Author/s:
Van Die, MD;Bone, KM;Emery, J;Williams, SG;Pirotta, MV;Paller, CJ

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Phytotherapeutic interventions in the management of biochemically recurrent prostate cancer: a systematic review of randomised trials.

M. Diana van Die[1], Kerry M. Bone[2,3], Jon Emery[1], Scott G. Williams[1,4], Marie V.Pirotta[1], Channing J. Paller[5]

1. University of Melbourne Department of General Practice, Parkville, Victoria, Australia; 2. Integria (MediHerb), Warwick, Queensland, Australia; 3. New York Chiropractic College; New York, USA; 4 Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; 5.The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore.

Email addresses: mvandie@unimelb.edu.au; kerry.bone@integria.com; jon.emery@unimelb.edu.au; Scott.Williams@petermac.org; m.pirotta@unimelb.edu.au; cpaller1@jhmi.edu

Correspondence: Dr Diana van Die, Department of General Practice, The University of Melbourne, 200 Berkeley St, Carlton, Victoria 3053, Australia. Email: mvandie@unimelb.edu.au

Keywords: prostate cancer, biochemical recurrence, phytotherapy, herbal medicine, systematic review, clinical trials

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Phytotherapeutic interventions in the management of biochemically recurrent prostate cancer: a systematic review of randomised trials.

ABSTRACT

Objectives

- To evaluate the evidence from randomised trials for the efficacy and safety of phytotherapeutic interventions in the management of biochemically recurrent prostate cancer, indicated by PSA progression, numbers progressing to/time to initiation of androgen deprivation therapy or salvage therapy.

Patients and Methods

- MEDLINE (Ovid), EMBASE (Ovid), AMED (Ovid), CINAHL (EBSCO) and the Cochrane Library databases were searched.
- Clinical trials investigating phytotherapeutic interventions as dietary supplements or dietary components, including multi-component herbal formulations, in men with biochemically recurrent prostate cancer were located.
- Eight of nine authors contacted for further information responded.
- Methodological quality was assessed using the Cochrane Collaboration's risk of bias assessment tool.
- The PRISMA statement for reporting systematic reviews was followed.

Results

- Of 23 full-text articles assessed for eligibility, five met the criteria for inclusion.
- Two studies were placebo controlled, two were active control trials, and one a high-dose/low-dose trial.
- The interventions were administered as isolated phytochemicals (sulforaphane), phytotherapeutic extracts (Pomi-T (pomegranate, turmeric, green tea and broccoli sprout extract), soy, lycopene and POMx (pomegranate)), or plant-derived dietary items (soy and lycopene).
- All studies found serum PSA levels to either stabilise, decrease or rise more slowly in a significant number of men, and three studies reported stabilising or lengthening of PSA-doubling time.
- Studies were generally of good quality, but sample sizes were predominantly small, and durations short.

Conclusions

- High quality studies in this area are lacking. Sulforaphane, lycopene, soy isoflavones, pomegranate and Pomi-T are safe and well tolerated. There is limited evidence that they can affect PSA dynamics. No recommendation can be made for the use of these agents in managing PrCa morbidity and mortality until high quality, fully powered studies are available.
- Recommendations are made for improving reproducibility and translation of findings with regard to study population, study endpoints, design and the reporting of phytotherapeutic interventions.

Keywords: prostate cancer, biochemical recurrence, phytotherapy, herbal medicine, systematic review, clinical trials

Introduction

Approximately 35% of men treated annually for localised prostate cancer (PCa) with definitive local therapies such as radical prostatectomy, brachytherapy, and external beam radiation therapy, will develop biochemical failure or biochemical recurrence (BCR) of disease[1], detected by a rising serum prostate-specific antigen (PSA) within 10 years after treatment[2]. This usually signifies the presence of incurable disease, and can indicate disease progression years before clinical signs or symptoms develop[2].

The small fraction (10–15%) of men with rapidly progressive biochemically recurrent PCa, signified by a PSA-doubling time (PSA-DT) of three months or less, have a high risk of clinical recurrence and cancer mortality. These are typically managed with early systemic therapy, usually in the form of androgen deprivation therapy (ADT) initially[3]. For the remainder with more indolent PSA dynamics, however, there may be a period of several years of observation prior to embarking on salvage ADT[4] with its associated toxicities[5].

Substantial anxiety during this period of watchful waiting[6] often drives patients to seek non-hormonal treatments. Complementary medicine use among men with PCa ranges from 8 to 90% (median 31%) with 8 to 50% (median 30%) using it specifically for cancer care[7]. With regard to herbal medicine use, the prevalence ranges from

1.2 to 24.5%. Evidence for the efficacy of non-hormonal herbal treatments (phytotherapies) is needed from studies in humans.

Scientific investigation of phytotherapeutic agents for potential benefit in PCa chemoprevention is increasing, especially for green tea (*Camelia sinensis*) catechins (GTCs), lycopene and soy (*Glycine max*) isoflavones, curcumin from turmeric (*Curcuma longa*), sulforaphane and indole-3-carbinol from broccoli (*Brassica oleracea*). Pre-clinical studies and/or clinical trials also suggest benefits for resveratrol from grape skins or *Polygonum cuspidatum*, pomegranate *(Punica granatum)* extract, silymarin (from St Mary's/milk thistle, *Silybum marianum*) and mushrooms such as reishi (*Ganoderma lucidum*), turkey tail (*Coriolus/Trametes*), and shiitake (*Lentinula edodes*).

Potential anti-cancer mechanisms of these agents have been extensively reviewed elsewhere[8-17]. These include inhibition of proliferation, induction of apoptosis and cell cycle arrest. Soy isoflavones, indole-3-carbinol and 3,3'-diindolylmethane from broccoli, lycopene (predominantly found in tomatoes), (-)-epigallocatechin-3-gallate (green tea polyphenols), and curcumin from turmeric are known to downregulate the signal transductions in AR, Akt, NF-κB, and other signal transduction pathways[18]. In vitro, sulforaphane can inhibit cancer cells through a variety of mechanisms including inflammation, angiogenesis and metastasis, and in vivo, its administration inhibited prostate cancer progression and metastasis in TRAMP mice[11]. Pomegranate polyphenols modulate Bcl-2 proteins, increase p21 and p27, and downregulate the cyclin-cdk network[12]. *Silymarin* (St Mary's/milk thistle) and its main active constituent, silibinin may enhance IGFBP-3 action and inhibit IGF-I-induced growth or affect levels of AR-regulating genes[10]. Mushroom polysaccharides stimulate T-cells, B-cells, neutrophils, and macrophage dependent immune system responses[16]. Systemic bioavailability is poor for curcumin and silibinin[10 17].

The objective of this systematic review was to evaluate the evidence from randomised trials of phytotherapeutic interventions in the management of biochemically recurrent prostate cancer for delaying disease progression, indicated by PSA progression, numbers progressing to/time to initiation of ADT or other salvage therapies.

METHODS

Data Sources

The following electronic databases were searched (earliest to May 2015): EMBASE (Ovid), Medline (Ovid), AMED (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL (EBSCO).

In addition, further relevant papers were identified using the 'related articles' function in PubMed, and by hand-searching reference lists of relevant journal articles and conference proceedings.

Search Strategy

Search strategy (in MEDLINE – adapted for other databases)

1. exp Prostatic neoplasms/
2. prostate cancer.mp.
3. 1 or 2
4. (herb$ or medicinal plant$ or plant extract$ or plant drug$ or botanic$ or phytotherap$).mp
5. (citrus or pomegranate or *Punica granatum* or indol-3-carbinol or broccoli or diindolymethane or DIM or glucosinolate$ or sulforaphane or polyphenol$ or resveratrol or grape or curcumin or turmeric or *Curcuma longa* or green tea or *Camellia sinensis* or catechin$ or isoflavone$ or phytoestrogen$ or genistein or daidzein or *Glycine max* or soy$ or lycopene or red clover or *Trifolium* or liquorice or licorice or *Glycyrrhiza* or garlic or *Allium sativum* or pycnogenol or shitake or mushroom$ or *Ganoderma* or *Trametes* or turkey tail or PSP or PSK or *Coriolus* or *Lentinula* or lentinan or *Agaricus* or silybin or *Silybum* or silymarin or silybin$ or flaxseed or linseed or Linum or viscum or mistletoe or Iscador).mp
6. 4 or 5
7. 3 and 6
8. limit 7 to (English and clinical trials, all)

English language restriction was imposed

Study Selection

Randomised clinical trials were eligible for inclusion in this review. Trials investigating phytotherapeutic extracts in combination with mainstream treatment were excluded.

Types of participants

Men with biochemically recurrent hormone sensitive prostate cancer following local therapy for histologically confirmed prostate cancer were included.

Types of intervention

Trials investigating phytotherapeutic extracts, isolated phytochemicals, and plant-derived dietary components/items were included. Data from studies investigating herbal formulations containing additional vitamins or minerals were excluded. Studies of PC-SPES, which has been discredited due to adulteration with synthetic drugs, and of herbs administered via non-oral routes were excluded.

Types of controls

Studies comparing interventions with inactive controls, (such as placebo, no treatment, standard care or a waiting list control) or active control interventions (such as a different variant of the same intervention or a different herbal intervention) were included.

