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REVIEW

Nutraceutical treatment and prevention of benign prostatic hyperplasia and prostate cancer

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Summary *During the last years, pharmaceutical innovations in primary care are dramatically less frequent and will be even more rare in the next future. In this context, preclinical and clinical research oriented their interest toward natural compounds efficacy and safety, supporting the development of a new "nutraceutical" science. Medicinal plants, in the form of plant parts or extracts of them, are commonly used for the treatment of prostate diseases such as benign hypertrophy, prostatitis and chronic pelvic pain syndrome.*

The pharmacological properties searched for the treatment of prostatic diseases are anti-androgenic, anti-estrogenic, anti-proliferative, antioxidant and anti-inflammatory. The most studied and used medicinal plants are Serenoa repens, Pygeum africanum and Urtica dioica. Other promising plants are Cucurbita pepo, Epilobium spp, Lycopersum esculentum, Secale cereale, Roystonea regia, Vaccinium macrocarpon. In parallel, epidemiological studies demonstrated that diet may play an important role on incidence and development of prostatic diseases. The Mediterranean diet is rich of elements with anti-oxidant properties that act as a protective factor for prostatic cancer. Similarly, low intake of animal protein, high intake of fruits and vegetable, lycopene and zinc are a protective factor for benign prostatic hyperplasia (BPH).

Serenoa repens in the treatment of symptoms of BPH has been tested either alone or, more frequently, in combination with other medicinal plants, alpha-blockers and inhibitors of 5-alpha reductase (5-ARI). Recent meta-analyses found the effectiveness of Serenoa repens similar or inferior of that of finasteride and tamsulosin but clearly higher than that of placebo in the treatment of mild and moderate low urinary tract symptoms (LUTS), nocturia and discomfort. Clinical trials showed potential synergistic effect of Serenoa repens with other medicinal plants and drugs. In addition to Serenoa repens, there are many other medicinal plants for which clinical evidence is still controversial. Urtica dioica, Pygeum africanum and Curcubita pepo can be considered as an adjunct to the common therapies and their use is supported by studies showing improvement of symptoms and flowmetric indices. Lycopene and selenium are natural products with antioxidant and anti-inflammatory action. The combination of lycopene and selenium with Serenoa repens was able to reduce inflammation in histological prostate sections and to further improve symptom scores and urinary flow in patients with BPH on tamsulosin treatment. Similar effects could be obtained with the use of other carotenoids, such as astaxanthin, and/or zinc. Efficacy on symptoms of patients with BPH of some polyphenols such as quercitin, equol and curcumin have been demonstrated by clinical studies. Pollen extract is a mixture of natural components able to inhibit several cytokines and prostaglandin and leukotriene synthesis resulting in a potent anti-inflammatory effect. Pollen extracts significantly improve symptoms, pain, and quality of life in patients affected by chronic pelvic pain syndrome and chronic prostatitis. Beta-sitosterol is a sterol able to improve urinary symptoms and flow measures, but not to reduce the size of the prostate gland.

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide-signaling molecule with anti-inflammatory and neuroprotective effects that can have an interesting role in the management of chronic pelvic pain syndrome and chronic urological pain.

Finally, several plant-based products have been subjected to preclinical, in vitro and in vivo, investigations for their potential pharmacological activity against prostate cancer. Some epidemiological studies or clinical trials evaluated the effects of beverages, extracts or food preparations on the risk of prostate cancer. Some plant species deserved more intense investigation, such as Camelia sinensis (green or black tea), Solanum lycopersicum (common tomato), Punica granatum (pomegranate), Glycine max (common soy) and Linum usitatissimum (linen).

KEY WORDS: *Medicinal plant; Prostate; Benign prostatic hyperplasia; Prostate cancer; Antiproliferative effect; 5α-reductase; Serenoa repens; Pygeum africanum; Urtica dioica; Cucurbita pepo; Lycopene; Selenium; Polyphenols; Pollen extract; Beta-sitosterol; Palmitoylethanolamide.*

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Introduction to nutraceutical prescription

(Arrigo F.G. Cicero)

During the last years, the pharmaceutical innovation in primary care are dramatically less frequent and will be even more rare in the next future. In this context, preclinical and clinical research oriented their interest toward natural compounds efficacy and safety, supporting the development of a new nutraceutical science. The term "*nutraceutical*" has been created by *Stephen De Felice* in 1989 from the union of the words "*nutrition*" and "*pharmaceutical*", to include dietary components or (more generically) botanical bioactive compounds with positive effects on well-being and health preservation, but also for the cure of some common health disorders (1).

The most part of nutraceuticals has been identified in vegetables (2) such as β-glucans, tocotrienols, plant sterols/stanols, polifenols (anthocyanins, proanthocyanidins, flavonols, stilbens, catechins, epicatechins, cumarins, ellagic acid, isoflavons, lignans, etc.) whose biological activities are numerous and often well-documented. Much less numerous are the nutraceuticals of animal origin, even if some of them, as the omega 3 polyunsaturated fatty acids are among the most used nutraceuticals around the world (4).

There are a large number of medical areas where nutraceuticals are currently used, among them urology and andrology. To warrant the consumer safety and to help the citizens to correctly choose the most adequate nutraceuticals, current laws state that the marketed products should be safe and adequately labelled.

Then, the *European Commission* promoted specific rules on the nutritional and healthy properties of dietary supplements that can be disclaimed on nutraceutical boxes (*Health Claims*) (*December 20th, 2006*) (5, 6).

The *European Commission* approved health claims are based on the opinions of an external agency, the *European Food Safety Authority* (EFSA), that periodically should organize meeting of expert panels selected to evaluate and re-evaluate health claims based on the available preclinical and clinical scientific data (7, 8).

Currently, the use of dietary supplements and functional foods for the health maintenance and disease prevention is in continuous increase and the number of available products in the market is growng even more intensively. So, how to navigate (as prescribers, sellers or consumers) among 20-30 products containing similar bioactives, in different combinations, that suggest similar effects but with costs often really different? For some of them we have (almost) complete preclinical and clinical pharmaco-toxicological dossiers, till the availability of meta-analysis of randomized clinical trials. However, in the most part of cases, what is known about single bioactives is transferred to the combined marketed products without any kind of test on the final formulation. The main reasons of this are resumed in Table 1.

