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Review

Is garlic a promising food for benign prostatic hyperplasia and prostate cancer?

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Prostate cancer is one of the most common male malignancies worldwide, and benign prostatic hyperplasia (BPH) is a common cause of lower urinary tract symptoms in elderly men. Garlic (*Allium sativum*) has been known to have anti-inflammatory, anti-cancer and antioxidant effects. Owing to these effects, garlic and its preparations have been used for the treatment of prostate cancer and relief of BPH symptoms for decades. It is thought that the mechanism(s) through which garlic may show anti-cancer and anti-inflammatory effects should be investigated further. Several researchers are attempting to demonstrate the useful properties of garlic and its mechanism(s) of action. This review aims to present the current studies related with the effects of garlic in prostate diseases, namely prostate cancer and BPH.

Keywords: Benign prostatic hyperplasia / Garlic / Natural foods / Nutrition / Prostate cancer

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1 Introduction

Benign prostatic hyperplasia (BPH) is a pathologic process contributing to lower urinary tract symptoms in elderly men, which is not a pre-malignant lesion. Histo-pathologically, BPH is characterized by increased number of stromal and epithelial cells in the periurethral area of the prostate. The increase in cell numbers may be due to the epithelial and stromal proliferation or impaired programmed cell death (apoptosis) leading to cellular accumulation [1].

Prostate cancer is known as one of the most common malignancies worldwide, and is the most common malignancy in men in the US and the second most common cause of cancer-related death in men in the US [2, 3]. It is suggested that both genetics and environmental factors play important roles in the development of prostate cancer. Inheritance, androgens, genetic polymorphisms, insulin-like growth factor-1, and diet are among the risk factors for prostate cancer [2]. High fat and calcium consumption may increase the risk of prostate cancer, however, it is stated that lycopene, selenium, vitamin E and green tea, which have strong antioxidant activity, may have protective effects against prostate cancer [2]. Prostate cancer is adenocarcinoma of the epithelial cells of the prostate gland, and high-grade prostatic intraepithelial neoplasia is the leading lesion for most peripheral-zone prostatic carcinomas [4]. At the early stages of prostate cancer, the cancer cells are dependent on androgen, and once the disease progresses, especially at metastatic stages, it becomes androgen independent [4].

Garlic (*Allium sativum*) is a vegetable known to have anti-cancer, antioxidant, anti-inflammatory, and cardio-protective effects. Garlic is composed of water (65% of fresh weight), carbohydrates, proteins, lipids, fiber, sulfur compounds (1.1–3.5% of fresh weight), vitamins and minerals [5]. Water soluble allicin, alliin, S-allyl cysteine (SAC) and S-allyl mercaptocysteine (SAMC), and oil soluble diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS) are among the major organosulfur compounds found in different garlic preparations. There are various garlic preparations such as aged garlic extract (AGE), garlic powder, garlic oil, garlic homogenate and raw garlic. Since SAC and SAMC are major organosulfur compounds found in AGE, which is the mostly used form of garlic, SAC can be used to standardize AGE preparations. These organosulfur compounds have been suggested to play a role in the antioxidant and possibly chemo-preventive properties of garlic [6, 7].

As emphasized above, prostate cancer is one of the most common malignancies in men and BPH is an important

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Abbreviations: **AGE**, aged garlic extract; **BPH,** benign prostatic hyperplasia, **CI**, confidence interval, **DADS,** diallyl disulfide; **DAS,** diallyl sulfide; **DATS**, diallyl trisulfide; **OR**, odds ratio; **PSA**, prostate-specific antigen; **ROS**, reactive oxygen species; **SAC**, S-allyl cysteine; **SAMC**, S-allyl mercaptocysteine

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health problem in elderly men. It has long been known that garlic has anti-cancer and anti-inflammatory effects in this regard. Therefore, in the present review is aimed to present recent studies related to the effects of garlic in prostate diseases, namely prostate cancer and BPH.

2 Use of garlic in BPH and prostate cancer

In the literature, there are many epidemiological, clinical and experimental studies aiming to investigate the effects of garlic and its derivatives in prostate diseases, specifically BPH and prostate cancer.