Types of outcome measures

The primary outcomes of this review were

- disease progression denoted by changes in PSA levels and PSA kinetics (PSA rise rate, PSA-DT)

Secondary outcomes included

- numbers progressing /time to initiation of mainstream treatments such as ADT or salvage therapies
- changes to prostate symptoms
- quality of life measures
- adverse events
- compliance

Outcomes excluded

- bioavailability/tissue levels
- mechanisms of action

Data extraction and methodological quality assessment

Two reviewers (DvD and CP or KB) independently screened the titles and abstracts of all articles returned from the search strategy. When necessary, full-text articles were obtained to determine eligibility of the study. Any disagreement between the two authors was to be resolved by a third author (KB). Data extraction from included studies was conducted by two investigators (DvD and KB). Excluded studies were reviewed by DvD and MP; discrepancies were checked by KB.

The following data were extracted from the included articles: intervention, patient characteristics at baseline, trial design, sample size duration, outcome measures, results and adverse events. Where necessary, authors were contacted for further details.

The quality of each study was assessed using the Cochrane Collaboration's risk of bias assessment tool[19]. Three reviewers (DvD, KB and CP) worked independently to determine selection, attrition, detection, performance and reporting bias. Any discrepancies were resolved by discussion between the reviewers. To supplement the quality assessment, additional criteria were assessed according to the proposed elaboration of CONSORT checklist item 4 for reporting randomized controlled trials of herbal medicines[20].

Data analysis

Lack of homogeneity across trials precluded any meaningful meta-analysis.

Figure 1. Flowchart of selection process

Table 1 Characteristics of identified randomised trials of phytotherapeutic extracts, isolated phytochemicals and dietary interventions in BCR

ADT – androgen deprivation therapy; AEs – adverse events; AS – active surveillance; BCR – biochemically recurrent; CRP -C-reactive protein; EBRT – external beam radiotherapy; GI – gastrointestinal; IGF – insulin-like growth factor; INF- international normalisation ratio; ITT – intention to treat; LHRH - luteinizing hormone

releasing hormone; M0- baseline; M6 – end of month 6;mths – months; NS – not significant; P – placebo; PCa – prostate cancer; POMx – pomegranate extract; PSA – prostate specific antigen; PSA-DT – PSA doubling time; pts – patients; RCT – randomised controlled trial; RP – radical prostatectomy; RT – radiotherapy; RTE – external radiotherapy; SF – sulforaphane; SHBG – sex-hormone binding globulin; VEGF: vascular endothelial growth factor; wk – week; WW –watchful waiting; yrs – years

RESULTS

Description of Studies

After the removal of duplicates, 318 articles were located and 23 full text articles were assessed, five of which met the selection criteria (Fig. 1)[11 20-23]. Key data extracted from the identified studies are included in Table 1. Of the five studies, two were placebo controlled[11 22], two compared the intervention with a different herbal intervention,[23 24] and one was a variant of the same intervention (high-dose/low-dose) trial[21]. Study durations were as follows: eight weeks[24], three of six months[11 22 23], and one study of up to 18 months[21]. However in the latter, only 58% completed either 18 months or met the protocol-defined progression.
Excluded studies (*n*=18) are shown in Table 2.

Participants

In total, 500 participants were randomised across these five studies, of which 489 were included in intention-to-treat analyses. Of these, 368 were patients with BCR PCa. One placebo-controlled randomised controlled trial (RCT) was conducted in each of UK[22] and France[11]; the other three were conducted in the USA [23 24 21].

One study (Pomi-T) included men prior to and following radical therapies, on active surveillance (AS) or watchful waiting (WW). The others included men following radical prostatectomy and/or radiotherapy therapy for localised PCa[11 21 23 24]. One of these also included men on hormone therapy (LHRH analogue)[23].

Four studies reported mean ages, which ranged from 69 to 75 years[11 21 23 24]. The other reported a median age of 75 years[23]. Mean baseline Gleason scores reported in two studies[21 22] were 6.4[22] and 6.45[21] respectively. Baseline PSA levels were specified in four studies: means of 0.76 ng/mL, 6.5 µg l^{-1}[22], 5.3 ng/mL[21], and a median of 6.5 ng/ml[23]. Baseline PSA-DT was reported in three trials: means were 14.4[11] and 14.7 months[21]; percentages of men with slow, moderate and fast rise rates were 38% (< 4 months), 32% (4-9 months), and 30% (>9 months) respectively[24].

PSA inclusion criteria were specified in four studies*:* PSA > 0.2 ng/ml and <5 ng/ml after radical prostatectomy (RP) ± external beam radiotherapy (EBRT)[11]; no PSA limits[24]; a minimum PSA of 10 ng/ml[23]; a PSA ≥0.4 ng ml^{-1} after RP or multiple therapies, PSA >1.5 ng ml^{-1} after primary radiation therapy (RT) or cryotherapy; PSA nadir plus 2 $ngml^{-1}$ following ERT with neo-adjuvant hormonal therapy[21].

Definitions of BCR were included in four studies: PSA at three successive measurements[11]; at least two consecutive increases in serum PSA [24]; three successive elevations at a minimum interval of two weeks or at least two PSA values at least two weeks apart [23]; rising PSA on three or more time points at least a month apart, within one year prior to enrolment[21].

Doubling time (DT) calculations were reported in three of the studies[11 21 24], and PSA rise rate calculations described in a fourth (linear mixed-effects modelling with logarithm of PSA[23]. PSA-DT was calculated either by fitting a simple linear regression model, using the slope, (the natural log of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA on time (months)[21], consistent with the Memorial Sloan Kettering Cancer Centre calculation[11], or by using only the difference of the first and last PSA values (the natural log(2) × time interval/log final PSA–log initial PSA[24]).

Current users of hormone therapy were included in one trial[24]. One study permitted LHRH analogue but not other hormones within the previous four weeks[23]. Three other studies included prior but not current users[11 21 22]. Two allowed hormone use in conjunction with radiotherapy[11 22] and the other at least one year prior to enrolment[21]. There was no significant difference across groups for current or prior use of hormone/anti-androgen therapy in any of the trials including this baseline data[11 21 23 24].

Interventions

Three types of interventions were identified in the studies: phytotherapeutic extracts, isolated phytochemicals, and plant-derived dietary items. Interventions were delivered either as monotherapies or in combinations. Two studies investigated

lycopene – dietary lycopene (tomatoes) 25+ mg/day, calculated according to a food worksheet vs. a powdered soy protein supplement 40 g/day (Solae Company, St. Louis, MO; product Number AB20 Soy 1.2; each 40 g packet contained 24 mg genistein, 12 mg diadzein, and 2 mg glycitein. Isoflavones were present in the aglycone form) for four weeks followed by the combination for a further four weeks (both arms)[24]; lycopene 30 mg/day (Lyc-o-mato^{R} ,15 mg orally twice daily) vs. a combination of lycopene at the same dose plus isoflavone capsules 80 mg daily (Solgen R 40 mg orally twice daily, LycoRed Company, Beer-Sheva, Israel)[23]. The other three studies investigated three different interventions: free stabilised sulforaphane (SF) 60 mg daily (Nutrinov^{TM})[11]; Pomi-T® (Power Heath Products Ltd, Pocklington, York), a combination of pomegranate (*Punica granatum*) extract, green tea (*Camellia sinensis*), broccoli sprouts (*Brassica oleracea*) and turmeric (*Curcuma longa*) – all 300 mg/day; and pomegranate (*Punica granatum*) extract 1 g or 3 g /day (POMx capsules, POM Wonderful LLC; 1 or 3/ capsules day, each containing 1000 mg of polyphenol extract, comparable to about 8 ounces pomegranate juice. 90% polyphenols)[21].

Controls/Comparators

Two studies were placebo-controlled trials (SF[11] and Pomi-T[22]) of six months duration; the pomegranate (POMx) study was a high dose/low dose study of up to 18 months duration[21]; and the remaining two compared lycopene with a different phytotherapeutic agent (soy protein) for eight weeks[24]/combination (lycopene plus soy isoflavones for up to six months)[23].

Effects of interventions

PSA levels

With all five interventions investigated, serum PSA levels either stabilised, decreased, or increased less than with placebo in a significant number of men on verum. PSA levels rose significantly less with sulforaphane (SF) than with placebo over six months, $p = 0.03$, and the log PSA slope was significantly lower between baseline and month 6, $p = 0.036$ and particularly months 3 and 6, $p = 0.011$[11]. In the Pomi-T study, mean PSA rose by 8.78% in the watchful waiting group on verum (95% CI –6.32 to 26.62), compared with a 80.34% rise in the placebo group (95% CI

50.54 o116.55); $p = 0.001$[22]. Serum PSA decreased in 25% men administered tomato/lycopene for four weeks followed by a combination of tomato and soy protein for a further four weeks, compared with 43% men administered soy protein for four weeks, followed by the combination for a further four weeks, (36% men overall)[24]. No partial (50% reduction) or complete (PSA≤4ng/mL) responses were observed with lycopene or lycopene plus soy isoflavones over six months[23]. However, 95% of patients in the lycopene group and 67% of the lycopene-isoflavones arm achieved stabilisation of serum PSA. Additionally, the rise rate of PSA significantly declined over the six months for both the hormone sensitive, $p = 0.015$, and hormone refractory men, $p = 0.017$. Lycopene only resulted in a significantly greater decline than the combination for the hormone refractory men, $p = 0.021$. In the pomegranate study, declining post-baseline PSA levels were observed in 13% (six patients in the low-dose arm and nine patients in the high-dose arm, and stable disease was seen in 36 patients (78%) in the low-dose arm and 40 patients (82%) in the high-dose arm[21].

