Complementary and alternative medicine in urology

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Complementary and alternative medicine (CAM) includes various practices, measures and products which are not presently considered to be a part of conventional (mainstream) medicine. Herbal products, vitamins, minerals and amino acids are increasingly popular as dietary supplements for the treatment, improvement and prophylaxis of urological diseases, and to improve general health and well-being. As these products are freely available without prescription, conventional healthcare providers are often unaware that their patients are using CAM. It is essential to know that some herbal supplements may act in the same way as chemical drugs, and that they originate 'from nature' does not mean that they are safe and/or with no potential harmful effects and/or toxicity. Eventual interactions with conventional medications and contamination with prescription drugs and metals have been reported. The active components of many phytotherapeutic preparations and their mechanism(s) of action are still being determined and evaluated. There is scientific evidence for the effectiveness of some CAM treatments, but for most there are important key questions yet to be answered through basic research and well-designed studies according to established guidelines. Because of the increasing popularity and use of CAM, conventional healthcare providers, including urologists, should not ignore it, and be well informed about the benefits and potential risks of dietary supplements, so that they can advise their patients about this developing field. Whenever necessary and possible, lifestyle and behavioural changes should be recommended before using CAM, and eventually be supplemented by CAM as a second step.

INTRODUCTION

An increasing interest in, and use of, complementary and alternative medicine (CAM) is widely documented for the management of numerous diseases, to relieve symptoms in various conditions and to improve general health and well-being, even in Western countries. More than a third of the population of the USA are using some form of CAM, with expenditures for these therapies currently in the USA estimated to exceed $50 billion/year, and with more visits to providers of CAM (mainly chiropractors, herbalists and acupuncturists) than to conventional primary healthcare providers, although most CAM therapies are not or only partly reimbursed by health insurance [1].

In the USA a National Center for Complementary and Alternative Medicine (NCCAM Clearinghouse; website: www.nccam.nih.gov) was instituted in 1998 by the USA National Institute of Health (NIH) to help the interested public to find information about this form of therapy [2,3]. The AUA established a ‘Committee on CAM’, with the late W.R. Fair, the ‘Father of CAM in Urology’, as its first chairman.

By definition, the term ‘complementary’ medicine does not mean ‘instead of’ conventional treatment, but rather a supplement to another treatment, while the term ‘alternative’ medicine also is used as a real alternative to conventional medicine. However, this was criticised by Fair, if alternative medicine was intended to replace conventional, established standard treatment [1]. Both terms are usually combined to the term CAM, meaning an integrated form of treatment in which CAM may complement other treatments. The NCCAM uses the term ‘integrative medicine’ for the combination of mainstream medical treatments and those CAM therapies for which there is some scientific evidence of safety and effectiveness.

CAM mainly includes diets, nutritional supplements (herbal products, vitamins, minerals, amino-acids), but also measures for stress reduction (e.g. yoga), acupuncture, aromatherapy and exercise therapy, sometimes given as a combination of two or more therapies, representing a holistic view of medicine and diseases [4,5].

WHO USES CAM?

In a USA survey, there was a more widespread use of CAM in younger people with higher educational and income levels than in uneducated and lower socio-economic classes [1]. Also in other Western countries, institutions and organizations have been established to provide the public and medical profession with information about CAM, which is easily accessible on the Internet, e.g. in the UK, there are various bodies; Institute for Complementary Medicine (www.i-c-m.org.uk), the Research Council for Complementary Medicine, founded in 1983 (www.rccm.org.uk), and The British Complementary Medicine Association (www.bcma.co.uk).

Interestingly, even politicians are noticing the rapidly spreading use of CAM and have discussed the issue. In 2000, The UK Parliament (Select Committee on Science and Technology of the House of Lords) published a detailed report on CAM, with suggestions for its use, and concerning future research, training of the medical profession and regulatory issues [6]. To improve the regulations of complementary and alternative healthcare, the British Government presented an official response [7] and the UK Department of Health provided more than GB £1.3 million for research in CAM to develop the evidence base for CAM in healthcare. An International Society for Complementary Medicine Research (www.iscmr.org/) and a journal ‘Evidence-based Complementary and Alternative Medicine’ (Oxford University Press) have also been founded.

