DOI: 10.4081/aiua.2025.13645

REVIEW

The effect of flavonoid and subclasses supplementation on prostate specific antigen (PSA), hormonal parameters and prostate cancer risk: A systematic review and meta-analysis of randomized controlled trials

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Summary

Introduction and objectives: *Prostate cancer (PCa) is a significant concern and burden worldwide. Several studies suggest that flavonoids have a significant potential as an anti-cancer agent, but the evidence remains controversial. This study aims to assess the effect of flavonoids and its subclasses supplementation on PCa risk parameters in men with biopsy-proven diagnosis of PCa or clinically determined to have a high risk of PCa.*

Materials and methods: *This systematic review and meta-analysis adhered to PRISMA guideline. A literature search was conducted across PubMed, ScienceDirect, Scopus and Cochrane utilizing PICO framework. Revised Cochrane's risk of bias tools (RoB2) was used for quality analysis. Review manager 5.4 was used for statistical analysis.*

Results: *Out of 1.117 articles, nine final studies (involving 420 patients) were included. Regarding total PSA, flavonoid provided a reduction of total PSA (MD: -0.64, $p < 0.05$), and sub-group analysis based on the supplementation duration showed flavonoid administration with a duration of ≥ 12 weeks significantly reduced total PSA compared to administration of < 12 weeks ($p < 0.05$). Meta-analyses of four studies, including men clinically at risk of PCa, revealed that flavonoid supplementation was associated with a significantly lower risk of developing PCa at endpoint (OR 0.41, $p < 0.05$). However, our results indicated no favorable effect in hormonal parameters.*

Conclusions: *The results of this meta-analysis suggest there may be a potential role for flavonoid in PCa risk reduction. Flavonoids supplementation also have been proven to be safe. However, further investigation is necessary to gain a clear understanding of the flavonoid impact on PSA and sex hormone parameters.*

KEY WORDS: *Prostate cancer; Oncology; Flavonoids; Meta-analysis.*

Submitted 18 January 2025; Accepted 1 February 2025

INTRODUCTION

Prostate cancer (PCa) represents a significant global health issue, being a primary contributor to illness and death among men, with a retrieved 1.6 million cases reported annually worldwide. PCa is recognized as the second most diagnosed malignancy and is the fifth leading cause of death attributed to cancer (1, 2). Several risk factors, including familial predisposition, ethnicity, aging, obesity, and dietary habits, influence PCa (3). While ethnic and racial disparities influence PCa risk, Northern Europe exhibits the highest rates of incidents (83.4 per 100.000) and mortality (13 per 100.000), while South Central Asia has a comparatively lower risk with incidents (6.3 per 100.000) and mortality at (3.1 per 100.000) (4).

The prevalence of PCa exhibits significant geographical variations, mostly attributed to disparities in dietary patterns. Essential nutrients, encompassing fats, proteins, carbohydrates, vitamins, and polyphenols, may influence the onset and advancement of PCa (5). *Mirza et al.* demonstrated that certain fruits, including dates, have the potential to induce apoptosis in the human prostate cancer cell line (PC3). This highlights the potential of certain fruits, which are rich in natural compounds, to exhibit strong anticancer properties (6).

At diagnosis, about 80% to 90% of PCa cases are androgen-dependent, which underpins the use of *androgen deprivation therapy* (ADT) as the primary treatment (7). The increasing prevalence of PCa and the limited treatment options available necessitate the exploration of novel supplementation and preventative strategies for the disease. Chemoprevention is an approach that uses naturally occurring substances found in fruits and vegetables to slow disease progression or even prevent cancer development (6).

Flavonoids are essential chemical components in plants, especially in fruits and vegetables. They are divided into six main subclasses: flavones, flavan-3-ols, flavanones, flavonols, anthocyanidins, and isoflavones (8). Various studies propose that these flavonoids may potentially benefit cancer therapy significantly (9). Flavonoids have also been found to reduce the development of the cell

cycle, cause apoptosis, and inhibit metastasis, invasion, and angiogenesis (10).

Although many studies have been published, the connection between flavonoids and PCa remains debated. This study conducted a meta-analysis to explore the effects of flavonoid supplementation and its subclasses on men diagnosed with PCa or considered high-risk, focusing on critical factors influencing PCa development and progression.

Methods

Literature search

On April 1, 2024, a literature study was conducted by three reviewers across multiple databases, including *PubMed, ScienceDirect, Scopus* and *Cochrane Library*. The search utilized keywords 'Prostate AND Cancer AND flavonoid OR flavonol OR flavone OR flavanone OR flavan-3-ol OR isoflavone. This study applied no restrictions regarding country or publication year. The protocol of this meta-analysis was registered in PROSPERO (CRD42024615073).

