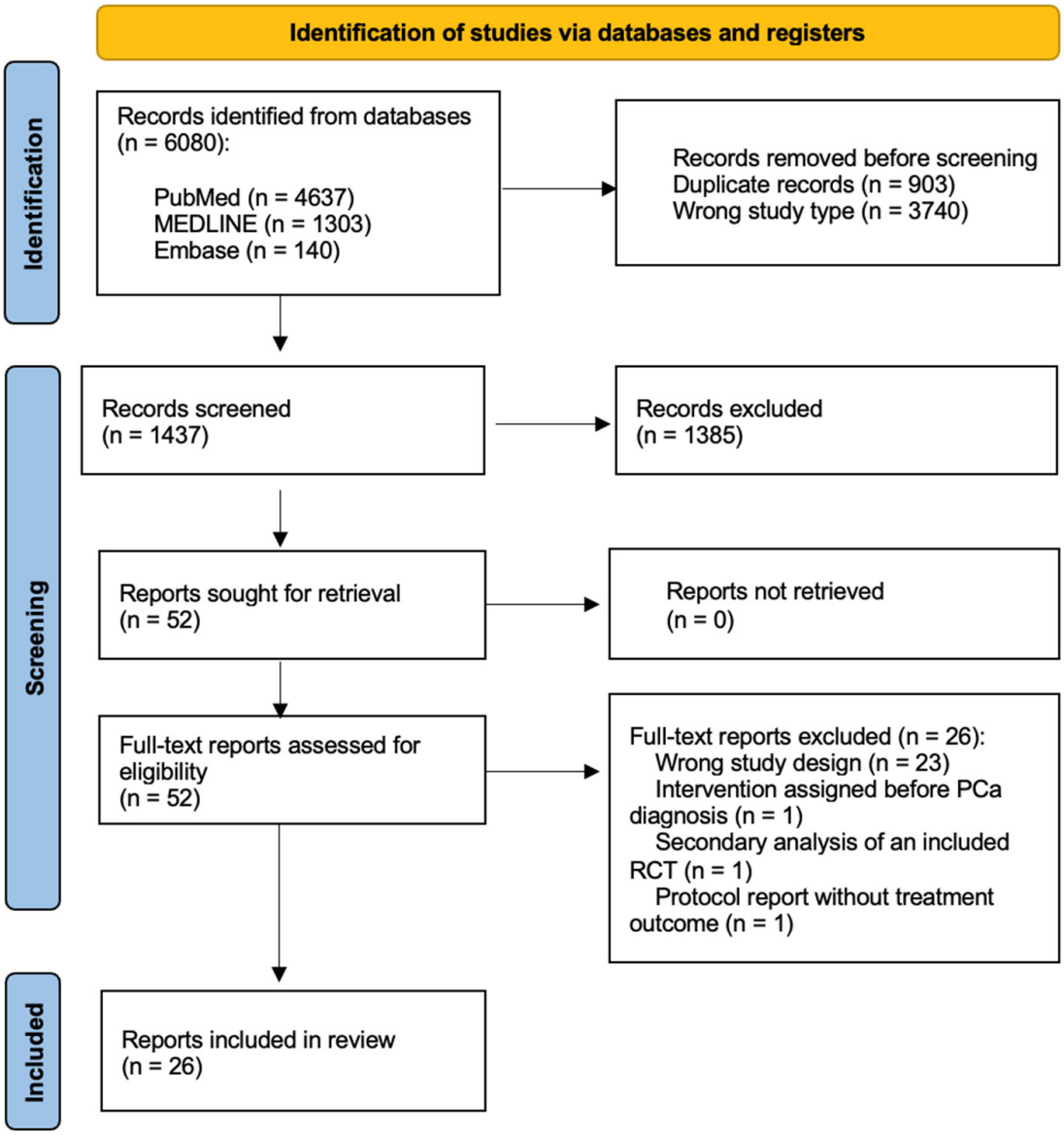


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection. PCa, prostate cancer; RCT, randomized controlled trial.