When searching ‘Google’ for the term ‘complementary medicine’ more than one million ‘hits’ are recorded, and searching the National Library of Medicine for ‘CAM’, more than 6 000 references can be retrieved.
An increasing use of CAM is also documented for different urological conditions and diseases, e.g. LUTS/BPH, cancer treatment and prevention, prostatitis, UTIs, erectile dysfunction (ED), urolithiasis and infertility. However, most urologists have been and remain reluctant to recommend CAM, for various reasons. The knowledge about CAM among urologists is limited, the effect of CAM is difficult to assess scientifically, and most CAM research and clinical studies are too short, too small and rarely double-blinded and placebo-controlled to fulfil the established prerequisites of evidence-based medicine. Moreover, many studies produce contradictory results and interpretation [8–10]. Safety aspects are another concern; the mechanism of action and pharmacodynamics and pharmacokinetics of most herbal preparations are unknown, their content and compositions are rarely standardized and quality-controlled and they may contain contaminants, some of which might interact with conventional medicines or even be toxic [11,12].

Thus for example the US Food and Drug Administration in 2002 warned consumers to stop taking the dietary/herbal product PC SPES and SPES, marketed as an ‘immune enhancer’ with suggested beneficial effects in the treatment of advanced and hormone-refractory prostate cancer, as some batches of the preparations were found to contain undeclared prescription drug ingredients (oestrogens, indomethacin and warfarin) [12,13].

There are many good reasons why urologists should increase their knowledge about CAM. CAM is increasingly popular and used by their patients; there are reports that >90% of patients referred to urological practices for LUTS/BPH were taking or had taken alternative medications. Usually, patients do not reveal this information, unless directly asked.

The urologist should be able to advise patients about the benefits and risks of CAM, especially as some preparations may eventually interact with prescription medications, or increase the risk of bleeding during surgery, while others have been reported to increase the risk of certain cancers or even all-cause mortality.

More attention should also be focused on detrimental lifestyle habits, e.g. excess overall calorie intake (leading to obesity), smoking, and the general life-threatening risks associated with both, as it makes more sense to motivate patients to make changes towards a healthy lifestyle than to try to correct or counteract bad lifestyle habits by CAM. There is significant evidence from many clinical trials that lifestyle changes have a much greater influence on the reduction of all-cause mortality and prevention of some cancers than any dietary supplements [1,14–20].

The NCCAM has grouped CAM into five major domains:

- Alternative medical systems, such as homeopathy, traditional oriental medicine and ayurveda;
- Mind-body interventions, such as meditation, prayer and mental healing;
- Biologically based therapies, such as the use of vitamins, minerals, amino acids, herbal and special dietary and non-dietary products with suggested anitineoplastic properties.
- Manipulative and body-based methods, such as chiropractic manipulation and massage;
- ‘Energy’ therapies, such as biofield therapies, Qui gong, Reiki and energy therapies with therapeutic touch.

The third category is the most important group in urology, as it contains products and preparations which are increasingly used in benign urological conditions, and as complementary methods for preventing and treating cancers. Detailed and extensive general and specific reviews have been published on the use of CAM in numerous urological conditions and diseases. The aim of this overview is to highlight only some aspects and controversies.

**CAM THERAPIES FOR PROSTATE DISEASES**

**DIET, GENERAL NUTRITION, VEGETABLES AND FRUITS**

There are many reports, suggesting that calorie-restricted diets with low levels of saturated fats, but rich in fibre, antioxidant-containing fruits and vegetables, phytoestrogens, and nutrition with high levels of isoflavones (soy products, green tea) and carotenoids may reduce the incidence and improve the course of LUTS, BPH, prostatitis and even prostate cancer. The differences in dietary composition and the consumption of green tea, together with different lifestyle habits, might explain the lower incidence of prostate diseases, especially clinically relevant prostatic cancer, in Asian than in Western populations. This observation is explained by diet-induced higher cellular apoptosis rates, lower free-radical induced DNA changes, lower cell proliferation by reduced IGF-1 production and inhibition of angiogenesis factors, 5α-reductase, aromatase and oestrogen receptor activities in the prostate in Asian than in Western diets [5,21].