In fact, the companies need to market new (at least apparently) "*unique*" products in a context where the registration and copyright are easily copied and scarcely protected. The cost of the high quality bioactives and the need to create original products often push the industries to add more and more low-dosed components in a single pill/tablet to make the product more complex ("*original*") trying to make up eventual synergies, almost never demonstrated. Of course, the use of low-dosed bioactives is a warranty of product safety and tolerability and to avoid the comparison to pharmacological drugs of natural origin, however it reduces the probability to observe a clinical effect. Thus, how to recognize a serious product?

Table 1.
Factors limiting the application of available scientific data to the combinations of nutraceutical products available in the market.

• No legal need to prove efficacy
• No legal possibility to declare efficacy (lack of approved health claim)
• Incomplete pharmaco-toxicological dossiers
• Cost of high quality bioactives and/or of pharmaceutical technologies used to make them bioavailable (for instance Coenzyme Q10, Resveratrol, Lycopene)
• Industry need to differentiate their product from the other ones
• Need to produce absolutely safe products (often limiting the dosage under the efficacy level)

As regards monocomponent products, it is relatively easy. The proposed nutraceuticals should have an adequate bibliography support that should include (at least):

– The description of the mechanism of action, eventually associated with notes on pharmacokinetic (for instance, resveratrol has an oral bioavailability near to zero, being the supplementation of the raw form of the molecule very doubtful);
– A therapeutic indication supported by randomized, double-blind, placebo-controlled clinical trials carried out on subjects similar to the ones we need to treat in regard to age, ethnicity, and disease profile;
– Quality (bioactive titration) and dosage similar to the one shown to be efficacious and safe in clinical trial.

As regards nutraceuticals in combination, the requirement are similar if the single components are all supported by scientific evidence of efficacy and safety, and if they are included in the same pill/tablet at the tested doses. If a kind of synergy of components is suggested, this has to be clearly demonstrated with specific trials or, alternatively, it should be never mentioned. Of course, the risk of interaction between the components of a combined nutraceutical should also been considered (9).

When the informative brochure of the product is complete and correct, this will help the prescriber to adequately select the more adequate product in the market, being also more protected from a legal point of view (10).

We have to remember that the final responsibility of the prescriber remains in the knowledge to of the effective dosages of the bioactives (based on the results of adequately designed clinical trials or their meta-analysis), of possible pharmacological interaction and adverse events, and of the adequate length of treatment (in particular, avoiding short cyclic treatment for chronic diseases).

Preclinical studies on medicinal plants, used in the treatment of prostatic diseases

(Annabella Vitalone, Olta Allkanjari)

Phytotherapy could be useful in the treatment and pre-

vention of mild to moderate prostatic diseases. The etiology of prostatitis, *benign prostatic hyperplasia* and hypertrophy (BPH) can be complex and the intervention is often multi-targeted.
The pharmacological properties useful for the treatment of the urinary tract diseases are anti-androgenic, anti-estrogenic, anti-proliferative, antioxidant and anti-inflammatory.
The most studied and used medicinal plants are: *Serenoa repens*, *Pygeum africanum* and *Urtica dioica*. Phytosterols and fatty acids are the pharmacologically active phytochemicals usually found in these plants; however, they are more used as a phytocomplex (total extract of the plant) than as isolated compounds. In preclinical research, *Serenoa* is responsible of numerous mechanisms of action, including: inhibition of the *dihydrotestosterone binding* (DHT) to its receptors present in the cytosol of prostatic cells, of 5α-reductase (both isoforms), of *cyclooxygenase* (COX) and of 5-*lipoxygenase* (LOX); it induces apoptosis of prostatic epithelial cells and it presents antiestrogenic activity, spasmolytic effect due to blockage of calcium channels and β-adrenergic antagonism (11). Similar mechanisms have been found for Pygeum and nettle, probably due to the presence of β-sitosterol and consisting in the inhibition of 5α-reductase, of prostatic cell proliferation, blockage of the cell cycle in the G2 phase and induction of apoptosis in prostate cancer cells (12, 13). Furthermore, atranorin and atraric acid, present in Pygeum, inhibit the androgen receptor nuclear translocation, endogenous PSA expression, and fibroblast proliferation in human prostate cells. Lignans, lectins and polysaccharides contained in nettle extract, seem to exert anti-proliferative and anti-inflammatory activity, and to inhibit the binding of sex hormones to the sex hormone binding globulin.
Other promising plants are *Cucurbita pepo*, *Epilobium spp* (14), *Lycopersum esculentum*, *Secale cereale*, *Roystonea regia*, *Vaccinium macrocarpon*. They have anti-inflammatory and anti-androgenic properties. In particular, the tomato fruit extract (containing lycopene, polyphenols, etc.) down-regulates 5α-reductase and inhibits COX.
The inhibitory properties against 5α-reductase appear also for *Roystonea regia*, probably exerted by the fatty acids. Furthermore, in vitro, antiproliferative, antimicrobial, antioxidant and radical scavenger properties seem encouraging for epilobio, tomato, pollen extracts of *Secale cereale* and *Roystonea regia* (15). Vaccinium macrocarpon inhibits aromatase and is helpful in the urinary tract infection, because it acidifies the urine and inhibits bacterial adherence to uroepithelial cells (16). The mechanism of action of the plants listed above has to be confirmed in in vivo models. Other specific plants and/or substances have still limited scientific evidence.

