Anti-prostate cancer protection and therapy in the framework of predictive, preventive and personalised medicine — comprehensive effects of phytochemicals in primary, secondary and tertiary care

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Abstract
According to the GLOBOCAN 2020, prostate cancer (PCa) is the most often diagnosed male cancer in 112 countries and the leading cancer-related death in 48 countries. Moreover, PCa incidence permanently increases in adolescents and young adults. Also, the rates of metastasising PCa continuously grow up in young populations. Corresponding socio-economic burden is enormous: PCa treatment costs increase more rapidly than for any other cancer. In order to reverse current trends in exploding PCa cases and treatment costs, pragmatic decisions should be made, in favour of advanced populational screening programmes and effective anti-PCa protection at the level of the health-to-disease transition (sub-optimal health conditions) demonstrating the highest cost-efficacy of treatments. For doing this, the paradigm change from reactive treatments of the clinically manifested PCa to the predictive approach and personalised prevention is essential.

Phytochemicals are associated with potent anti-cancer activity targeting each stage of carcinogenesis including cell apoptosis and proliferation, cancer invasiveness and metastatic disease. For example, their positive effects are demonstrated for stabilising and restoring mitochondrial health quality, which if compromised is strongly associated with sub-optimal health conditions and strong predisposition to aggressive PCa sub-types. Further, phytochemicals significantly enhance response of cancer cells to anti-cancer therapies including radio- and chemotherapy. Evident plant-based mitigation of negative side-effects frequently observed for conventional anti-cancer therapies has been reported. Finally, dual anti-cancer and anti-viral effects of phytochemicals such as these of silibinin have been demonstrated as being highly relevant for improved PCa management at the level of secondary and tertiary care, for example, under pandemic conditions, since PCa-affected individuals per evidence are highly vulnerable towards COVID-19 infection.

Here, we present a comprehensive data analysis towards clinically relevant anti-cancer effects of phytochemicals to be considered for personalised anti-PCa protection in primary care as well as for an advanced disease management at the level of secondary and tertiary care in the framework of predictive, preventive and personalised medicine.

Keywords Prostate cancer management · Metastatic disease · Predictive Preventive Personalised Medicine (PPPM/3PM) · Sub-optimal health condition · Health-to-disease transition · Risk assessment · Phenotyping · Primary secondary tertiary care · Phytochemicals · Plant-based food · Clinical trials · Molecular mechanisms · ROS · Stress · Mitochondrial health · Anti-cancer protection · Radiation and chemotherapy · Tailored treatments · Cost-efficacy · COVID-19 · Silibinin · Health policy

Preamble
Prostate cancer (PCa) represents one of the most frequent cancer types in men in both incidence and mortality [1]. Following lung cancer, PCa is the second most frequently occurring cancer in men globally. According to the GLOBOCAN
statistics presented for 2020, 1,414,259 new PCa cases accounted for 14.1% of all cancer sites in men. Moreover, PCa was the most often diagnosed cancer in men in 112 countries. Similarly, in 2020 PCa accounted for 375,304 new deaths and thus represented the fifth most frequent cause of cancer death in men accounting for 6.8%. PCa was the leading cause of cancer-related death in 48 countries. The highest PCa incidence rates are found in Northern and Western Europe, The Caribbean, Australia/New Zealand, Northern America, and Southern Africa while the lowest incidence rates are in Asia and Northern Africa. Further, the highest mortality rates are in the Caribbean, Central and South America (e.g. Ecuador, Venezuela, Chile), and Sweden. The role of Western African ancestry in the modulation of PCa risk is supported by the highest global incidence of PCa in black men in the USA and Caribbean. To this end, national PCa diagnostics standards strongly contribute to PCa incidence-to-mortality statistics varying between countries and continents [2]. Moreover, PCa incidence is permanently increasing in adolescents and young adults (aged 15–40 years). Also, the rates of metastasising PCa are steadily growing up in the young population [3, 4].

Socio-economic burden is enormous: PCa treatment costs increase more rapidly than for any other cancer [3]. To this end, anti-cancer mRNA-based therapy is a promising approach based on experience collected during the last couple of months from the anti-COVID-19 vaccination. However, consideration of short- and long-term effectiveness of this kind of vaccination and its potential side effects will take years or even decades, in order to optimize the treatment condition for each cancer subtype individually [3]. In order to reverse current trends in exploding PCa statistics and treatment costs, pragmatic decisions should be made, to advance populational screening programmes and to force an effective anti-Pca protection at the level of the health-to-disease transition (sub-optimal health conditions) demonstrating the highest cost-efficacy of treatments. For doing this, the paradigm change from reactive treatments of the clinically manifested PCa to a predictive approach and personalised prevention [3].

Here, we present a comprehensive data analysis towards clinically relevant anti-cancer effects of phytochemicals [5–9] to be considered for personalised anti-PCa protection in primary care as well as for advanced disease management at the level of secondary and tertiary care in the framework of predictive, preventive and personalised medicine (PPPM/3PM).

Plant-based anti-cancer intervention — the general view

Phytochemicals are secondary plant metabolites, non-nutritive compounds produced by plants [10]. Main phytochemical classes are including polyphenols, carotenoids, alkaloids, and organosulfur compounds as recently analysed by Mazurakova et al. (2022) [9]. Current evidence highlights potent anti-cancer effects of phytochemicals and plant-based anti-cancer intervention [5, 7, 11, 12]. Recent reviews and original articles discuss the anti-cancer effects of phyto-substances demonstrated in preclinical in vitro and in vivo evaluations, including remarkable impacts on PCa prevention, inhibition of the disease progression and stimulating effects of phyto-substances on anti-cancer therapies [13–16]. Identification of health beneficiary effects as well as precise mechanism of the anti-cancer action by phytochemicals are essential for associated drug development and recommendations for personalised dietary supplements [5, 9, 10].

Phytochemicals are associated with potent anti-cancer activity affecting each of the multistage process of carcinogenesis, including apoptosis, proliferation, and invasion of cancer cells and related processes of cancer angiogenesis and metastasis [5–7, 17]. Moreover, oxidative stress overload associated with PCa development and progression results from molecular and sub-cellular changes synergistically leading to compromised mitochondrial health quality [18]. The key role of mitochondrial health quality control in the targeted anti-PCa protection can be illustrated by the capacity of apigenin to induce apoptosis of PCa cells in vitro [19]. Noteworthy, prostate tissue analysed in African American men has been associated with reduced mitochondrial DNA (mtDNA) content compared to Caucasian American while men. This may help to explain higher incidence rates and more aggressive PCa subtypes in African American men. Compromised mitochondrial health related to mtDNA depletion results in defective OXPHOS, uncontrolled ROS production, and extensive mutations to mtDNA. Dysfunctional mitochondria are also associated with increased metastatic potential and stemness of PCa cells as well as significant radio-resistance of related prostate malignancies [20].

Abundant evidence indicates a potent role of phytochemicals in both — mitochondrial health quality support on the one hand and on the other hand significantly enhanced response of cancer cells towards anti-cancer therapies including radiotherapy and chemotherapy; also an evident mitigation of negative side-effects frequently observed for conventional anti-cancer therapies have been reported [21–26].

Figure 1 depicts the anti-cancer effects of phytochemicals and their impact on each of the processes of carcinogenesis including apoptosis, oxidative stress, angiogenesis, metastasis, and affecting the effectiveness of conventional anti-cancer strategies. As is discussed below, clinical evaluations of anti-cancer capacity of phytochemicals provide evidence of their efficacy in each of the illustrated processes of carcinogenesis in PCa primary and secondary care as well as in combination with conventional anti-cancer therapeutic modalities.
Protection against clinical manifestation of PCa: phytochemicals for primary care

The preventable nature of most PCa cases represents a platform for effective risk assessment, disease-predisposition, and effective preventive and personalised strategies [1, 3]. For example, pre-cancerous lesions, such as high-grade intraepithelial neoplasia (HGPIN), can be detected years before the progression to PCa. Therefore, targeted prevention and early diagnosis are essential strategies to reduce PCa [27]. Naturally occurring phytochemicals are widely known for their anti-cancer effects on all of the multistep processes of carcinogenesis, including cancer initiation, promotion, and progression [5, 6, 8]. The study published at the end of the twentieth century evaluating the data from three case–control studies points to a potential association between plant foods (green and cruciferous vegetables, tomatoes, and beans) and whole-grain bread and reduced PCa risk [28]. A year later, legumes and specific vegetable categories were suggested to protect against PCa [29]. Moreover, Ambrosini et al. (2008) observed a decreased PCa risk with increasing intake of vegetable rich in vitamin C (bell peppers and broccoli) [30]. Furthermore, as discussed below, current evidence provides the clinical evaluations of anti-cancer effects of other plant-based food subtypes in PCa management.

