

Applications of Curcumin in the Treatment of Prostate Cancer

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Abstract. A polyphenolic compound curcumin, which is extracted from turmeric, has been proven to have dual effects of inhibiting tumor cell proliferation and inducing apoptosis. Prostate Cancer (PCa) which in the male urinary and reproductive systems was recognized as the most common malignant tumors, seriously affects men's daily lives. At present, there is still a lack of highly effective and low-side-effect clinical drugs. Current research indicates that curcumin significantly stops the PCa from growing by regulating miRNA and key enzyme activities, controlling the androgen receptor (AR) signaling pathway. Particularly, nanocarrier technology can greatly enhance its bioavailability and targeting. However, the current research still lacks large-scale clinical validation, standardized dosing regimens, and the ability to overcome the problem of its low bioavailability. This article systematically reviews the research progress on the molecular mechanism of curcumin in the prevention and treatment of PCa and the clinical efficacy data, providing a basic direction and feasibility for future research, and also creating a mechanistic blueprint to guide drug development against PCa.

Keywords: Prostate cancer, curcumin, molecular mechanism, treatment

1. Introduction

Prostate Cancer (PCa), as a major threat to men's health worldwide, has seen its incidence and mortality rates rise year by year. Each year, there are over 1.6 million new cases and 366,000 deaths [1]. Family history, obesity, old age and race are risk factors for this disease. Epidemiological data show that the incidence rate is higher among men in Europe, Australia, North America and African America, while the prevalence rate is lower in Asia [2].

Surgical resection, radiotherapy and targeted therapy are currently the main treatment methods. However, these methods are often accompanied by varying degrees of side effects, and the prognosis of patients in the advanced stage is poor. In recent years, curcumin, as a polyphenolic compound extracted from the rhizome of *Curcuma* (*Curcuma longa* L.), has received extensive attention due to its anti-inflammatory, antioxidant and anti-tumor properties. Experimental data indicate that curcumin demonstrates significant potential in inhibiting the progression of PCa, especially showing multi-target effects in regulating tumor proliferation, angiogenesis, stromal microenvironment and immune response [3]. Curcumin is widely recognized in various forms and applied in different fields worldwide, including food, medicine and other daily uses. Its therapeutic effects have been proven

in many chronic diseases: inflammation, arthritis, metabolic syndrome, liver diseases, obesity, neurodegenerative diseases (NDDs), especially several types of cancer. Against this research backdrop, curcumin demonstrates significant potential for drug development. It can be used as an effective anti-cancer drug on its own or in combination with other drugs to inhibit tumor cell growth by influencing different signaling pathways and molecular targets involved in the development of multiple cancers [4].

However, the side effects of curcumin are also issues that cannot be ignored in treatment, some patients experience gastrointestinal reactions and neurological symptoms during clinical treatment, which are urgent problems to be solved in clinical application. Due to its poor bioavailability and low water solubility, its clinical development is also restricted. Therefore, systematically exploring its molecular mechanism and clinical application prospects is of great significance for promoting the development of curcumin as an anti-cancer drug.

Based on the pathogenesis of PCa, this article explores the disease-resistant mechanism of turmeric in the treatment of PCa and summarizes the clinical efficacy data, with the aim of deepening the understanding of the pharmacological properties of curcumin.

2. The pathogenesis of PCa

The most prominent feature in the process of tumor development is the deletion of human chromosomal tumor suppressor genes caused by gene mutations. In addition, tumor cells obtain energy through metabolic reprogramming to meet the needs of proliferation and metastasis. A large number of research results in recent years have revealed that long chain non-coding RNAs (LncRNA) plays an indispensable role in the occurrence and development of PCa. This type of non-coding RNA exerts regulatory effects on a series of core biological processes such as cell proliferation, apoptosis and migration through complex molecular mechanisms, thereby profoundly influencing the growth trajectory of PCa. For instance, LncRNA small RNA host gene 1 (SNHG1) shows significantly high expression in PCa tissues and cell lines, promoting tumor cell proliferation. Through quantitative analysis in vitro experiments, it was found that the proliferation activity and invasion ability of prostate cancer cells both showed statistically significant enhancement [5].

The formation of new blood vessels is a necessary condition for tumor growth and spread. The normal growth of PCa is regulated by androgen receptors (AR). Antagonizing AR and depriving androgens are the main targets of anti-angiogenesis at present [6]. Stromal cells are important sources of nutrients and signals during tumor development. For instance, tumor-associated fibroblasts (CAFs) promote tumor invasion and angiogenesis, and reshape the microenvironment by secreting factors such as TGF- β , thereby influencing the progression of PCa. Adipocytes, as an energy source, also affect the proliferation, metastasis, and immune evasion activities of PCa in the tumor environment [7].