Nutritional epidemiological studies and prostate diseases

(Giorgio Ivan Russo, Gaetano Largana)

Prostatic diseases, like *prostatic cancer* (PCa) and *benign prostatic hyperplasia* (BPH), are influenced by different factors, like age, hormone profile and genetics. Several epidemiologic studies demonstrated how diet may play an important role in prostatic diseases incidence and development.
Knowledge of the different kind of effects of foods on prostate could help us to understand how better prevent and treat these diseases, exploiting synergic effects of specific drugs.
PCa represented the most common incident cancer in men in developed countries in 2013 (17).
Western diet, characterized by high intake of energy, red and processed meats and fat but low intake of fibres has been associated to an increased risk to develop an advanced PCa (18, 19). Instead, *Mediterranean diet* (MeDi), that is characterized by use of olive oil and high intake of fibres, fish, fruits, vegetables, legumes and cereals in association with moderate to low intake of dairy products and moderate intake of wine, is a diet rich of components with anti-oxidant proprieties that could protect from PCa (20). In fact, countries following MeDi, particularly Southern European countries, have a lower incidence and mortality from PCa, compared to other European countries (21, 22).
A 2015 review included several papers evaluating the effect of single components of MeDi on incidence and development of PCa: olive oil, an unsaturated fat, was not associated with the risk of advanced PCa, that was increased for saturated fat (23-26); in a 2010 metanalysis (27) there was an association between fish consumption and a significant reduction of PCa-specific mortality; higher intake of legumes and cereals has been associated with a decreased risk of several cancer (28) , included PCa (29, 30); there was a positive association between dairy product consumption and PCa (31); a 2010 review showed how a moderate daily intake of alcohol, 3 drinks per day, does not appear to influence PCa risk (32); lastly *Russo et al.* showed how consumption of food rich of phenolic acids, like fruits, vegetable, coffee, tea and cacao were associated to a reduced risk of PCa development (33).
BPH is one of the most common medical conditions in older men (34). A study evaluating more than 3500 patients showed that total protein intake (particularly animal protein) is positively associated with the risk of BPH, while in men who consumed at least 4 servings per day of fruits and vegetable, there was a lower risk of BPH (35-38). Lycopene, contained in tomatoes, seems to help to reduce *lower urinary tract symptoms* (LUTS) and to inhibits BPH progression, as well as epigallocatechin-3-gallate, contained in green tea (39, 40). The human prostate gland contains higher level of zinc than other tissues and *Kristal et al.* (38) showed that zinc could have a protective role for BPH, although excessive consumption may significantly increase the risk of advanced PCa (41-43). Like fot PCa, high alcohol intake may be associated with BPH (44).
In conclusion, epidemiologic studies demonstrated that diet habits could help to prevent PCa and BPH incidence and their development and could be used in a multimodal therapy to prevent and treat these diseases. Particularly, MeDi, a diet rich of elements with anti-oxidant properties related to use of olive oil, high intake of fibres, fish, fruits, vegetables, legumes and cereals, moderate to low intake of dairy products and moderate intake of wine, is a protective factor for PCa. Similarly,

low intake of animal protein, high intake of fruits and vegetable, lycopene and zinc are a protective factor for BPH. Instead, high intake of saturated fats and animal meat, and excessive alcohol consumption could be a risk for both PCa and BPH development.

Clinical use of Serenoa repens in BPH treatment

(Kostantinos Stamatiou)

A variety of phytotherapeutic agents are used in traditional and alternative medicine to treat lower urinary tract symptoms. The most commonly used preparations originate from the species Saw palmetto. Their extract *Serenoa repens* (SR) exhibits marked anti-inflammatory, anti-androgenic and anti-proliferative effects. For this reason, it has been the subject of clinical and experimental research on the treatment of symptoms of benign prostatic hyperplasia.

A non-systematic search was performed in electronic libraries for clinical trials, experimental studies and systematic reviews on the topic. Main outcomes of the abovementioned studies are displayed in Table 2.

SR in the treatment of symptoms of BPH has been tested either alone or, more frequently, in combination or in comparison with other phytotherapeutics, alpha-blockers and inhibitors of 5-α reductase (5-ARI).

With regard to studies using SR extract as monotherapy for men with BPH an confirmed *lower urinary tract symptoms* (LUTS), *Lopatkin et al.* and *Giulianelli et al.* showed significant improvement in symptom scores (IPSS ans IIEF-5) and uroflowmetry at 6-month follow up (45, 46). Accordingly, *Sinescu et al.* (47) demonstrated a significant improvement of mild or moderate LUTS, *quality of life* (QoL), urinary flow, residual urinary volume and erectile function and *Gerber et al.* demonstrated improvement in urinary symptoms compared with placebo (but no measurable effect on urinary flow) (48). On the contrary, the large trial of *CAMUS Study Group* found no differences between improvements of urinary symptoms between SR extract and placebo group at 72-week follow-up (49) in accordance to other placebo-controlled trials (50, 51). Recently, *Ye et al.* (52) in a double blind, placebo-controlled study found significant improvements in the urinary flow, IPSS, male sexual function (MSF-4 and IIEF scores) in the SR extract group. In none of these studies significant side effects of SR were observed. Higher doses of SR cannot influence neither the impact on LUTS nor the quality of sexual performance (53, 54).

Efficacy of SR was compared to other treatments. *Alcaraz et al.* (55) found equivalent efficacy with respect to alpha-blockers and 5-ARI in LUTS improvement; *Pytel et al.* (56, 57) confirmed similar results as measured by IPSS, QoL, index of sexual function (MSF-4), size of the prostate, urodynamic parameters (but no change of plasma sexual hormones). A prospective multicentre double-blind randomized study comparing tamsulosin (0.4 mg/24h) with SR (320 mg/24h) found no differences in IPSS, urinary flow and PSA at 12-month follow up (58). SR was used in combination with other treatment. The addition of dietary supplements or other phytotherapeutic agents improved the effect of SR (59, 60). The combination of SR with alpha-blockers agents (tamsulosin, silodosin) was more effective than monotherapy according to some Authors (61, 62) although others were not able to demonstrate no extra benefits by combination therapy (63-68).

Recent meta-analyses found the effectiveness of SR similar or inferior of that of finasteride and tamsulosin but clearly higher than that of placebo in the treatment of mild and moderate LUTS, nocturia and discomfort (69-71).