Eligibility criteria

The systematic review followed the PICO framework with the following eligibility criteria: (1) the study included participants diagnosed with *prostate cancer* (PCa) or classified as high-risk due to clinical indicators; (2) intervention using rich-food or purified flavonoid and its subclasses; (3) comparing with placebo; (4) outcome including PSA parameters, hormonal parameters (testosterone, estradiol and *Sex Hormone Binding Globulin* (SHBG), developing biopsy-detectable PCa and reporting adverse events; (5) randomized controlled study; (6) published in Indonesian or English.

Selection process

After the initial search, duplicate studies were identified and excluded. At least three independent reviewers screened the remaining studies for eligibility based on their titles and abstracts. Studies that fulfilled the predetermined inclusion criteria were incorporated into the analysis, whereas those that did not meet these criteria were excluded. Discrepancies regarding study classification were addressed through collective discussion among the research team. The literature review process adhered to the PRISMA guidelines (11).

Data collection

Data collection was performed independently by each author, with cross-checking by others to address any inconsistencies through discussion. If any information was unclear, the study authors were contacted for clarification, and studies with no response were excluded with the consent of the other reviewers. The data gathered included the first name of author, year, study design, population characteristics, mean age, type of intervention, control type, reported outcomes, and adverse events from all included studies.

Quality analysis

Revised Cochrane *Risk of Bias* tool (RoB2) was used for quality analysis, with each study being assigned a risk of bias rating of low, high, or some concerns at each evaluation point.

Publication bias

Publication bias was evaluated with a funnel plot analysis. Publication bias considered to be high if the distribution of studies was asymmetrical. Conversely, if the study distribution was evenly distributed and symmetrical, publication bias was considered to be low.

Statistical analysis

Meta-analyses were conducted to evaluate the impact of flavonoids or their subclasses on PCa risk, comparing them to a placebo in Review Manager 5.4. The first meta-analyses assessing the effect between groups in PSA parameters and hormonal parameters were performed by entering the mean ± SD to measure the mean difference (95% CI) and were sub-grouped by effect of duration (< 12 weeks or ≥ 12 weeks) if the data was sufficient. The second meta-analysis was performed by entering the incidence of biopsy-detectable PCa in populations clinically determined as having PCa risk to measure the odds ratio (95% CI) between groups. The heterogeneity of the statistical analysis was evaluated by the I^2 value. The fixed-effects model was employed when I^2 was less than 50%, whereas the random-effects model was utilized when I^2 was equal to or greater than 50%. The findings were illustrated through a forest plot, and an overall effect was deemed statistically significant if the p-value was less than 0.05 (12).

Results

Literary search and examination results

A total of 1.117 studies were initially identified from various databases. The studies included in this analysis were published prior to April 1, 2024. After removing 125 duplicates, two reviewers independently screened the remaining 1.052 study by titles and abstracts. Of these, 1.043 studies were excluded for failing to meet the eligibility criteria. As a result, nine studies were deemed eligible and included in the qualitative and quantitative analysis. A detailed overview of the search and filtering results is presented in Figure 1.

Characteristics of eligible studies

The nine studies were RCTs done in various countries, involving a cumulative sample size of 420 participants including 186 men with PCa biopsy-proven diagnosis and Gleason score ≥ 6 in four studies (13-16), 218 men at elevated risk of PCa (elevated PSA, ASAP, HGPIN or negative prostate biopsy) in four studies (17-20) and 16 men with a history of radical prostatectomy less than 3 years before with elevated PSA (≥ 0.1 ng/ml) in one study (21). In all studies flavonoid or its subclasses in various form were given, eight studies used a purified isoflavone rich-food (14-16, 19-21) or isoflavone supplement in capsule or tablet (13, 18), only one study (17) used a Flavan-3-ols subclass of flavonoid with PolyE capsule containing *Epigallocatechin gallate* (EGCG). In all trials most controls