An estimated 30–75% of all patients with cancer worldwide, and up to two-thirds of patients with prostate cancer, use CAM therapies, including dietary approaches, herbal and other biologically based treatments, to prevent, palliate and treat their disease.

The incidence and course of bacterial prostatitis may be ameliorated by the reduction of inflammatory arachidonic acid-by-products, prostaglandin E2 and leukotriene levels, suggested to be induced by certain herbal products.

**PHYTOTHERAPY IN LUTS/BPH**

There are many publications on the use of phytotherapeutic preparations in men with LUTS/BPH and prostatitis [22–27]. Plant extracts are commonly prescribed as the first choice of therapy in many European countries, totally or partly reimbursed by health insurance, and are increasingly used in the USA, where these agents are classified as not reimbursable, and off-prescription dietary supplements, available over the counter in an increasing number of health-food stores and vitamin shops. They are usually less expensive than chemical drugs (α-blockers, 5α-reductase inhibitors) and have gained wide popularity, mainly because they are regarded as ‘natural’ products, supposedly having no significant side-effects.

In Europe alone, >100 different botanical preparations, made from >30 plants, are available. The most popular preparations are extracted from the seeds, roots, fruits or bark of the plants listed in Table 1. Some extracts are produced from one species, others contain components from two or more species, often with additives of minerals (selenium, zinc), vitamins (vitamin E) and amino acids, although there is insufficient scientific and/or...
Clinical evidence to support the use of these combinations. The extraction procedures, components and additives in the final product differ among the various producers, making general conclusions and comparisons difficult without adequate clinical studies. Therefore, even sophisticated basic research and clinical studies with one specific product cannot automatically be transferred to a preparation from another manufacturer, even if it derives from the same botanical species.

Moreover, although several specific components of plant extracts have been identified it is still speculative which are or could be the essential and active ones for the various effects described in vitro and in vivo. The components identified are:

- Phytosterols (β-sitosterol, campesterol, stigmasterol, Δ5-sterols, Δ7-sterols).
- Phytoestrogens; lignans, flavonoids, isoflavonoids (genistein, daidzein).
- Fatty acids (lauric and myristic acid).
- Lectins.
- Plant oils.
- Polysaccharides.
- Lupene.
- Lupeol.
- Terpenoids.

Phytosterols (plant sterols) are a class of compounds found in the cells and membranes of plants; there are ≈250 different sterols and related compounds in plant materials, with the most common being β-sitosterol, stigmasterol and campesterol. Phytosterols block the absorption of cholesterol and, when ingested in large doses, reduce blood cholesterol levels. Phytosterols, having similar molecular, compete with cholesterol for absorption in the small intestine. However, phytosterols themselves are practically not absorbed by humans.

The suggested modes of action of plant extracts are:

- Overall anti-androgenic effect.
- Androgen and oestrogen receptor inhibition.
- 5α-reductase I and II inhibition.
- General reduction in prostatic urethral resistance.
- Action on α-adrenergic receptors.
- Overall anti-inflammatory effect.
- Anti-oedema effect.
- Overall interference with prostaglandin metabolism.
- Inhibition of phospholipase A2 and 5-lipoxygenase enzymes.
- Blockage of arachidonic acid release.
- Overall suppression of prostate cell metabolism and growth.
- Inhibition of growth factor-induced prostatic cell proliferation.
- Inhibition of prolactin-induced prostatic growth.
- Protection and strengthening of detrusor muscle.
- Aromatase inhibition.
- Alteration of cholesterol metabolism.
- Decrease of sex-hormone binding globulin.
- Free-radical scavengers/membrane stabilization.
- Induction of apoptosis.