The ability of SR to reduce prostatic size is controversial, although the association with other natural compounds (such as lycopene, other carotenoids and selenium) could enhance the activity of SR alone by augmenting pro-apoptotic effects and suppressing growth factors expression in hyperplastic prostates (72). The evaluation of the results of BPH treatment with SR is made difficult by the variability of the composition of products of different brands in relation the concentration of free fatty acids and the method of extract preparation.

Table 2.
Design of studies of Serenoa repens for BPH treatment.

	Placebo	SR	5ARI	Alpha-blockers	Pinus + Crocus +SR	SR+LY+ +SE	Alpha-blocker SR+LY+ SE	Alpha-blocker SR
Dedhia (50)	+	+						
Bent (51)	+	+						
Ye (52)	+	++						
Barry (53)	+	+						
Alcaraz (55)		+	+	+				
Debruyne (58)		+		+				
Cai (59)		+			++			
Morgia (60)		+				++		
Morgia (61)				+		+	++	
Ryu (63)				+				++
Boeri (62)		+		+				++
Argirovic (64)		+		+				+
Bertaccini (67)		+						+
Gerber (48)	+	++						
Helfand (49)	+	+						
Glemain (65)		+		+				+
Hizli & Uygur (66)		+		+				+

Clinical use of other medicinal plants for BPH treatment: Urtica dioica, Pygeum africanum e Cucurbita pepo

(Gian Maria Busetto)

Alongside the traditional 5α-reductase and β-blockers, medical therapy for LUTS secondary to BPH, is based on nutraceuticals and compounds. In addition to Serenoa repens, which has been extensively studied, there are many other substances for which scientific evidence is often controversial.

Urtica dioica has the capability to decrease testosterone conversion to *dyhdrotestosterone* (DHT), interact with *sex hormone-binding globulin* (SHBG) and block the conversion of androgens to estrogens. Other studies report even an antiproliferative action on prostate cancer cells.

Pygeum africanum is rich in phytosterols and antioxidants. An inhibitory effect on prostate growth factors, on androgenic hormones and an effect on the contractility of

Table 3.
Symptoms, IPSS and flowmetric indices after treatment with Urtica dioica, Pygeum africanum and Cucurbita pepo.

Author, year	Study design	Patients & Controls n° and response rate	Comparator	Outcomes measured
Safarinejad 2005 (73)	**Urtica dioica** Double-blind placebo-controlled randomized Patients with LUTS secondary to BPH	305 (287 evaluable) **Urtica dioica** 315 (271 evaluable) placebo	Placebo	Urtica dioica vs placebo - Improved LUTS 81% vs 16% ($p < 0.001$) - IPSS 19.8 to 11.8 vs 19.2 to 17.7 ($p = 0.002$) - Peak flow rates +8.2 mL/s vs +3.4 mL/s ($p < 0.05$) - PVR 73 to 36 ml vs no change ($p < 0.05$) - PSA and testosterone unchanged in both groups - Prostate volume by TRUS 40.1 to 36.3 cc vs no change ($p < 0.001$) - No side effects
Pavone 2010 (74)	Serenoa repens 320 mg + **Urtica dioica 120 mg** + Pinus pinaster 5 mg for 30-365 days in LUTS associated to BPH (46%) or CP/CPPS (43%) or other conditions (11%)	320 patients (80 evaluable)	-	Symptom score significant benefit in 85% No change of prostate volume and Q_{max}
Lopatkin 2005 (75)	160 mg sabal fruit extract (Serenoa) + **120 mg urtica root extract** 2 capsule/day RCT 24 weeks	129 (127 evaluable) 128 (126 evaluable)	Placebo	Treated vs placebo IPSS -6 points vs -4 points ($p = 0.003$) - excellent tolerability
Lopatkin 2007 (76)	160 mg sabal fruit extract (Serenoa) + **120 mg urtica root extract** 2 x 1 capsule/day open-label extension of RCT for 96 weeks	219 subjects	-	I-PSS -53% ($p < 0.001$) Peak and average urinary flow +19% ($p < 0.001$) PVR -44% ($p = 0.03$) adverse events 1/1,181
Changping 2016 (77)	Metanalysis of 5 papers LUTS associated with BPH	1128 patients	Placebo	Standardized mean difference (SMD) IPSS 10.47 (95% CI 18.12 to -2.82, $p = 0.007$) Peak urinary flow rate (Q_{max}) 4.37 (95%CI = 1.55 to 7.19, $p = 0.002$) Prostate volume 3.63 (95%CI = -4.67 to -2.57, $p < 0.00001$) PSA 0.08 (95%CI = -0.23 to 0.07, $p = 0.31$)
Barlet 1990 (78)	Pygeum africanum extract (50 mg) or placebo (1 capsule BID) double-blind 60 days 8 centres (Germany, France, Austria)	263 patients	Placebo	micturition improvement 66% vs 31% $p < 0.001$ gastrointestinal side effects in 5 patients
Barth 1981 (79)	Pygeum africanum	215 patients		Improvement Nocturia, Q_{max}, PVR
Wilt & Ishani 1998 (80)	Pygeum africanum Metanalysis of 18 RCTs Treatment of BPH	1562 patients mean study duration was 64 days (range, 30 to 122 days)	Placebo	Effect size of combined outcome of urologic symptoms and flow measures (-0.8 SD [95% CI -1.4 to -0.3) (n = 6 studies) improvement symptoms (RR = 2.1, 95% CI = 1.4 to 3.1) nocturia - 19%, residual urine volume - 24%, peak urine flow + 23% mild adverse effects
Hong 2009 (81)	Pumpkin seed oil 320 mg day randomized, double-blind, placebo-controlled trial 12 months BPH patients	47 patients	Placebo Saw palmetto oil Pumpkin+Saw Palmetto	IPSS & QoL reduced after Pumpkin, Saw Palmetto, Pumpkin+Saw palmetto PSA reduced after Pumpkin+Saw palmetto Q_{max} increased after Pumpkin and Saw Palmetto Prostate volume no change
Friederich 2000 (82)	Pumpkin seed extract multicentric clinical trial BPH (stage I to II according to Alken) 12 weeks	2245	-	IPSS decreased by 41.4% life quality improved by 46. 1% no side effects in 96%
Vahlensieck 2015 (83)	Pumpkin seed 5 gr BID or Pumpkin seed extract 500 mg BID Randomized partially blinded placebo-controlled parallel-group trial 12 months patients with LUTS suggestive of BPH	1431	Placebo	Responders (IPSS decrease > = 5 points) pumpkin seed vs placebp 58.5% vs 47.3% no difference between pumpkin seed extract and placebo
Damiano 2016 (84)	Narrative review	6 clinical studies	-	IPSS and uroflowmetry improvement in 6 studies QoL improvement in 4 studies

the detrusor musculature of the bladder have been hypothesized. Some authors have also reported an improvement in the parameters of the semen, in particular on sperm motility.

