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REVIEW

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Insights of Curcumin in Prostate Cancer with update: Review

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Abstract

Prostate cancer is the most common type of uncontrolled slow-growing cancer in men at 99% cases. The risk of developing prostate cancer is 74 percent higher in African Americans than in non-Hispanic Caucasian men. Prostate cancer patients with the age of 66 to 80 years old show cancerous symptoms who usually die. The natural agent curcumin and its derivatives are widely used for the treatment of prostate cancer. Although the bioavailability of Curcumin is very poor, it shows high efficacy in prostate cancer patients. The clinical trials demonstrate a well-tolerated safety at a high dose 12g/day after oral administration in the patients with malignant or pre-malignant lesions. These studies show minor adverse events such as nausea and diarrhea without other complications. The androgen receptor (AR) gene binding to the prostate-specific antigen (PSA) gene is highly expressed in prostate cancer patients which is found downregulated after the treatment of curcumin. In this review, we have discussed the broad impact and indication of curcumin for the treatment of prostate cancer.

Key Words: prostate cancer, curcumin, clinical trial, androgen receptor

Introduction

Prostate cancer is the development of non-cutaneous cancer in the walnut-sized gland located below the bladder and in front of the rectum (Centers for Disease Control and Prevention, 2019). It is the most common type of cancer among men in United States. Generally, prostate cancers are slow-growing; but in most of 99% cases, it grows out of control and forms a tumor (Espiritu et al., 2018). Prostate adenocarcinomas are found in the prostate fluid-secreting glands found in semen (Wagenlehner, Pilatz, Weidner, & Naber, 2017). The other types of prostate cancer consist of sarcomas, small cell carcinomas, neuroendocrine tumors, and transitional cell carcinomas (Li, & Wang, 2016). It is estimated that one in five African-American men and one in six white Americans will be diagnosed with this cancer (Hoffman et al., According to GLOBOCAN 2018, the incidence of prostate cancer is very high all over the world. It is estimated that 1276106 new cases of prostate cancer were reported in 2018, where 7.1% of prostate cancers were in men (Bray, Ferlay, Soerjomataram, Siegel, Torre, & Jemal, 2018). Moreover, in African Americans, the risk of developing prostate cancer is 74 percent higher than in non-Hispanic Caucasian men (Shenoy, Packianathan, Chen, & Vijayakumar, 2016). The incidence rates of prostate cancer are lower in Asia and Africa as compared to the United States, Europe, and Oceania. The age-standardized age rate in Asia and Africa was estimated as (26.6 and 11.5) while in the United States (73.7), Europe (62.1) and Oceania were recorded as 79.1/100,000 individuals (Rawla, 2019). The symptoms of prostate cancer include incontinence, difficulties in urination, frequent urination, blood in urine and semen, burning during urination, painful ejaculation, and erectile dysfunction (Canadian Cancer Society, 2020). The age at which men are more likely to display signs of prostate cancer ranges from 66 to 80 years old (Stangelberger, Waldert, & Djavan, 2008). 80 years old man

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Public interest statement
Curcumin has significant efficacy for the treatment of prostate cancer in men. The importance of curcumin in diet and its safety and bioavailability is described in this review.

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are mostly affected and die from prostate cancer. Additionally, men whose father or brother is diagnosed or had prostate cancer are at double the risk of developing this fatal disease. Moreover, men who inherited mutations in their breast cancer genes (BRCA1 and BRCA2) also have a greater chance of developing a prostate malignancy.

Curcumin is a polyphenolic molecule extracted from rhizome of the plant *Curcuma Longa*. It is a yellow spice mainly used as an ingredient for curries and for centuries used as an anti-inflammatory agent for the Chinese, Ayurvedic, and Hindi medicine (Bhowmik, Chiranjib, Kumar, Chandira, & Jayakar, 2009). Curcumin consists of several properties such as anti-oxidant, chemo-preventive, anti-inflammatory, anti-angiogenic, anti-microbial, anti-cancer and as anti-proliferative agent (Tomeh, Hadianamrei, & Zhao, 2019). Currently, anti-tumor activity of curcumin and its by-products are used for preclinical studies on prostate cancer. In this literature review, the information available regarding the impact of curcumin on prostate cancer in men and additional studies that included curcumin in diet, its analogs, safety and bioavailability for prostate cancer prevention or treatment would be discussed respectively.