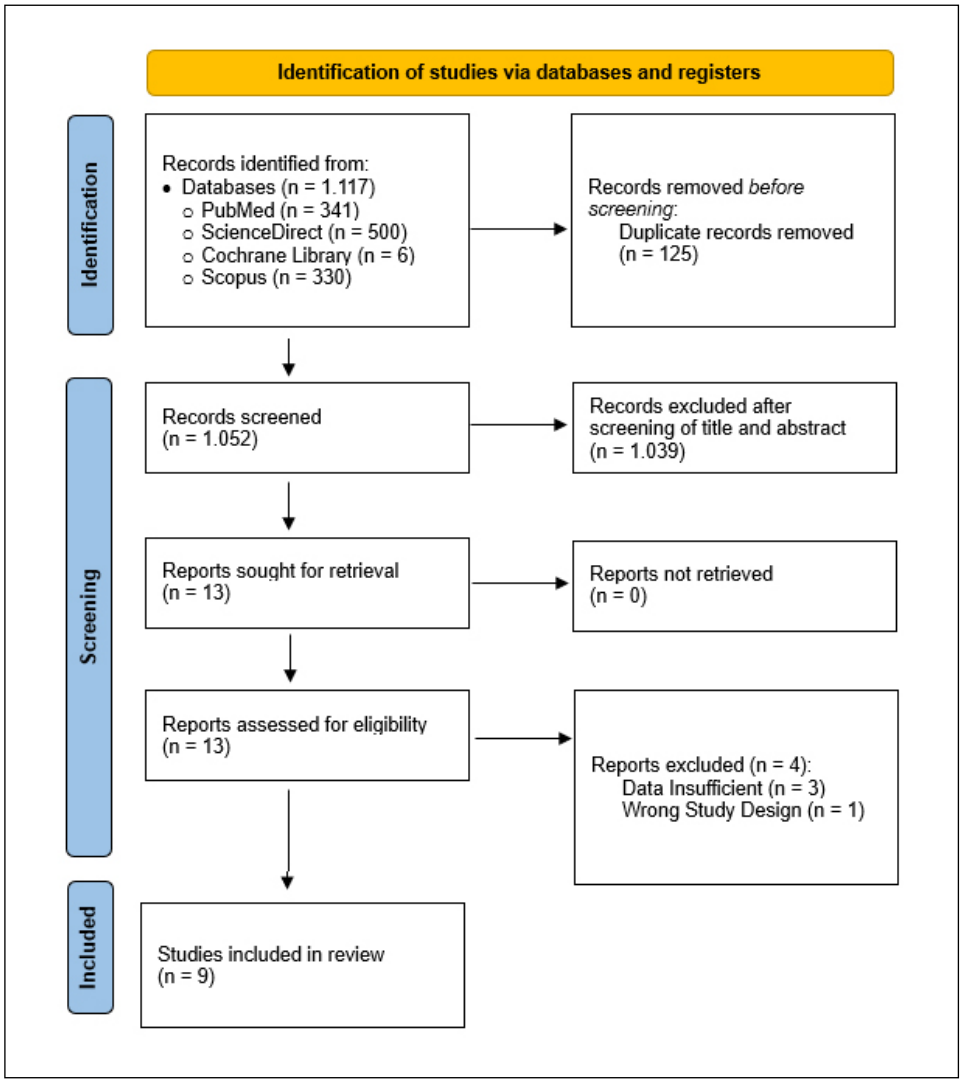


Figure 1.
Flow of literature search and selection based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

used placebo. Most studies used 12 weeks or more as an end-point outcome, only two studies had < 12 weeks intervention duration (13, 16). The outcomes assessed total PSA in six studies (13, 15-17, 19, 21) and free PSA in three studies (15, 16, 19), as well as hormonal parameters, which consist of total testosterone observed in four studies (13, 15, 16, 20), free testosterone in four studies (13-15, 20), total estradiol in four studies (13-15, 20) and SHBG in five studies (13, 15, 17, 18, 20).
Additionally, three studies (17, 18, 20) provided data on the incidence of PCa at the end of intervention of men clinically at risk of PCa. Only four studies (13, 14, 17, 18) have reported data on the flavonoid intervention side effects, with the majority reporting a small sample size of 1-2 grade side effects.
Full details regarding the details of studies are presented in Table 1.

Study quality results
The risk of bias assessment results indicated that all studies generally had a low risk of bias. However, one study raised some concerns regarding its overall risk, as shown in Figure 2.

Publication Bias results
Funnel plot results of studies on Total PSA (***Supplementary Figure 1A***) and SHBG (***Supplementary Figure 2D***) showed an asymmetrical distribution. The other results of the studies showed a symmetrical distribution as shown in ***Supplementary Figures***. Therefore, it can be concluded that the results of this analysis have a low risk of publication bias.

Statistical analysis (Meta-analysis)

PSA parameters
There were two outcomes in the assessment of PSA parameters: total PSA and free PSA. The result of the forest plot revealed that in the comparison between flavonoid supplementation and placebo, there was a significant difference in total PSA (MD: -0.64, $p < 0.05$). Sub-group analysis based on the supplementation duration showed that flavonoid administration with a duration of ≥ 12 weeks significantly reduced total PSA compared to administration of ≤ 12 weeks ($p < 0.05$). However, no significant statistical difference was revealed for free PSA (MD: 0, $p = 0.99$). Figure 3 shows the detailed forest plot of PSA parameters.

Table 1.
Baseline characteristics data of included studies.