Green tea phytochemicals

The main phytochemicals in green tea are known as green tea catechins (GTC), which include epigallocatechin-3-gallate (EGCG), epicatechin (EC), epigallocatechin (EGC), and epicatechin-3-gallate (ECG). Several authors reviewed GTC as effective in reducing PCa risk, especially in Asian populations characterised by increased intake of green tea [31, 32]. However, the overall clinical data neither confirm nor refute the protective effects of green tea against PCa. A case–control study in southeast China that was published in 2004 demonstrated declined risk of PCa with increasing frequency, duration, and quantity of green tea consumption [33]. Similarly, the potential effectiveness of GTC in PCa prevention was supported by McLarty et al. (2009) who demonstrated that the administration of Polyphenon E, a mixture of tea catechins, decreased serum levels of PSA, HGF, and VEGF with no elevation in liver enzymes in men with PCa [34]. Oxidative DNA damage plays an important...
role in carcinogenesis [35]. Moreover, prostate tissue is suggested to be more vulnerable to oxidative damage due to the fewer DNA repair enzymes, faster cell turnover, and chronic inflammation of prostate epithelial cells. Indeed, 8-hydroxy-2′-deoxyguanosine (8-OHdG) is the product of oxidative damage of the DNA base 2′-deoxyguanosine(dG) [35]. Therefore, 8-OHdG is considered a marker of oxidative stress and has been observed to be expressed more highly in PCa tissue when compared with benign prostate tissues [36]. However, decreased 8-OHdG is associated with human leukocytes in individuals consuming food rich in antioxidants [35]. Indeed, green tea resulted in altered PCa development and progression biomarkers — decreased NFκB in radical prostatectomy tissues, systemic antioxidant effect (reduced urinary 8OHdG), and a small but significant decrease in serum PSA levels [37]. Also, Nguyen et al. (2012) suggested that green tea chemo-preventive abilities in PCa may not be mediated by direct means or occurs without accumulation. However, the authors concluded the need for long-term interventions, repeated doses for more constant exposure, or evaluations in pre-cancerous models [38]. However, these results must be interpreted with caution due to the inconsistency of the results of other studies. For example, results of the placebo-controlled, randomised clinical trial (2015) evaluating the potential anti-cancer effectiveness of Polypehenol E demonstrated that EGCG accumulated in plasma and was well tolerated but did not reduce PCa risk in men with HGPIN and/or atypical small acinar proliferation (ASAP) [39]. Also, recent 3-week-long pre-prostatectomy intervention (2020) evaluating the combination of quercetin with green tea extract for 4 weeks revealed no significant increase in EGCG or EGC concentrations or decrease in GTP methylation in prostate tissues [40]. Moreover, fatty acid synthase (FAS) catalyses final step in fatty acid synthesis de novo. In tumour cells, the rate of fatty acid synthesis is greater. Also, FAS gene was found to be upregulated by hypoxia in tumour cells. Therefore, overexpressed FAS appears to play important role in PCa [41]. As FAS is hypothesised to be associated with chemo-preventive effects of fish oil and green tea, Zhang et al. (2016) evaluated their effects in PCa patients. However, the results demonstrated no effects of fish oil and green tea supplement (EGGC) administered during a short duration on FAS or Ki67 in PCa [41].

**Carotenoids**

The evidence suggests the PCa protective role of tomato or tomato phytochemicals such as lycopene, a non-provitamin A carotenoid [42, 43]. Beynon et al. (2019) demonstrated the efficacy of lycopene in lowering pyruvate levels. Indeed, decreased pyruvate is related to reduced PCa risk as supported by Mendelian randomisation suggesting the association between genetically predicted higher pyruvate levels and increased risk of PCa [44]. Moreover, study results published in 2008 indicated that lycopene may inhibit disease progression in patients with benign prostate hyperplasia [45]. Similarly, *Serenoa repens*, derived from the saw palmetto tree berries, selenium, and lycopene, may exert anti-inflammatory effects that could benefit the treatment of chronic prostatic inflammation in benign prostate hyperplasia and/or PIN/ASAP [46]. The evaluation of the effects of red or yellow tomato paste and purified lycopene resulted in increased circulating lycopene only after consuming red tomato paste and purified lycopene. At the same time, antioxidant status, PSA, and insulin-like growth factor-1 (IGF-1) did not modify by tomato paste consumption. However, upregulated IGFBP-3 and Bax/Bcl-2 ratio and decreased cyclin-D1, p53, and Nrf-2 after ex vivo cell incubation with sera from healthy men who consumed red tomato paste [47]. As recently demonstrated by Fraser et al. (2020), the consumption of canned and cooked tomatoes that contain more available lycopene may reduce the PCa risk. However, the inability to distinguish between PCa molecular subtypes limits the study results [48]. On the contrary, another study demonstrated the role of tomato sauce in the reduction of *TMPRSS2:ERG*-positive PCa [49]. On the contrary, the results of a small pilot, randomised-controlled trial demonstrated no effects of a tomato-enrich diet, lycopene, or green tea to affect serum levels of IGF-I, IGF-II, IGFBP-3, or IGFBP-2 [50]. Paradoxically, Gontero et al. (2015) observed three times higher incidence of PCa at re-biopsy and microRNAs associated with PCa progression in men with primary multifocal HGPIN and/or ASAP administered with high non-toxic doses of lycopene, green tea catechins, and selenium when compared with participants without supplementation. However, the evaluation of three compounds does not allow the precise analysis of individual substances [51]. However, Morgia et al. (2017) did not show the evidence of deleterious effects of selenium and lycopene in increasing PCa risk after 2 years of therapy, nor supported the protective role [52]. Similarly (2011), the associations between serum lycopene and PCa prevention have not been supported in nested case–control study in the Prostate Cancer Prevention Trial either [53]. Several other studies (2007, 2015) reflect no effects of tomato or lycopene on decreasing PCa risk [54, 55].

In addition to lycopene, the evidence on the association between other carotenoids and retinol and PCa risk is inconsistent [56]. Neuhouser et al. (2009) provided modest evidence of the association between increased PCa risk and high-dose β-carotene (30 mg/day) and retinyl palmitate (25,000 IU/day) administered for lung cancer prevention plus at least one other dietary supplement [57]. Moreover, Nash et al. (2015) described an increased PCa risk in men with higher serum retinol and α-carotene [56]. Also, a recent study by Chadid et al. (2022) concluded...
common circulating carotenoids and retinol as not useful in preventing PCa through the modulation of intraprostatic inflammation [58]. However, serum levels of α-carotene, retinyl esters and lycopene have been demonstrated to be associated with PSA biomarkers in US men and thus could be useful in early PCa detection [59].

**Isoflavones of soy**

Soy is a rich source of isoflavones while the main soy isoflavone — genistein — is associated with potent anti-cancer efficacy [60–62]. It is known that prostate tissue can concentrate genistein and other phytochemicals [63]. In 2012, Lazarevic et al. supported the chemo-preventive role of genistein in PCa demonstrated through the modulation of biomarkers related to prediction and progression of the disease — including reduced KLK4 in tumour cells and a non-significant decrease in androgen and cell cycle–related biomarkers [62]. Importantly, soy isoflavones (administered to PCa patients in a neo-adjuvant setting for 2 weeks before prostatectomy) resulted in gene expression changes (decreased prostate COX-2 mRNA and increased p21 mRNA) with a significant correlation between COX-2 suppression and p21 stimulation in serum and the level of serum isoflavone. These results, supported by in vitro studies, highlight the role of soy isoflavones in PCa chemo-prevention or treatment through modulation of COX-2 and prostaglandin pathway [64]. Moreover, the role of isoflavones in reducing PCa risk was demonstrated by decreased or unchanged PSA and free testosterone in early stage PCa patients in the isoflavone group when compared with placebo [65].

**Broccoli isothiocyanates**

Broccoli is a rich source of biologically active isothiocyanates, including sulforaphane and iberin. Importantly, broccoli consumption interacts with glutathione S-transferase mu 1 (GSTM1) genotype modulating signalling pathways associated with inflammation and carcinogenesis in the prostate; the authors also observed changes in TGFβ receptor pathway, insulin signalling, and EGF receptor signalling in men on the broccoli diet. These results provide a mechanistic basis for the effects of broccoli in decreasing PCa risk [66]. Furthermore, a recent study (2020) evaluating chemo-preventive effects of broccoli sprout extract (BSE) demonstrated 40 differentially expressed genes correlating with BSE treatment, including *AMACR* and *ARLNC1*, two genes implicated in PCa development. However, the authors observed no effects on other evaluated markers, such as HDAC activity [67].