In localized presurgical disease, trials evaluated soy or isoflavones [12–16], pomegranate [17], lycopene or tomato products [18,19], vitamin E and selenium [20], low-fat diet with fish oil [21], flaxseed [22], cranberry [23], and tea [24]. Active surveillance or localized-disease trials evaluated soy or isoflavones [25,26], pomegranate [27], selenium [28], the multi-ingredient Pomi-T formulation [6], and vitamin D [29]. Trials in biochemical recurrence or following local treatment evaluated soy [30], pomegranate [31,32], tomato and soy [33], and muscadine grape-skin extract [34]. Curcumin was evaluated during radiotherapy [35], while lycopene with or without soy was evaluated in recurrent or hormonally treated disease [36].

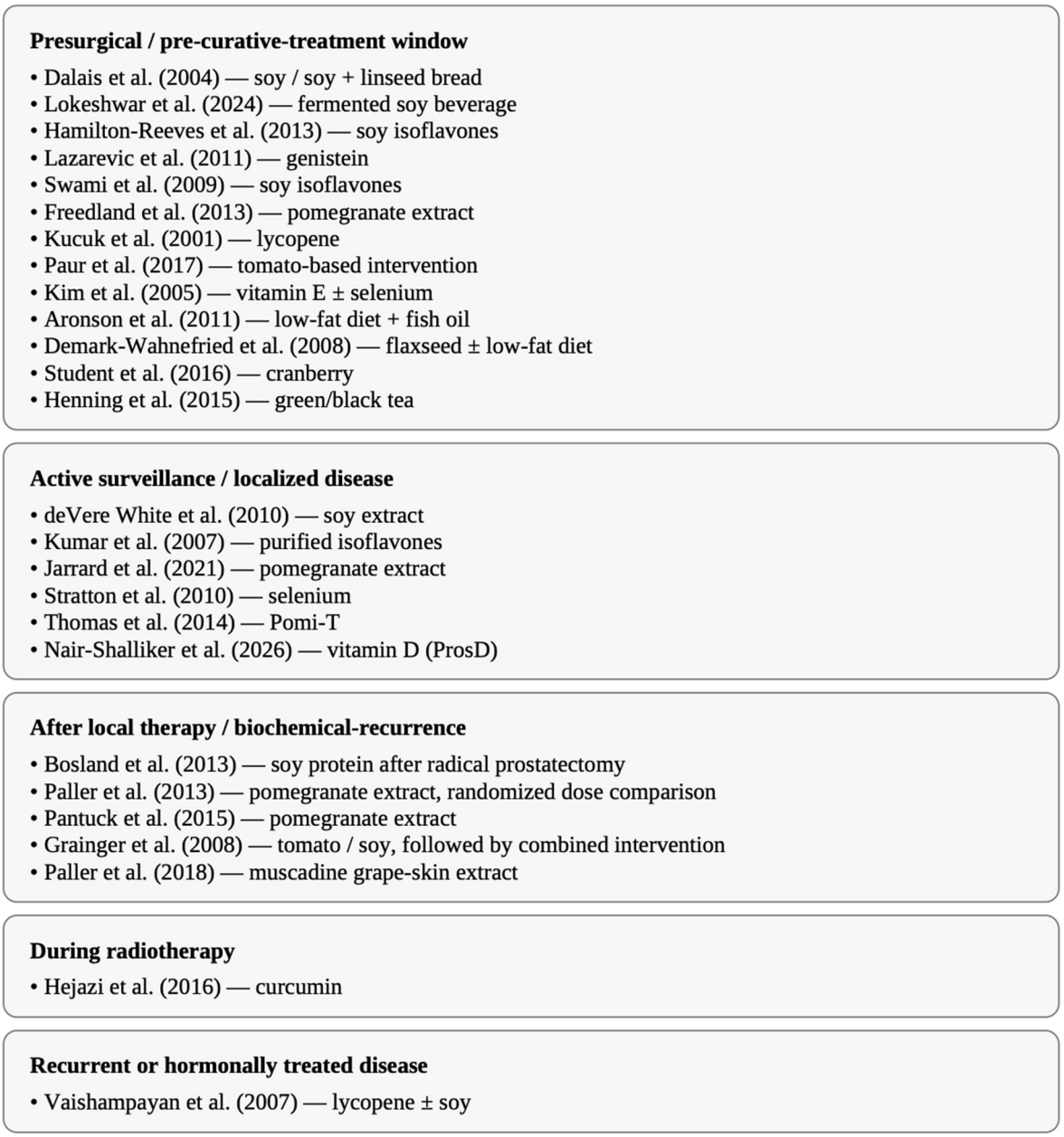


Figure 2. Included RCTs grouped by phase of prostate cancer management [6,12–36]. ProsD, High-Dose Vitamin D Supplementation and Prostate Cancer Progression; RCT, randomized controlled trial.