Numerous clinical studies have been published during the last decades with different brands of plant extracts for the treatment of BPH/LUTS. Only a minority included an adequate number of patients with long-term observation, and only a few were placebo-controlled and conducted according to the recommendations of the International Consultations on BPH [24]. Moderate improvements of symptoms, flow rates and nocturia rates with questionable clinical significance were described in some, with 'dramatic' effects in single studies, which urgently need confirmation. Even large meta-analyses support the persisting need for further long-term studies to conclusively evaluate the efficacy of plant extracts in the treatment of BPH/LUTS [22,23]. To date, herbal products have not (yet?) been documented to reduce BPH-related complications, clinical progression or the need for surgical intervention. Of all products investigated, extracts from the fruits of saw palmetto (Serenoa repens), preparations with high levels of β-sitosterol as ‘leading marker component’ and pumpkin seeds (Cucurbita pepo) have some statistical evidence of efficacy and tolerability. There is less evidence for extracts of the African plum bark (Pygeum africanum) and products made of stinging nettle roots (Urtica dioica) and rye pollen, which, due to the suggested anti-inflammatory effect, is also recommended for patients with prostatitis [22–28].

For these reasons, the USA National Institute of Diabetes, Digestive and Kidney Diseases started a large randomized, double-blind, placebo-controlled clinical trial in ≈3000 men with BPH over 4–6 years to study the effects of S. repens and/or P. africana extracts to prevent the clinical progression of BPH. This study ‘Complementary and Alternative Medicine for Urological Symptoms’ (CAMUS-Trial) will meet the prerequisites, also proposed by other authors working in evidence-based medicine and the International Consultations on BPH [24], demanding that phytotherapy should be tested according to the same general research principles and standards as conventional drugs.

**TABLE 1**

<table>
<thead>
<tr>
<th>Plant (species)</th>
<th>Part used</th>
<th>Table 1: The origin of phytotherapeutic preparations used for treating LUTS/BPH and prostatitis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>American dwarf palm/Saw palmetto (Sabal serrulata/Serenoa repens)</td>
<td>fruit</td>
<td></td>
</tr>
<tr>
<td>African plum tree (Pygeum africanum)</td>
<td>bark</td>
<td></td>
</tr>
<tr>
<td>South African star grass (Hypoxis rooperi)</td>
<td>root</td>
<td></td>
</tr>
<tr>
<td>Pine, spruce (Pinus, Picea)</td>
<td>root</td>
<td></td>
</tr>
<tr>
<td>Stinging nettle (Urtica dioica)</td>
<td>root</td>
<td></td>
</tr>
<tr>
<td>Rye* (Secale cereale)</td>
<td>pollen</td>
<td></td>
</tr>
<tr>
<td>Pumpkin (Cucurbita pepo)</td>
<td>seed</td>
<td></td>
</tr>
</tbody>
</table>
soil where the plants are grown or animals raised, as selenium can also be found in meats and seafood.

Observational studies indicate that death rates from cancer, including colorectal, lung and prostate cancer, are lower among people with higher blood levels or intake of selenium [1,29]. Results of The Nutritional Prevention of Cancer Study, a double-blind trial of dietary selenium supplementation, whose primary goal was to determine whether or not selenium supplements might reduce the incidence of nonmelanoma skin cancer in high-risk individuals, showed a statistically significant lower incidence (63%) of prostate cancer than in those receiving placebo, although there was no beneficial effect on skin cancer [30–33]. Moreover, selenium had a significant effect on the reduction of lung, colon cancers, total carcinoma incidence and mortality. The incidence of nonmelanoma skin cancer was higher in areas of the USA with a low soil selenium content. However, not all studies have documented a correlation between selenium intake and cancer.

Some studies showed that selenium supplements provide a benefit only for those individuals who have lower levels of baseline plasma selenium [1]. Over-dosage of selenium may be toxic and result in a condition called 'selenosis' with gastrointestinal complaints, fatigue, irritability, hair and nail loss.