**Milk thistle (silibinin)**

Milk thistle (*Silybum marianum*) is a therapeutic herb with a 2000 history of use. Milk thistle contains a mixture of flavonolignans known as silymarin while silibinin (also known as silybin) represents its main component [68]. A flavonoid silibinin exerts anti-cancer efficacy including potent inhibitory effects on apoptosis, proliferation, angiogenesis or metastasis associated with prostate carcinogenesis [69]. Recent study also demonstrated the effects of silibinin in decreasing aggressive phenotype in an in vitro model of obesity and PCa. Indeed, silibinin mitigated increased cell growth and invasive capacity of PCa cells exposed to sera of the obese and overweight males. These results indicate the beneficial PCa-protective effects of silibinin in obese or overweight males [70]. Therefore, based on the potent results of preclinical anti-cancer evaluations, silibinin advanced into clinical trials [71]. The evidence of initial clinical evaluations of the effects of silibinin in advanced PCa patients demonstrated oral silybin-phytosome, a commercially available formulation that contains silibinin, in a dose of 13 g daily delivered in three divided doses to be safe and well tolerated [72]. Moreover, a phase II study revealed that the same dose of oral silybin-phytosome achieved high blood concentrations transiently but low levels in prostate tissue of patients with localised PCa [73].

Table 1 provides a detailed overview of the above-discussed effects of phytosubstances/plant-based interventions in primary PCa care as well as the summary of potential adverse events associated with the intervention and major study limitations that need to be carefully evaluated when interpreting the results and proposing a possible implementation into clinical practice.