PSA-DT

All three studies reporting on PSA-DT found prolongation in a number of men[11 21 24]. An estimated 78% PSA-DT increase was observed with sulforaphane (21.7 months) compared to placebo (12.2 months)[11]. Median PSA-DT extended from 14.26 to 28.9 months over six months. With tomato or soy protein for four weeks followed by a combination of the two for a further four weeks, prolongation of PSA-DT occurred in 58% men, 65% of the tomato group, and 51% of the soy arm[24]. The percentage of men whose PSA-DT was classified as slowest (> 9 months) increased from 30% to 48 %, $p = 0.08$, over the eight week period. Administration of pomegranate capsules (1 g or 3 g/day) resulted in a median lengthening of PSA-DT from 11.9 to 18.5 months over the study period of up to 18 months, $p < 0.001$, with no significant difference between the dosage regimens[21]. In the 1g-POMx group, 76% of patients had stable or lengthening PSA-DT and 46% had increases of 100% or more in PSA-DT. In the 3g-POMx group, 82% of patients had stable or lengthening PSA-DT and 41% had 100% or greater increase in PSA-DT.

Other

No significant effect was observed on testosterone levels with sulforaphane, pomegranate or lycopene and soy protein[11 21 24]. With administration of pomegranate capsules, oestradiol trended higher in the high-dose group from 28.0 to 32.3 pg ml^{-1}, but not in the low-dose group. Sex-hormone-binding globulin increased in both groups (42.5–54.7 nmole l^{-1} in the 3g-POMx group and 42.8–49.2 nmole l^{-1} in the 1g-POMx) with no significant difference between groups[21]. Lycopene plus soy resulted in reductions in serum vascular endothelial growth factor (VEGF) in both treatment arms, $p < 0.04$, and total cholesterol[24].

Adverse Events

Adverse events were predominantly grade I gastrointestinal events, that were not significantly more frequent than with placebo in the RCTs. As shown in Table 1, other events were minor in nature.

Risk of Bias

Risk of bias analysis was conducted in accordance with the Cochrane Collaboration guidelines for systematic reviews as an assessment of the validity of findings, and is summarised in Figures 2A and 2B. Most were categorised as low risk (60%) or unclear (20%). Random sequence generation was only described in two of the five studies. The two unblinded active-comparator studies were assessed as high risk on selection, performance and detection bias criteria[23 24]. In the sulforaphane study, it would appear the trial product manufacturer had involvement in data analysis and interpretation[11].

Reporting according to elaboration of CONSORT for trials of herbal interventions

All identified studies were assessed according to the elaborated CONSORT statement for trials of herbal interventions[20]. Generally compliance was low (Table 3). All studies reported the common names of the plant (4A.1iv), the propriety product name or extract name and name of manufacturer of the product (4A.2), and dose and duration of administration (4Ci) and ii)), but none included the botanical

family (4A.1iii), the type and concentration of extraction solvent (where relevant); or a description of the practitioners (4F).

Figure 2A. Risk of bias summary of included studies

Figure 2B. Risk of bias graph of included studies

Table 2 Characteristics of excluded studies

ADT– androgen deprivation therapy; ALP – alkaline phosphatase; Apo – apolipoprotein; AS –active surveillance; AST – aspartate amino-transferase; BCR – biochemical recurrence; DHEA – dehydroepiandrosterone; GGT – gamma-glutamyltransferase ; GI – gastrointestinal; HR – hormone refractory; HT – hormone therapy; IGF – insulin-like growth factor; LDL –low density lipoprotein;LH – luteinising hormone; mths – months; M- months; P – placebo; PCa – prostate cancer; PP – per protocol analysis; PSA – prostate specific antigen; PSA-DT – PSA doubling time; pt/s –patient/s; QoL – quality of life; RP – radical prostatectomy; RT – radiotherapy; SF - sulforaphane ; SHBG – sex-hormone-binding globulin; SME - Shiitake Mushroom Extra

ADT – androgen deprivation therapy; ALP – alkaline phosphatase; Apo – apolipoprotein; AS –active surveillance; AST – aspartate amino-transferase; BCR – biochemical recurrence; DHEA – dehydroepiandrosterone; GGT – gamma-glutamyltransferase ; GI – gastrointestinal; HR – hormone refractory; HT – hormone therapy; IGF – insulin-like growth factor; LDL –low density lipoprotein;LH – luteinising hormone; mths – months; M- months; P – placebo; PCa – prostate cancer; PP – per protocol analysis; PSA – prostate specific antigen; PSA-DT – PSA doubling time; pt/s –patient/s; QoL – quality of life; RP – radical prostatectomy; RT – radiotherapy; SF - sulforaphane ; SHBG – sex-hormone-binding globulin; SME - Shiitake Mushroom Extract; TAG – trigylcerides

Discussion

There is growing interest in researching phytotherapeutic interventions for BCR prostate cancer, especially ones that do not interfere with hormone receptors. Many men who experience PSA relapse following local treatment for prostate cancer turn to herbal and other complementary medicines in an attempt to delay the need for androgen deprivation therapy with its attendant side-effects, to prolong the time to metastases, and/or reduce prostate cancer-specific morbidity and mortality. We have presented the results of a systematic review of the evidence from randomised trials of phytotherapeutic extracts, isolated phytochemicals, and plant-derived dietary items in the context of biochemically recurrent prostate cancer. To our knowledge, this is the first review of phytotherapeutic interventions in this cohort.

Of the 22 identified clinical studies, five met the criteria for inclusion. No two were identical in terms of intervention and comparator, thus precluding any meaningful meta-analysis. Overall, the quality of the studies was good, although generally sample sizes were small and durations short. Interventions investigated were sulforaphane; lycopene versus soy (*Glycine max*) protein; lycopene with soy isoflavones; Pomi-T®, which is a combination of pomegranate (*Punica granatum)*, green tea (*Camellia sinensis*), broccoli sprouts (*Brassica oleracea*) and turmeric (*Curcuma longa*); and pomegranate (*Punica granatum)* extract. Despite small sample sizes, all studies found serum PSA levels to stabilise, decrease or rise more slowly in a significant number of men. Statistically significant results were found for a decrease in mean PSA slope compared with placebo with sulforaphane, mean PSA change with Pomi-T, and PSA rise rate in both hormone sensitive and hormone refractory PCa with lycopene and lycopene plus soy isoflavones. Prolongation of PSA doubling time was observed in all three studies reporting on this endpoint[11 21 24], and reached statistical significance with sulforaphane, and pomegranate extract. In the third, the 8-week study of tomato vs. soy protein, it should be noted that PSA was not the main endpoint of interest, but rather metabolism and absorption[24]. Importantly, in the three studies that monitored testosterone levels across the treatment phase, no significant changes were found. With pomegranate extract[21], both dosage regimens resulted in non-significant increases in sex-hormone binding globulin levels. Only one study measured changes to VEGF, and found significant

reductions with both dietary lycopene and soy protein[24]. Safety and tolerability were very good for all interventions. However, these findings should be treated with caution pending replication of results from further adequately powered studies.

Limitations

Consistent with the findings of other reviews on phytotherapeutic interventions in prostate cancer[42-44], limitations include the number of studies identified, sample sizes and length of follow-up, and lack of power in some studies to detect clinically meaningful changes in PSA or other biomarkers of disease progression. One study included men on both active surveillance (pre-local therapy) and watchful waiting (post local therapy), without consistent reporting of sub-population analysis, thereby limiting our ability to determine the impact on the rising PSA population post local therapy[22].

In addition, comparison of results across studies is hindered by the variety of ways used to report PSA endpoints: mean change in PSA/percentage change from baseline; percentage lower than control arm; percentage of men experiencing a decrease in PSA; number of/percentage of men demonstrating a partial (>50% reduction) or complete PSA response; time to PSA progression. PSA-doubling time was defined as mean or median log slope; the number of men moving from one risk category (slow, moderate or fast) to another; median or mean number of months' prolongation; and percentage change from baseline.

With regard to adherence to the proposed elaboration of CONSORT checklist item 4 for trials of herbal medicine, reporting was inadequate for information relating to the herb name, characteristics of the herbal product, quantitative description and qualitative testing. Lack of complete and transparent reporting impacts on reproducibility of studies as well as translation into clinical practice.

Abstracts published in proceedings of professional meetings were searched but not included in the review. As none of these was a negative study, this is unlikely to reflect publication bias. However, publication bias cannot be ruled out.

The key issues identified with phytotherapeutic research in this area are summarised in table 4.

The overall aim of this review was to examine the evidence for phytotherapeutic interventions in prolonging metastasis-free survival in men with BCR prostate cancer. The attempt to pool or compare results from the identified studies highlighted several barriers to comparability of findings from phytotherapy research in this cohort, namely variations in study population, intervention, design and endpoints. As most studies do not concurrently measure other markers of tumour progression in participants, the possibility of the interventions masking PSA kinetics cannot be excluded.