Vitamin E is the term used to describe a group of related fat-soluble tocopherol and tocotrienol natural vitamin E isoforms. According to Moyad [34], vitamin E is a prevalent natural form of vitamin E, while Moyad [34] reported that a large portion of vitamin E found in the diet is γ-tocopherol. In most of the trials with vitamin E, the reduction in risk of heart disease and prostate carcinoma was primarily in individuals with high levels of γ-tocopherol. Synthetic α-tocopherol is suggested to have different biological properties from the natural vitamin E isoforms. According to Moyad [34], the level of γ-tocopherol, deriving from natural sources, is possibly more important for preventing prostate carcinoma than the supplementary intake of α-tocopherol. This was also shown in a study in which men who ingested larger amounts of dietary vitamin E (γ-tocopherol) had a greater reduction of prostate cancer risk than men with supplements of α-tocopherol and/or selenium. This might also be explained in that a high intake of synthetic α-tocopherol can lower plasma and tissue levels of γ-tocopherol.

The basic mode of action of tocopherols in the tissue is to prevent the oxidation of polyunsaturated fatty acids by trapping free radicals. Moreover, vitamin E down-regulates cellular adhesion molecules, reduces inflammation and smooth muscle cell proliferation, induces apoptosis and enhances cell-mediated immunity [35].

Vitamin E is known to interact with other nutrients which are also in the pathway of oxidation processes. Vitamin C, selenium and zinc interact synergistically with vitamin E. Results from animal studies and epidemiological studies in humans suggest that vitamin E may protect against cancer. The role of vitamin E in reducing the incidence of cancer came into focus in 1998, when the main results of the Alpha-Tocopherol-Beta Carotene Cancer Prevention (ATBC) study were published [35–37]. In this trial, 29 000 Finnish men who smoked were followed for up to 8 years, to evaluate whether either vitamin E (50 mg of α-tocopherol) and/or β-carotene (20 mg) supplements could prevent lung cancer. Instead of preventing lung cancer, it was surprising that there was a 32% reduction in the incidence and a 41% decrease in mortality from prostate cancer. In a recent analysis of the levels of vitamin E in the blood of ATBC study participants at the start of the trial, men with the highest levels of vitamin E (γ-tocopherol) in their blood had a lower risk of prostate cancer. A commonly neglected fact of this trial was that men with excessive overweight had a 39% greater incidence in prostate cancer.

Although the relation between vitamin E and prostate cancer is the most exciting observation for urologists, it is also important to know the potential correlation of vitamin E and other dietary supplements with cardiovascular risks and the risk of non-urological cancers.

In March 2005 results of a sub-analysis of the Heart Outcomes Prevention Evaluation Study (HOPE) were published [38]. HOPE was originally a placebo-controlled 4.5-year clinical trial of ≥9500 men and women aged ≥55 years with vascular disease or diabetes, to evaluate whether the risk of heart disease could be decreased by the intake of the blood-pressure lowering angiotensin-converted enzyme inhibiting drug ramipril and/or vitamin E. At the end of the initial study, ramipril showed a clear benefit in reducing heart disease outcome. The study was extended, and those participants who had not taken ramipril were offered the drug and asked to continue taking vitamin E or a vitamin E placebo for 2.5 more years (HOPE-TOO) [38]. Analyses showed no clear evidence that men and women who took 400 IU of vitamin E daily for 7 years reduced their overall risk of cancer compared to others who took a placebo. Unfortunately, the study was not large enough to determine if vitamin E could prevent specific cancers. Although there were no differences in the pre-specified major heart disease outcomes, there was a 13% greater risk of heart failure events in the group of participants taking vitamin E than in the placebo-group.

It was shown that men with high levels of vitamin E have significantly lower testosterone, androstenedione and oestrone levels. In the ATBC study, this could mean that vitamin E may prevent prostate cancer in smokers by altering the hormonal milieu (lowering androgen levels).

Side-effects of vitamin E over-dosage have been reported. When combined with anticoagulant drugs, the risk of bleeding may be increased. Moreover, supplementary intake of >1 g vitamin E/day may reduce the absorption of other antioxidants, e.g. vitamin C, resulting in a pro-oxidant effect of vitamin E over-dosage, which may increase the risk of cancer.

A recent study on vitamin E provoked considerable criticism and controversy, presenting the results of a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality, by using data from 19 randomized, controlled trials, including 135 967 participants [39]. This dose-response analysis showed a statistically significant positive relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages of >150 IU/day, with the conclusion, that "high-dosage (>400 IU/day) vitamin E..."
may increase all-cause mortality and should be avoided. The design and the conclusions of this meta-analysis were rigorously discussed and heavily criticised in numerous responses, after publication of the article, reviving the controversies about vitamin E supplementation and illustrating the well known problems of drawing conclusions from meta-analyses [40-43].