No	Study (Author)	Study Design	Population	Mean Age (years)		Total Sample (Flavonoid vs Control)	Treatment Type		Intervention Duration	Outcome Assesments							Adverse Events Reported
				Flavonoid	Control		Flavonoid	Control		Total PSA (ng/mL)	Free PSA (ng/mL)	Total Testosterone (nmol/L)	Free Testosterone (nmol/L)	Total Estradiol (pg/ml)	SHBG (nmol/L)	PCa Incidence	
1	*Bosland et al. (2022)*	RCT	Men all age with elevated PSA with a history of radical prostatectomy	65.8 (CI: 60.2 - 71.3)	63.8 (CI:58.5 - 69.0)	16 (8 vs 8)	Soy isoflavone purified (Isoflavone 40 mg/day)	Placebo	32 weeks	✓	-	-	-	-	-	-	-
2	*Kumar et al. (2020)*	RCT	Men aged 30-80 with a biopsy-proven diagnosis of localized PCa	58.8 ± 7.5	59.1 ± 7.4	62 (31 vs 31)	Isoflavone capsule (Isoflavone 40 mg/daily)	Placebo	3- 6 weeks	✓	-	✓	✓	✓	✓	-	Only grade 1-2 (nausea, elevated liver enzyme etc) adverse event in intervention group reported
3	*Kumar et al. (2015)*	RCT	Men aged 30-80 with a biopsy-proven diagnosis of HGPIN and/or ASAP	62.0 ± 7.9	64.1 ± 7.9	94 (49 vs 48)	PolyE capsule (EGCG 400 mg/day)	Placebo	24 weeks & 48 weeks	✓	-	-	-	-	-	✓	Only grade 1-2 (nausea, etc) adverse event in intervention group reported
4	*Miyanaga et al. (2012)*	RCT	Men aged 50-75 with elevated serum PSA level of 2.5-10.0 and negative prostate biopsy	66.5 (52.0-75)	65 (50-75)	89 (42 vs 47)	Isoflavone tablet (Isoflavone 60 mg/day)	Placebo tablet	48 weeks	-	-	-	-	-	-	✓	Grade 3 adverse event in intervention group (1 patient: iliac artery stenosis) reported
5	*Kumar et al. (2007)*	RCT	Men aged 50-80 with a biopsy-proven diagnosis of localized PCa	71.75 ± 6.39	71.92 ± 5.59	49 (22 vs 27)	Isoflavone purified (Isoflavone 80 mg/day)	Placebo	12 weeks	-	-	-	✓	✓	✓	-	Only grade 1-2 (nausea, etc) adverse event in intervention group reported
6	*Hamilton-Reeves et al. 1 (2007)*	RCT	Men aged 50-85 with a high-grade PIN and/or ASAP	68 ± 8	68 ± 7	35 (18 vs 17)	Soy isoflavone (Isoflavone 107 mg/day)	Milk protein isolate	12 weeks & 24 weeks	✓	✓	-	-	-	-	✓	-
7	*Hamilton-Reeves et al. 2 (2007)*	RCT	Men aged 50-85 with a high-grade PIN and/or ASAP	68 ± 8	68 ± 7	35 (18 vs 17)	Soy isoflavone purified (Isoflavone 107 mg/day)	Milk protein isolate	12 weeks & 24 weeks	-	-	✓	✓	✓	✓	-	-
8	*Fabien et al. (2004)*	RCT	Men all age with a biopsy-proven diagnosis of PCa scheduled to undergo radical prostatectomy	61.7 ± 5.1	60.5 ± 5.2	16 (8 vs 8)	Soy bread isoflavone purified (Isoflavone 117 mg/day)	Wheat bread placebo	3- 4 weeks	✓	✓	✓	-	-	✓	-	-
9	*Kumar et al. (2004)*	RCT	Men aged 45-85 diagnosed with PCa with gleason score of 6	72.5 ± 5.0	70.9 ± 5.3	59 (29 vs 30)	Isoflavone soy purified (Isoflavone 60 mg/day)	Placebo	12 weeks	✓	✓	✓	✓	✓	✓	-	-

ASAP: Atypical Small Acinar Proliferation; CI: Confidence Interval; EGCG: Epigallocatechin gallate; PCa: Prostate Cancer; PIN: Prostatic Intraepithelial Neoplasia; PSA: Prostate Specific Antigen; RCT: Randomized Controlled Trial; SHBG: Sex Hormone Binding Globulin.