3.2. Soy and Isoflavones

Eight trials evaluated soy protein, soy foods, fermented soy, or purified isoflavones [12–16,25,26,30]. Bosland et al. randomized 177 men after radical prostatectomy; 159 were evaluable, and soy protein did not reduce biochemical recurrence compared with placebo (hazard ratio: 0.96, 95% confidence interval: 0.53–1.72; $p = 0.89$) [30]. deVere White et al., Hamilton-Reeves et al., and Lokeshwar et al. found no significant overall PSA benefit [13,14,25]. Dalais et al. reported a −12.7% PSA change with soy bread versus +40% with the wheat control ($p = 0.02$), whereas Lazarevic et al. reported a borderline between-group difference in percentage PSA change ($p = 0.051$) [12,15]. Swami et al. found decreased cyclooxygenase-2 (COX-2) and increased p21 messenger RNA expression in prostate tissue, without assessing clinical oncological outcomes [16]. Kumar et al. found that purified isoflavones were well tolerated over 12 weeks [26].

The exploratory meta-analysis included Dalais et al., Hamilton-Reeves et al., and Lokeshwar et al., comprising 100 participants with available short-term post-intervention PSA data [12–14]. Soy-based interventions were not associated with a significant difference in post-intervention serum PSA compared with placebo or control (mean difference: −0.50 ng/mL, 95% confidence interval: −2.14 to 1.14; $p = 0.55$; $I^2 = 0\%$; Figure 3).

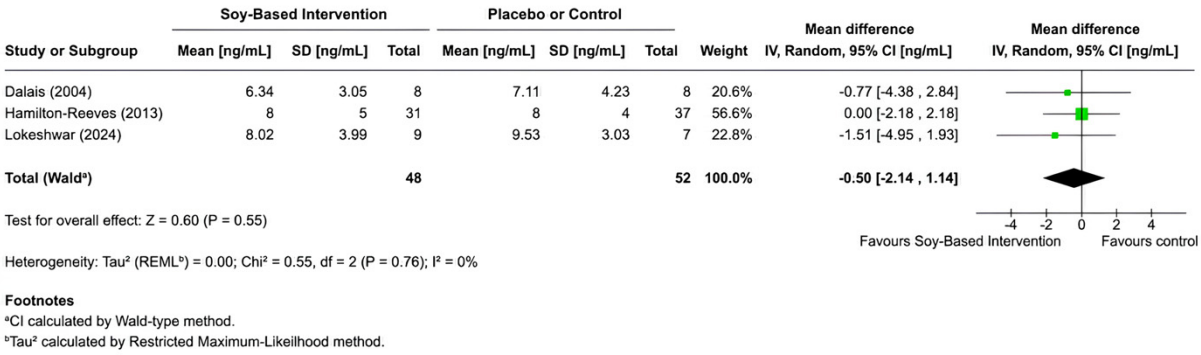


Figure 3. Exploratory random-effects meta-analysis of post-intervention prostate-specific antigen compared with placebo or control [12–14]. IV, inverse variance; CI, confidence interval; REML, restricted maximum likelihood.

Leave-one-out sensitivity analyses did not change the interpretation, and pooled mean differences remained nonsignificant when Dalais et al. (−0.43 ng/mL, 95% CI: −2.28 to 1.41), Hamilton-Reeves et al. (−1.16 ng/mL, 95% confidence interval [CI]: −3.65 to 1.33), or Lokeshwar et al. (−0.21 ng/mL, 95% CI: −2.07 to 1.66) were excluded. Further meta-analysis was not considered appropriate because of substantial clinical and methodological heterogeneity across the remaining trials, including differences in interventions, patient populations, treatment settings, follow-up durations, outcome definitions, and reporting methods.

The GRADE certainty of evidence for the nutraceutical and defined dietary interventions is shown in Supplementary Table S4.