Role of Curcumin in Prostate Cancer

Curcumin is considered as a natural nutritional supplement, with chemo-preventive and anti-cancer drug (Devassy, Nwachukwu, & Jones, 2015). It helps to decrease the incidence of cancer by reducing treatment-related side effects and mortality. These naturally occurring substances are usually found in foods such as fruits, spices, seeds, and vegetables (Devassy, Nwachukwu, & Jones, 2015). There are currently no prognostic indicators of prostate cancer but the role of the androgen receptor (AR) is well-known and well-founded in the initiation and development of prostate cancer (Tamburrino et al., 2012). Curcumin limits the androgen receptor (AR) gene binding to the prostate-specific antigen (PSA) gene by downregulating AR expression (Nakamura et al., 2002).

Moreover, it reduces the prostate-specific antigen (PSA) expression in LNCaP cells which are the androgen-sensitive prostate glandular cancer cells that are epithelial adherent cells growing in clusters and as a single cell (Davis, Kucuk, & Sarkar, 2002). The reported studies revealed that curcumin and its analogs inhibit the effect on CWR-22Rv1 androgen receptor (AR) and delay tumor cell growth by suppressing the AR expression in an LNCaP xenograft mouse model (Schmidt, & Figg, 2016).

Nowadays, clinical trials are conducted on curcumin for prostate cancer in humans. The clinical trials have illustrated that the patients with malignant or pre-malignant lesions presented the curcumin as a well-tolerated and safe molecule even at a high dose such as 12g/day after oral administration with few adverse events such as nausea and diarrhea within several months (Teiten, Gaascht, Eifes, Dicato, & Diederich, 2010). Several curcumin derivatives such as desmethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin, hexahydro curcumin, and octa hydro curcumin are evaluated as androgen receptor antagonist and suppress growth of prostate tumor due to 17a-substituted dihydrotestosterone function (Ohtsu et al., 2002).

Curcumin was shown to induce a marked alteration in the microfilament and cell motility in PC-3 and LNCaP cells and increase the stress fibres of f-actin causing inhibition of angiogenesis and metastasis in prostate cancer (Holy, 2004). Furthermore, several studies reveal that the treatment of prostate cancer by curcumin down-regulate Bcl-2 and Bcl-xL apoptosis suppressor protein and results in the release of cytochrome c, Smac/DIABLO, caspase 3 activation, reactive oxygen species activation, a decline in mitochondrial membrane potential and Bax and p53 translocation to mitochondria (Khan, Adhami, & Mukhtar, 2010). Hence, it is significantly evident through several studies that the use of curcumin causes prostate cancer cells to undergo apoptosis by down-regulating murine double minute 2 (MDM2) protein and mRNA. Furthermore, curcumin analogs have anti-oxidant potential for the induction of phase 2 enzymes by regulating nuclear factor erythroid-2-related factor (NRF2) (Ma, Wu, Gao, & Loor, 2018).

According to Oliver et al (2016), the use of curcumin may protect and reduce the risk of cardiovascular disease by improving the endothelial functions in individuals. A randomized controlled double-blind parallel study was conducted and fifty- nine healthy participants were enrolled and were assigned to placebo for 8 weeks. They were orally administering 50 mg or 200 mg of curcumin. The higher dose of 200 mg curcumin significantly showed improvement in endothelial functions when measured by flow-mediated dilation with 3.0% increase (90% CI 0.7 to 5.3%, p = 0.032). The lower dose of 50 mg did not show any clinical signs but

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displayed an increase in flow-mediated dilation by 1.7% (−0.6 to 4.0%, p = 0.23; 25: 1).