Recommendations

Greater consensus among researchers designing clinical trials is needed to permit meta-analyses and meaningful comparisons of studies that would assist clinicians in advising patients of the risks and/or benefits of phytotherapeutic interventions in biochemically recurrent prostate cancer. Four areas are candidates for such consensus:

i) definitions of biochemical recurrence, and number and frequency of PSA readings over time: The authors propose that researchers use the American Urological Association (AUA) definition of BCR post radical prostatectomy (PSA > 0.2 ng/mL measured 6 – 13 weeks after RP, followed by a confirmatory test showing persistent PSA > 0.2 ng/mL"[45]). Researchers should also follow the AUA-recommendation for defining BCR post radiation therapy by using the ASTRO definition of BCR (the midpoint between PSA nadir and the first of three consecutive rises in PSA)[5].

ii) stratification: Because metastasis-free survival is strongly influenced by PSA doubling time and Gleason score, it is important to stratify patients on these two factors (PSADT < 9 months vs ≥ 9 months and Gleason 3+4 and below vs 4+3 and above)[2 3].

iii) methods of calculating PSA-DT: As recommended by the Prostate-Specific Antigen Working Group's Guidelines on PSA Doubling Time, the calculation of PSA-DT is the natural log of 2 divided by the slope obtained from fitting a linear regression

of the natural log of PSA on time (months) for at least three values of PSA all > 0.2 ng/mL and all taken within 12 months[46].

iv) reporting of results: Results should include, where available, change in PSA doubling time, 30% and/or 50% decline in PSA and metastasis-free survival in accordance with the Prostate Cancer Working Group definitions[47].

Endpoints

Although PSA-DT is likely the most important prognostic factor in metastases-free survival and overall survival[2], further evidence is needed to confirm findings that changes in PSA-DT following initiation of a therapy are prognostic for metastasis-free survival in patients with BCR disease[5 48]. Inclusion of metastases-free survival as an endpoint is encouraged despite necessitating lengthy follow-up periods. To determine whether effects endure, adequate follow-up periods, and non-treatment follow-up beyond the treatment phase are needed. Where interventions have potential phytoestrogenic activity, the inclusion of sex hormones and sex-hormone-blinding globulin is recommended.

To ensure that interventions are not simply suppressing PSA, but also impacting on cancer progression, routine prostate imaging through CT and bone scans 1-2 years, depending on PSA kinetics, is recommended.

Design

The importance of a placebo arm and adequate sample size to overcome the possibility of type II errors due to natural PSA variability is emphasised by the finding that calculated PSA-DT in BCR PCa may naturally increase over time in the absence of therapy and may be influenced by duration of PSA follow-up[49].

Intervention

In 2006, an elaboration of CONSORT item 4 was proposed for reporting on clinical trials of herbal interventions[20]. As biologically defined agents, crude phytotherapeutic drugs vary in chemical composition according to agricultural practices and growing conditions. Other factors that determine whether different

phytotherapeutic extracts achieve phyto-equivalence, (the same therapeutic activity), include plant part used, extraction methods, solvents, ratio of crude herbal drug to solvent, presence or absence of standardisation, and the quantity of herbal product constituents per dosage unit form. Disclosure of this information is essential for researchers wishing to replicate studies, as well as for clinicians prescribing on the basis of published findings to have confidence that they are using an equivalent agent/product. However, reporting according to this checklist remains poorly-done[50]. Improved reporting according to the proposed elaboration of CONSORT item 4 for reporting on clinical trials of herbal interventions is therefore urgently required.

Conclusion

There is growing interest in finding safe and effective phytotherapeutic therapies that can delay time to metastases and reduce PrCa-specific mortality and morbidity in men with BCR PrCa following local treatment. High quality studies in this area are lacking. Sulforaphane, lycopene, soy isoflavones, pomegranate and Pomi-T are safe and well tolerated. There is limited evidence that they can affect PSA dynamics. No recommendation can be made for the use of these agents in managing PrCa morbidity and mortality until high quality, fully powered, placebo controlled studies are available.

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None

Conflict of Interest

Prof Kerry Bone works as a consultant director of Research and Development for MediHerb (Integria) Australia, manufacturers of herbal medicines. He and Dr Diana van Die are in-laws.

Abbreviations

ADT – androgen deprivation therapy; AEs – adverse events; Akt– protein kinase B; ALP – alkaline phosphatase; Apo – apolipoprotein; AR – androgen receptor; AS – active surveillance; AST – aspartate amino-transferase; ASTRO – American Society for Radiation Oncology; AUA – American Urological Association; Bcl-2– B-cell lymphoma 2; BCR – biochemically recurrent; CAM – complementary and alternative medicine; CRP -C-reactive

protein; cyclin-cdk– cyclin-dependent kinase complex; DHEA– dehydroepiandrosterone; EBRT – external beam radiotherapy; GGT – gamma-glutamyltransferase; GI – gastrointestinal; GTCs – green tea catechins; HR – hormone refractory; HT – hormone therapy; IGF – insulin-like growth factor; IGFBP3– insulin-like growth factor-binding protein 3; INF- international normalisation ratio; ITT – intention to treat; LDL –low density lipoprotein; LH – luteinising hormone; LHRH - luteinizing hormone releasing hormone; M- months; M0- baseline; M6 – end of month 6; MSKCC – Memorial Sloan Kettering Cancer Centre mths – months; NF-κB– nuclear factor-kappaB; NS – not significant; P – placebo; PCa – prostate cancer; POMx – pomegranate extract; PP – per protocol analysis; PSA – prostate specific antigen; PSA-DT – PSA doubling time; pts – patients; QoL – quality of life; RCT – randomised controlled trial; RP – radical prostatectomy; RT – radiotherapy; RTE – external radiotherapy; SF – sulforaphane; SHBG – sex-hormone binding globulin; SME - Shiitake Mushroom Extract; TAG – trigylcerides; VEGF: vascular endothelial growth factor; wk – week; WW –watchful waiting; yrs – years

Table 3 Reporting according to the Proposed Elaboration of CONSORT checklist Item 4 for reporting randomized controlled trials of herbal medicine

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Table 1 Characteristics of identified randomised trials of phytotherapeutic extracts, isolated phytochemicals and dietary interventions in BCR

First author, year & country	***Intervention, extract & dosage vs. comparator***	***Diagnosis & participant characteristics***	***Study design, participants (n) & duration***	***Endpoints***	***Main results***	***Adverse events***	***Authors' conclusions***
Intervention compared with an inactive control intervention (e.g. placebo, no treatment, standard care, or a waiting list control)							
PLACEBO CONTROLLED							
Monotherapies							
Cipolla et al., 2013[17] France	***Sulforaphane*** (SF) 60 mg daily SF ***vs. placebo***	BCR PCa - rising PSA (at 3 successive measurements) after RP (*n*=29) or RP & RT(*n*=39) or RP & RT & hormone therapy (*n*=10) *Current or prior*	double-blind, randomized, placebo controlled trial *n*=81/78 (SF *n*=38; placebo *n*=40) Duration: 6	Primary: .012 log (ng/ml)/ month decrease in the log PSA slopes in the SF arm vs. placebo arm Secondary	- Primary end-point was not reached using 4 values (M0, M1, M3, M6). - The adjusted median log PSA slope in SF group was 38.5% lower than in the placebo group. -Mean PSA change between M6 and M0	Only grade 1 GI toxicity (bloating) in the SF arm (*n*=17) but not statistically different from placebo (*n*=10)	*This stabilized SF was shown to significantly delay PSA progression after RP ± RT. The decrease the PSA slope was most marked after 3 months treatment.*

		hormone therapy? Yes, in conjunction with RT (*n*=10) PSA >0.2 and <5 ng/mL Mean: 0.76 ng/mL PSA-DT >5 and <36 mths. Mean: 14.4 mths *Gleason score:* ≤8 *Mean age:* 69 ±6 yrs	mths	- Difference in M6 –M0 PSA values - PSA-DT - testosterone	was significantly lower in the SF group than placebo (0.099 ± 0.34 vs 0.62±1.47 ng/ml; *p* = 0.043). - PSA-DT was 86% longer in the SF than in the placebo group (28.9 and 15.5 months respectively). -Testosterone levels: no difference between arms - Very good tolerance.		
Multi-component Interventions							
Thomas et al., 2013[21] UK	***Pomi-T:*** pomegranate green tea, broccoli sprouts and turmeric (Pomi-T) – all 300 mg.day ***vs. placebo*** (P)	Localised PCa managed with active surveillance (AS) (*n*=121/60%) or watchful waiting (WW) (*n*=78/40%) following a PSA relapse post-radical treatments	RCT – placebo controlled *n*=203/199 (136/134 active;67/ 65 placebo) Duration: 6	-PSA levels -Average PSA change -Number remaining on active surveillance -cholesterol	- PSA levels were stable or lower than baseline more often in the Pomi-T group (46% vs. 14%; *p* = 0.00001). - In the AS sub-group (*n*=121) mean PSA dropped by 0.14% (95% CI –7.57 to 7.95)	-No statistically significant difference in AEs between arms:34 (24%) in Pomi-T and 23 (34%) in P group. - No grade 3-4 toxicities, but one	*This study found a significant short-term, favourable effect on the percentage rise in PSA in men managed with AS and WW following ingestion of this*

	RT, *n*=65; RP & RT, *n*=8; brachytherapy, *n*=9). *Current or prior hormone therapy?* No current use; prior use included. *PSA, mean:* 6.5 µg l^{-1} *PSA-DT:* not specified *Gleason score, mean:* 6.4 *Mean age:* 72 (active); 76 (placebo) yrs [overall: 73 yrs]	mths	-blood glucose -CRP -blood pressure	in Pomi-T, but rose by 46.98% in P group (95% CI 28.51 to 68.31); p = 0.001; in the WW subgroup, (*n*=78) mean PSA rose by 8.78% in Pomi-T (95% CI –6.32 to 26.62), cf 80.34% in P group (95% CI 50.54 o116.55); p = 0.001. –Median increase in PSA was 63.8% lower in the supplement groups than in P group (14.7% vs. 78.5%; p =.0008) at 6 mths. -More men in the Pomi-T group than in P group continued on AS or WW (92% vs. 72%). -No significant differences between groups for cholesterol, serum glucose, CRP, or	grade 2 (diarrhoea) with Pomi-T. -GIT events in 21 (15.5%) in Pomi-T cf. 5 (7.5%) in the P group. (NS) -No effect on INR in 30 men on warfarin. -	*food supplement*.