3.3. Pomegranate

Four randomized trials evaluated pomegranate products [17,27,31,32]. Paller et al. reported an overall within-group increase in PSADT from 11.9 to 18.5 months, but the study lacked a placebo group and found no difference between the groups given 1 g and 3 g of pomegranate extract ($p = 0.554$) [31]. Pantuck et al. found no significant overall PSADT benefit versus placebo ($p = 0.14$). In an exploratory subgroup analysis, median PSADT increased from 13.6 to 25.6 months among men with the Manganese Superoxide Dismutase (MnSOD) AA genotype receiving pomegranate extract ($p = 0.03$) [32]. Freedland et al. observed nonsignificant reductions in benign-tissue 8-hydroxy-2′-deoxyguanosine (8-OHdG) (16% lower; $p = 0.095$) and cancer-tissue 8-OHdG (23% lower; $p = 0.372$) [17]. Jarrard et al. found no significant between-group effect on plasma insulin-like growth factor 1 (IGF-1), PSA, PSADT, or biopsy outcomes [27].

3.4. Lycopene and Tomato Products

Four trials evaluated lycopene or tomato-based interventions [18,19,33,36]. In a small presurgical trial, Kucuk et al. found organ-confined disease in 73% of lycopene-treated men versus 18% of controls ($p = 0.02$), although the between-group PSA difference was not significant [18]. Paur et al. found no overall PSA effect; a post hoc intermediate-risk subgroup showed a PSA change of −2.9% with tomato versus +6.5% with control ($p = 0.016$) [19]. Vaishampayan et al. observed no complete or partial PSA responses and

did not demonstrate additional benefit from adding soy to lycopene [36]. Grainger et al. reported PSA and vascular endothelial growth factor changes in a small sequential dietary study without a concurrent placebo comparison [33].

3.5. Vitamins, Minerals, Flaxseed, and Dietary-Fat Interventions

Selenium did not improve PSA velocity in men on active surveillance at either 200 or 800 µg/day; among men in the highest baseline-selenium quartile, 800 µg/day increased PSA velocity ($p = 0.018$) [28]. Kim et al. reported a shift in serum proteomic patterns with combined vitamin E and selenium, but no validated clinical oncological endpoint was assessed [20]. Nair-Shalliker et al. randomized 123 men with newly diagnosed low- to intermediate-risk PCa undergoing active surveillance that were treated with monthly oral cholecalciferol (50,000 IU; $n = 81$) or placebo ($n = 42$). Vitamin D supplementation did not significantly improve active therapy-free survival (log-rank $p = 0.44$) or progression-free survival (log-rank $p = 0.60$), and adverse-event occurrence was similar between groups. Reductions in selected lymphocytic markers of genome damage were observed in the vitamin D group, but these biomarker changes were not accompanied by evidence of reduced clinical disease progression [29]. A low-fat diet with fish oil supplementation reduced tumor Ki-67 compared with a Western diet ($p = 0.026$), although the primary serum IGF-1 endpoint was not significantly different [21]. Flaxseed-containing interventions reduced tumor proliferation ($p < 0.002$), whereas low-fat dietary restriction alone did not [22].

3.6. Other Phytochemicals and Multi-Ingredient Formulations

Cranberry supplementation was associated with a 22.5% within-group PSA reduction, but a clear between-group PSA treatment effect was not established and tissue markers were unchanged [23]. Curcumin increased total antioxidant capacity during radiotherapy (adjusted mean difference: 1.3, 95% confidence interval: 0.3–2.4; $p = 0.014$), but the trial did not assess oncological efficacy [35]. The Pomi-T formulation produced a smaller median PSA rise than placebo over 6 months (14.7% vs. 78.5%; $p = 0.0008$), representing a 63.8% difference in PSA change; this single study does not establish synergy or long-term clinical benefit [6]. Green tea did not significantly alter tissue proliferation, apoptosis, or oxidative-damage markers; however, secondary analyses showed reductions in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) staining, urinary 8-OHdG, and serum PSA [24]. Muscadine grape-skin extract did not improve overall PSADT ($p = 0.81$). In an exploratory Superoxide Dismutase 2 (SOD2) Ala/Ala subgroup analysis, median PSADT increased by 6.4 months in the pooled treatment groups and by 1.8 months in the placebo group, but the between-group difference was not statistically significant [34].