Curcubita pepo mainly contain fatty acids, specific sterols, tocopherol, carotenoids, vitamins and micronutrients. It is mainly the high Δ-7-sterol content that has the therapeutic effect and that has been shown to reduce prostate volume in the main animal models.

These treatments can be considered as an adjunct to the common therapies and their effect is supported by improving symptoms, IPSS and flowmetric indices (Table 3) (73-84). Their action on the volume of the prostate gland and on inflammation is more controversial. The literature is lacking data and double-blind placebo-controlled studies able to improve levels of evidence. It is therefore necessary to continue studying these substances, commissioning adequate trials with

high statistical power, strict inclusion and exclusion criteria and with adequate case studies.

Carotenoids and mineral supplements

(Vittorio Magri)

Lycopene and selenium are two natural products with antioxidant and anti-inflammatory action. Lycopenes are carotenoids, natural pigments widely distributed in the environment that are synthesized both by plants and bacteria, but not by the animals that must take them with the diet. Lycopene accumulates in the prostate and is secreted in the seminal fluid. Dietary supplementation of rats resulted in accumulation of lycopene in all prostatic lobes, but preferentially in the lateral lobes. Lycopene concentrations are gradually increased and interfered with local prostate androgenic signaling, IGF-1 expression, and inflammatory mediators (85, 86). Selenium has an essential role in some enzymatic activities such as glutathione-peroxidases (87, 88) that can reduce hydrogen peroxide, and lipid and phospholipid hydroperoxides, counteracting free radical damage and *oxygen-reactive species* (ROS). Furthermore, selenium is important for maintaining an efficient immune response (89, 90). Studies *in vitro* and on animal models, have shown that *Serenoa repens-Selenium-Lycopene* (SeR-Se-Ly) administered in combination, are synergistic and amplify their action both on the inflammatory and proliferative component (91-93). Some clinical studies have confirmed the efficacy of the SR-Se-Ly association in patients with BPH. In the FLOG study the administration of SR-Se-Ly in patients who had to undergo prostatic rebiopsy due to suspected prostate cancer showed a significant reduction in inflammation and the number of lymphocytes and macrophages in histological sections (94).
In the PROCOMB study (61), patients treated with SR-Se-Ly + tamsulosin had a greater reduction in the IPSS score, an increase in Q_{max} and a reduction in the post-voiding urinary volume, compared to those treated with tamsulosin alone. A randomized double-blind study of patients with BPH treated with an herbal mixture that also contains lycopene showed a significant reduction in the total IPSS score, pollakiuria and nocturia in treated patients (95).
Similar effects to those obtained with lycopene and selenium could be obtained with the use of other carotenoids and/or zinc. Astaxanthin, at low concentration, was able to inhibit in vitro 5α-reductase by 98% and to decrease growth of cultured prostate cancer cell lines (96). The accumulation of zinc in prostate tissue depends, more than on dietary intake, on the activity of specific transporters (ZnT4 and ZIP4) that can be modulated by natural products as diadzein and genistein (97, 98). In patients with symptomatic BPH a combination of zinc, daidzein and Isolase (a mixture of enzymes that increases the bioavailability of plant polyphenols) improved at 6-month follow up IPSS score, peak urinary flow rate and quality of life (99).
The close correlation between prostatic inflammation and LUTS associated to BPH, as demonstrated by MTOPS and REDUCE clinical studies (100, 101), suggests a new systematic approach to the medical therapy of symptomatic BPH based on the association of a drug with anti-inflammatory activity to alpha-blockers and/or 5ARI drugs. Considering the side effects of *non-steroidal anti-inflammatory drugs* (NSAID), the use of natural substances with a low risk of complications is attractive. Further studies are needed to evaluate the short and long-term efficacy of this approach to validate its use in the daily clinical practice for treatment of benign prostate diseases.

Polyphenols

(Alberto Trinchieri)

Polyphenols are a large class of organic chemicals (> 8000) characterized by the presence of large multiples of phenols structural units. They can be differentiated according to the chemical structure of the polyphenol skeleton. Flavonoids, lignins, phenolic acids, stilbenes and other polyphenols belong to this class (Table 4). Polyphenols can act on prostatic hyperplasia with different mechanisms: inhibition of 5α-reductase; decreased expression of growth factors (IGF-I and IGF-II); anti-inflammatory action (reduction of interleukin levels IL 1-β, IL 6, IL-I6 and tumor necrosis factor TNF-α, inhibition of COX-2 and 5-lipogenase, increased synthesis of nitric oxide and expression of nitric oxide synthase); induction of apoptotic activity (increased expression of pro-apoptotic caspase-3 protein, up-regulation of peroxisomal proliferation receptors PPAR α and γ, increased expression of G protein estrogen receptor 1 coupled GPER); increased antioxidant activity (superoxide dismutase, glutathione peroxidase). Experimental evidences based on in vitro studies on homogenates of hyperplastic prostate cells or prostatic cell lines demonstrated prevalent inhibitory effect of 5α-reductase type 2 of isoflavones (phytoestrogens), while flavonols and flavones show inhibitory effect of 5α-reductase type 1 but also anti-inflammatory ant antioxidant effects and induction of apoptosis (102, 103). Phenolic acids and lignins also have a combined action on 5α-reductase and induction of apoptosis (104). In experimental models of BPH in rats, the efficacy of cocoa extract, soy-derived isoflavones, quercitin, a mixture of baicalin and catechin (flavocoxid), equol, anthocyanins derived from black soy, flavonoids extracted from Garcinia kola (kolaviron), epigallocatechin-3-gallate, secoisolariciresinol and curcumin was demonstrated (105-115). Clinical studies in patients with BPH have demonstrated the efficacy of quercitin, a flavonol contained in various foods such as onions, citrus fruits, cranberry, spices, tea and red wine (116), of equol (a metabolite of daidzein which is a soy isoflavon) (117), a flaxseed extract containing the lignin *secoiso-lariciresinol diglucoside* (SDG) (118) and of curcumin, a derivative of the spice Curcuma longa (119). Conversely, resveratrol has not been shown to be effective in reducing prostate volume and levels of testosterone, didrotestosterone (DHT) and PSA (120). Different types of polyphenols are contained in medicinal plants that have been used in the treatment of IPB, such as epliobium (121) and extract from the bark of French maritime pine (122).