Based on the above results, despite the original assumptions about the effectiveness of phytochemicals in PCa prevention, we observe very inconsistent results in the accumulation of phytochemicals or their metabolites in prostate tissue and effects on PCa prevention. However, primary care is at the forefront of a paradigm change from reactive to the cost-effective predictive approach in PCa management. The crucial importance of a personalised approach in PCa management can be illustrated with an example of soy isoflavones in PCa risk assessment provided in a study by Ahn-Jarvis et al. (2015) who described that a characterisation of isoflavonoid metabolic phenotypes is essential to decipher heterogeneity in biological responses among individuals in clinical studies. Therefore, such approaches provide a framework to study isoflavone (phytochemical)-metabolizing phenotypes as a strategy for identification of individuals that might benefit or show resistance to cancer preventive strategies using soy (dietary intervention) [74].
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (n = number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|-----------------------------------------------|--------------|------|--------------------------------|----------------|-------------------------------|------------------------|-----|
| Plant foods (green vegetable, cruciferous vegetable, tomatoes, beans) and whole-grain breads | Data from three case–control studies | 1999 | Incident PCa cases (n = 617) and controls (n = 636) | Reduced PCa risk | Not available | Multiple comparisons — some findings could occur as significant by chance | [28] |
| Fruit (cryptoxanthin) | | | | | | | |
| Legumes (not limited to soy) and certain vegetables | Multicentre, multiethnic, case–control study | 2000 | Confirmed PCa cases (n = 1619) and controls (n = 1618) | Legumes and certain categories of vegetables may protect against PCa | Not available | Not available | [29] |
| Fruit, vegetable, vitamin A | Follow-up on cohorts of former workers and residents of Wittenoom Gorge since 1975, to document the epidemiology of asbestos-related diseases | 2008 | PCa cases (n = 1985) | Decreased PCa risk with increasing intake of vegetable rich in vitamin C (bell peppers and broccoli); fruit, other vegetable, vitamin A not observed a strong factor in PCa development | Not available | Analysed 'total fruit and vegetable' intakes analysed may not be directly comparable to typical definitions of total fruit and vegetable intakes; Repeated assessments of dietary intake would improve the study; Required careful interpretation (some results may arise by chance) | [30] |
| Green tea | Case–control study (epidemiological study) | 2004 | Adenocarcinoma of prostate cases (n = 130) and controls (n = 274) | Declined PCa risk with increasing frequency, duration, and quantity of green tea vs controls | Not available | Not available | [33] |
| Polyphenon E (800 mg of EGCG and lesser amounts of other GTC, totally 1.3 g of tea polyphenols/day) administered during the interval between prostate biopsy and radical prostatectomy | Open-label, single-arm two-stage phase II clinical trial | 2009 | Men with positive prostate biopsies (n = 26) | Decreased PSA, VEGF, HGF with no elevation in liver enzymes | No adverse effects (only 1 patient reported mild nausea) | Not available | [34] |
| Green tea (6 cups/day) or water (control) prior to radical prostatectomy | Randomised exploratory, open label, phase II trial | 2015 | Men diagnosed with PCa (n = 113) prior to radical prostatectomy randomised into brewed green tea, black tea, or water control | Decreased NFκB in radical prostatectomy tissues, reduced urinary 8OHdG, decrease in serum PSA vs control | No serious adverse event reported | Not blinded study | [37] |
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (n = number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|---------------------------------------------|-------------|------|---------------------------------|----------------|-------------------------------|------------------------|-----|
| Polyphenon E (800 mg of EGCG/day) or placebo for 3–6 weeks until the day before surgery | Randomised, double-blind, placebo-controlled trial | 2012 | Men with PCa scheduled to undergo radical prostatectomy (n = 50) | Low bioavailability and/or bioaccumulation of green tea polyphenols in prostate tissue; Insignificant changes in PSA, serum insulin-like growth factor, oxidative DNA damage in blood leukocytes | Well tolerated, minimal adverse events (nausea, diarrhoea, headache, 1 patient had a mild ALT elevation) | Short duration of intervention | [38] |
| Polyphenon E (400 mg of EGCG/day) for 1 year | Placebo-controlled, randomised clinical trial | 2015 | Men with HGPIN and/or ASAP (n = 97) | EGCG accumulated in plasma; no effects on PCa prevention | Well tolerated | Low completion rate | [39] |
| Quercetin and green tea (1 g of green tea extract with 800 mg of quercetin or placebo (green tea + placebo) for 4 weeks | Prospective randomised, open label, parallel two arm intervention study | 2020 | Men scheduled for prostatectomy (n = 31) | No significant increase in EGCG or EGC or decrease in GTP methylation in prostate tissues | No serious adverse effects | Not reported participant food intake (foods containing quercetin or green tea) | [40] |
| EGCG (600 mg/day) and/or fish oil or placebo | Double-blinded, randomised controlled trial | 2016 | Men scheduled for repeat prostate biopsy following an initial negative prostate biopsy (n = 89) | No significant changes in FAS or Ki67 | No grade ≥ 3 adverse events | Limited sample size, hospital-based design among men scheduled for repeat prostate biopsy may restrict the generalizability of results | [41] |
| Lycopene and green tea (6 months) | ProDiet randomised controlled trial | 2019 | Men with raised PSA levels but PC-free (n = 128) | Lycopene lowered pyruvate levels → suggested effects on reduced PCa risk | Not available | ProDiet RCT originally designed to test the feasibility of a dietary intervention (not to detect an effect of the intervention on metabolite levels), small sample size, | [44] |
| Lycopene (15 mg/day) or placebo for 6 months | Randomised clinical pilot study | 2008 | Patients with benign prostate hyperplasia (n = 40) | Inhibited disease progression vs placebo | Well tolerated, no adverse events | Not available | [45] |
| Profluss® (Serenoa repens + selenium + lycopene) | | 2013 | Patients with benign prostate hyperplasia and/or PIN/ASAP (n = 168) | Anti-inflammatory effects | Not available | Lack of placebo controlling | [46] |
| Phytosubstance/plant-based supplement (dosage) | Study design                        | Year | Study participants (n = number) | Effects/results                                                                 | Adverse events of phytosubstance | Major study limitations                                                                 |
|---------------------------------------------|-------------------------------------|------|--------------------------------|---------------------------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------|
| Red/yellow tomato paste, purified lycopene (yellow and red tomato paste 200 g/d, which provided separated by 2 weeks of washout, in a parallel design first group purified lycopene 16 mg/d for 1 week and second group placebo) | Randomised, single-blinded crossover study for tomato paste studies and a parallel study for lycopene studies, ex vivo study (incubation of LNCaP cells with sera from healthy volunteers) | 2010 | Healthy men (n = 30) | Upregulated IGFBP-3 and Bax/Bcl-2 ratio and decreased cyclin-D1, p53, and Nrf-2 after cell incubation with sera from health men who consumed red tomato paste | No side effects reported | Not available [47] |
| Tomato consumption (canned and cooked) more than 4 times/week | Prospective study (food frequency questionnaire) | 2020 | Incident cases of PCa (n = 1 2020 | Canned and cooked tomatoes may reduce PCa risk (more available lycopene) | Not available | Dietary habits information only from the enrolment questionnaire (repeated measures not provided), not distinguishing between molecular PCa subtypes, relatively low number of aggressive PCa limits power to evaluate risk with good precision [48] |
| Tomato sauce | Prospective cohort of men from the Health Professionals Follow-Up Study (food frequency questionnaire) | 2016 | n = 46 719 | Tomato sauce may play a role in TMPRSS2:ERG-positive PCa reduction | Not available | Possible misclassification of diet, restricting cases to men treated with radical prostatectomy rendered the entire population of men who did not develop PCa an inappropriate comparison group [49] |
| Tomato-enrich diet, lycopene (15 mg capsules/day), or green tea (600 mg/day) for 6 months | Pilot, randomised-controlled trial | 2019 | Men with PSA between 2.0 and 2.95 ng/ml or negative biopsies (n = 266) | No effects on serum levels of IGF-I, IGF-II, IGFBP-3, or IGFBP-2 | Not available | Trial not set up to investigate IGFs as a primary outcome and designed as a feasibility pilot study [50] |
| Lycopene (35 mg/day), green tea catechins (600 mg/day), and selenium (55 μg/day) or placebo for 6 months | Double-blind Phase I–II randomised controlled trial | 2015 | Men with primary multifocal HGPin and/or ASAP (n = 60) | Higher incidence of PCa at re-biopsy and microRNAs associated with PCa progression vs placebo | Well tolerated | Small number of patients, simultaneous use of three compounds (not allowed precise evaluation of each substance, absence of PCa family history), not performed molecular analysis [51] |
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants \((n = \text{number})\) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|-----------------------------------------------|--------------|------|-----------------------------------------------|-----------------|-----------------------------|----------------------|-----|
| Selenium and lycopene or control for 1 year  | Post-hoc analysis of the Procomb trial | 2017 | Patients who underwent prostate biopsy when ≥ 4 ng/ml and/or PCa suspicion \((n = 209)\) | No detrimental effects on increasing PCa risk; no protective effects | Not available | Lack of measurement of serum levels of selenium or other micronutrients, low rate PCa diagnosed | [52] |
| Serum lycopene                                | Nested case–control study in the Prostate Cancer Prevention Trial, a placebo-controlled trial | 2011 | PCA cases \((n = 1683)\) and controls \((n = 1751)\) | No evidence on association between serum lycopene and PCa | Not available | Not available | [53] |
| Lycopene-rich tomato extract (30 mg/day) for 6 months | Phase II randomised, double-blind, placebo-controlled trial | 2015 | Men with HGPIN \((n = 58)\) | Large differences in serum lycopene but no treatment effects | Not available | Small size and restricted statistical power, presence of HGPIN as an endpoint | [54] |
| Lycopene-rich tomato supplement (30 mg of lycopene/day) | Phase II trial | 2007 | Androgen-independent PCa patients \((n = 46)\) | Not effective in androgen-independent PCa | Less severe — appeared more plausibly related to lycopene (diarrhoea, nausea, abdominal distension, flatulence, vomiting, anorexia, dyspepsia) | Stable PSA in several patients (unclear whether due to lycopene), PSA decline as primary endpoint | [55] |
| Retinol and α-carotene (serum)                | Nested case–control study – data from PCPT, a multicentre, randomised, placebo-controlled SWOG-coordinated trial | 2015 | \(n = 18,880\) | Increased PCa risk in men with higher level of serum retinol and α-carotene | Not available | Small number of high grade cancers, limited differences by race or ethnicity | [56] |
| β-carotene (30 mg/day) and retinyl palmitate (25,000 IU/day) for lung cancer prevention | Randomised controlled trial | 2009 | CARET participants | Increased PCa risk associated with high-dose β-carotene and retinyl palmitate plus at least one other dietary supplement | Not available | Only evidence whether participants used or not supplements — inability to investigate which particular place person at a risk, underpowered to examine PCa deaths | [57] |
| Common circulating carotenoids and retinol    | Men from the Prostate Cancer Prevention Trial placebo arm | 2022 | Men with negative end-of-study biopsy \((n = 235)\) | Not useful in PCa prevention through the modulation of intraprostatic inflammation | Not available | Inability to assess whether circulating carotenoids reflect prostate tissue levels (circulating levels and tissue inflammation not measured concurrently) | [58] |
| Genistein (30 mg/day) or placebo for 3–6 weeks | Phase 2 placebo-controlled, double-blind clinical trial | 2012 | Early PCa patients before prostatectomy \((n = 47)\) | Reduced KLK4 in tumour cells and a non-significant decrease in androgen and cell cycle-related biomarkers vs placebo | Not available | Small number of cases, short time of intervention | [62] |
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (n = number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|---------------------------------------------|--------------|------|---------------------------------|----------------|-------------------------------|------------------------|-----|
| Soy isoflavones (27.2 mg isoflavone aglycones per tablet, 3 tablets/day) or placebo for 2 weeks | Pilot randomised double blind clinical study | 2009 | PCa patients (n = 25) | Decreased prostate COX-2 mRNA and increased p21 mRNA | Not available | Not available | [64] |
| Soy isoflavones (soy beverage protein containing 60 mg of genistein) or placebo for 12 weeks | Prospective randomised, placebo-controlled clinical trial | 2004 | PCa patients (n = 76) | Decreased or unchanged PSA and free testosterone vs placebo | Not available | Not available | [65] |
| Broccoli (400 g/week) or peas (400 g/week) for 6 months | Parallel, dietary intervention study | 2008 | Male volunteers with previous diagnosis of HGPIN (n = 22) | Interaction with GSTM1 genotype modulating signalling pathways associated with inflammation and carcinogenesis, changes in TGFβ, insulin signalling, and EGF (decreasing PCa risk) | Not available | Men within both arms exerted significant changes in androgen receptor pathway (but this can be associated with aging independently of diet), informative stratification of global gene expression profiles, other dietary phytochemicals could interact with plasma signalling peptides | [66] |
| BSE (200 µmol/day) or a placebo for 4–8 weeks | Double-blind, randomised controlled trial | 2020 | Men scheduled for prostate biopsy (n = 98) | Differentially expressed genes correlating with BSE treatment — AMACR and ARLN1 (implicated in PCa development) | Bloating, headache, no grade ≥ 3 adverse events | Short treatment duration | [67] |
| Milk thistle — silybin-phytosome (2.5–20 g daily in 3 divided doses) | Phase I trial | 2007 | PCa patients (n = 13) | 13 g of oral silybin-phytosome is well tolerated and recommended to phase II dose | Hyperbilirubinemia (grade 1—2 bilirubin elevations in 9 of 13 patients), ALT elevation (grade 3 toxicity) in one patient; no grade 4 toxicity | Not available | [72] |
| Milk thistle – silybin-phytosome (13 g/daily in 3 divided doses) | Clinical trial | 2010 | PCa patients planning for prostatectomy (n = 12) | High-dose oral silybin-phytosome achieves high blood concentrations transiently, but low levels in prostate tissue | Mild (diarrhoea, hyperbilirubinemia). One patient developed grade 4 post-operative thromboembolic event | Short duration | [73] |

**Abbreviations:** ALT, alanine aminotransferase; ASAP, atypical small acinar proliferation; BSE, broccoli sprout extract; CARET, The Carotene and Retinol Efficacy Trial; COX-2, cyclooxygenase-2; DNA, deoxyribonucleic acid; EGC, epigallocatechin; EGCG, epigallocatechin-3-gallate; EGF, epidermal growth factor; FAS, fatty acid synthase; GSTM, glutathione S-transferase mu 1; GTC, green tea catechins; GTP, green tea polyphenols; HGF, hepatocyte growth factor; HGPIN, high-grade prostatic intraepithelial neoplasia; IGF, insulin-like growth factor; IGF-BP, insulin-like growth factor binding protein; KLK4, kallikrein-related peptide 4; mRNA, messenger RNA; NF-kB, nuclear factor-kB; PCa, prostate cancer; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; TGFβ, transforming growth factor beta; VEGF, vascular endothelial growth factor; 8-OHdG, 8-Hydroxy-2'-deoxyguanosine; g, gram; mg, milligram; µg, microgram
Phytochemicals in PCa management: secondary and tertiary care

Numerous clinical trials evaluate the potential effects of phytochemicals in already diagnosed PCa patients or patients with recurrent or metastatic disease aimed at the evaluation of their impact on the disease progression [35, 75–79]. Indeed, the effective PCa secondary care highlights the need for the differentiation between non-metastatic and aggressive metastatic disease that requires personalised treatment algorithms. Tertiary PCa care mainly focuses on the palliative care [3]. However, current clinical evidence on the effects of phytochemical in palliative PCa care is lacking. The search on medical database provided only the evidence of phytochemicals affecting the adverse events associated with conventional PCa treatment modalities [22–26] — therefore potentially improving the quality of life during therapy.