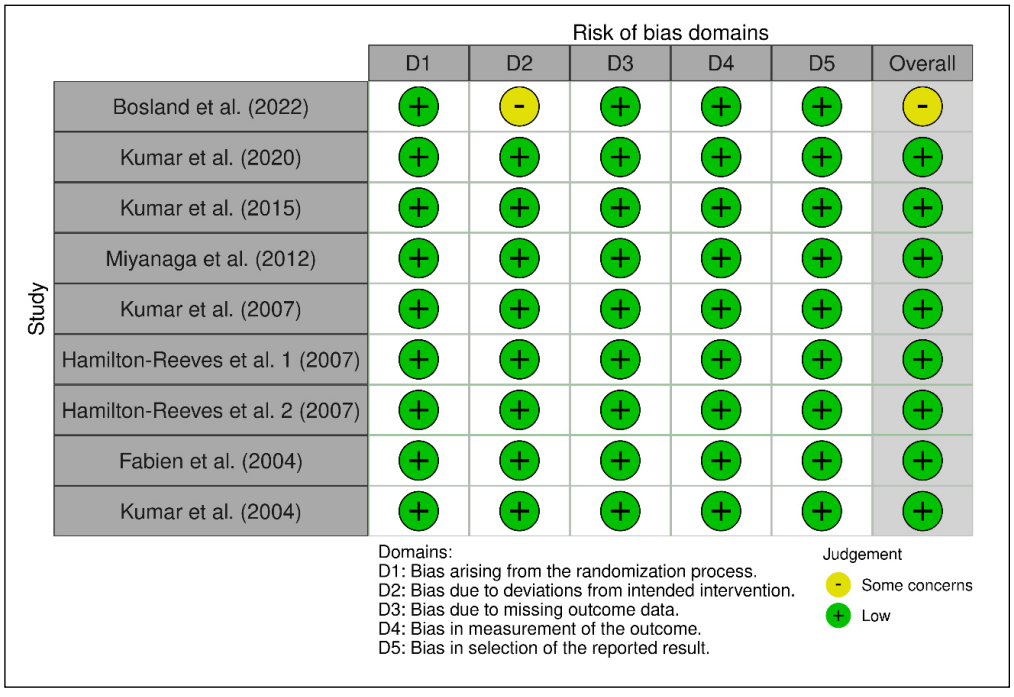
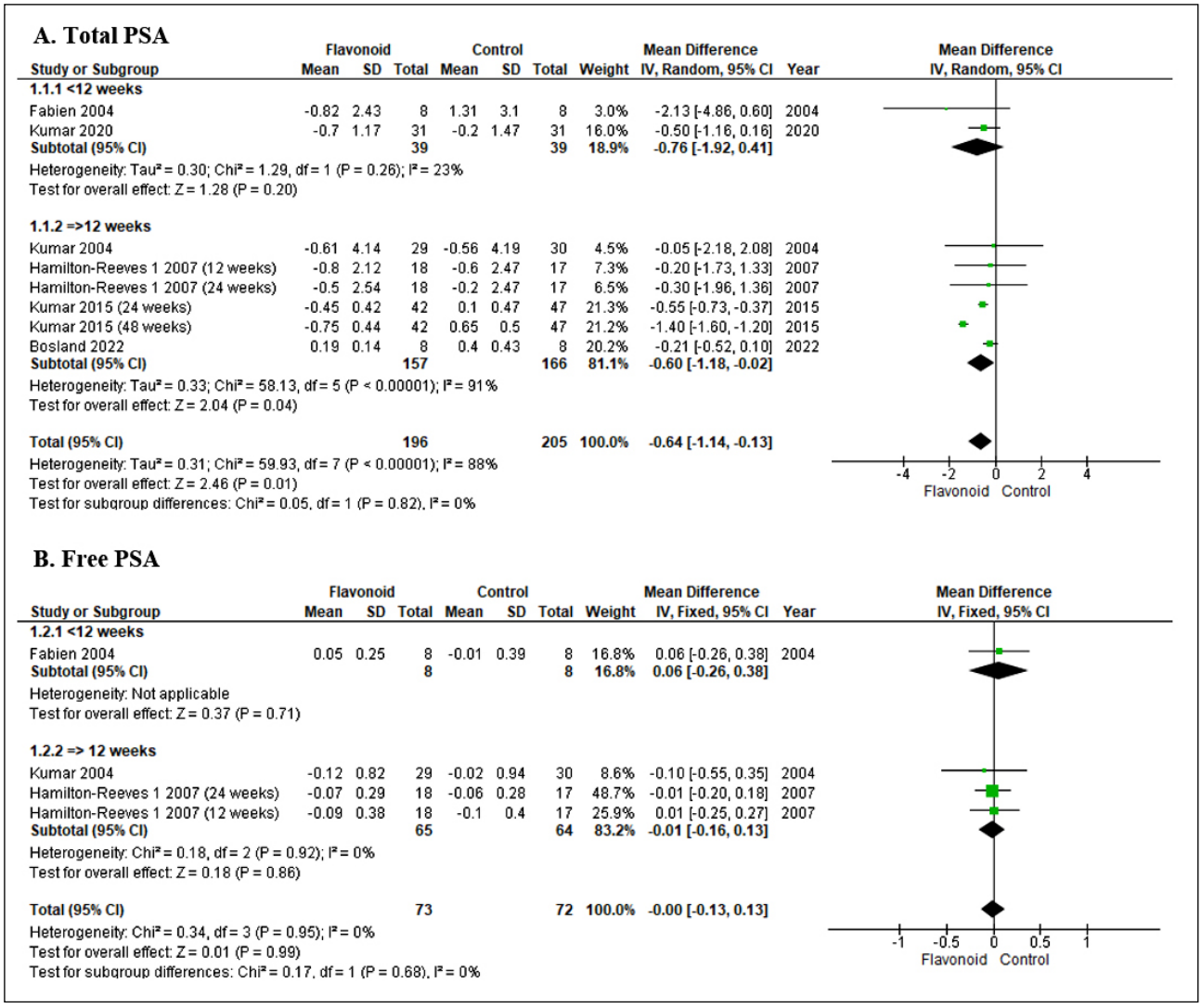


Figure 2.
Risk of bias assessment using the revised Cochrane risk-of-bias tool algorithm for randomized trials (RoB 2.0).