3.7. Risk of Bias

The specific outcome selected for RoB 2 assessment for each included trial is reported in Supplementary Table S3. RoB 2 was used to assess 26 included RCTs. Four studies (15.4%) were judged to be at low risk of bias, 15 (57.7%) had some concerns, and seven (26.9%) were judged to be at high risk (Figure 4). The most common concerns related to missing outcome data, for which 13 studies had some concerns and four were at high risk. Concerns regarding the randomization process were identified in 13 studies, predominantly because allocation concealment or sequence implementation was insufficiently described. Four studies were at high risk because of deviations from the intended interventions, commonly owing to post-randomization exclusions, poor adherence, or analyses that did not preserve the randomized groups. Three studies were at high risk for selective reporting because multiple outcomes or analyses did not have a clearly prespecified analysis plan. All studies were judged to be at low risk of bias for outcome measurement, reflecting the predominantly objective laboratory, pathological, and PSA-based outcomes. The traffic-light plot is shown in Figure 5.

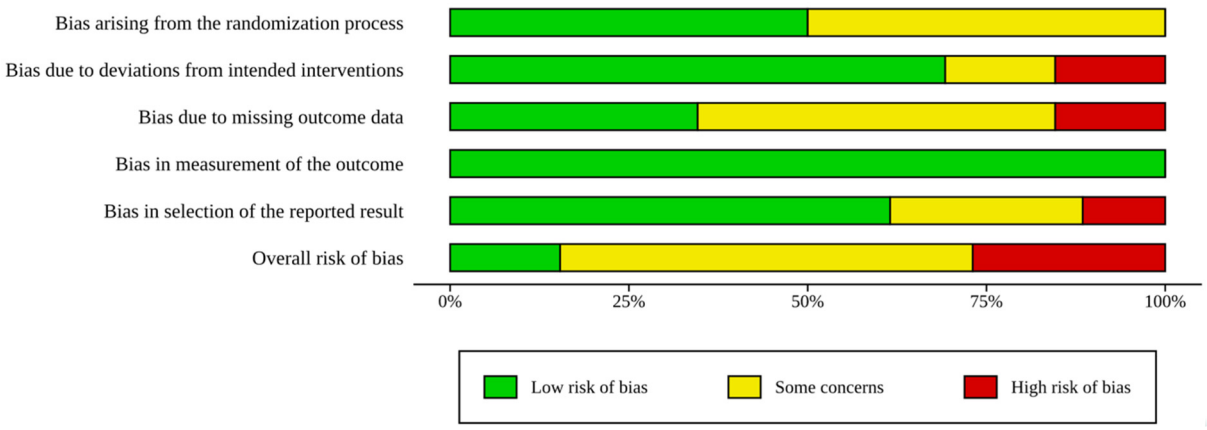


Figure 4. Study-count-weighted summary of the Cochrane Risk of Bias 2 assessment of the included randomized controlled trials.



Figure 5. Traffic-light plot of the Cochrane Risk of Bias 2 assessment for the selected outcome for each included randomized controlled trial [6,12–36]. Green (+) indicates low risk of bias, yellow (?) indicates some concerns, and red (−) indicates high risk of bias. D1, bias arising from the randomization process; D2, bias due to deviations from intended interventions; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result.

4. Discussion

4.1. Principal Findings

This review of 26 RCTs involving 2188 men found inconsistent evidence that nutraceutical and defined dietary interventions improve PCa-related outcomes. The exploratory meta-analysis of three presurgical soy trials showed no statistically significant difference in short-term post-intervention serum PSA. Across the wider evidence base, several interventions altered tissue, oxidative-stress, inflammatory, or PSA-related biomarkers, but the available evidence was insufficient to establish validated benefits for progression, metastasis, cancer-specific survival, or overall survival. These findings should be interpreted as an absence of established evidence of clinical benefit rather than evidence that the interventions have no effect.

This interpretation is also influenced by the developmental phase of several included studies. Some trials were phase II studies, which are designed to assess biological activity or preliminary efficacy rather than to provide evidence of clinical benefit. Therefore, biomarker-related findings from these trials should not be interpreted as conclusive evidence for or against long-term oncological efficacy.

