



## Does Oral Lycopene Reduce Benign Prostate Enlargement/Hyperplasia (BPE/BPH)?

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Please note that the LactoLycopene in The Tomato Pill is highly bioavailable. See page 3 for the benefits of lycopene on Prostate size.

### Abstract

**Aims:** Lycopene is a potent antioxidant found in 'Mediterranean diets' with evidence suggesting a beneficial effect on the prostate. Our objective was to critically appraise the current literature as to whether Lycopene has a beneficial effect on benign prostatic enlargement.

**Methods:** We searched PubMed electronic databases for articles published from 2000. The following key words were used: lycopene and prostate or prostate cancer or prostatitis or BPH or BOO or LUTS or LUTD or BPE, *in vitro* or *in vivo*, animal study.

**Results:** The literature search identified 91 articles for analysis, 24 *in vitro*, 9 *in vivo*, 43 clinical and 15 review articles. We analyzed the papers with regards to bioavailability of lycopene, laboratory findings and clinical results of lycopene supplementation.

**Conclusions:** Lycopene has beneficial effects on prostate and several mechanisms of action have been identified in laboratory and clinical studies. However, the most important issue regarding future trials with lycopene is bioavailability.

**Keywords:** Lycopene; Diet; Prostate; Prostate cancer; LUTS; Supplementation; Tomato; BPH

### Introduction

Lycopene is an active carotenoid component of tomatoes giving them their familiar red colour. It is a potent antioxidant with a singlet-oxygen quenching ability twice that of  $\beta$ -carotene and ten times that of Vitamin E due to its structure. It is known to be a promising nutritional chemoprevention agent for prostate cancer [1]. However, during the 1990s the lycopene studies were based around lycopene products, which were considered to have poor or variable bioavailability, which led to inconsistencies in study outcomes [2]. Specifically, food based interventions involving consumption of large volumes of tomato products (e.g. juice or paste) or by the use of heterogeneous tomato extracts containing mixtures of carotenoids were unstandardized [2,3]. Clinical evidence for prostate health benefits of lycopene has been limited to patients with prostate cancer or high-grade prostatic intraepithelial neoplasia [4,5]. Epidemiological studies have established an association between tomato product intake, lycopene levels and prostate cancer risk reduction [1,2] but larger intervention trials are needed to determine the effect size of lycopene supplementation [6]. However, *in vitro* and animal studies have revealed several mechanisms of action of lycopene in the prostate that may play a role in prostate cancer initiation, promotion and progression. Some of these may also play a role in benign prostate hyperplasia (BPH). BPH and clinically associated lower urinary tract symptoms/dysfunction (LUTS/D) is a common disease of elderly men affecting 50 to 90% of all men between 50 and 80 years of age. These men will be treated by a variety of medications with associated side effects such as loss of libido, sexual dysfunction, hypotension and others. There are no known serious side-effects of lycopene, hence lycopene supplementation seems favorable if efficacy on LUTS/D and/or BPH is proven. Nutritional supplements and botanicals are widely used for symptom relief in LUTS/D and some, either as single intervention or combination, have shown promising results. However, the evidence level of clinical studies still precludes guideline recommendation of their use [7]. Although human and animal studies point to beneficial

effects on BPH, the mechanism of action of many plant-derived agents are not yet fully understood [8]. A possible beneficial role of lycopene in patients diagnosed with benign prostate hyperplasia (BPH), has been studied *in vitro* [9-11] and by clinical randomized trials [12]. Several issues complicate the interpretation of the results. First, lycopene has been studied as single intervention or combined with other plant-derived agents (e.g. *serenoa repens*) or vitamin E. Secondly, the dose of lycopene and mode of supplementation (tomato-derived food product or extract) varies across the studies. The latter has a significant effect on the bioavailability of lycopene that may consequently lead to different results. Thus, our aim was to assess the published evidence of the effect of lycopene on BPH and associated LUTS/D by performing a critical review of the literature.

### Methods

We searched PubMed electronic databases for articles published from 2000. Four main categories of studies have been selected: *in vitro* studies, *in vivo* studies, clinical studies and review articles. The results were confirmed by the similar search through Google. For clinical studies and review articles we used the following key words for search: lycopene and prostate or prostate cancer or prostatitis or BPH or BOO or LUTS or LUTD or BPE. For *in vitro* and *in vivo* models we used key words like lycopene and prostate, *in vitro* or *in vivo*, animal study.

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The final list of clinical studies was created considering several criteria available in an article, the level of lycopene in serum, information about the source of lycopene, protocol of a study and clear outcome results. For non-human studies any innovative studies adding value to the understanding of the mechanism of action of lycopene in prostate *in vitro* or *in vivo* models were included.

## Results

The literature search identified 91 articles for analysis, 24 *in vitro*, 9 *in vivo*, 43 clinical and 15 review articles. Sixty-seven original articles addressed prostate cancer and the findings were included in the analysis when potentially applicable to BPH. We analyzed the papers with regards to bioavailability of lycopene, laboratory findings (i.e. mechanisms of action) and clinical results of lycopene supplementation. The results of the literature search are shown in tables 1 and 2 for laboratory and clinical studies.