					blood pressure. Compliance was excellent (96.5% Pomi-T, and 98.4% P).		
Intervention compared with an active control intervention (e.g. a different variant of the same intervention, a different drug, a different kind of therapy)							
COMPARATOR A DIFFERENT HERBAL INTERVENTION							
Monotherapies							
Grainger et al., 2008[22] USA	***Dietary lycopene (tomatoes)*** (T) ***vs. soy protein*** (S) Lycopene 25+ mg/day or soy protein 40 g/day for 4 weeks, followed by combined tomato-rich diet and soy supplements for a further 4 weeks	Biochemically recurrent PCa after local therapy (at least 2 consecutive increases in serum PSA); asymptomatic *Current or prior hormone therapy?* Yes, current: (*n*=20;[T *n*=9] S *n*=11]) *PSA:* not specified *PSA-DT:* 38% < 4	Randomised trial *n*=41/40 Lycopene (20) vs. soy protein (21) Duration: 8 wks	-Serum PSA -PSA-DT -VEGF -IGF-1 -testosterone -cholesterol -compliance	-Serum PSA decreased for 14 / 41 men (36%) over 8 wks. (T *n*=5/20 (25%); S *n*=10/20(50%)) - Prolongation of PSA-DT occurred in 23/40 (58%) men over 8 wks.(T (65%); *n*=13/20); S (51%) *n*=10/21) -No. of men with slowest PSA-DT increased from 12	No grade II - IV toxicities were observed. Constipation (Grade I) in 3 men (7%) while on soy protein.	*Prostate cancer patients will consume diets rich in tomato products and soy with excellent compliance and bioavailability of phytochemicals.*

	(both arms).	mths; 32% 4-9 mths; 30% >9mths *Gleason score:* not specified *Mean age:* 70±7 yrs			(30%) to 19 (48 %) (p = 0.08) over the 8 wks. - A reduction in mean serum VEGF Wks 0-4, 4-8 (p < 0.04), with no effect of group observed . -No significant changes in testosterone or IGF-1 for either hormone therapy naıve or refractory men. -A clinically small decrease in serum total cholesterol (p = 0.009). -Excellent compliance.		
Multi-component Interventions							
Vaishampayan et al., 2007[23]	***Lycopene*** (L) 15 mg ***vs.***	PCa with rising serum PSA (3	Randomised phase II clinical	-Serum PSA	- No partial (.50% reduction) or	-No significant treatment-related	*Lycopene and soy isoflavones may*

USA.	***Lycopene plus soy isoflavones*** (LI) 40 mg twice daily	successive elevations at ≥2 wk intervals or at least 2 PSA readings of 10 ng/ml or more) following local therapy or while on hormone therapy (LHRH analogue) *Current or prior hormone therapy?* Yes, at least 4-6 wks prior: *n*=14 (36%) L; *n*=11(33%) LI *PSA, median:* 6.5 ng/ml. *PSA-DT:* not specified *Gleason score:* not specified *Median age*: 75 yrs	trial *n*=71/70 (*n*=38, L; *n*=33 LI) Duration: median 6 mths in L arm; 5.5 mths in LI arm	-PSA rise rate	complete PSA (PSA ≤4 ng/ml) response in either group. - 35/37 (95%) pts in the L group and 22/ 33 (67%) pts in the LI group achieved stabilization in serum PSA. - PSA rise rate significantly declined from pre- to post-therapy, *p* = 0.015 in the hormone sensitive group, and *p* = 0.017 in the hormone refractory group; in the latter group, L only resulted in a significantly greater decline than LI (*p* = 0.02)..	toxicities -Both regimens were very well tolerated. -1 patient reported a Grade 1 headache that was possibly related to therapy.	*delay progression of both hormone - refractory and hormone-sensitive PCa in men with PSA relapse, but there may not be an additive effect when the two are co-administered*

RANDOMISED HIGH-DOSE/LOW-DOSE TRIALS							
Monotherapies							
Paller, et al., 2013[24] USA	***Pomegranate (Punica granatum) extract (***POMx) ***1 g or 3 g*** of POMx (90% polyphenols), stratified by baseline PSA-DT and Gleason score	Biochemically recurrent PCa (rising PSA on ≥3 time points at least a month apart, within previous year) following primary therapy for localised PCa. (RP *n*=52; RP & RT *n*=12; RT *n*=54; cryotherapy *n*=2; brachytherapy *n*=19) *Current or prior hormone therapy?* Yes, at least 1 year prior: *n*=28/101 (1-g *n*=11/50; 3-g *n*=17/51) PSA: 5.3 ng/mL	Randomized, multi-centre, double-blind phase II, dose-exploring trial *n*=104/101/ 95ITT (*n*=46 low; *n*=49 high) Duration: up to 18 mths [92% of pts completed 6 mths, 70% completed 12mths; 58% completed 18 months or met the protocol]	-PSA-DT -testosterone -oestradiol -SHBG	-Median PSA-DT lengthened from 11.9 mths at baseline to 18.5 mths after treatment ($p < 0.001$). (In the low-dose group from median 11.9 to 18.8 months and median 12.2 to 17.5 months in the high-dose group, with no significant difference between dose groups ($p = 0.554$). -PSA-DT increases >100% of baseline were observed in 43% of pts. -Declining PSA levels were	No clinically significant toxicities were seen. Diarrhoea of grade ≤2 was seen in 1.9% and 13.5% of patients in the 1-g and 3-g dose groups, respectively, and deemed drug-related in only 5 patients (all 3-g POMx). In 1-g group: l case of reflux disease; in the 3-g group: 6 pts reported GI events - nausea (4 pts) ; abdominal pain,	*POMx treatment was associated with 6 month increases in PSADT independent of dose level without adverse effects. The significance of this on-study slowing of PSADT remains unclear.*

	(1-g 4.79; 3-g 5.74) *PSA-DT mean:* 14.7 mths *Gleason score, mean*: 6.5 *Mean age:* 74.5 yrs	observed in 13 patients (13%). -No significant changes occurred in testosterone. oestradiol trended higher in the 3-g group (28.0 to 32.3 pg ml-1; - SHBG increased in both groups (42.5–54.7 nmole l^{-1} in 3g-POMx group and 42.8–49.2 nmole l^{-1} in 1g-POMx) Difference: NS - -defined progression.	constipation, frequent bowel movements, stomach discomfort and vomiting (one case each).	

ADT – androgen deprivation therapy; AEs – adverse events; AS – active surveillance; BCR – biochemically recurrent; CRP -C-reactive protein; EBRT – external beam radiotherapy; GI – gastrointestinal; IGF – insulin-like growth factor; INF- international normalisation ratio; ITT – intention to treat; LHRH - luteinizing hormone releasing hormone; M0- baseline; M6 – end of month 6;mths – months; NS – not significant; P – placebo; PCa – prostate cancer; POMx – pomegranate extract; PSA – prostate specific antigen; PSA-DT – PSA doubling time; pts – patients; RCT – randomised controlled trial; RP – radical prostatectomy; RT – radiotherapy; RTE – external radiotherapy; SF – sulforaphane; SHBG – sex-hormone binding globulin; VEGF: vascular endothelial growth factor; wk – week; WW –watchful waiting; yrs – years

Table 2 Characteristics of excluded studies, grouped by reason excluded

First author, year & country	*Intervention, extract & dosage vs. comparator*	*Diagnosis & inclusion of ADT*	*Study design & duration*	*Endpoints*	*Results*	*Adverse events*
Non-randomised studies of herbal extract or isolated phytochemicals						
Clark et al., 2006[1] USA	***Lycopene*** capsule of escalating doses: 15/30/45/60/90 or 120 mg/ day	Biochemically recurrent PCa after surgery or radiotherapy *Current or prior hormone therapy?* Previous yes, but no new HT within 6 months pre-enrolment *Evidence of metastases?* No *PSA, median*: 4.4 ng/mL *PSA-DT:* 3.7 years *Gleason score:*	Phase I-II prospective dose-escalating (within-groups) trial *n*=36 (6 cohorts of 6 patients) *Duration:* 1 year	-PSA response ≥ 50% reduction -PSA response as a function of lycopene dose; -duration of PSA response; -time to PSA progression - PSA-DT or slope -toxicity	-No PSA responses -Median time to progression was not reached. -PSA-DT before-to- after NS - PSA slopes before-to-after : NS - Toxicity was mild - Compliance 100%	Well tolerated. One pt discontinued due to diarrhoea (grade 2 toxicity). Seven grade 2 transient abnormalities of serum glucose (*n*= 5) or creatinine (*n*=2).

		not specified *Median age:* 74 yrs				
Flaig et al., 2007[2] USA	***Silybinin from St. Mary's thistle (Silybum marianum):*** Silybin phytosome (Siliphos®) 2.5-20 g daily	PCa, progressive disease following surgery, radio-therapy(+/- ADT , and life expectancy ≥ 3 mths *Current or prior hormone therapy?* Yes, prior; LHRH analogues permitted *Evidence of metastases?* Uncontrolled brain metastases excluded *PSA, median:* 4.3 ng/mL *PSA-DT:* not specified	Phase I dose-escalation and pharmacokinetic study *n*=13 *Duration:* 12 – 52 wks (3-13 courses)	-PSA response (50% reduction) -toxicity -tolerability	- No objective PSA responses - 1 case elevated ALT -Hyper bilirubinaemia in 10/24 courses (41.67%); at 15g and 20g dose levels, but only in 2 of 32 courses (6.25%) with dose reduction to 13g; no grade 34 bilirubin toxicity. -Grade 1 elevation in creatinine (6 cases) usually resolved spontaneously. Grade 1 hypercalcemia. (6 cases), mild and self-limiting - Good follow-up compliance	Well tolerated. Minor halitosis in 2 pts, attributed to silybin-phytosome.