There is another recent landmark study in which a 24% reduction in cardiovascular death, but no significant effect of vitamin E on total mortality, non-fatal heart attacks and non-fatal strokes in women, was reported; the participants received 600 IU of vitamin E or aspirin, or placebo, every other day. The study was conducted from 1992 to 2004 on 39 876 healthy women aged >45 years (Women's Health Study) [44]. There was no effect of vitamin E on total cancer or on the most common cancers in women, i.e. breast, lung and colon cancers. The conclusion of the study was that at present, vitamin E cannot be recommended for preventing cardiovascular disease or cancer.

Nevertheless, although there is no clear scientific evidence to propagate their general supplemental use and specific dosage, selenium and vitamin E are probably two of the most popular dietary supplements suggested for reducing the risk of prostate cancer. A large USA NIH-sponsored long-term, placebo-controlled study, the 'Selenium and Vitamin E Cancer Prevention Trial' is currently underway in North America to evaluate whether the risk of prostate cancer in healthy men can be reduced. Selenium (200 µg) and a placebo resembling a vitamin E tablet are given as a daily supplement to one group, while another will receive 400 mg of vitamin E with a placebo resembling the selenium dose. A third group takes both selenium and vitamin E and the fourth group receives two placebo preparations. The study will run from 2001 to 2013 and will include >35 000 healthy men from 400 different sites in the USA and Canada. Although this study hopefully will show whether selenium and/or vitamin E reduce the risk of prostate cancer, its current justification and design has already been heavily criticised [34].

Carotenoids are compounds which are not synthesized in animals but biosynthesized by plants and micro-organisms. About 700 naturally occurring carotenoids have been identified, ~10% of which can be found in the human diet. The predominant carotenoids observed in the plasma are β-carotene, lycopene, lutein, cryptoxanthin and α-carotene.

The main known functions of some carotenoids, e.g. β-carotene, are to serve as an important source of vitamin A, and as light-absorbing pigments and protection against photosensitization. Moreover, antioxidant, anti-carcinogenic and immune-enhancing activities were reported. The average human intake of β-carotene is 1.8 mg/day, the main dietary sources being carrots, oranges, tomatoes and dark green vegetables. Although various epidemiological studies in humans and animals support the idea that β-carotene can prevent cancer [45], supplemental β-carotene actually increases lung-cancer incidence and mortality in smokers, as was shown in the Finnish ATBC study. The risk was particularly higher in heavy smokers than light smokers. For this reason and because of similar results in other chemoprevention trials, the use of β-carotene as a supplement should be regarded with caution in smokers, because of the greater risk in the incidence and mortality of lung cancer. Moreover, in the same study, those subjects receiving β-carotene supplements had a 23% increase in prostate cancer incidence with a 15% increase in mortality. While the assumption is generally accepted that the intake of more fruits and vegetables, rich in carotenoids, supports general health, and that individuals who have high levels of β-carotene have a lower risk of cardiovascular diseases, no clinical trial of β-carotene as a single agent showed a lower risk of cancer at any specific site.

In another analysis, which was a part of the ATBC study, the effects of α-tocopherol and β-carotene supplementation on the incidence of gastric cancer were evaluated [46]. There was no significant effect of either supplementation on the overall incidence of gastric cancer, but subgroup analyses by histological type suggested a greater risk from β-carotene on intestinal-type cancers.

Raw and processed tomatoes are the predominant natural source for carotenoids, especially lycopene. Several case-control and prospective studies suggest that the intake of tomatoes and tomato products may be associated with a lower risk of prostate cancer [47]. It is possible, but not certain, that lycopene is responsible for these observations, as other carotenoids or phytochemicals, including phytoestrogens, contained in tomatoes, may also contribute to the suggested positive effects. Tomato processing may enhance the beneficial effect by increasing the bioavailability of these components [48].