Figure 3.
Forest plots of PSA parameter: (A) Total PSA sub-group based on the duration of intervention (< 12 weeks or ≥ 12 weeks). (B) Free PSA.



CI: Confidence interval; IV: Inverse variance; SD: Standard deviation.

Hormonal parameters

There were four outcomes in the assessment of hormonal parameters. The total testosterone forest plot revealed a difference between groups in total testosterone (MD: 1.49, $p < 0.05$) and free testosterone (MD: -0.47, $p < 0.05$). There was no statistical significance regarding total estradiol (MD: 0.61, $p = 0.38$) and SHBG (MD: -0.02, $p = 0.99$). Figure 4 shows the detailed forest plot of hormonal parameters.

Prostate cancer risk

There were four included studies dealing with a population of men clinically at risk of PCa that reported data on the incidence of PCa biopsy-proven diagnosis at the end of intervention. The forest plot revealed that the group of patients who received flavonoid supplementation was associated with a markedly reduced risk of developing PCa (OR 0.41, $p < 0.05$). The estimated analysis associated with the incidence of PCa is presented in Figure 5.

Discussion

The objective of this study was to evaluate the findings from RCTs regarding the impact of flavonoids and their various subclasses in male individuals diagnosed with PCa or those classified as at risk for developing PCa. This systematic review included nine RCTs in total. Four studies recruited men with biopsy-proven diagnosis of PCa, four studies included men who were considered to have a risk of PCa and one study included men with a history of radical prostatectomy with elevated PSA. Our findings suggest that flavonoid consumption may lower total PSA serum levels and reduce the incidence of PCa. A subgroup analysis revealed that flavonoid supplementation for more than 12 weeks significantly reduced the risk of PCa.

While previous meta-analyses found no link between flavonoid intake and PCa risk, the limitations of these studies may have influenced their conclusions. Notably, all the studies included in that meta-analysis were observational studies. The amounts of flavonoid consumption