		Gleason score, mean: 7.6 *Median age:* 70 yrs			
deVere White et al., 2002[3] USA	***Shiitake Mushroom Extract*** (SME) polysaccharide/oligosaccharide complex, 8 g/day for a 70-kg man, adjusted at the rate of 1 g/10 kg body weight.	PCa and two consecutive elevated PSA readings; AS; WW; hormone therapy; hormone refractory (HR) *Current or prior hormone therapy?* Yes *Evidence of metastases?* Yes (*n*=21) *PSA, mean*: 10.5 after RP; 12.3 after RT; 13.9 AS; hormonal 10.7; HR 41.5 *PSA-DT:* not specified	Non-randomised, open label study *n*=62/61 *Duration:* 6 mths	-Change in PSA levels: complete = undetectable PSA; partial >50% decrease; stable response 50% change or less in PSA level; progression- 50%+ increase	- No effect : No appreciable difference in level of PSA or in the rate of change in the PSA level after treatment initiation - 61/62 evaluable pts for PSA

		Gleason score: mean not calculable *Mean age:*71.5 yrs				
Kamoto et al., 2010[4] Japan	***Mushrooms:*** *Agaricus blazei* Murill [Senseiro (KyowaWellness, Tokyo, Japan)] vs. *Ganoderma lucidum* mushroom [Rokkaku Reishi (Suntory Holdings, Osaka, Japan)]	Men with biochemical failure after radical treatment *Current or prior hormone therapy?* Yes, prior to radical therapy only. *PSA, mean:* not specified *PSA-DT* not specified*:* *Gleason score:* not specified *Mean age:* not calculable	Open label study *n*=51 *(n*=34 Senseiro*; n*=17 Reishi) *Duration*: Senseiro: 6 mths + 2–32 mths; Rokkaku Reishi 7 mths + 6–25 mths	-PSA partial response (> 50% reduction) -PSA-DT -serum testosterone	- No patient showed a partial response of serum PSA -For both *Senseiro* and *Rokkaku Reishi,* PSA-DT at 6 months was significantly longer than that at study entry (p = 0.03; median, 8.3–9.6 mths; and p = 0.02; median, 5.8–10.7 mths respectively). -30% pts on *Senseiro* and 12% of pts on *Rokkaku Reishi* showed a 20+% reduction in testosterone -Alteration of PSA-DT did not correlate with that of serum testosterone levels. .	No serious adverse effects were observed, but three pts withdrew following a rapid rise in serum PSA.

Twardowski,et al., 2015[5]	***White button mushroom (Agaricus bisporus)*** at 6 doses: 4/6/8/10/12, and 14 g/d.	BCR PCa/PSA failure following RP or RT. [PSA ≥0.2 ng/mL post RP, or ≥2.0 ng/mL above post-RT nadir. *Current or prior hormone therapy?* Yes, prior. Up to 9 months of neoadjuvant or adjuvant treatment, completed at least 6 months prior to registration *Evidence of metastases?* No *PSA, median:* 1.9 ng/mL *PSA-DT:* not reported *Gleason score, mean:* not	Phase I dose-escalation study *n*=36 *Duration*: 3 months	-PSA progression -DHT, DHEA and estrogen - cytokine multiplex - myeloid-derived suppressor cells in peripheral blood mononuclear cells -toxicity	- 11% overall PSA response rate. Complete response (CR) to undetectable levels in two pts on 8 and 14 g/d. Partial response (PR) in two pts on 8 and 12 g/d . 13 (36%) experienced some PSA decrease below baseline after 3 mths. -CR and PR demonstrated higher levels of baseline IL-15 than non-responders, and associated declines in MDSCs. -PSA responses did not correlate with serum testosterone, DHT or DHEA levels	Minimal side effects, mostly limited to grade 1 abdominal bloating. 1 case of grade 3 hyponatremia at dose of 8 g/d. Pt was taken off protocol.

		specified *Median age:* 68				
Guess et al., 2003[6] USA	***Modified Citrus Pectin (MCP),*** Pecta-Sol 14.4 g/day in divided doses	Recurrent adenocarcinoma of the prostate and low but progressively rising PSA following RP, external beam RT, RP & RT or cryosurgery *Current or prior hormone therapy?* Yes, previous. *Evidence of metastases?* No Up to stage 3c *PSA, mean:* 1.03 *PSA-DT, mean:* 6.9 mths *Gleason score, mean:* 6.9 *Mean age:* 69.6	Non-randomised phase II pilot study *n* =13/10 *Duration:* 12 mths	-PSA -PSA-DT	-No decreases in absolute PSA. - An increase in PSA-DT in 8 of 10 evaluable pts, but only seven (70%) were statistically significant (p≤0.05). -Compliance excellent (Pt subjective report)	Well tolerated. No serious side-effects but three pts (23%) withdrew due to side effects (two with mild abdominal cramps, one with mild diarrhea) that resolved soon after stopping the MCP.

		yrs				
Hussain et al., 2003[7] USA	***Soy isoflavones*** (200 mg/day) orally	PCa and rising PSA (i) under watchful waiting; or (ii) increasing serum PSA following local therapy, or (iii) while receiving hormone therapy *Current or prior hormone therapy?* Yes, prior. Current LHRH analogues permitted. *Evidence of metastases?* Yes *PSA, mean:* 13.3 ng/ml. *PSA-DT:* Not specified *Gleason score:* Not specified	Pilot study *n*=41 *Duration:* 0.8 – 6 mths	-PSA levels -Biomarkers (IGF and oxidative stress markers) -Toxicity	-No complete (normalisation of PSA) or partial (≥50% reduction) PSA responses. - serum PSA rise rate decreased in whole group (p = 0.01). - no significant change in the level of 5-OH-mdU or plasma levels of IGF-1 and IGFBP-3 - no observed changes in serum testosterone	Very well tolerated, with no toxicity attributable to Novasoy treatment. No grade 3+ adverse events.

		Mean age: 73 yrs				
de Vere White et al., 2004[8] USA	***Genistein-rich extract,* 5 g/day*:*** 40% isoflavones (Novasoy) added to a mushroom (*G. lucidum*) mycelia culture - a total of 450 mg/day of genistein, plus an additional 450 mg/day of other aglycone isoflavones	Five treatment groups: failed RP; failed RT; intermittent hormonal therapy; combination RP and RT; AS or WW. *Current or prior hormone therapy?* not specified *Evidence of metastases?* Yes *PSA, mean:* 7ng/mL *PSA-DT:* not specified *Gleason score, mean:* not calculable *Mean age:*74.5 yrs	Open label pilot study *n*=52 *Duration*: 6 mths	-PSA levels - Clinical chemistries (ALP, AST, total bilirubin, creatinine, cholesterol, and GGT)	-One AS pt had ≥ 50% reduction in PSA -7 AS pts had PSA reductions < 50%. -Pts in AS group had PSA levels on average 27% lower than otherwise predicted (p=0.026); -Clinical chemistries were all unaltered	3 pts withdrew due to adverse events (diarrhea).

Kwan et al., 2010[9] Canada	***Soy beverage,*** 500 mL/day, equivalent to approximately 50–100 mg isoflavones	Rising PSA after curative radical radiation for prostate cancer but no clinical evidence of distant disease *Current or prior hormone therapy?* Yes, during primary treatment *Evidence of metastases?* No *PSA, median*: 5ng/mL *PSA-DT, median:* 18.2 mths *Gleason score, median:* 6 *Median age:*78 yrs	Phase II non-randomised study *n*=34/29 *Duration*: 6 mths	-PSA -PSA-DT -Tolerability -Compliance	- PSA showed a declining trend in 4 patients (13.8%), -Eight pts (27.6%) had > 100% prolongation of PSA-DT, but PSA-DT also showed a 50% or more shortening in 5 patients (17.2%). - Mean consumption of the assigned soy beverage 29 subjects who had more than 1 mth soy was 93%.	Well tolerated. Most common AE was grade I GI complaints; Hives (1 case) and weight gain (4pts) also reported.
Pendleton et al., 2008[10] USA	***Soy milk*** containing soy milk containing 141 mg isoflavonoids per day	PSA recurrent prostate cancer after previous local	Phase II non-randomised clinical trial	-PSA -PSA-DT -serum	- PSA reduced in 6 pts but increased in 13 pts. -PSA slope significantly	One pt (5%) withdrew due to diarrhoea.