Pollen extract, Beta-sitosterol and Palmitoylethanolamide (PEA)

(Tommaso Cai)

Pollen extract is a mixture of natural components, such as amino acids, carbohydrates, lipids, vitamins, phytos-

Table 4.
Classification, sources, biological and clinical activity of polyphenols used for BPH treatment.

Classification	Name	Source	*In vitro* 5-AR	*In vitro* other effects	Animal models	Clinical studes
FLAVONOIDS	**C6–C3–C6 general structural backbone with two C6 units of phenolic nature**					
Flavonols	Quercitin	onions citrus cranberry spices tea red wine	5-AR type 1 inhibition (?) Decreased DHT by androgen-independent effect SHBG	Antinflammatory (decrease cytochines, suppressed TNF-alfa and MCP-1 expression by NF-kappa B inhibition) Antioxidant Proapoptotic (TGF increase)	Decreased prostate volume	IPSS decreased Q_{max} increased
	Mirecitin	red wine	5-AR type 1 inhibition	-	No	
	Fisetin	strawberry apples grapes	5-AR type 1 inhibition	-	No	
Flavanons	GB1 e GB2 kolaflavonone binaringenina (Kolaviron)	Garcinia kola	-	Antioxidant	Decreased prostate volume	
Flavan-3-ols	Epigallocatechin-gallate	Green tea		Antinflammatory (decreased IL-Iβ, IL-I6, and TNF-α) Antioxidant Decreased IGF-I e IGF-II Proapoptotic PPAR-α e PPAR-γ up-regulation	Decreased prostate volume	
Flavones	Baicalin	Scutellaria baicalensis and Scutellaria lateriflora	5-AR type 1 inhibition	Antinflammatory (inhibition cicloxigenase 2 and 5-lipooxigenase Decrease growth factors	Decreased prostate volume by a mixture of baicalin and catechin (flavocoxid),	
	Kaempferol	Apples broccoli, onions, tomatoes	5-AR type 1 inhibition		No	
Anthocyanidins	Antocianin	Black soy		Proapoptotic	Decreased prostate volume	
Isoflavones (phytoestrogens)	Daidzein	Soy	5-AR type 2 inhibition		Decreased prostate volume by soy-derived isoflavones	
	Genistein	Soy Fava beans	5-AR type 2 inhibition			IPSS decrease
	Biocanin A	Soy Peanuts	5-AR type 2 inhibition			DHT
	Equol	Soy	5-AR type 2 inhibition		Decreased prostate volume	Decrease
STILBENS	**Hydroxylated derivatives of stilbene with C6–C2–C6 structure**					
	Resveratrol	Grapes Red wine				No decrease prostate volume No effect on testosterone and DHT
LIGNANS	**Two units of a phenylpropene derivative**					
	Secoisolarici-resinol diglucoside	Flaxseed		Proapoptotic Increased GPER expression	Decreased prostate volume	
	Enterolactone	Sesame Flaxseed	5-AR type 2 inhibition		No	
FENOLIC ACIDS	**Phenolic ring and an organic carboxylic acid function (C6-C1 skeleton)**				No	
	Caffeic Acid Phenethyl Ester (CAPE)	Propoli	5-AR type 2 inhibition			
OTHER POLYFENOLS	Curcumin	Curcuma lunga (spice)		Decreased growth factors (VEGF, TGF-ß1, and IGF1).	Decreased prostate volume	IPSS decrease

terols and minerals (123). The compound of the pollen extract is able to inhibit several cytokines, such as prostaglandin and leukotriene synthesis and this effect is comparable to that of diclofenac and indomethacin and approximately 10 times higher than that of aspirin (124). The pharmacological effects are due to the inhibiting activity of carvacrol, a pollen extract component, on the NF-KB (*Nuclerar Factor Kappa Light Chain Enhancer of Activated B Cells*). The inhibition of NF-KB reduce the levels of prostaglandin E2 and increase the production of beta-endorphins with inflammation decrease and pain relief (125). Moreover, several authors demonstrated that pollen extract has a possible pro-apoptotic effect on the prostate via the androgen metabolism. In particular, it protects acinar prostate epithelial cells and inhibits stromal proliferation in association with enhanced apoptosis. Finally, several in vitro studies demonstrated that pollen extract is able to inhibit the prostate cancer cell growth

Table 5.
Pre-clinical and clinical trials about the use of pollen-extract.