Hence, the researcher concluded that oral intake of curcumin supplementation can help to decrease risk of cardiovascular disorders. In another study, curcumin efficacy was found to be similar to statins, and curcumin is also used for treatment of statin-associated muscle symptoms (SAMS). Curcumin administration prevents and reduces the delayed onset of muscle soreness by blocking the nuclear factor inflammatory route. It also attenuates muscular atrophy and muscle fiber regeneration after injury.

Curcumin increases number of mitochondrial DNA duplications in skeletal muscle cells due to increase in the levels of cyclic adenosine monophosphate. Therefore, curcumin serves as an additional therapy with statin in patients suffering from SAMS. It lowers low-density lipoprotein cholesterol and reduces statin doses due to lipid-altering properties (Sahebkar, Saboni, Pirro, & Banach, 2017).

According to the epidemiological study by Mishra and Palanivelu (2008), effect of curcumin (turmeric) has a positive impact on Alzheimer's disease. Curcumin supplements play a major role in prevention and treatment of Alzheimer's disease by improving the brain functions by crossing the blood-brain barrier and decreasing the beta-amyloid plaques, microglia formation. Curcumin also delays the neuron degradation and metal-chelation. These lipophilic actions of curcumin help to improve the memory of Alzheimer's disease (AD) patients. Therefore, turmeric benefit for cognitive functions is well established.

A pilot study conducted by Di Pierro, Rapacioli, Di Maio, Appendino, Franceschi and Togni (2013) showed that 2 g of curcumin had an analgesic effect in subjects with acute pain of osteoarthritis. At this dose, the activity was higher than that associated with 500 mg acetaminophen. Analgesic effect was visible after 2 hours of curcumin dose administration with no adverse effects as compared to NSAIDs which cause gastrointestinal symptoms. 1.5 g or 300 mg of curcumin gave only minimal pain relief but by using 2 g of curcumin, can provide relief of pain and is considered as a significant substitute to NSAIDs (Di Pierro, Rapacioli, Di Maio, Appendino, Franceschi, & Togni, 2013). Therefore, curcumin and turmeric extracts can be recommended for relieving the symptoms of osteoarthritis as they result in similar improvements in the symptoms as compared to NSAIDs.

Extract of turmeric can be used alone or in combination with other pharmaceutical drugs for the prevention and treatment of different forms of cancers such as breast, colorectal, pancreatic, lung, multiple myeloma and for oral cancer. It is used as an anticancer agent as it targets multiple pathways as per Table:1 (Devassy, Nwachukwu, & Jones, 2015). Moreover, by anti-inflammatory, anti-oxidant, antiproliferative, and proapoptotic mechanisms it inhibits cell proliferation and leads to cancer cell death.

Although curcumin has a significant impact on prostate and other forms of cancers but due to poor bioavailability and low aqueous solubility the clinical development becomes limited. By conducting preclinical and in-vivo studies, the bioavailability of curcumin is greatly affected by several barriers such as poor absorption, rapid metabolization, and systematic elimination (Liu et al., 2018). These researchers have implemented various approaches such as curcumin liposomal and nanoparticles, by structural modification and use of piperine as an adjuvant therapy still it has poor bioavailability. In a randomized clinical trial, a dose of 8 g/day was administered in participants orally. Researchers found a low level of free curcumin (<2.5 ng/mL) in plasma due to rapid metabolites transformation (Kunati, Yang, William, & Xu, 2018). Even though curcumin has visibly shown poor bioavailability, but several preclinical studies still focus on therapeutic effect of curcumin.