The heterogeneous findings may partly reflect differences in biological targets, formulation, bioavailability, dose, and intervention duration. Soy isoflavones and other phytoestrogens may influence hormone-dependent signaling and gene expression, whereas polyphenol-rich interventions have been investigated for effects on oxidative stress and inflammatory pathways. Lycopene, selenium, vitamin E, green-tea constituents, curcumin, omega-3 fatty acids, and vitamin D act through distinct metabolic and cellular pathways. Consistent with these proposed mechanisms, several included trials demonstrated changes in intermediate biomarkers such as COX-2, p21, Ki-67, 8-OHdG, NF-κB, total antioxidant capacity, and lymphocytic genome-damage markers. However, changes in these biological markers did not consistently translate into changes in PSA or clinically meaningful oncological outcomes. Differences in baseline nutritional status, host genotype, tumor biology, disease setting, concomitant treatment, adherence, treatment duration, and supplement formulation may further contribute to variability between trials.

4.2. The Validity of PSA as a Clinical Endpoint

A major limitation of the current literature on nutraceutical and defined dietary interventions is its reliance on short-term changes in serum PSA concentration, PSA velocity, or PSA doubling time as primary efficacy outcomes. Although PSA is clinically useful for monitoring PCa, aggregate randomized-trial analyses have shown that biochemical-failure-based intermediate endpoints do not meet accepted surrogacy criteria for overall survival in localized disease, whereas metastasis-free survival has demonstrated stronger surrogacy [37]. Consequently, a favorable PSA response should not be interpreted as evidence of meaningful oncological benefit without corresponding improvements in radiological, pathological, or long-term clinical outcomes. Metastasis-related clinical endpoints are also directly relevant to contemporary studies of metastasis-directed therapy [38].

Recent systematic reviews have reached similarly cautious conclusions. Lin et al. reviewed prospective cohort studies and randomized trials of dietary patterns across PCa prevention and management and highlighted substantial heterogeneity across interventions and outcomes [2]. Allen et al. reviewed postdiagnosis diet and lifestyle studies and found suggestive associations with progression and mortality, while emphasizing the need for more robust interventional evidence [7]. Htet et al. similarly identified heterogeneity and risk-of-bias concerns across studies of dietary patterns after non-metastatic PCa diagnosis [8]. Together, these contemporary reviews reinforce the need to distinguish biological or surrogate-endpoint signals from established clinical benefit.

Our findings reinforce these concerns. Several included trials reported changes in tissue-level biomarkers, including markers of proliferation, oxidative stress, inflammation, and gene expression. However, these findings were not consistently accompanied by improvements in pathological stage or disease progression. Favorable PSA or tissue-biomarker changes should therefore be interpreted as biological signals of uncertain clinical significance rather than evidence of oncological benefit.

4.3. The Role of Precision Nutrition and Genotypes

Variation in response to nutraceutical interventions may partly reflect differences in host genetics and metabolism. In the pomegranate and muscadine grape-skin trials, exploratory genotype-defined subgroup analyses suggested possible differences in PSA kinetics [32,34]. However, these findings were derived from small subgroups and were not supported by significant overall treatment effects. Current evidence is insufficient to support genotype-guided selection of nutraceutical interventions outside clinical trials.

4.4. Multi-Ingredient Formulations

The Pomi-T trial reported one of the largest short-term PSA effects among the included RCTs [6]. However, the trial did not establish radiological or pathological benefit, and the observed difference in progression to conventional treatment may have been influenced by PSA changes rather than independently confirmed disease progression. Because all four components were administered together, the contribution of each ingredient could not be determined, and the design could not distinguish additive from synergistic effects. The findings therefore apply only to the specific formulation and dose evaluated and do not establish that multi-ingredient supplements are superior to single-agent interventions.

4.5. Safety

Serious toxicity was not reported in the included trials that systematically assessed adverse events; however, most studies were relatively small and of short duration and were not designed to exclude uncommon, delayed, or cumulative harms. Accordingly, the absence of observed serious adverse events should not be interpreted as establishing the safety of these interventions. Safety may also vary according to formulation, dose, baseline nutritional status, and treatment duration.