Author, year	Study design	Patients & controls n° and response rate	Comparator	Outcomes measured
Buck AC, 1989 (132)	Prospective trial (phase II)	15 (86.6)		Pollen extract effective in the treatment of chronic prostatitis and prostatodynia
Cai T, 2013 (133)	Prospective trial (phase II)	20 (90.0)		Pollen extract significantly improved total symptoms, pain, and QoL in patients with non-inflammatory CP/CPPS without severe side effects
Cai T, 2014 (134)	Randomized controlled trial	41 (75.6) 46 (41.3)	Ibuprofen	Pollen extract significantly improved quality of life of patients when compared with those treated with ibuprofen (treatment difference in the NIH-CPSI pain domain, -2.14 ± 0.51, p < 0.001; QoL scores, p = 0.002)
Elist J, 2006 (135)	Randomized controlled trial	30 (73.3) 28 (64.2)	Placebo	Pollen extract is superior to placebo in providing symptomatic relief in men with chronic nonbacterial prostatitis/chronic pelvic pain syndrome
Iwamura H, 2015 (136)	Randomized placebo-controlled trial	50 (78.1) 50 (88.2)	Eviprostat (phyto-thera-peutic agent)	Pollen extract significantly reduced the symptoms of category III CP/CPPS without any adverse events, in terms of NIH-CPSI, IPSS, and QoL
Jodai A, 1988 (137)	Prospective trial (phase II)	32 (75.0)		Pollen extract significantly reduced the symptoms in 75.0% of all treated patients
Monden K, 2002 (138)	Prospective trial (phase II)	24 (91.6)		Pollen extract significantly reduced the symptoms of chronic prostatitis group
Rugendorff EW, 1993 (139)	Prospective trial (phase II)	90 (62.2)		Pollen extract significantly reduced the symptoms of category III CP/CPPS without any adverse events, in terms of urinary symptoms and QoL
Suzuki T, 1992 (140)	Prospective trial (phase II)	25 (96.0)		Pollen extract significantly reduced the symptoms of prostatitis patients without any adverse events
Wagenlehner FM, 2009 (141)	Randomized controlled trial	70 (70.6) 69 (49.3)	Placebo	Pollen extract significantly improved total symptoms, pain, and QoL in patients with inflammatory CP/CPPS without severe side-effects

and this effect is even more pronounced in the hormone-independent models, suggesting that there might be a place for the pollen extract in the control of abnormal growth in hormone-insensitive cells (126-130).
On the clinical point of view, pollen extracts significantly improve symptoms, pain, and quality of life in patients affected by chronic pelvic pain syndrome and chronic prostatitis. These evidences have been done by a recent systematic review and meta-analysis (131) of 4 RCTs, that demonstrated that the use of flower pollen extracts in the management of CP/CPPS patients is associated with a high rate of clinical response without any significant adverse events. The Table 5 of all pre-clinical and clinical trials about the use of pollen-extract. No side effects are reported in all clinical trials (132-141).
Beta-sitosterol is a sterol commonly present in the almost all plants, such as rice bran, wheat germ, peanuts, corn oils, soybeans, saw palmetto, rye grass pollen and pygeum. Its activity is due to the fact that cannot be converted to testosterone and inhibits aromatase and 5α-reductase (142). Due to these pharmacological properties, beta-sitosterol is able to improve urinary symptoms and flow measures, as demonstrated by a Cochrane Review (143). On the other hand, beta-sitosterol is not able to reduce the size of the prostate gland. In general, no adverse effects are reported during therapy, even if gastrointestinal side effects are the most common. However, we need consider that this compound can enhance the cholesterol-lowering effects of antihyperlipidemic medications.
Palmitoylethanolamide (PEA), an endogenous fatty acid amide-signaling molecule has well-known anti-inflammatory and neuroprotective effects. The clinical anti-inflammatory effect is due to the downregulation of mediator release from mast cells, monocytes and macrophages. In particular, in recent experience, PEA seems to have interesting activities in regulation of neurogenic and neuropathic pain. It has been demonstrated that PEA is able to act on TRPV1 channels, by indirect activity and desensitization. Several authors showed an interesting role in the management of chronic pelvic pain syndrome and chronic urological pain (144-146).

Medicinal plants for prevention and treatment of prostatic carcinoma

(Gianpaolo Perletti)

Medicinal plants and herbal products, in the form of plant parts or extracts of them, are commonly used for the treatment of prostate diseases such as benign hypertrophy, prostatitis and chronic pelvic pain syndrome. Over the past 20 years, dozens of plant-based products

have been subjected to preclinical in vitro and in vivo investigations for their potential pharmacological activity against *prostate cancer* (PCa). Less numerous but worthy of special attention are epidemiological studies or clinical trials in which plant species, administered in the form of beverages, extracts or food preparations, have been studied for their effect on prostate cancer. Here follows an example of plant species which have been subjected to deeper investigation.

Camelia sinensis (CS), in the form of unfermented (green) or fermented (black) tea, is rich in polyphenols, the most representative and investigated being epigallocatechin-3-gallate (EGCG; green tea contains about 10-fold ECGC compared to black tea). A number of epidemiological and clinical studies have attempted to investigate the preventive effect of CS intake on prostate cancer. Such studies have been pooled in at least 6 meta-analyses, among which the work of *Fei et al.* (147), including 29 data series, appears to be the most comprehensive.

We deemed interesting to integrate such meta-analysis with the more recent studies of *Lassed et al.* (280 patients, risk ratio = 0.51; 95% CI: 0.14-1.82) and *Sen et al.*, (142, 196 men, of which 7036 PCa cases; risk ratio: 1.06; 95% CI: 0.98-1.14) (148, 149). Our metanalysis (Figure 1) (150) shows that, in contrast to the significant data of *Fei* and coworkers (147), (risk ratio = 0.84; 95% CI: 0.71-0.98), the addition of the *Lassed* and *Sen* (148, 149) trials results in a non-significant pooled risk ratio (0.89; 95% CI: 0.77-1.02). The publication bias for this pooled analysis is not significant (Egger's test: p = 0.542; Begg&Mazumdar's test: p = 0.311), but the analysis shows substantial heterogeneity (I2 = 0.69).

More focused analyses, investigating the effect of high doses of green tea catechins, tested in the frame of randomized-controlled studies, resulted in a significant protective effect against PCa.

Thus, whereas studies about consumption of CS infusions in the general population have given contradictory results – probably also due to uncertain dosage, length of therapy, herb quality, patient compliance, etc. –, rigorous, controlled clinical trials seem to provide encouraging evidence about the antitumor activity of CS catechins.