Lao et al., (2006) has shown through dose-escalating studies that consuming 12 g/day of curcumin leads to no detrimental effects, and curcumin consumption is considered safe and effective to treat cancers. In another clinical trial study, curcumin had beneficial effects on cancer by consuming a dose of 100 mg/d to 6 g/d. The dosage of 2-3 g/d curcumin lead to beneficial effects for cancer treatment. Moreover, if want to achieve increase in curcumin bioavailability than low dose of curcumin would be enough to treat cancer (He, Shi, Wen, Li, Wang & Wang, 2011). According to the reviews, there is an advantage to use curcumin to prevent or treat prostate cancer. Based on current studies, it is evident that the use of curcumin and its derivatives is associated with a reduction in the incidence of prostate cancer but still

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Types of Cancer	Proliferative Proteins	Transcription Factors	Apoptotic Proteins	Growth Factors	Protein Kinase
Breast (Nee Chakraborty, Ghosh, Bhattacharyy, Bhattacharyy, Dey, & Roy, 2007).	↑ TIMP-1, p21, p27	↓ NF-κB, AP-1, COX-1, COX-2, VEGF, FGF, cyclin E, IL-6, IL-11, TGF-β, MMP-2, MMP-9, MMP-13	-	-	-
Pancreatic (Thakkar, Sutaria, Grandhi, Wang, & Prabhu, 2013).	-	↓ NF-κB, cyclin-D1, c-myc protein, Bcl-2, Bcl-xL, cIAP-1, MMP, COX-2, VEGF, Sp-1, Sp-3, Sp-4, survivin, VEGF, PGE2, miR-21	↑ caspase-3, PARP, P-ERK1/2, c-Jun protein, p38 MAPK, p53 protein, miR-200	-	-
Colorectal (Patel & Majumdar, 2009; Patel, Misra, Patel & Majumdar, 2010)	-	↓ COX-2, NF-κB, Bcl-2, Bcl-xL, cyclin D1, c-myc, VEGF, IL-8, MMP-9, PGE2	-	↑ DR-5, IGF-1R, IGFBP-3	↑↓ EGFR
Prostate (Teiten, Gaascht, Eifes, Dicato, & Diederich, 2010)	↑ Bcl-2 L1, Bcl-2 L11, BAK1, BAX, BBC3, PMAIP 1, p53 protein	↓ NFKBIA, AKT 1, Bcl-2, BIRC4, BIRC5, PTEN, NKX 3A, CSF 1R, EGFR, NF-κB	↑↓ caspase-3, caspase-8	-	-
Multiple Myeloma (Tomeh, Hadianamrei, & Zhao, 2019)	↓ IkBα, Bcl2, Bcl-xL, cyclin D1, IL-6, COX-2, NF-κB	-	↑ caspase-7, caspase-9, PARP	-	-

further research is required concerning the trials including placebos for the use of curcumin for prostate cancer.

Conclusion

The literature review suggests that the use of curcumin is found beneficial and has an apoptosis effect on prostate cancer cells. Reduction in incidence of prostate cancer due to use of curcumin has been widely documented throughout the literature. A major limitation is that further epidemiological assessment is required by conducting deep analysis and improving the reporting system. Though current clinical studies support the use of curcumin as discussed above, however, further research is required to assess increase in curcumin bioavailability for low doses. Additionally, it would provide a solid base and fill gaps for future research and help to justify the use of curcumin to treat prostate cancer in men by providing us with a robust and credible data.

Additional Information

Author Contribution

M. S. S. Khan made substantial contributions to the conception and design of the manuscript, review of the literature, and drafting of the manuscript and figures. C. I. Cazzonelli made equally substantial contributions to the conception and design of the manuscript, review of the literature, and drafting of the manuscript and figures. H. Kurata made significant contributions to the collection of citations related to plant and human metabolism and participated in drafting relevant sections of the manuscript. M. B. Badsha made substantial contributions to the collection of citations related to metabolism and computational information and in drafting the relevant sections of the manuscript. C. G. Li provided in depth input on the acquisition and interpretation of the literature on safety of herbal medicine and participated in the preparation of the manuscript. G. Munch provided interpretation of the literature on herbal medicine value and participated in the preparation of the manuscript. A. M. S. Abdul Majid supervised every step in the design, structure and preparation of the manuscript and gave the final approval of the version to be published. All authors read and approved the final manuscript.

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Competing financial interests

The author(s) declare no competing financial interests.

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