Kumar et al. reported that purified soy isoflavones administered at 80 mg/day for 12 weeks were well tolerated in men with localized PCa, with no significant clinical toxicity identified [26]. Similarly, the Pomi-T trial found no significant difference in overall adverse events between the intervention and placebo groups, and no grade 3 or higher toxicity was reported during the six-month study period [6]. In the High-Dose Vitamin D Supplementation and Prostate Cancer Progression (ProsD) trial, adverse-event occurrence was also similar between the vitamin D and placebo groups over 24 months [29].

The potential for harm may increase when supplements are administered at high doses or in patients with already adequate or elevated baseline nutrient levels. Stratton et al. found that selenium supplementation did not improve PSA velocity and that 800 µg/day was associated with increased PSA velocity among men with high baseline selenium concentrations [28]. Although this represents an unfavorable biomarker effect rather than a conventional toxicity endpoint, it suggests that excessive supplementation may be ineffective or potentially detrimental in selected patients.

Evidence from the broader literature also indicates that concentrated green-tea extracts can cause hepatocellular liver injury, with susceptibility influenced by dose, formulation, and administration conditions such as fasting [39]. Product purity and manufacturing consistency are additional concerns. The experience with PC-SPES demonstrated that

biologically active nutraceuticals may be compromised by contamination or undeclared pharmacologically active ingredients [5].

4.6. Limitations

The included studies showed substantial clinical and methodological heterogeneity, particularly in disease stage, treatment setting, nutraceutical formulation, dosage, and intervention duration. This variability reduced the number of studies suitable for quantitative synthesis and precluded broader pooled analyses. Methodological quality was variable, and several included studies were early-phase trials that were not powered to assess definitive clinical outcomes. Most studies also relied on PSA kinetics or surrogate tissue biomarkers, whose relationships with long-term clinical outcomes remain uncertain. In addition, the soy meta-analysis pooled post-intervention PSA values rather than change-from-baseline or baseline-adjusted effects, so chance baseline imbalances may have influenced the estimate. The pooled analysis should therefore be considered exploratory and cannot establish absence of a treatment effect. The small number of studies in the quantitative synthesis precluded meaningful assessment of small-study effects. Also, this review was restricted to English-language publications, which may have introduced language bias.

4.7. Future Directives

Future studies should prioritize larger, randomized trials using standardized formulations, well-defined doses, and longer follow-up. PSA kinetics should not be used as the sole efficacy endpoint. Studies should also assess meaningful oncological outcomes, including radiological or pathological progression, progression-free survival, cancer-specific survival, and overall survival. Potential differences in response according to genotype and baseline nutrient status should be tested in trials designed and powered for subgroup analyses. Future trials should also include standardized adherence assessment, comprehensive adverse-event reporting, and evaluation of interactions with conventional PCa treatments.

5. Conclusions

The current randomized evidence is insufficient to establish a clinically meaningful benefit of nutraceutical or defined dietary interventions in PCa management. The exploratory meta-analysis found no significant difference in short-term post-intervention serum PSA following soy-based interventions, while other interventions produced inconsistent results on PSA kinetics and tissue biomarkers. Although some interventions demonstrated biological activity, the available evidence is insufficient to establish meaningful oncological or survival benefits. Larger, well-designed trials using standardized interventions and clinically relevant endpoints are required.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/siuj7050071/s1, Table S1: Summary of search strategy. Table S2: Characteristics and principal findings of the included randomized controlled trials. Table S3: Outcome-specific Cochrane RoB 2 assessments. Table S4: Summary of Findings and GRADE Certainty of Evidence for Nutraceutical and Defined Dietary Interventions in PCa Management. Supplementary File S1: PRISMA 2020 Checklist.

Author Contributions: Conceptualization, N.L., H.Z. and S.Z.; Methodology, H.Z. and S.Z.; Formal Analysis, H.Z. and S.Z.; Investigation, H.Z. and S.Z.; Data Curation, H.Z. and S.Z.; Writing—Original Draft Preparation, H.Z. and S.Z.; Writing—Review and Editing, J.C. and N.L.; Visualization, H.Z. and S.Z.; Supervision, N.L. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article. All data analysed were extracted from previously published studies, which are cited in the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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