Solanum lycopersicum, the common tomato, contains high quantities of lycopene, a carotenoid antioxydant hydrocarbon (C40H56) devoid of vitamin-A activity. Lycopene, investigated in the frame of meta-analyses of epidemiological studies, doesn't seem to show a significant PCa preventive activity (151, 152). However, single studies suggest that lycopene shows indeed protective activity (153), and can as well lower PSA levels in prostate cancer

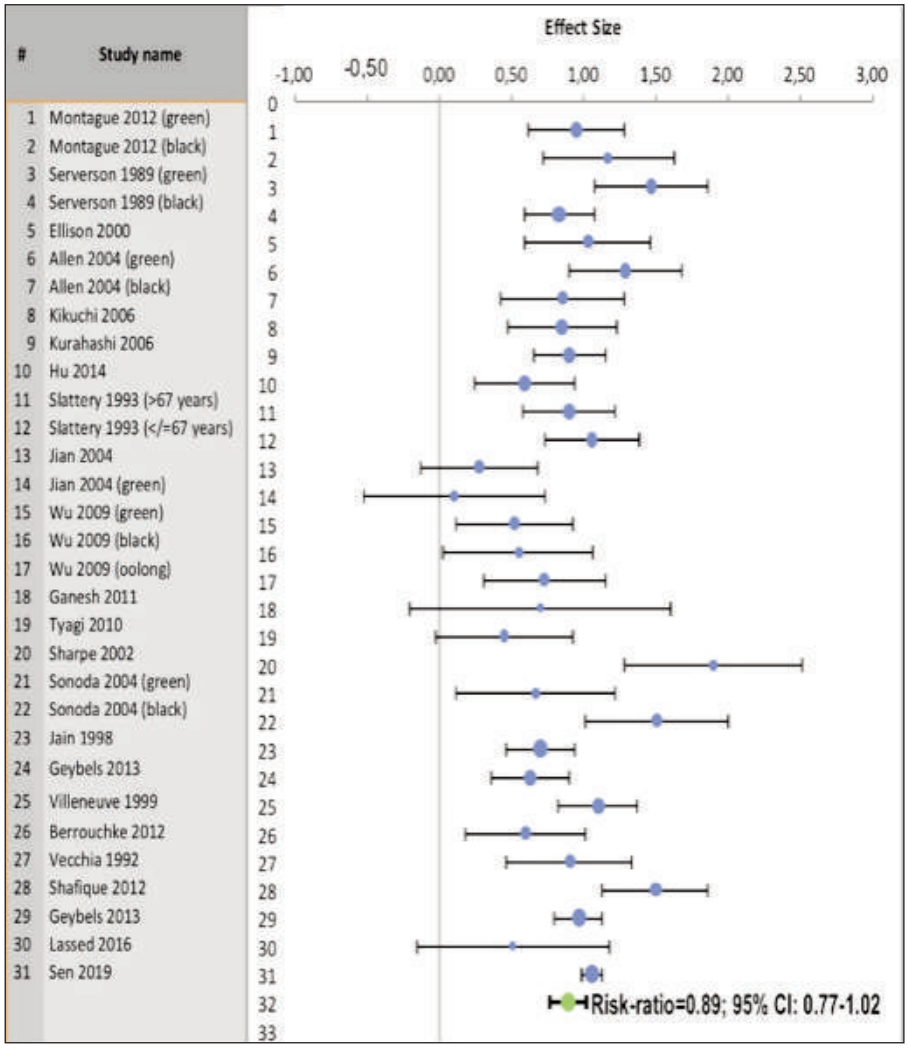

Figure 1.
Forest plot.
Risk-ratio for the association between the consumption of various preparations of tea (beverage, concentrates, etc.) and prostate cancer, assessed by pooling 23 epidemiological studies (31 data series).
The values at the right of the no-effect unit (n = 1) show an increased relative risk for prostate cancer, whereas data plotted on the left show a protective effect of tea intake against prostate cancer.
Arch Ital Urol Androl, this issue.
Random effect model, Mantel-Haenszel statistics, Meta-Essentials software.

patients (154). *Punica granatum*, *pomegranate* (PG), contains a number of active polyphenol compounds (e.g., elagitannins) and fatty acids (punicic acid). Promising preclinical results have not been translated so far into sound clinical evidence. Whereas in earlier clinical studies PG seemed to significantly prolong the PSA doubling time in patients with localized PCa (155), recent placebo-controlled trials failed to show increased PSA doubling times by PG preparations, compared to placebo (156, 157).
Glycine max, the common soy, and *Linum usitatissimum*, known as flax or lineseed, contain isoflavones (e.g., genistein) and lignans which are known to act as phytoestrogens. These compounds, which have been hypothesized to be active against PCa growth, have been tested in the frame of clinical trials in PCa patients. It is not clear whether soy extracts show any effect on PCa and PSA, as clinical data produced so far didn't show univocal therapeutic effects (158, 159). Similarly, single clinical trials and meta-analyses suggest that flax lignans do not seem to have a significant therapeutic activity (160). However, a metanalysis of observational studies by He and coworkers has evidenced a significant association between high serum levels of the lignan metabolite enterolactone and a reduced odds of prostate cancer (OR = 0.76, 95% CI: 0.60-0.97) (*He et al.*).
In conclusion, *Camelia Sinensis catechins*, *Solanum lycopersicum lycopene* and the flax lignan metabolite enterolactone have shown some chemopreventive or therapeutic activity against PCa. The major limitation of the clinical studies and meta-analyses produced so far is the great variability of key elements such as (i) compound quality (poor standardization), (ii) patient compliance (virtually unknown in observational studies), (iii) active drug dosages (extremely diverse according to dietary customs worldwide), and (iv) preparation modalities. Randomized controlled trials versus placebo or versus compounds of established efficacy are still scant. To draw any final conclusion concerning the efficacy of medicinal plants and fruits for preventing or treating PCa, additional well-designed, adequately powered clinical trials are urgently needed.

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