## Discussion

### Bioavailability of lycopene

A healthy diet is a common, general advice for patients with disease. Increasing the intake of vegetables has no side-effects and increases the intake of protective dietary factors like lycopene [13]. Dietary adherence to tomato product consumption increases plasma levels of lycopene [14]. In men in active surveillance for prostate cancer, a telephone-based dietary intervention (one serving of tomato product per day) increases lycopene levels [15]. Diet change towards a vegetable-rich diet can be challenging for men. Mindfulness training programs can be feasible to support a dietary change over time [16]. The absorption of lycopene is a complex issue involving release from the food microstructure matrix, dissolution into mixed micelles, intestinal uptake and incorporation into chylomicrons. Lycopene is distributed to e.g. prostatic tissue and the liver, where it is re-secreted into VLDL, which are progressively transformed into LDL. Increased intake of lycopene increases both plasma levels and lycopene content of prostate tissue [17,18]. The plasma half-life of lycopene is approximately 2 weeks [19]. The best food sources providing lycopene in a bioavailable form are tomato-derived food products, whereas lycopene from other sources such as fresh tomatoes and unheated tomato juice is poorly absorbed. The bioavailability of lycopene from tomato products is greatly enhanced after mechanical texture disruption and thermal processing. Such treatment increases the accessibility of the lycopene but also helps to disperse the liposoluble lycopene in the food matrix. In concentrated tomato extracts, the poorly soluble lycopene is predominantly crystallized and the crystalline form of carotenoids has been found to be one of the primary factors that reduce their bioavailability. However, if the particle size of lycopene is minimized, its bioavailability will be enhanced. Unprocessed tomatoes contain mostly all-trans lycopene isomer while lycopene found in prostate tissue predominantly is cis-isomers suggesting a better bioavailability for cis-lycopene [20]. Tangerine tomatoes contain more cis isomers. Interestingly, tomato products from tangerine tomatoes increase the uptake of both cis and trans lycopene [21]. Both tomato food products and lycopene extracts have been shown to increase plasma levels of lycopene. However, in a study using tomato-based juice as lycopene source, 80% of the subjects absorbed only 6 mg of lycopene, even when given doses of up to 120 mg of lycopene [22]. Lycopene supplementation in tablet form may be more attractive for some since a regular intake of tomato-paste or sauce is not necessary. Richelle et al., tested the bioavailability of lactolycopene, crystalline lycopene embedded in a whey protein matrix, in a randomized fashion compared to tomato paste and placebo. The

formulation of lactolycopene decreases the crystal size of lycopene significantly, resulting in a probable better resorption. After 3 weeks of supplementation with 25 mg of lycopene, administered as either tomato paste or lactolycopene in 36 healthy subjects, lycopene levels increased equally in both groups (2.6 and 2.7 times, respectively). There was no increase in the placebo group [20]. Thus, lycopene supplementation is possible without the need for consumption of large quantities of tomato paste.

### Laboratory findings

Several mechanisms of action of lycopene in prostate cells have been described. Lycopene is a potent antioxidant and has antiproliferative, pro-apoptotic properties in the prostate. Several animal studies, mostly using transgenic rat models have documented reduced tumour growth [23-25] and altered gene expression counteracting carcinogenesis [24-27]. Lycopene affects the insulin-like growth factor system which has a proposed key role in carcinogenesis in the prostate. An inverse association between lycopene intake and IGF-1 levels has been observed in men [28] suggesting a link between lycopene deficiency and prostate cancer. Lycopene also influences the insulin-like growth factor system in normal prostate cells. In cultured prostate cancer cell lines and normal prostate epithelium cells, lycopene inhibits the insulin-like growth factor 1 (IGF-1) stimulated cell growth by reducing dihydrotestosterone stimulated IGF-1 production [29]. However, in a clinical study of lycopene supplementation in 97 men with low burden prostate cancer under active surveillance, only a third of the patients randomized to 3 months lycopene supplementation had a twofold decrease of IGF-1 gene expression in prostatic tissue compared to placebo, resulting in an overall not significant decrease of IGF-1 gene expression by lycopene [30]. This result may be due to the size of the study or, potentially, the effect of lycopene on IGF-1 production is diluted from bench to bedside. In normal rats, lycopene supplementation reduces IGF-1 expression, local prostatic androgen signaling and inflammatory signals without affecting prostate growth [11,31]. Anyhow, lycopene appears to have multiple effects on the IGF-system. In a study by Talvas et al., sera from healthy men supplemented with lycopene upregulated IGF1binding protein in prostate cancer cell cultures while the expression of IGF-1 was unchanged [32]. Although there is little data on lycopene's effect on the IGF-system in BPH, this mechanism of action may counteract prostate growth in BPH. Qiu et al. have investigated proteomics in normal prostate epithelium cells exposed to lycopene vs. placebo and found that lycopene reduces oxidative stress in the cells, upregulates proteins that can promote apoptosis and down-regulates several proteins that are involved in anti-apoptosis [33]. In a study on cell viability and apoptosis in prostate cancer cell cultures, lycopene induces cell cycle arrest and apoptosis compared to placebo. However, no such effect was observed in BPH cells [34]. The promotion of cell cycle arrest and apoptosis by lycopene in prostate cancer cells is supported by another similar study [35]. Some of the potential health benefits of lycopene have been attributed to the potent antioxidant properties. As lycopene is accumulated in prostate tissue, an antioxidant effect should be detectable in the prostate. For instance, the receptor for advanced glycation end products (RAGE) and the soluble form (sRAGE) is, among many organs, expressed in prostate tissue. Activation of RAGE induces oxidative stress. Pathological conditions such as diabetes, vascular disease and cancer are associated with increased expression of sRAGE. In a study in healthy volunteers and normospermic male partners from infertile relationships, lycopene supplementation reduced sRAGE levels in seminal plasma both groups but not in blood plasma [36]. This suggests a specific antioxidative effect of lycopene in the prostate. However, in a randomized controlled