A. The anti-cancer effects of phytochemicals on PCa progression

The potential effects of plant-based interventions or phytochemicals in PCa patients have been clinically evaluated for several decades. At the beginning of the twenty-first century, the small study by Saxe et al. (2001) provided evidence on plant-based diet within Mindfulness-Based Stress Reduction (MBSR) intervention decreasing PSA increase and potential in slowing the progression in patients with recurrent PCa [80]. Similar data were concluded in 2006 supporting the role of plant-based diet and stress reduction in attenuation of PCa progression [81]. As provided below, available data provide evidence of clinical trials evaluating the potential effects of other phytosubstances.

Carotenoids

Tomato products and lycopene revealed controversial effects in PCa prevention; however, studies evaluating their efficacy in PCa treatment or prevention of the disease progression demonstrated more concise effects. Earlier published study (2001) described interesting results indicating a role of tomato sauce constituents (especially lycopene) in the short-term treatment of PCa demonstrated by reduced leukocyte and prostate tissue oxidative DNA damage and decreased PSA levels in men with the high-lycopene tomato sauce intervention compared to randomly selected patients [35]. Also, Ansari and Gupta (2003) compared the effects of lycopene plus orchidectomy with orchidectomy alone in metastatic PCa. Indeed, orchidectomy plus lycopene resulted in more reliable and consistent reduction in serum PSA, shrinkage of primary tumour and diminution of secondary tumours, improving survival and better relief from bone pain and symptoms of lower urinary tract when compared with orchidectomy alone [75]. Furthermore, dietary intervention with tomato-products alone or combined with selenium and 3-fatty acids for 3 weeks lowered PSA in non-metastatic PCa patients. The authors suggested that the effects may depend on the aggressiveness of the disease and blood levels of lycopene, omega-3 fatty acids, and selenium. Thus, the control of blood concentrations after dietary interventions seems to be important due to the detection of largest PSA reduction in patients with highest lycopene, selenium, and C20:5 n-3 (eicosapentaenoic acid) increase [76]. Moreover, lycopene and soy isoflavones demonstrated activity in PCa patients with PSA relapse disease demonstrated by PSA stabilisation with the conclusion supporting the potential delay in progression of both hormone-refractory and hormone-sensitive PCa. Besides, the authors suggested no additive effects of the two compounds [82]. On the contrary, lycopene exerted no clinical benefits in PCa patients in advanced stages but two-thirds of patients experienced improved or unchanged situation independently of clinical course or PSA [83].

In addition to tomato products, increased plasma level of β–cryptoxanthin, trans–β–carotene, cis–lutein/zeaxanthin, all–trans–lycopene, and α–tocopherol resulted in lower PSA levels in men with biochemically defined PCa recurrence. Also, higher antioxidant score was observed to be related with lower PSA levels. The results highlight the role of phytochemicals in slowing the PCa progression demonstrated through PSA as a marker of disease progression in men with recurrent PCa [84].

Flavonoids of soy and red clover

Isoflavone supplementation revealed potential benefits in men with biochemically recurrent PCa after radiation therapy or radical prostatectomy demonstrated through a decline in PSA slope [85]. Moreover, genistein exerted effects on genome-wide DNA methylation and gene expression, specifically differentially methylated sites and expressed genes involved in developmental processes, stem cell markers, proliferation, and transcriptional regulation (NOTCH3, JAG1, ADCY4, and NEU1) as well as reduced MYC activity and increased PTEN activity in genistein group; thus affecting molecular pathways of prostate tumorigenesis [86]. Furthermore, genistein in a dose that can be obtained from a diet rich in soy reduced serum PSA level in patients with localised PCa when compared with placebo [77]. Also, soy-based dietary supplementation (soy, isoflavones, lycopene, silymarin, antioxidants) delayed the progression of PSA when compared with placebo in men with PCa history and rising PSA after radical prostatectomy or radiotherapy [87]. Similarly, soy beverage intervention (containing 50–100 mg of isoflavones daily) for 6 months was associated with a declining
trend or more than two times prolongation of PSA doubling time in 41% of patients with rising PSA after radical radiation [88]. On the contrary, short-term intervention with soy isoflavone resulted in no significant changes in selected parameters (PSA, testosterone, cholesterol) in patients with localised PCa [78]. Moreover, high-dose aglycone-rich soy extract elevated serum genistein and daidzein levels but no PSA level changes in men with low-volume PCa [89]. Jared et al. (2002) described that dietary red clover-derived isoflavones might be effective in halting PCa progression by inducing apoptosis in low to moderate-grade tumours and also in potential contribution to lowering the incidence in Asian men [90]. In addition to the above-mentioned entrance of milk thistle phytochemicals into PCa research [72, 73], another study revealed potent efficacy of silymarin (silibinin) against PCa progression. Silymarin combined with selenium administered in patients after radical prostatectomy, reduced low-density lipoprotein and total cholesterol, two markers related to PCa progression [91].

**Pomegranate polyphenols**

Pomegranate is a rich source of polyphenolic compounds, including tannins, anthocyanins, and flavonoids [92]. Pomegranate extract exerted an effect on ≥ 6-month increases in PSA doubling time (PSADT) without adverse effects in men with primary PCa. Indeed, almost one-half of patients who underwent primary therapy for localised PCa is associated with rising PSA levels, indicating PCa recurrence. Gleason scores, time from local treatment to biochemical recurrence, and PSADT functions as a predictor of metastasis-free survival and overall survival. PSADT can be suggested as a predictive factor of PCa progression [93]. However, PSADT is still a controversial primary endpoint in clinical trials [79]. On the contrary, the administration of pomegranate extract before radical prostatectomy revealed no significant changes in the oxidative stress biomarker — 8-OHdG. However, the hypothesis of the protective effect of pomegranate extract against oxidative damage was supported by the capability of its metabolite — Urolithin A of absorption and accumulation in prostate tissues, while high Urolithin A levels correlated with lower 8OHand levels [94]. Nevertheless, the results from a recent study by Jarra et al. (2021) concluded that pomegranate compounds could affect biomarkers of oxidative stress demonstrated by reduced 8OHdG and androgen receptor expression in prostate tumour associated with pomegranate fruit extract in men with organ-confined, favourable-risk PCa [95]. In comparison with pomegranate impact discussed above in men with rising PSA following initial PCa therapy [93], daily pomegranate demonstrated no effect on PSA levels in recurrent and advanced PCa patients compared with placebo [96]. In addition, Muscadine-Plus, a preparation of pulverised muscadine grape skin, did not prolong PSADT in biochemically recurrent PCa patients [79].

The assumption of potent anticancer effectiveness of individual polyphenol-rich foods was extended by Thomas et al. (2014) who evaluated the effects of an oral capsule with a combination of pomegranate, green tea, broccoli, or turmeric in men with localised PCa either with primary active surveillance (AS) or with watchful waiting (WW) after previous interventions. Finally, the results revealed the beneficial but short-term effect of the capsule containing pomegranate, green tea, broccoli, and turmeric on PSA in men with AS or WW [97].

**Broccoli phytochemicals — sulforaphane**

Glucoraphanin-rich broccoli soup consumption for a year affected gene expression in men on active surveillance, while these changes were consistent with a reduced risk of PCa progression [98]. Also, sulforaphane demonstrated promising results in decreasing PSA progression in PCa patients and biochemical recurrence after definite radical prostatectomy [99]. However, Alumkal et al. (2015) described sulforaphane-rich extracts not being associated with ≥ 50% PSA decline in most recurrent PCa patients conducted in the study. Nevertheless, the authors recommend performing studies evaluating higher doses of the substance [100].