		therapy *Current or prior hormone therapy?* ADT not within 12 months of study entry *Evidence of metastases?* No *PSA, median:* 9.2 ng/mL *PSA-DT, median* 15 mths: *Gleason score, median:* 7 *Median age:* 73 yrs	*n*=20 *Duration:* 12 mths	testosterone, lipids, -quality of life	decreased in 6 pts ($p<$ 0.05), but significantly increased in 2 patients ($p<$ 0.05). -Improvements in PSA-DT in 14 pts (p = 0.044) -Free testosterone (median 10.3 vs. 9.7 ng/ml, p = 0.031), but no change in total testosterone or cholesterol -QoL: no significant change -Compliance high; only two pts did not ingest the required amount of soy milk	No other side-effects.
Pantuck et al., 2006[11] USA.	***Pomegranate (Punica granatum)*** (Wonderful variety, 570 mg total polyphenol gallic acid equivalents per 8 ounces(250 mL) of	Rising PSA [PSA>0.2 and <5 ng/mL] after surgery or radiotherapy. *Current or prior*	Phase II, Simon two-stage clinical trial *n*=46 *Duration:* 6 – 40 mths (until	-PSA -PSA-DT - hormone levels (testosterone, androstenedione, oestradiol,SHBG,	- From both stages, 16 (35%) achieved a PSA decrease (mean, 27%). Four of these achieved a PSA decline >50%. -Mean PSA-DT increased	Well tolerated. No serious adverse events.

	pomegranate juice daily	*hormone therapy?* No *Evidence of metastases?* No *PSA, mean:* 2.23 ng/mL *PSA-DT, mean:* 14.3 mths *Gleason score:* 5-7 in 94% pts *Mean age:* not specified	disease progression)	DHEA, IGF)	from 15 to 54 months post-treatment ($p <$ 0.001). -No significant difference in pre- and post-treatment hormone levels ~~-A 12% decrease in cell proliferation and a 17% increase in apoptosis ($p =$ 0.0048 and 0.0004, respectively)~~	
Intervention combined with vitamins/minerals						
Schroder et al., 2005[12] Netherlands	***Soy isoflavones*, *lycopene, silymarin and antioxidants vs. placebo***	Prostate cancer and rising PSA after RP or RT *Current or prior hormone therapy?* No *Evidence of metastases?* Not specified *PSA, mean:* 3.3	RCT crossover study - tertiary prevention *n*=49/46 *Duration:* 10 wk treatment phases separated by a 4-wk washout.	- PSA slope - PSA-DT - hormone levels (testosterone, DHEA, SHBG, LH)	-Significant decrease in non-transformed PSA slope ($p = 0.03$) and ^{2}log PSA slope ($p = 0.041$) [PP analysis] -A 2.6 fold increase in the PSA–DT for placebo and supplement periods (PP) - No changes in hormone levels	The few adverse events (eg GI complaint) were judged not related to the dietary supplement.

		ng/mL *PSA-DT:* not specified *Gleason score:* not specified *Mean age:* 70 yrs			- Two pts were withdrawn for < 80% compliance. -Compliance was >90% in 41/46 pts.	
Kranse et al.,[13] 2005 Netherlands	***Isoflavones plus green tea extract, lycopene, antioxidants*** *including carotenoids, selenium, phytosterol, alpha tocopherol* and margarine ***vs. placebo***	Hormonally untreated men with PCa and rising PSA after RP or RT or under watchful waiting. *Current or prior hormone therapy?* No *Evidence of metastases?* No *PSA, median:* 3.24 ng/mL *PSA-DT:* not specified *Gleason score:* not	RCT crossover study *n*=37 *Duration:* 6 wk treatment phases separated by a 2wk washout	- PSA, total and free - PSA-DT -male sex hormone levels	--Free PSA decreased during verum (p = 0.02). -Total PSA-DT unaffected, but NS increase from 41 weeks during placebo period to 44 weeks during verum. -In men in whom the free androgen index decreased (21/32), there was a significant decrease in the slopes of both total and free PSA (p = 0.04). -Male sex hormone levels lower with verum (p = 0.02) – (DHT:-0.11 nmol/L, p = 0.005;	No serious adverse events; one patient withdrew due to abdominal pains.

		specified *Median age:*70 yrs			testosterone:-1 nmol/L, *p* = 0.02).	
Barber et al, 2006[14] UK	***Lycopene*** whole-tomato lycopene supplementation 10 mg/day (two tablets of Lycoplus – each tablet contains 5mg lycopene, 100mg vitamin C, 1.25mg vitamin E, 0.83mg phytoene and phytofluene and 0.21mg β-carotene).	Men with localised PC on clinical surveillance (AS or BCR/WW) *Current or prior hormone therapy?* Yes, at least one year prior *Evidence of metastases?* No *PSA, mean:* 23.3 ng/ml *PSA-DT:* Not specified *Gleason score, mean:* 6 *Mean age:* 73 yrs	Phase II clinical within-groups pilot study *n*=37 *Duration, mean:* 10.4 mths	- PSA velocity - PSA-DT -toxicity	-Regression slops of (log) PSA vs. time decreased in 26/37 patients (70%), (p-0.0007)., -PSA-DT: non- significant increase (median increase of 174 days) -No toxicity	Discolouration of faeces.
Dorff et al, 2013[15] USA	***Prostate Health Cocktail*** (PHC), a supplement containing	BRC, rising PSA post RT or RP or both with doubling	Open label pilot study *n*=40/39	-PSA response -PSA-DT - circulating	-No men had complete or partial PSA response -15/39 men (38%) had a	Grade 1 or 2 liver enzyme elevations [transient], grade 1

	vitamin D & E, saw palmetto, lycopene, green tea and soy extracts	time between 3 and 36 months, *Current or prior hormone therapy?* Yes, at least 3 mths prior with testosterone recovery *Evidence of metastases?* No *PSA, median:* 2.8 ng/mL *PSA-DT, median:* 9.4 mths *Gleason score:* 23% had Gleason >7 *Median age*:67 yrs	*Duration:* 4 week cycles (1-13, median 10)	tumour cells -DHT -testosterone	PSA decline (1.1%-55% max decrease); median change at 12 weeks was 18.1%; -PSA-DT median 6.7 mths; 12/37 (32%) had slower PSA-DT Circulating tumor cells in 16/33 pts . No change in testosterone or DHT	or 2 GIT symptoms (9), grade 1 weakness/ dizziness/pain (5), and grade 1 fatigue (2).
Risk of BCR PCa						
Bosland et al[16]; 2013 USA	***Soy protein isolate vs. placebo***	Men at high risk of recurrence after RP	RCT – placebo controlled *n*=177/159	-Biochemical recurrence rate (defined as development of	-28.3% developed BCR within 2 years (close to the a priori predicted rate of 30%) [22 (27.2%) in	Trial stopped after 45 men developed BCR due to lack of treatment effect.

		Current or prior hormone therapy? Not specified *Evidence of metastases?* Yes *PSA, mean pre-op:* 7.4 *PSA-DT:* Not specified *Gleason score, mean*: 7 *Mean age:* 61 yrs	(81soy;78 P) *Duration*: up to 2 years	PSA >0.07 ng/mL) over first 2 ys following randomisation - time to recurrence - adherence	the intervention group and 23 (29.5%) in P group.] -Self-reported adherence was excellent, with 152 pts (96%) reporting having consumed more than 90% of the packets supplied.	Six potentially related GI issues but no difference to P group.
Vidlar et al., 2010[17] Czech Republic	***Silymarin*** [St. Mary's thistle***;*** *Silybum marianum* (SM)] 570 mg, *combined with* ***selenium (Se)*** 240 µg as selenomethionine ***vs. placebo***	Men with PCa after radical prostatectomy *Current or prior hormone therapy?* Not specified *Evidence of metastases?* Not specified *PSA, mean:* Not	RCT -placebo controlled *n*=37 (*n*=19, SM-Se group) (*n*=18, P) *Duration:* 6 mths	-QoL, -haematology & basic clinical chemistry (ALT, AST and GGT, cholesterol, TAG, ApoA1 and ApoB) -oxidative stress markers -testosterone	-Improved QoL -decreased LDLs and total cholesterol from baseline in SM-Se group, $p<0.05$ increase from baseline in erythrocyte count and hemoglobin in SM-Se group, $p<0.05$ -No change to	No adverse events reported.

		specified *PSA-DT:* Not specified *Gleason score:* Not specified *Mean age:*63.8 yrs			testosterone or antioxidant status	
Advanced PrCa						
Stenner et al., 2012[18] Switzerland	***Pomegranate (Punica granatum)*** juice, 500 ml or 500 mL placebo beverage/day for 4 weeks, followed by 250mL pomegranate juice/day (both arms) for a further 4 weeks.	Early PSA rise after initial therapy, and PSA ≥ 5 ng/ml *Current or prior hormone therapy?* Yes, both *Evidence of metastases?* Yes *PSA, mean:* 74.6 ng/mL *PSA-DT:* Not specified *Gleason score:* ≥ 8 in 49%	RCT - double blind, placebo controlled phase IIb *n*=103/98 *Duration*: 8 wks	-PSA values -pain scores -adherence	-No differences between groups for PSA values or pain scores - Adherence to protocol was good, with 94 pts (96%) completing the first period (days 1-28), and 87 pts (89%) completing both periods (days 1-56).	No grade 3 or higher toxicities. Bowel disturbances (1 case obstipation and 1 diarrhoea in verum group) most frequently reported.