trial in African American healthy men aged 50-83 years receiving 30 mg lycopene or placebo, lycopene levels in prostate tissue increased significantly but there was no evidence of oxidative stress reduction. In detail, products of DNA oxidation and lipid peroxidation were not altered by increased lycopene levels [17]. Thus, increased levels of lycopene in the prostate do not prevent products of oxidative stress but there is evidence of oxidative stress reduction by lycopene supplementation, depending on the markers measured. Clearly, there is a need for further research to understand mechanisms of action of lycopene in reducing oxidative stress and their clinical significance.

### Clinical studies

Over the past 15 years, the question whether lycopene supplementation is associated with prostate cancer risk reduction has been investigated in major epidemiological trials. The largest trials, as for instance the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the Prostate Cancer Prevention Trial, have not been able to document a certain association between higher levels of lycopene and prostate cancer risk reduction [37-39]. However, some epidemiological studies have shown a risk reduction with increased tomato product intake [1,2]. A Cochrane database systematic review of randomized trials concluded that there is still insufficient evidence to support or refute lycopene supplementation for prostate cancer risk reduction [40]. In clinical studies, a prostate-specific antigen (PSA) lowering effect of lycopene has been observed both in men with high risk for prostate cancer [41], known prostate cancer [42,43] and BPH [44]. A decrease in PSA during lycopene supplementation may be due its anti-inflammatory and anti-proliferative effects seen in laboratory studies. An accumulation of lycopene in the prostate is already evident after 3 weeks of tomato product enriched diet e.g. in men consuming tomato-sauce daily 3 weeks before radical prostatectomy [45]. However, do the potential beneficial effects of lycopene translate to clinical improvement of LUTS/D? There are few randomized, controlled trials investigating clinical effects of lycopene. In the PROCOMB trial, Profluss® was tested in men with symptomatic LUTS/D. Profluss® contains a combination of *serenoa repens* (berries of the American dwarf palm), selenium and lycopene. The rationale for this combination arises from a BPH rat model where the ingredients were given solely and in combination and the pro-apoptotic effects were measured. The combination of the three ingredients had the most pronounced effect [46]. Patients were randomized to receive Profluss®, Tamsulosin or both for one year. Both interventions improved International Prostate Symptom Score (IPSS) significantly, especially in combination [47]. Profluss® also appears to have anti-inflammatory effects, evident from less inflammation in histology after treatment [48] and clinical improvement of chronic pelvic pain syndrome [49]. Schwarz et al., investigated lycopene as single intervention in men with BPH. Patients were randomized to 15 mg lycopene vs placebo. PSA was significantly reduced in the lycopene group and prostate volume was unchanged after 6 months. In the placebo group, a 24% increase of prostate volume was observed. Thus, lycopene can potentially inhibit disease progression in BPH. Interestingly, IPSS scores improved in both groups with a slightly greater improvement in the lycopene group. This may be due to rather low IPSS scores at inclusion and clinical improvement not being a primary endpoint.

### Conclusions

Lycopene has beneficial effects on prostate. Preventive effects on prostate cancer are still a matter of debate. Many laboratory findings are theoretically of importance in disease progression in BPH and LUTS/D. Larger clinical trials are needed to explore the clinical

benefit. However, the most important issue regarding future trials with lycopene is bioavailability. To date, most studies have been undersized or have used unstandardized methods of lycopene supplementation as a variety of tomato products. The best available mode of lycopene supplementation in clinical trials appears to be lactolycopene. There is documentation on good bioavailability [20], plasma levels can be monitored by non-invasive spectroscopy [50] and it has already been utilized in clinical trials. In a recent randomized, controlled trial in patients with cardiovascular disease and healthy volunteers, lycopene supplementation with lactolycopene restored endothelial dysfunction [51]. This points out potential health benefits of lycopene that are yet unexplored.

### Author contribution

WE and AB searched the medical literature and extracted the data used in the study. HP and SM analysed the data extraction, confirmed the searches were valid. SM and HP produced the initial manuscript and final manuscript. HP is guarantor for the study and the senior author.

### Conflict of interest

HP received an educational grant from Camnutra (Cambridge, UK) to undertake the study.

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