**Green tea**

Patients with androgen-independent prostate carcinoma are associated with limits in treatment options and limited life expectancy. Therefore, it is essential to introduce novel treatment strategies for these patients. However, evaluated green tea exerted limited anticancer capacity demonstrated by a decline in PSA among patients with androgen-independent prostate carcinoma that were asymptomatic and manifested progressive PSA elevation with hormone therapy [101].

**Flaxseed and curcumin**

Flaxseed is a rich source of the plant lignans secoisolariciresinol and matairesinol that are, after ingestion, converted by aerobic intestinal microflora into the enterolignans, enterolactone, and enterodiol. These are suggested to possess potent anticancer effects. Indeed, flaxseed-derived enterolactone is inversely associated with the proliferation of tumour cells in men with localised PCa and possible reduction in angiogenesis [102]. In addition, oral curcumin intake suppressed PSA elevation but had no effects on PCa patients’ overall off-treatment duration of intermittent androgen deprivation (IAD) [103].

Table 2 shows a detailed overview of the above-discussed results of clinical trials evaluating the potential effectiveness of phytosubstances/plant-based interventions in secondary PCa care — especially in individuals with localised,
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (n = number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|---------------------------------------------|--------------|------|---------------------------------|-----------------|-------------------------------|------------------------|-----|
| Plant-based diet within MBSR intervention for 4 months | Non-randomised clinical trial | 2001 | PC patients with biochemical recurrence after prostatectomy (n = 10) | ↓ rate of PSA increase | Any adverse events described | Small sample size, lack of randomisation, a short period of intervention | [80] |
| Plant-based diet and stress reduction for 6 months | Non-randomised, whole-food intervention arm of an ongoing placebo-controlled clinical trial for the evaluation of lycopene as an in vivo antioxidant | 2006 | Recurrent PCa patients (n = 14) | ↓ rate of PSA increase | Not available | Small sample size, a short period of intervention, lack of randomised control group | [81] |
| High-lycopene tomato sauce-based pasta dishes (30 mg of lycopene/day) for 3 weeks | Non-randomised | 2001 | PC patients preceding radical prostatectomy (n=32) | ↓ leukocyte and prostate tissue oxidative DNA damage, ↓ PSA levels vs randomly selected patients | Minor gastrointestinal problems (3 of 32 patients) | Small sample size, more robust analysis required | [35] |
| Lycopene plus orchidectomy (starting at the day of orchidectomy, 2 mg/ twice a day) for 6 months | Clinical trial | 2003 | Patients with metastatic PCa (n = 54) | More reliable and consistent reduction in serum PSA, shrinkage of the primary tumour and diminution of secondary tumours, improved survival and better relief from bone pain and symptoms of lower urinary tract vs orchidectomy alone | No adverse effects | Appropriate long-term randomised studies are required | [75] |
| Lycopene-rich tomato intervention (tomato products containing 30 mg lycopene per day, or tomato products plus selenium, omega-3 fatty acids, soy isoflavones, grape/pomegranate juice, and green/black tea, or control diet) for 3 weeks | 3-arm randomised controlled trial | 2017 | Non-metastatic PCa patients (n = 79) prior to curative treatment | Lowered PSA (tomato products alone or in combination with selenium and n-3 fatty acids) | No side effects (only 1 patient discontinued the fish oil supplement intake due to regurgitation) | Products available in Norway — might not reflect the content of lycopene in products of other countries | [76] |
| Lycopene and soy isoflavones, tomato extract capsule (15 mg of lycopene alone) or together with a capsule (40 mg of soy isoflavone mixture) twice/day max for 6 months | Phase II clinical trial | 2007 | PC patients with 3 successive rising PSA levels or a minimum PSA of 10 ng/ml at 2 successive evaluations before starting therapy (n = 71) | Stabilisation of PSA levels | Not available | Small sample size, lack of stratification for prognostic factors, lack of a placebo arm | [82] |
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (n = number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|-----------------------------------------------|--------------|------|---------------------------------|-----------------|-------------------------------|------------------------|-----|
| Lycopene (15 mg/day) for 6 months             | Prospective, open phase II pilot study | 2009 | Patients with progressive hormone refractory PCa (n = 18) | No clinical benefits | Well tolerated | Not available | [83] |
| Diet and physical activity (plasma carotenoids and tocopherols) for 6 months | Intervention trial | 2015 | Recurrent PCa patients (n = 39) | Plasma level of α–tocopherol, β–cryptoxanthin, trans-β–carotene, cis-lutein/zeaxanthin, and all-trans-lycopene → lower PSA | Not available | Small sample size, short duration, and the lack of plasma carotenoid and tocopherol data at 6 months (prohibited evaluation of temporal associations) | [84] |
| Isoflavone supplementation (soy milk containing 47 mg of isoflavonoid per 8 oz serving three times/day) for 12 months | Open-labelled, Phase II, non-randomised trial | 2008 | Patients with rising PSA after prior local therapy (n = 20) | A decline in slope of PSA | Minimal (1 patient — diarrhoea) | A small study that was terminated early due to poor accrual, no control group, and therapy was neither randomised nor blinded, with serum PSA as the primary endpoint | [85] |
| Genistein (30 mg/day) or placebo for 3–6 weeks before prostatectomy | Randomised, placebo-controlled, double-blind clinical trial | 2017 | PCa patients (n = 20) | Differentially methylated sites and expressed genes (between genistein and placebo group) involved in developmental processes, stem cell markers, proliferation, and transcriptional regulation (NOTCH3, JAG1, ADCY4, and NEU1). Reduced MYC activity and increased PTEN activity in genistein group | Not available | Small number of patient samples | [86] |
| Genistein (dose that can be obtained from a diet rich in soy) or placebo for 3–6 weeks before prostatectomy | Placebo-controlled, block-randomised double-blind phase 2 study | 2011 | Patients with localised PCa before radical prostatectomy (n = 54) | Decreased serum PSA level, no effects on hormones in genistein group vs placebo | No adverse effects of clinical significance, only mild (in genistein arm 5 events — 3 gastrointestinal, 1 cardiovascular, and 1 general) | A small number of patients | [77] |
| Phytosubstance/plant-based supplement (dosage)                                                                 | Study design                        | Year | Study participants (n = number)                                                                 | Effects/results                                                                 | Adverse events of phytosubstance                                                                 | Major study limitations                                                                 | Ref |
|-----------------------------------------------------------------------------------------------------------------|-------------------------------------|------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----|
| Soy-based dietary supplement (soy, isoflavones, lycopene, silymarin, antioxidants) for 10 weeks, 4 weeks wash-out period, and 10 weeks | Randomised, double-blind, placebo-controlled crossover study | 2005 | Patients with PCa history and rising PSA after radical prostatectomy (n = 34) or radiotherapy (n = 15) | Delayed PSA progression vs placebo                                                   | Few adverse events that occurred were not related to the use of the dietary supplement     | A limited number of patients, more extensive studies, better standardisation, and characterisation of the effects of each compound on PCa biology are required for recommendations for the general public | [87]|
| Soy beverage (500 ml/day containing app. 50–100 mg of isoflavones) for 6 months                                 | Phase II trial                      | 2010 | PC with rising PSA after radical radiation (n = 34)                                             | Declining trend or more than 2 times prolongation of PSA doubling time in 41% of patients | Well tolerated                                                                            | Not measuring the intake of other phytochemicals that could potentially affect PSA, the use of PSADT as a surrogate endpoint | [88]|
| Soy isoflavone capsules (82 mg/day of total isoflavones) or placebo for 4 weeks before prostatectomy            | Double-blinded, randomised, placebo-controlled trial | 2013 | Localised PCa patients (n = 86)                                                                | No changes in serum total testosterone, free testosterone, total oestrogen, oestradiol, PSA, and total cholesterol | Safe, only mild adverse effects (gastrointestinal and general)                              | Lack of stratification of results based on Gleason score, pathologic stage, or PSA, a small number of tissue samples analysed | [78]|
| High-dose aglycone-rich soy extract — treatment group (supplement containing 450 mg genistein, 300 mg daidzein, and other isoflavones/day) for 6 months or placebo | Double-blind, placebo-controlled, randomised trial | 2010 | Men with low-volume PCa (n = 53)                                                               | Elevated serum genistein and daidzein levels; no changes in PSA level                | Well tolerated (only loose stools are the most common complaint from a small number of men) | A small number of patients                                                                 | [89]|
| Red clover-derived isoflavones (160 mg of isoflavones daily consisting of 4 tablets/day containing 40 mg of standardised red clover-derived isoflavones) for 20 days (median) | Non-randomised, non-blind trial with historically matched controls from archival tissue | 2002 | Treated and untreated control PCa specimens (n = 36)                                           | Induced apoptosis (higher apoptosis in radical prostatectomy specimens from treated patients vs control) | No adverse effects reported                                                                 | Observational study on a small cohort of Australian men                                           | [90]|
| Silymarin (570 mg) and selenium (240 µg) or placebo for 6 months                                           | Placebo-controlled double-blind clinical trial | 2010 | PC patients after radical prostatectomy (n = 37)                                                | Reduced low-density lipoprotein and total cholesterol                                | No adverse effects reported                                                                 | Not available                                                                                       | [91]|
| Pomegranate extract (1 or 3 g) for up to 18 months                                                           | Randomised, multi-centre, double-blind phase II, dose-exploring trial | 2013 | Men with rising PSA following initial PCa therapy (n = 104)                                     | Lengthened PSADT independently of dose and without adverse effects                  | No adverse effects                                                                        | Lack of placebo arm (placebo-controlled trials needed, e.g. NCT00732043 or NCT00719030)               | [93]|
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (n = number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|-----------------------------------------------|--------------|------|---------------------------------|-----------------|---------------------------------|------------------------|-----|
| Pomegranate extract (2 tablets/day — each capsule contains 1000 mg of pomegranate extract powder that contains up to 600 mg of polyphenol from extract) or placebo | Phase II, randomised, double-blind trial | 2013 | PC patients prior to radical prostatectomy (n = 70) | No significant changes in 8OHdG levels; however, Urolithin A capable of absorption and accumulation in prostate tissues - high Urolithin A level correlated with lower 8OHdG levels | No serious adverse effects, only grade I (mostly nausea, diarrhoea) | The primary end-point is an intermediate surrogate biomarker end-point (unclear clinical relevance of 8OHdG), the number of men included was modest (limiting statistical power), the duration of pomegranate extract therapy was short and the dose was modest) | [94] |
| Pomegranate fruit extract (1000 mg capsule/day) or placebo for 52 weeks | Randomised, placebo-controlled trial | 2021 | Active surveillance patients—men with organ-confined, favourable-risk PCa (n = 30) | Reduced 8OHdG and androgen receptor | Side effects felt to be unrelated to the administration of the study drug | No preliminary data on the calculation of the sample size for each treatment arm upon which to estimate treatment effect size, period of administration (1 year) is relatively short to generate large effects, 35.7% and 40% of patients in the treatment arms did not display carcinoma at the end of study biopsies | [95] |
| Pomegranate juice (500 ml/day of juice or placebo for 4 weeks), then all patients pomegranate juice (250 ml/day) for 4 weeks | Phase IIb, double-blinded, randomised placebo-controlled trial | 2013 | Recurrent and advanced PCa patients (n = 97) | No effect on PSA | Well tolerated (bowel disturbances most frequently reported) | Certain heterogeneity of the included patient cohort | [96] |
| Polyphenol-rich oral capsule 3 times/day (containing broccoli powder 100 mg, turmeric powder 100 mg, pomegranate whole fruit powder 100 mg, green tea 5:1 extract 20 mg equivalent to 100 mg of green tea) for 6 months | A double-blind, placebo-controlled randomised trial | 2014 | Men with localised PCa with AS or WW (n = 199) | Short-term favourable effect on PSA rise vs placebo | Gastrointestinal events | No proven long-term effects | [97] |
| MuscadinePlus (muscadine grape skin extract) for 12 months | 12-month, multicentre, placebo-controlled, two-dose, double-blinded trial | 2018 | Men with biochemically recurrent PCa (n = 125) | No prolongation of PSADT | Adverse effects judged to be unrelated or unlikely related to the study product | Dependence on PSADT as the primary endpoint | [79] |
Table 2 (continued)

| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (n = number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|-----------------------------------------------|--------------|------|--------------------------------|----------------|-------------------------------|-----------------------|-----|
| Glucoraphanin-rich broccoli soup (300 ml) consumption for a year | 3-arm parallel randomised double-blinded intervention study | 2019 | Men on active surveillance (n = 61) | Changes in gene expression in men on active surveillance while these changes were consistent with reduced risk of PCa progression | Not available | Small sample size, not met target recruitment to achieve the original power estimation, biopsies analysed were all considered nonneoplastic, based on directly adjacent histology | [98] |
| Sulforaphane (60 mg) for 6 months followed by 2 months without treatment | Double-blinded, randomised, placebo-controlled multicentre trial | 2015 | PC with increasing PSA levels after radical prostatectomy (n = 78) | Promising results on the effectiveness in decreasing PSA progression in PCa with biochemical recurrence after definite radical prostatectomy | Gastrointestinal adverse events (bloating) | Use of PSA as an endpoint (but PSA is the only available follow-up marker in this setting) | [99] |
| Sulforaphane-rich extracts (200 μmoles/day) for max 20 weeks | Single arm trial | 2015 | Recurrent PCa patients (n = 20) | No significant effects on PSA reduction | Safe with no grade II adverse events, gastrointestinal disorders (bloating, diarrhoea, dyspepsia, flatulence) | Lack of a placebo control arm limits interpretability | [100] |
| Green tea (6 g/day) | Phase II clinical trial | 2003 | Asymptomatic PCa patients with manifested progressive PSA elevation with hormone therapy (n = 42) | Limited anticancer efficacy of green tea | Well tolerated for the most part (grade 1 or 2 and included nausea, emesis, insomnia, fatigue, diarrhoea, abdominal pain, and confusion), but there were six episodes of Grade 3 toxicity (insomnia, confusion, diarrhoea, fatigue, and abdominal pain) and one episode of Grade 4 toxicity (confusion) | Not available | [101] |
| Oral curcumin (1440 mg/day) or placebo for 6 months | Randomised, double-blind, placebo-controlled trial | 2019 | PC patients who received IAD (n = 80) | No effect on overall off-treatment duration of IAD; suppressed PSA elevation | Adverse events were higher in the placebo group | Included subjects were from different clinical situations (biochemical recurrence after localized treatments and metastatic disease) | [103] |
B. Stimulating effects of phytochemicals on anti-cancer chemo- and radiotherapy in PCa management

Currently, incurable metastatic PCa is considered a therapeutic challenge. Most advanced PCa patients have a good initial response to androgen deprivation therapy with luteinizing hormone-releasing hormone analogs, orchietomy, and/or testosterone receptor antagonists. But patients consequently progress into castration-resistant PCa characterised by a median survival of 2–2.5 years. The disease in most patients, however, further progress despite anti-androgenic therapy, and these patients require the administration of cytotoxic agents, such as docetaxel [21].

The capacity of phytochemicals to potentially improve the efficacy of conventional anti-cancer treatment has been described in various cancer types [9, 104]. The study evaluating the combination of docetaxel, prednisone, and curcumin in patients with castration-resistant PCa described good tolerability and patient acceptability [22]. However, a recent study by Passildas-Jahanmohan et al. (2021) observed no effects of adding curcumin to treatment strategies (docetaxel) for patients with castration-resistant PCa in improving patient outcome and prognosis [23]. On the contrary, lycopene plus docetaxel exerted favourable effects in metastatic castrate-resistant PCa patients. The synergistic activity of lycopene with docetaxel is based on the effects on downregulation of IGF-I signalling inhibition and decrease in survivin expression. Indeed, previous evidence from PCa models describes that lycopene could suppress IGF-I, thus promoting docetaxel response [21].

C. Phytochemicals mitigate adverse effects of chemo- and radiotherapy

Evidence supports the role of phytochemical in mitigating adverse effects of conventional anti-cancer treatment modalities, e.g. radiotherapy or chemotherapy that are usually associated with various adverse events [9]. Indeed, ellagic acid reduced toxicity induced by chemotherapy (neutropenia) in hormone-refractory PCa patients. Moreover, the results also support the potential anti-cancer action of ellagic acid due to the observed decrease in serum PSA and a positive trend toward objective response and overall survival in the experimental group compared to the control [24].