	*Mean age:*72.5 yrs

ADT– androgen deprivation therapy; ALP – alkaline phosphatase; Apo – apolipoprotein; AS –active surveillance; AST – aspartate amino-transferase; BCR – biochemical recurrence; DHEA – dehydroepiandrosterone; GGT – gamma-glutamyltransferase ; GI – gastrointestinal; HR – hormone refractory; HT – hormone therapy; IGF – insulin-like growth factor; LDL –low density lipoprotein;LH – luteinising hormone; mths – months; M- months; P – placebo; PCa – prostate cancer; PP – per protocol analysis; PSA – prostate specific antigen; PSA-DT – PSA doubling time; pt/s –patient/s; QoL – quality of life; RP – radical prostatectomy; RT – radiotherapy; SF - sulforaphane ; SHBG – sex-hormone-binding globulin; SME - Shiitake Mushroom Extract; TAG – trigylcerides

Table 3 Reporting according to the Proposed Elaboration of CONSORT checklist Item 4 for reporting randomized controlled trials of herbal medicine

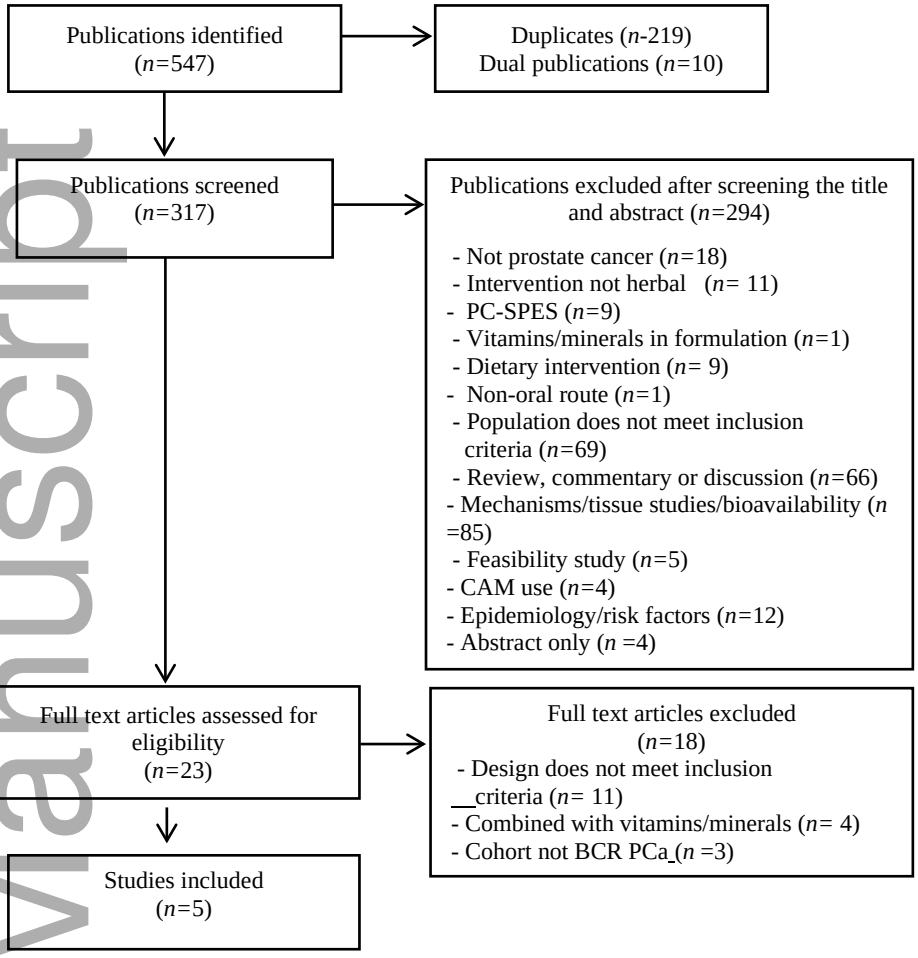
	Cipolla et al., 2014	Thomas et al., 2014	Grainger et al., 2008	Vaishampayan et al., 2007	Paller et al., 2013
4A: Herbal medicinal product name:					
1. *i) Latin binomial;*		Yes			Yes
ii) botanical authority;					Yes
iii) family;					
iv) common names	Yes	Yes	Yes	Yes	Yes
2. *The propriety product name (brand name) or extract name and name of manufacturer of the product*		Yes	N/A	Yes	Yes
3. *Whether the product is authorised (licensed or registered) in the country in which the study was conducted.*		Not required	N/A		
4B: Characteristics of the herbal product:					
1. *Plant part used in extract*		Yes/No	Yes/No		
2. *Type of product eg raw, (fresh or dry) extract;*			Yes		
3. *i) Type and concentration of extraction solvent use (eg 80% ethanol etc)*; *and*			N/A		
ii) the ratio of herbal drug to extract (eg 2:1)		Green tea –Yes Others N/A			
4. *The method of authentication of raw material, the lot number of raw material; whether a voucher specimen was retained; details of where deposited and reference number.*		Available on request			

4C: Dosage regimen and quantitative description: 1. *I) The dosage of the product;*	Yes	Yes	Yes	Yes
ii) duration of administration; and	Yes	Yes	Yes	Yes
iii) how these were determined		Yes		Yes
2. *The content of all quantified herbal product constituents per dosage unit form. Added materials such as binders etc.*	No/Yes	Yes		
3. *For standardised products the quantity of active/marker constituents per dosage unit form*	N/A	N/A	N/A	N/A
4D: Qualitative testing: 1. *i) Products chemical fingerprint and methods used;*		Yes		
ii) who performed the chemical analysis;		Yes		
iii) whether a sample of the product was retained; iv) if so, where	Yes			
2. *i) Description of any special testing/purity testing undertaken;*	Presented to reviewers			
ii) which unwanted components were removed, and iii) how				
3. *i) Standardisation: what to standardise; and ii) how*				
4E: Placebo/control group: • *The rationale for the type of control/placebo used*	Yes	N/A	N/A	N/A
4F: Practitioner/s: • *A description of the practitioners (training and practice experience) who are a part of the intervention*				

Table 4 Key limitations identified with phytotherapeutic research in this area

small sample sizes
short follow up periods
inadequate power
significant variations in study populations
significant variations in intervention
significant variations in design
significant variations in endpoints
publication bias cannot be ruled out
bias sometimes difficult to establish due to incomplete reporting
some manufacture driven trial data
type and concentration of extraction solvent use not commonly reported
extraction methods and actual bioavailability of compounds are variable
the ratio of herbal drug to extract not commonly reported
equivalence of product with expected bioactivity is variable

Figure 1. Flowchart of selection process



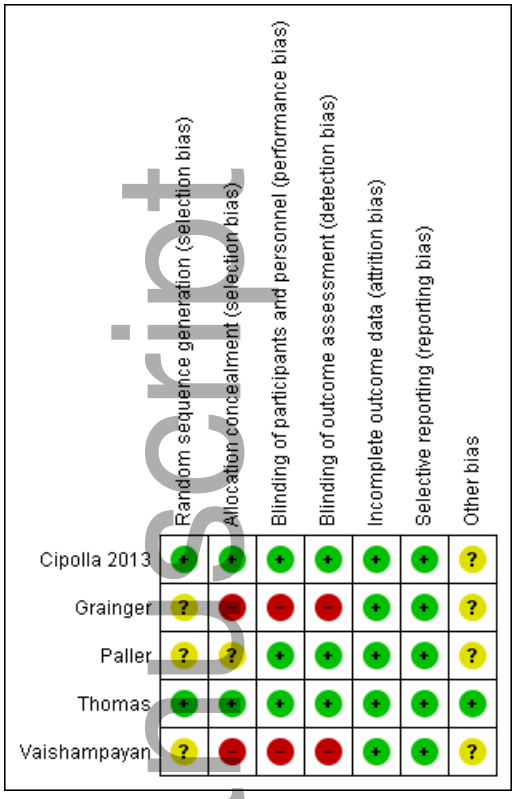


Figure 2A. Risk of bias summary of included studies

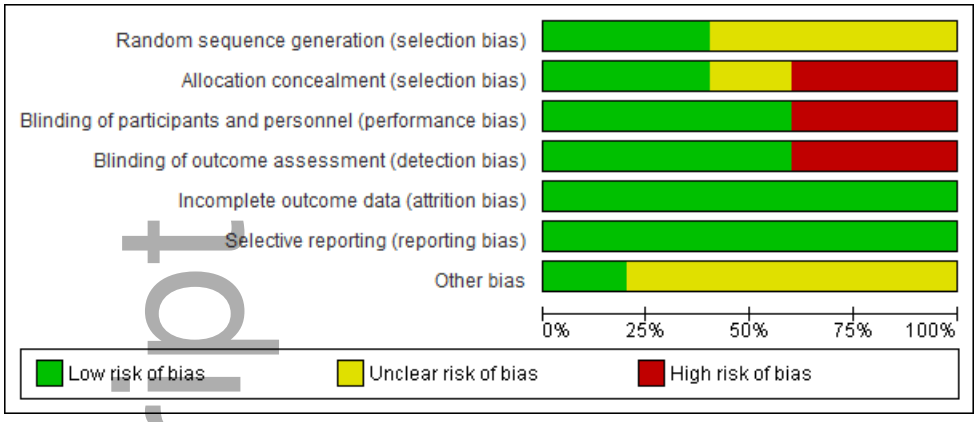


Figure 2B. Risk of bias graph of included studies