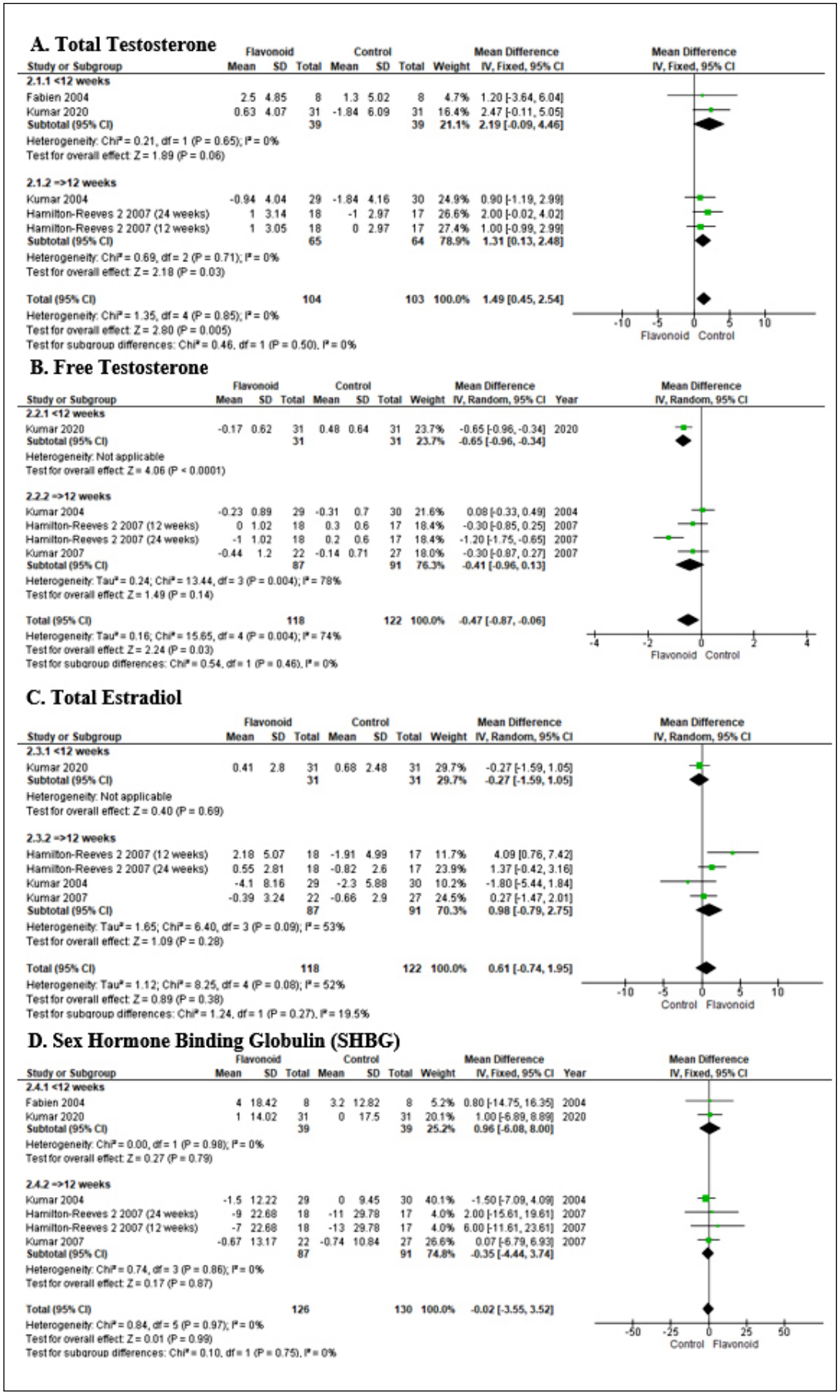
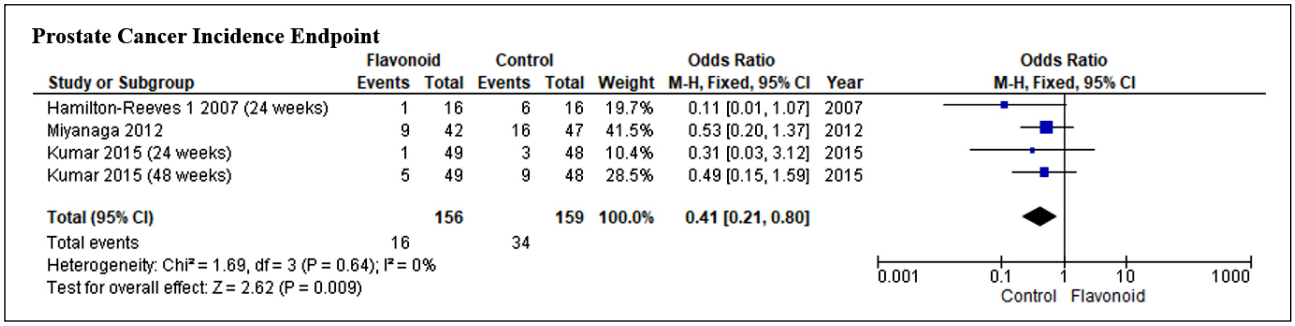


Figure 4.
Forest plots of hormonal parameter: (A) Total testosterone sub-group based on the duration of intervention (< 12 weeks or ≥ 12 weeks). (B) Free testosterone. (C) Total estradiol. (D) Sex hormone binding globulin (SHBG).

CI: Confidence interval; IV: Inverse variance; SD: Standard deviation.

Figure 5.
Forest plot of studies about subjects who had a risk of developing prostate cancer (PCa) becoming biopsy-detectable PCa at the endpoint.



CI: Confidence interval; IV: Inverse variance; SD: Standard deviation.

were derived from self-reported data provided by the participants, without a standardized method of categorization. Additionally, the research participants were categorized based on their various levels of flavonoid consumption, and the author was unable to evaluate the impact of higher flavonoid intake on the risk of PCa (22).

Flavonoids are a major category of dietary polyphenols that are found naturally in plant-based food, including fruits, vegetables, tea, and wine. Dietary products have a well-documented historical precedent as preventive agents in the fight against various forms of cancer. Natural substances such as green tea, grape skin, pomegranate, dates, and soy are known for their chemo-preventive properties. Scientific evidence strongly supports that consuming diets rich in plant-based foods may significantly lower the chance of developing many types of cancer. The precise mechanism via which these foods provide protection against the formation of tumours and the development of cancer is not yet understood. However, one possibility is that they may contain phytochemicals with potential anticancer properties (23). In addition, according to laboratory research conducted on fruits such as dates, which are rich in flavonoids, it has been shown that they can induce apoptosis in the PC3 cells of the human body. Flavonoids are suggested to have the ability to trigger apoptosis in tumour cells, which might potentially have a preventive impact against PCa (6).

