



# Dietary Botanicals for Chemoprevention of Prostate Cancer

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Prostate cancer typically develops later in life. Hence, identifying the botanical compounds that can prevent or delay disease progression may have a positive effect on the quality of life and reduce the healthcare costs of the aging population.<sup>[1]</sup> Supporting the statement, it could be accepted that the burden of increasing morbidity and mortality due to prostate cancer imposes a need for new, effective measures of prevention in daily life. Chemoprevention, a prophylactic approach that uses nontoxic natural or synthetic compounds to reverse, inhibit, or prevent cancer by targeting specific steps in the carcinogenic pathway, is gaining traction among healthcare practitioners.<sup>[2]</sup> The World Health Organization (WHO) estimates that 80% of the population of developing countries relies on traditional medicine for their primary care needs. The emergence of resistance to cancer chemotherapy has forced researchers to turn to natural products of plant and marine origin.<sup>[3]</sup> Additionally, treatments for advanced disease are limited to hormone ablation techniques and palliative care. Thus, new methods of treatment and prevention are necessary for inhibiting disease progression to a hormone refractory state. One of the approaches to control prostate cancer is prevention through diet, which inhibits one or more neoplastic events and reduces the cancer risk.

For centuries, Ayurveda has recommended the use of bitter melon (*Momordica charantia*) as a functional food to prevent and treat human health related issues.<sup>[4]</sup> A study conducted by Ru *et al.* demonstrated that prostate cancer cells treated with bitter melon extract (BME) delayed the progression to high-grade prostatic intraepithelial neoplasia in transgenic adenocarcinoma of mouse prostate (TRAMP) mice by 31%. Prostate tissue from BME-fed mice displayed approximately 51% reduction of proliferating cell nuclear antigen expression. Together, results suggest that oral administration of BME inhibits prostate cancer progression in TRAMP mice by

interfering with cell cycle progression and proliferation.<sup>[5]</sup>

Pomegranate juice (PJ) components luteolin, ellagic acid, and punicalic acid together inhibit growth of hormone-dependent and hormone-refractory prostate cancer cells and inhibit their migration and chemotaxis toward stromal cell-derived factor 1 $\alpha$  (SDF1 $\alpha$ ), a chemokine that is important in prostate cancer metastasis to the bone. Furthermore, they increase several well-known tumor-suppression microRNAs (miRNAs), decrease several oncogenic miRNAs, and inhibit the chemokine receptor type 4 (CXCR4)/SDF1 $\alpha$  chemotaxis axis.<sup>[6]</sup> PJ has been associated with prostate-specific antigen (PSA) doubling time (PSADT) elongation in men with prostate cancer in a phase II trial.<sup>[7]</sup> Additionally, Bhandari has reviewed the beneficial role of pomegranate in other disorders including prostate cancer.<sup>[8]</sup>

Gugulipid (GL), an extract of Indian Ayurvedic medicinal plant *Commiphora mukul*, has been used to treat a variety of ailments. Treatment with GL significantly inhibited the viability of human prostate cancer cell line LNCaP (androgen-dependent) and its androgen-independent variant. The GL-induced growth inhibition correlated with apoptosis induction and cleavage of poly (ADP-ribose) polymerase. The GL-induced apoptosis was associated with reactive oxygen species (ROS) production and c-Jun NH (2)-terminal kinase (JNK) activation.<sup>[9]</sup> The  $\alpha$ -guggulsterone treatment inhibited capillary-like tube formation (*in vitro* neovascularization) by human umbilical vein endothelial cells (HUVEC) and migration by HUVEC and DU145 human prostate cancer cells in a concentration- and time-dependent manner. These results provide compelling rationale for further preclinical and clinical investigation of  $\alpha$ -guggulsterone for its efficacy against prostate cancer.<sup>[10]</sup>

S-allylcysteine (SAC), a potent compound derived from garlic, suppressed the proliferation of PC-3 cells and led to cell cycle arrest at the G0/G1 phases, as well as induced cell apoptosis, which was

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accompanied by the decreased expression of Bcl-2 and increased expression of Bax and caspase 8. This demonstrates the chemopreventive activity of SAC *in vitro*, and that SAC may be a promising candidate for prostate cancer treatment.<sup>[11]</sup> Diallyl disulfide (DADS) is another major component of an oil-soluble allyl sulfide garlic (*Allium sativum*) derivative. Inhibitory effects of DADS on prostate carcinoma LNCaP cells motility and invasiveness were found to be associated with increased tightness of the tight junctions (TJ), which was demonstrated by an increase in transepithelial electrical resistance (TER).<sup>[12]</sup> Additionally, results of the study conducted by Singh *et al.* indicate that oral administration of diallyl trisulfide (DATS) prevents development of poorly differentiated carcinoma and multiplicity of pulmonary metastatic lesions in TRAMP mice without causing weight loss or affecting T-antigen expression.<sup>[13]</sup>

Ginger (生薑 Shēng Jiāng; *Zingiber officinale*) is an excellent source of several bioactive phenolics, including non-volatile pungent compounds such as gingerols, paradols, shogaols, and gingerones. Ginger has been known to display anti-inflammatory, antioxidant, and antiproliferative activities, indicating its promising role as a chemopreventive agent. Whole ginger extract (GE) exerts significant growth-inhibitory and death-inductory effects in a spectrum of prostate cancer cells. GE perturbed cell cycle progression, impaired reproductive capacity, modulated cell cycle and apoptosis regulatory molecules, and induced a caspase-driven, mitochondrially mediated apoptosis in human prostate cancer cells. Remarkably, daily oral feeding of 100 mg/kg body weight of GE inhibited growth and progression of PC-3 xenografts by approximately 56% in nude mice, as shown by measurements of tumor volume. Thus, bioactive compounds from ginger show protective effects in both *in vivo* and *in vitro* prostate cancer models by modulation of proteins involved in apoptosis pathway.<sup>[14]</sup>

An analog of mahanine (alkaloid from *Murraya koenigii*, curry leaf) potently inhibited human prostate cancer cell proliferation *in vitro*, and dosing at 10 mg/kg reduced human xenograft tumor volume by about 40%.<sup>[15]</sup>

Furthermore, curcumin and silibinin too have been demonstrated to possess prostate cancer chemopreventive potential.<sup>[16,17]</sup>

Thus, cancer chemoprevention by phytochemicals could be one of the most reasonable methods for cancer control. Phytochemicals obtained from vegetables, fruits, spices, teas, herbs, and medicinal plants have been established to suppress experimental carcinogenesis in several organs, including prostate, in pre-clinical models. Current studies have shown that mechanisms fundamental to chemopreventive potential might be a blend of antioxidant, anti-inflammatory, immune-enhancing, and hormone modulation effects. Moreover, alteration of drug metabolizing enzymes and effects on cell cycle and cell differentiation too are responsible. Stimulation of apoptosis, suppression of proliferation and angiogenesis also play a role in the initiation and secondary modification stages of neoplastic development. Particular features of prostate cancer, such as high prevalence and long latency period, offer sufficient prospects for chemopreventive agents to work

at different stages of disease development. Finally, appropriate populations with applicable risk factors, including the presence of pre-malignant lesions and genetic predispositions, need to be well characterized for future chemopreventive interventions.

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