2.1 Population studies

In the last ten years, a few population based diet studies were established to investigate the association between the intake of some foods, including garlic, and the risk of prostate cancer. In one of them, a case-control study was conducted to determine the relation of a high intake of total or saturated fat with the risk for prostate cancer in men in England [8]. It also aimed to establish whether the risk would decrease with a high intake of carotene or lycopene, and other foods including garlic. For this aim, 328 men diagnosed with prostate cancer before the age of 75 years and 328 age-matched population controls, were interviewed between February 1990 and July 1994. Cases were identified by searching histopathology records and controls were chosen from lists of the cases' general practitioner. The mean ages of cases and controls were 68.1 years. The questions asked during the interview were related to demographic details, *i. e.* smoking, family history of prostate cancer, and usual food intake in the previous five years. The researchers found no evidence for an association between fat intake and risk of the disease, whilst a higher intake of carotene was associated with decreased risk. Lycopene was found not to be associated with the risk. However, they observed important associations for garlic consumption and prostate cancer risk. The odds ratio (OR), which is used to estimate relative risk, for the subjects ingesting garlic as a food ≥2 servings/week to the ones consuming none was 0.56 (95% confidence interval (CI) = 0.33–0.93; $p_{trend} = 0.038$), and for the subjects consuming garlic supplements ≥2 servings/week to none was 0.60 (95% CI = 0.37–0.96; $p_{trend} > 0.05$), indicating decreased risk in the subjects taking garlic or its supplements. However, by adjusting for social class it was found that OR for the subjects ingesting garlic as a food ≥2 servings/week to the ones consuming none was 0.64 (95% CI = 0.38–1.09; $p_{trend} > 0.05$). It was suggested that the study did not support the hypothesis that fat increased risk and was unclear in relation to carotene intake. They also proposed that the possible relations of garlic consumption with risk for prostate cancer should be further investigated [8]. In a previous review, it was concluded that according to the results of the above mentioned study garlic supplements were not related to a risk of prostate cancer [9]. However, in that review, the authors suggested that there was an inverse correlation between consumption of garlic and gastric and colorectal cancers, and additional studies would be required for the role of garlic and garlic supplements in cancer etiology [9].

In another population based case-control study conducted in China, the relation between the intake of allium vegetables including garlic and the risk of prostate cancer was investigated. For this aim, 238 men diagnosed with histologically confirmed prostate cancer and 471 men as population control subjects were interviewed to determine their dietary habits. It was reported that men (highest category) consuming allium vegetables >10 g/day had a significantly lower risk of prostate cancer than those (lowest category) consuming <2.2 g/day (OR = 0.51; 95% CI = 0.34–0.76; $p_{trend} < 0.001$). For garlic and scallions consumption, the findings were similar in that men consuming garlic, >2.14 g/day, had a significantly lower risk for prostate cancer than those consuming no garlic (OR = 0.47; 95% CI = 0.31–0.71; $p_{trend} < 0.001$) and men consuming scallions >2.14 g/day had a significantly lower risk for prostate cancer than those consuming no scallions (OR = 0.30; 95% CI = 0.18-0.51; $p_{trend} < 0.001$). The ORs were adjusted for age and total calorie intake. As a conclusion of that study, it was suggested there was a reduced risk for prostate cancer in Chinese men consuming allium vegetables, especially garlic and scallions [10].

Recently, Galeone *et al.* investigated the role of allium vegetables, namely onion and garlic, in the etiology of several cancers in Italy and Switzerland [11]. One of their studies performed on prostate cancer included 1294 cases and 1451 controls. The median ages for cases and controls were 66 and 63 years, respectively. Questionnaires used in interviews included information about sociodemographic factors, anthropometric variables, smoking, alcohol usage, lifestyle habits, problem oriented medical history, physical activity and history of cancer in their relatives. Information on diet was taken by using food-frequency questionnaire and referred to two years prior to diagnosis. They divided frequency of garlic consumption into three groups of none or low, intermediate and high use and scored as 1, 2 and 3, respectively. According to the garlic scores, the OR for the highest score *vs*. the lowest score was 0.81 (95% CI = 0.64–1.00; $p_{trend} = 0.05$) for prostate cancer. Hence, Galeone *et al.* suggested that allium vegetables, garlic and onion, have protective roles on the risk of several cancers including prostate cancer in Western countries as well as Eastern countries [11].