Radiotherapy represents a vital PCa treatment modality [25]. External beam radiation therapy is associated with recurrent, or advanced PCAs. The Table also includes the data about the study limitations or adverse events associated with the interventions, information that is essential to provide a complex overview of the significance of clinical trials for the clinical practice or future research.
acute and subacute toxicities, including intestinal and urinary adverse effects and erectile dysfunction. However, Ahmad et al. (2010) concluded that soy isoflavones in conjunction with radiation therapy could reduce urinary, sexual, and intestinal adverse effects of radiation therapy in PCa patients [26]. Besides, up to 75% of patients receiving radiotherapy develop symptoms related to acute radiation-induced proctitis. The evaluation of potential effects of nano curcumin in PCa patients undergoing radiotherapy has not concluded effects neither to prevent and/or mitigate radiation-induced proctitis nor in radiation-induced cystitis, duration of radiation toxicities, hematologic nadirs, and tumour response. These results provide the translational insight to bridge the gap between clinical and laboratory practice despite any significant effect observed. Therefore, the authors conclude that studies with many patients and long-term pre-treatment with nano curcumin could clarify if the curcumin functions as radiosensitizer or radioprotector [25].

Table 3 provides a detailed overview of the above-discussed clinical evaluations of the effects of phytosubstances/plant–based on the anti-cancer effectiveness or mitigating the adverse effects of conventional PCa therapeutic modalities, with the overview of potential adverse effects of the phyto-interventions and significant study limitations that need to be carefully evaluated when interpreting results of the trials and their potential implementation into clinical practice.

Conclusions in the framework of predictive, preventive and personalised medicine (PPPM/3PM)

Utilisation of phytochemicals as potent anti-cancer agents represents the cornerstone in implementing novel, highly effective, well-tolerated, safe, and cost-effective measures in multi-faceted anti-PCa protection and disease management.

Primary care

Effective PCa management requires a paradigm change from reactive to predictive, preventive, and personalised medicine [1]. PCa is a systemic multi-factorial disease that results from an imbalance between excessively accumulated health risks and insufficient protection [4]. To this end, PCa develops over years or even decades via health-to-disease transition. Sub-optimal health conditions are characterised by a reversible damage to health presenting the opportunity for primary care to implement innovative tools of personalised risk assessment followed by cost-effective personalised anti-PCa protection tailored to the individual risks [106]. Contextually, targeted anti-PCa protection is at the forefront of the paradigm change from reactive to the predictive, preventive and personalised approach in PCa management. Phytochemicals are associated with potent anti-cancer activity targeting each stage of carcinogenesis starting with sub-optimal health conditions. For example, their positive effects are demonstrated for stabilising and restoring mitochondrial health quality, which if compromised is strongly associated with sub-optimal health conditions and strong predisposition to aggressive cancer sub-types [105]. An absolute majority of altogether 30 clinically relevant studies dedicated to phytochemicals in the PCa primary prevention which we have identified in the literature, demonstrated positive effects and potentially reduced risks of the disease development such as listed by references [33, 34, 45, 49]. To this end, we do strongly recommend the stratification of affected individuals in sub-optimal health conditions by phenotyping for targeted PCa-prevention and identification of the most effective plant-based treatment options [3, 49, 105, 107].

Secondary care

A rapid increase in PCa incidence and lack of adequate patient stratification to differentiate between non-metastatic PCa (no necessity for expensive treatments) and aggressive PCa subtypes requiring personalised treatment algorithms contribute to the enormous socio-economic burden currently caused by sub-optimal PCa management [3]. Consequently, risk assessment, patient stratification, targeted prevention of metastatic disease and treatment algorithms tailored to the person are the main pillars of PPPM strategies which would significantly advance secondary care in overall PCa management with potential to reverse current economic trends [3].

The effects of plant-derived phytochemicals were evaluated for secondary care particularly focused on reducing risks of the disease progression. By evaluating randomly selected clinical trials (29 studies in total), almost 70% were identified as demonstrating positive effects of phytosubstances in reducing risks of PCa progression such as listed by references [35, 76]. Moreover, several studies included in our review highlighted supportive and stimulating effects of conventional anti-cancer therapy as well as an evident mitigation of their adverse effects [21–26].

Tertiary care

Reactive medical services require biggest budgets, in particular dedicated to the last life year of the PCa patients [3]. Therefore, the intention of PPPM concepts is to treat affected individuals at the initial care levels (primary and secondary prevention). Nevertheless, the motivation of palliative care is to make palliative medicine to the management of chronic disease. For reaching the goal, treatment algorithms should consider comprehensive individualised patient profiles utilising big data analysis and machine learning approach [108]. To this end, application
| Phytosubstance/plant-based supplement (dosage) | Study design | Year | Study participants (number) | Effects/results | Adverse events of phytosubstance | Major study limitations | Ref |
|---------------------------------------------|-------------|------|-----------------------------|----------------|-------------------------------|------------------------|----|
| Docetaxel, prednisone, and curcumin (6000 mg/day–12 curcumin capsules/day for 7 consecutive days) | Non-randomised, open-label, phase II trial | 2016 | Patients with progressing castration-resistant PC | High response rate, good tolerability, and patient acceptability (tumour objective response in 40% and a PSA response in 59% of men) | Well tolerated curcumin, without systemic toxic effects | Single-arm, non-randomised design of the study, the low number of patients | [22] |
| Docetaxel plus curcumin (6 g/day) or docetaxel plus placebo in first-line treatment for 7 consecutive days every 3 weeks | Double-blind, randomised, phase II study | 2021 | Patients with metastatic castration-resistant PCa (n = 50) | No effects of adding curcumin to treatment strategies in improving patient outcome and prognosis | Most common: anaemia, asthenia, diarrhoea, and alopecia. Nothing relevant was noted between the two groups of patients, except less lymphopenia and less hypocalcaemia in the experimental arm | Small sample size, titration of curcumin performed for only a few patients | [23] |
| Docetaxel every 21 days plus lycopene daily (30 mg/day) | Interventional Phase II clinical trial | 2021 | Metastatic castrate-resistant PCa patients (n = 13) | Favourable effects, synergistic activity of lycopene with docetaxel (downregulation of IGF-I signalling inhibition and decrease in the expression of survivin) | Not available | Small sample size | [21] |
| Soy isoflavones (200 mg/day) or placebo for 6 months, beginning with the first day of radiation therapy | Double-blind, placebo-controlled, randomised trial | 2010 | PC patients (n = 42) | Reduced urinary, sexual, and intestinal adverse effects of radiation therapy | Not available | A small number of subjects, study coordinators should assist patients with the administration of study questionnaires for better compliance | [26] |
| Ellagic acid (180 mg/day) throughout the chemotherapy cycles and during the period between cycles | Clinical trial | 2005 | Hormone refractory PCa patients (n = 48) on standard chemo-therapy using vinorelbine and estramustine phosphate | Reduced toxicity induced by chemo-therapy (neutropenia) | Not available | Not available | [24] |
| Nanocurcumin (120 mg/day) or placebo 3 days before and during radiotherapy | Randomised, double-blind, placebo-controlled phase II trial | 2019 | PC patients (n = 64) | No effect on preventing and/or mitigating radiation-induced proctitis or in radiation-induced cystitis, duration of radiation toxicities, hematologic nadirs, and tumour response | Well tolerated, no drug-related severe adverse effects | Single-centre design (not representing the entire population), a small number of patients, under-powered trial to accept or reject the study hypothesis | [25] |

**Abbreviations:** PCa, prostate cancer; g, gram; mg, milligram.
of natural compounds based on flavonoids and their nanotechnologic derivatives may significantly contribute to improved individual outcomes and extended life expectation in the tertiary care of PCa. Corresponding therapeutic modalities consider their immune-modulating and drug-sensitising effects as well as excellent capacity to increase sensitivity of cancer cells and to reverse cancer resistance against anti-cancer therapies [109].

Finally, PCa-affected individuals per evidence are highly vulnerable towards COVID-19 infection [3]. Therefore, dual anti-cancer and anti-viral effects of phytochemicals such as these of silibinin are highly relevant for improved PCa management at the level of secondary and tertiary care under pandemic conditions [110]. Silibinin forms a stable complex with SARS-CoV-2 spike protein RBD being capable to interact with the active site of Mpro inhibiting, therefore, viral entry and replication. Further, silibinin may reduce pro-inflammatory effects and endothelial dysfunction by regulating expression patterns of TNF-α, IL-6 and ET-1 in blood plasma [110]. Figure 2 highlights the key concepts of the PPPM approach in primary care (anti-PCa protection) and advanced management of the clinically manifested diseases.

Author contribution O.G. was responsible for the conception. The manuscript was drafted by A.M., L.K., E.K., and K.B. and critically revised by D.B., P.K., R.A.I., F.A.G. and M.P. O.G. has contributed with PPPM/3P medicine expertise and data interpretation in the framework of PPPM. P.K. provided skilled assistance and supervised the overall preparation of the manuscript. The figures was designed and prepared by M.S.

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Declarations

Ethics approval and consent to participate Not applicable.

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