Zinc is an essential mineral that is found in almost every cell; it stimulates the activity of ≈100 enzymes. Zinc is found in a variety of foods; oysters contain more zinc per serving than any other food, but red meat and poultry provide most of the zinc in Western diets. Some seafood, beans, nuts, whole grains and breakfast cereals also contain zinc, but zinc absorption is greater from a diet high in animal protein than a diet rich in plant proteins. Low zinc status has been reported in vegetarians, and in alcoholics, as alcohol decreases the absorption of zinc and increases loss of zinc in urine. Severe zinc deficiency depresses immune functions. The recommended dietary allowance (average daily intake level that is sufficient to meet the nutrient requirements of 98% of healthy individuals) is 11 mg for men. Signs of zinc deficiency include hair loss, diarrhoea, impotence and loss of appetite.

The concentration of zinc in the prostate gland is higher than in any other human tissue. Zinc levels in prostate cancer tissue are lower than in BPH tissue, which could suggest that some form of zinc deficiency might play a role in the occurrence and growth of prostate cancer, which possibly could be corrected by a greater zinc intake [20]. However, some studies showed that zinc supplementation potentially may also increase prostate carcinoma risk and disease progression [49]. Men who consumed zinc supplements for ≥10 years also had a significantly higher risk of advanced prostate cancer, suggesting that chronic zinc oversupply may play a role in prostate carcinogenesis [49]. About 15% of the USA population ingest dietary supplements that contain zinc; 10% of men who use zinc supplements have an average daily zinc intake that is two to three times higher than the recommended dietary allowance [49]. Increased zinc intake might also increase the risk of BPH, possibly by higher androgen uptake in the prostate, as suggested by some laboratory studies. High intakes of zinc (150–450 mg/day) are toxic, being associated with lower copper status, reduced immune function, increased levels of low-density lipoproteins.
and reduced levels of high-density lipoproteins (the ‘good cholesterol’).

CAM IN ED

The placebo effect of all medical treatments is well known and also demonstrable in the treatment of ED; placebo-controlled trials with newer oral chemical drugs showed placebo responses of 25–41%. A comparable placebo effect was shown in trials of LUTS and BPH. The use of CAM for treating ED does not give greater ‘success rates’ than in the placebo group of clinical trials with chemical drugs. Thus, small studies with acupuncture, supplements of androstanedione, dehydroepiandrosterone, zinc supplements, ginkgo extracts, yohimbine (extracted from the bark of the West African yohim tree), and products made from Korean red ginseng, as well as other herbal preparations, have provided no evidence of superiority over placebo. The urologist should know that herbal products from ginseng may contain numerous compounds, some of which have anticoagulative potential. However, treatment with supplements of L-arginine, an amino-acid, that is a precursor to nitric oxide, had some benefit over placebo in some randomized trials, which awaits confirmation by larger studies [20]. Some dietary supplements, marketed for sexual enhancement and claimed to be ‘natural’, were found to contain amounts of unlabelled sildenafil and/or tadalafil.

CRANBERRY JUICE AND UTIs

Cranberry juice is supposed to reduce the incidence of UTIs by preventing bacteria from adhering to the bladder endothelium. The active components for this action are suggested to be proanthocyanidins [50]. A randomized, double-blind, placebo-controlled trial of 153 elderly women suggested that the use of cranberry beverage reduced the frequency of bacteriuria with pyuria. In a systematic review, conducted by the Cochrane renal group, overall results indicate that, compared to placebo, cranberry juice and tablets may reduce the risk of developing symptomatic UTIs in sexually active women, and the risk of developing a UTI after 6 months in women who have frequent UTIs. The results of other studies were less convincing, partly due to poor methods. Thus, although evidence of its effectiveness is limited, cranberry juice is widely used to prevent UTIs. However, it is suspected that cranberry juice may affect the absorption and metabolism of antibiotics used to treat UTIs. A clinical study was initiated by the USA NIH to further investigate this question. Side-effects after excessive intake may include gastrointestinal discomfort and upset, diarrhoea and an increased risk of renal stone formation. Moreover, five cases of increased bleeding, in individuals taking warfarin (coumadine), after consuming cranberry juice were reported.