2.2 Clinical studies

In a clinical study performed by our group previously, the effects of aqueous garlic extract supplementation on the dis-

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ease parameters in the patients with prostate diseases were investigated [12]. In that study, 27 volunteer patients with BPH and nine volunteer patients with prostate cancer were given aqueous garlic extract at a daily dose of 0.2 g raw garlic/kg body weight for one month. At the end of the study period, it was observed that the mass of the prostate was significantly lowered in the BPH group. It was also found that urinary frequency and international prostate symptom score values decreased, maximum and average rates of urine flow increased after the extract consumption. In the prostate cancer group, significantly lowered total and free prostate-specific antigen (PSA) values were measured after the extract consumption. In this group, urinary frequency, maximum and average rates of urinary flow and international prostate symptom score values were also found to significantly improve after the experimental period. As a result of that study, it was suggested that garlic supplementation or its regular daily consumption might improve the disease parameters of the patients with BPH and prostate cancer [12].

2.3 Animal studies

Arunkumar *et al.* conducted an animal study to evaluate the effects of DADS on prostate carcinogenesis in Sprague–Dawley rats. In that study, it was shown that DADS, one of the organosulfur compounds of garlic, has considerable potential to inhibit cancer induction in the rat prostate. They concluded that DADS had chemo-preventive effects in rat prostate carcinogenesis [13]. In a recent study, the antioxidant potential of DAS against testosterone-induced oxidative stress in prostate and liver tissues from Swiss albino mice was investigated. As a conclusion of that study, it was suggested DAS was effective in exerting antioxidant effects by inhibiting testosterone-induced oxidative stress in both tissues and might be helpful in the prevention of prostate cancer [14].

2.4 Cell line studies

In recent years, many cell line studies have been conducted to elucidate the mechanisms through which garlic derivatives have exerted their effects on prostate cancer cells. In one of the studies performed in androgen independent prostate cancer cell lines (PC-3 and DU145), it was demonstrated that SAC and SAMC, water soluble garlic derivatives, could suppress the invasion ability of prostate cancer cells. It was also shown that the inhibitory effect of the prostate cancer cell invasion was mediated via restoration of E-cadherin expression [15]. In previous studies, it was suggested that inactivation of E-cadherin was one of the main characteristics of metastatic prostate cancer [16–19]. Chu *et al.* showed that E-cadherin expression was induced by the garlic derivatives in some other human cancer cell lines including ovarian, nasopharyngeal and esophageal cancer cell lines [15]. Hence, they concluded that garlic derivatives namely SAC and SAMC might be effective agents in the treatment of invasive cancers including prostate cancer [15]. In another recent cell culture study, Arunkumar *et al.* demonstrated that DADS suppressed the proliferation of PC-3 cells, an androgen-independent human prostate cancer cell line, in a dose-dependent manner by induction of cell cycle arrest at G_2/M phase transition. They concluded that DADS had the potency to inhibit proliferation of prostate cancer cells through cell cycle arrest [20]. It was demonstrated in another study that DATS caused G_2/M phase cell cycle arrest in the human prostate cancer cells (PC-3 and DU145) through the generation of reactive oxygen species (ROS) and hyperphosphorylation of cell division cycle 25C (Cdc25C) protein [21]. Similarly, in our previous studies which were performed in the chronic myeloid leukemia cell line (32Dp210), we observed that AGE, at 0.4% concentration, caused apoptotic and anti-proliferative effects on the cells, and created oxidant stress which was reflected by significant increases in malondialdehyde level and xanthine oxidase enzyme activity in the cells. Our findings suggested that oxidant potential of the garlic extract which was created by increased xanthine oxidase activity and/or its own ingredients might play an important role in the anticancer property of garlic. This property of garlic was supposed to be a potential chemo-preventive force in chronic myeloid leukemia [22, 23]. In another study, it was concluded that DATS-induced ROS generation in human prostate cancer cells was mediated by an increase in labile iron due to the degradation of ferritin [24]. Additionally, researchers showed that c-Jun N-terminal kinase signaling axis, which is known to have a role in the control of cell survival [25], was involved in the regulation of DATS-induced ROS generation [24]. In another study, the same research group revealed that DATS-induced apoptosis in human prostate cancer cells (PC-3 and DU145) was mediated by Akt inactivation leading to mitochondrial translocation of BAD (one of the pro-apoptotic proteins) and mediated by activation of caspases 3 and 9 (apoptotic proteins [26]) [27]. It was also observed that DATS activated both the G_2 and M phase checkpoints in human prostate cancer cells (PC-3 and DU145) independent of their p53 tumor suppressor protein status [28], which was thought to play a role in the regulation of G_2/M transition [29]. They suggested the existence of a checkpoint kinase 1-dependent mechanism for DATS, induced mitotic arrest in human prostate cancer cells [28]. It has been reported that DATS has inhibitory effects on angiogenic features of human umbilical vein endothelial cells [30], and its administration has inhibited growth of androgen-independent PC-3 human prostate cancer xenograft (implanted to athymic mice), correlated with the induction of Bax and Bak apoptotic proteins *in vivo* [31]. In another study conducted in androgen-dependent prostate cancer cell line LNCaP, it has been observed that DADS inhibited the growth of prostate cancer cells *in vitro* [32]. In a previous study, it was determined that SAMC led