Researchers have identified PSA as a biomarker for the initial detection and prognosis of PCa. Prostatic luminal epithelial cells produce it and it plays a role in regulating semen coagulation. PSA is thought to be elevated due to cellular architecture disruptions, and it circulates in both free and complex forms (24). Reports indicate that some flavonoids have the ability to prevent the production of PSA by the BT-454 cell line. This may explain the notable correlation between consumption of flavonoids and a reduced risk of PCa (25). Our findings indicated a statistically significant difference in total PSA (MD: -0.64, $p < 0.05$) between study groups. A sub-group analysis based on the length of supplementation showed that giving flavonoids for more than 12 weeks significantly decreased total PSA compared to giving them for less than 12 weeks ($p < 0.05$). However, free PSA showed no significant statistical difference ($p = 0.99$).

The results of our meta-analyses showed that there were no significant impacts on sex hormone levels. The results align with a 2013 meta-analysis of researches on isoflavones, which concluded that there was no significant influence on reproductive hormones in individuals with PCa (26). In contrast, a research investigation on the administration of soy isoflavone supplements at a dosage of 60 mg per day resulted in a reduction in testosterone and 5α-*dihydrotestosterone* (DHT) levels, while simultaneously increasing SHBG levels in a group of healthy males aged 30 to 59 years (27). These data do not provide a clear understanding of the impact of sex hormone levels. Looking at each of these, the pooled results of several small studies showed no significant changes.

In line with a previous meta-analysis by *Van Die et al.*, which examined the cancer risk in men clinically determined to be at risk (including those with a single negative prostate biopsy at the start of a 12-month study or those with ASAP or HGPIN over a 6-month period), it was found that soy isoflavones significantly reduced the likelihood of developing PCa. This conclusion was supported by a statistically significant analysis ($RR = 0.49$, $p < 0.05$) (26). In our analysis, four studies were included, focusing on men clinically at risk of PCa. The forest plot analysis showed that individuals who received flavonoid supplementation exhibited a markedly lower risk of developing PCa ($OR = 0.41$, $p < 0.05$). These findings suggest a significant association between flavonoid intake and a lower risk of PCa.

Testosterone and DHT work through the androgen receptor to control cell proliferation and differentiation. Androgens play a pivotal role in the normal development of the prostate gland, but they also contribute to the proliferation of prostate tumors, which is the primary target of *androgen deprivation therapy* (ADT). The implementation of ADT is associated with various side effects that can significantly impact both the quality of life and overall health of patients. Certain dietary supplements may provide benefits for persons undergoing ADT. Research has shown that flavonoids, such as phytoestrogen, have the ability to mitigate certain adverse effects linked to ADT. Research conducted by *Durreger et al.* found that dietary treatments including certain natural compounds might be beneficial in the adverse effects associated with ADT (7). Our study also demonstrated the safety of flavonoid sup-

plementation and its potential for use in PCa patients undergoing ADT.

It is important to address some limitations in our study. First, out of all the interventions available, only the flavonoid subclass isoflavone and flavan-3-ols were available from our included studies due to the limited number of published articles. This implies that our included study does not provide an analysis of other subclasses of flavonoids. Second, our inclusion studies have a relatively small overall sample size. Furthermore, the examination of some results revealed significant heterogeneity, which is to be expected considering the variability in the impact of flavonoids depending on the length of supplementation. Consequently, dividing into subgroups based on 12-week periods decreased the heterogeneity.

Conclusions

The findings of this study indicate that flavonoids and their respective subclasses may contribute to the reduction of PCa risk. Flavonoid supplementation is effective in lowering total PSA levels, particularly when administered for ≥ 12 weeks. Additionally, flavonoids appear to reduce the risk of PCa incidence in populations clinically identified as high-risk. Flavonoid supplementation has also been shown to be safe. Nonetheless, additional investigations are warranted to determine the optimal dose and duration of flavonoid supplementation.

Declarations

Ethical approval: *This study did not need any of ethical approval.*

Availability of data and material: *All data and materials from this research are available to the researcher and we will provide it upon request if the researcher needs it.*

Competing interests: *The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.*

Funding: *All funding for this research comes from researchers without receiving research costs or research grants from third parties.*

Authors' contributions:

Contribution Details

	AA	ASA	HR	LH	SB	AB	AAZ
Concepts	√	√	√	√	√	√	√
Design	√	√	√	√	√	√	√
Definition of intellectual content	√			√	√		
Literature search	√			√	√		
Data acquisition	√	√	√	√	√		
Data analysis	√			√	√		
Statistical analysis	√			√	√		
Manuscript preparation	√	√	√	√	√		
Manuscript editing	√			√	√		
Manuscript review	√	√	√	√	√	√	√
Guarantor	√	√	√	√	√	√	√

Acknowledgments: *We as authors would like to thank all parties involved in this study, including the Department of Urology, Faculty of Medicine, Hasanuddin University and also Hasanuddin University Hospital.*

Conference Presentation: *This article has not been presented at any conference.*

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