RED WINE CONSUMPTION AND PROSTATE CANCER

By contrast with earlier studies, which had shown a positive correlation between alcohol consumption and rectal and lung cancers, a recent study [51] reported that red wine consumption may reduce the risk of prostate cancer. The alcohol history of 753 men aged 40–64 years and with prostate cancer was compared to a similar number of control subjects without prostate cancer. In the group drinking red wine there was a 24% lower risk of being diagnosed with prostate cancer, with a statistically significant 6% decrease in relative risk for each additional glass of red wine consumed per week, amounting to halving of the risk for men who consume four or more glasses per week.

A previous study from Australia showed that women who drink one or more glasses of wine per day (!) have a 40% reduction in the risk of developing ovarian cancer [52]. Another study reported that long-term consumption of more than one wine drink per day was associated with a 70% reduction in the incidence of non-Hodgkin’s lymphoma in men [53]. The studies concluded that the inverse association of cancers with alcohol consumption was solely due to wine, as there was no protective effect for beer or spirits (liquor). The agent responsible for this effect of wine is supposed to be the polyphenol resveratrol, a naturally occurring plant antibiotic found in grape skins and red wine. The effects of resveratrol seem to include antioxidant activity, immunomodulation, growth-inhibiting activity, anti-androgenic, anti-inflammatory and inhibition of angiogenesis. These reports suggest overall health benefits from moderate wine consumption, while it is less clear at what levels wine consumption becomes harmful due to the well known adverse effects of excessive alcohol ingestion.

CONCLUSIONS

An increasing use of, and interest in, CAM is apparent worldwide and especially in Western countries. CAM includes a broad range of therapies; some offer complete and alternative treatment options to conventional management, others complement conventional treatments with various supportive products and treatment regimens. Only a few studies have suggested some evidence for the efficacy of CAM, e.g. phytotherapy for LUTS/BPH. However, most are not (yet?) evidence-based, as with vitamin E and selenium for the prevention/treatment of prostate carcinoma. Conventional healthcare providers, including urologists, should become more familiar with CAM therapies, their potential usefulness, their weaknesses and their risks, especially as some may have effects on the cardiovascular system, overall mortality and non-urological cancers. There is insufficient high-quality CAM research and some attempt should be made to accumulate an evidence base with the same rigour as is required and used for conventional medicine.

Apart from the suggested benefits, there are several potential risks for the people and patients when using CAM therapies. One is that patients could miss appropriate relevant diagnoses and established, evidence-based conventional standard therapy; another is that patients often do not reveal to their conventional healthcare provider that they are using CAM therapy, and may thus risk complications from drug and CAM-product interaction or toxicity. Urologists must inform their patients that the belief that all ‘natural products’ are generally safe and without toxicity is not in principle correct. Food supplements, e.g. synthetic vitamin E, may differ from those contained in normal diets, and over-dosage may carry substantial risks. Thus, instead of using vitamin E supplements intended to prevent heart attacks and strokes, leading to a decrease in overall mortality, people should focus on well proven means of preventing heart disease, including leading or changing to a more healthy lifestyle, consuming healthy natural diets, reducing obesity, practising exercise, stopping smoking and controlling risk factors such as high
cholesterol and high blood pressure, whenever necessary and possible.

Drinking an additional glass or two of red wine per week seems to be a harmless and enjoyable form of dietary supplementation, with some evidence of efficacy in preventing prostate cancer, at least until another study suggests an association between red wine intake and increased prostate cancer risk.

More research and evidence-based regulations on the use of CAM are needed, and adequate information must be provided to the medical profession, including conventional healthcare providers, patients and the public, as to what is effective or does not work, and what are the benefits and risks of any specific form of CAM.

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Abbreviations: CAM, complementary and alternative medicine; NCCAM, National Center for Complementary and Alternative Medicine; NIH, (USA) National Institute of Health; ED, erectile dysfunction; ATBC, Alpha-Tocopherol–Beta Carotene Cancer Prevention (study); HOPE, Heart Outcomes Prevention Evaluation Study.