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to a decrease in the growth of androgen-dependent LNCaP human prostate cancer cells and caused a decreased PSA secretion which was disproportionately greater compared to the cell growth inhibition [33].

Chu *et al.* recently performed a study aiming to investigate the effects of SAC on CWR22R, human androgen independent prostate cancer xenografts, in castrated nude mice. They reported that SAC treatment resulted in inhibition of the growth of CWR22R xenograft which was correlated with decreases in serum PSA level and proliferation rate of the xenograft. Additionally, they observed an inhibition of the cancer invasion via the restoration of E-cadherin and γ-catenin, adhesion complexes, expression. They concluded that SAC might be a chemotherapeutic agent for suppressing androgen-independent prostate cancer [34]. In another recent study, Howard *et al.* showed that SAMC is an anti-metastatic agent for androgen-independent prostate cancer. They used PC-3 cells implanted orthotopic severe combined immunodeficient mouse model of advanced androgen-independent prostate cancer, and determined that SAMC inhibited the growth and progression of prostate cancer xenografts *in vivo* [35]. This finding is very important since it shows anti-metastatic properties of garlic in an animal model *in vivo*.

3 Conclusions and future targets for the use of garlic in BPH and prostate cancer

In summary, garlic and its derivatives have long been known to have antioxidant, anti-inflammatory and anti-cancer properties and possibly because of these properties, they are commonly used by patients with prostate diseases, namely BPH and prostate cancer. It is also known that garlic is mostly consumed, raw or cooked, in combination with foods like tomatoes and olive oil in salads and sauces as a part of a modern diet strengthening its preventive effects against the carcinogenesis [11]. As emphasized above, many experimental cell line studies as well as a few animal studies were performed in an attempt to elucidate action mechanism(s) of garlic derivatives against prostate cancer. Additionally, some clinical and epidemiological studies have been directed to determine the therapeutic use of garlic as a vegetable in daily diet and/or its preparations as supplements in patients with BPH or prostate cancer in the last ten years. Unfortunately, it is not exactly understood yet what active components of garlic are responsible for the observed beneficial effects of garlic in BPH and prostate cancer. Secondly, it is not well known how it exerts its protective effects in prostate diseases. However, present data suggest that garlic consumption before prostate cancer initiation may be more useful. We suppose that further studies should be directed to this subject.

We think that in future, new *in vitro* and *in vivo* studies should be conducted to establish which active components of garlic play a role in the therapeutic effects against prostatic diseases, and to elucidate whether garlic as a whole, or its active components, are more suitable. In conclusion, we recommend that men at risk for BPH or prostate cancer consume more garlic in their daily diets, and those who are diagnosed with BPH or prostate cancer should consume it to support their medical therapies.

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