The immune system plays a key role in tumor immune surveillance, but its function is often disrupted by the immune escape mechanism of tumor cells. Studies have shown that various immune cells in the tumor microenvironment (such as T cells, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs)) exhibit functional heterogeneity: they can not only mediate anti-tumor immune responses but also promote tumor progression through immunosuppression [3]. Especially during the development of PCa, the formation of this immunosuppressive microenvironment will lead to the gradual decline of the body's anti-tumor immune function. Therefore, regulating the function of immune cells to reshape the tumor microenvironment has become a current research hotspot in PCa immunotherapy.

3. The pharmacological properties and anti-tumor mechanisms of curcumin

Curcumin, a hydrophobic polyphenolic compound extracted from the rhizome of *Curcuma longa* L., a plant of the Zingiberaceae family, is classified as a blood-activating and stasis-resolving drug among blood-activating and stasis-resolving drugs in the theory of traditional Chinese medicine (TCM). It is known that recent pharmacological research has demonstrated curcumin has strong antioxidant and anti-inflammatory qualities and exerts its effects by regulating multiple signaling pathways and molecular targets [8]. The therapeutic value of curcumin in the fields of oncology, cardiology and neurodegenerative diseases has been preliminarily verified, and its application prospects in the clinical transformation of prostate cancer are particularly clear.

3.1. Analysis of bioactive components

Curcumin is a polyphenolic compound with significant biological activity. Chemically, it belongs to the diarylheptanoids. The molecular formula of this compound is $C_{21}H_{20}O_6$, and its relative molecular mass is 368.38. The unique chemical structural characteristics of curcumin, especially the presence of its β -dione group and phenolic hydroxyl group, form the molecular basis for its extensive pharmacological activities [4].

3.2. Anti-tumor mechanisms

According to vitro experiments we can know that the growth of human PCa LNCaP and DU145 cells will also be restricted by curcumin in exhibiting both time-dependent and dose-dependent characteristics, arresting tumor cells at G2 or M phase, significantly elevate the reactive oxygen species (ROS) level in cells, and prompt apoptosis of PCa cells [9]. When the concentration reaches $25\mu\text{mol/L}$ and $50\mu\text{mol/L}$, curcumin can completely inhibit the growth of these two types of cells, reduce the levels of testosterone and dihydrotestosterone, and regulate the signal transduction of PCa by up-regulating the expression of aldosterone reductase 1C2 (AKR1C2) in LNCaP cells [10].

In addition, turmeric also shows significant inhibitory effects on the proliferation, migration and invasion of PCa cells PC-3 and LNCaP, promotes their apoptosis, and can induce autophagy at the same time. The study quantitatively analyzed the effect of different concentrations of curcumin (0, 12.5, 25, $50\mu\text{mol/L}$) on the apoptosis of LNCaP and PC-3 PCa cells after 24 hours of treatment by flow cytometry. The results showed that curcumin significantly induced apoptosis of LNCaP cells in a dose-dependent manner. Compared with the control group ($0\mu\text{M}$), the apoptosis rates of the treatment group increased to 11.41%, 12.55%, and 36.64%, respectively ($p < 0.05$). Similarly, in PC-3 cells PC-3, the apoptosis rates increased to 3.59%, 9.20% and 31.05% respectively ($p < 0.01$). These data confirm that curcumin can effectively induce apoptosis of PCa cells in a concentration-dependent manner. Through LC-MS technology, non-targeted metabolomics analysis was conducted on PC-3 cells in each group. The results indicated that curcumin could significantly affect the metabolic network of tumor cells. By interfering with lipid metabolism such as glycerophospholipid metabolism, linoleic acid metabolism and alpha-linolenic acid metabolism, it regulated the cysteine-methionine metabolic cycle and inhibited the cholesterol biosynthesis pathway [11]. These synergistic metabolic alterations collectively constitute the important molecular basis for curcumin's inhibition of PCa cell growth and induction of apoptosis, providing a theoretical basis for its clinical application. These multi-target mechanisms highlight the unique advantages of curcumin in the fight against PCa.

4. Clinical research progress and combination therapy potential of curcumin

Clinical studies have shown that curcumin exhibits good tolerance through oral administration, intravenous injection and other routes of administration, and no dose-limiting toxicity has been observed. Nonetheless, there are individuals who may experience diarrhea or high levels of serum alkaline acid enzymes and serum lactate dehydrogenases. When curcumin at a daily dose of 3.6 grams demonstrated systemic pharmacological activity, suggesting its preventive potential against non-gastrointestinal malignancies [12].

A randomized controlled trial involving 85 patients confirmed that curcumin and soy isoflavones combined could have a significantly effect on tumor progression by down-regulating the expression levels of prostate-specific antigen (PSA) and androgen receptor (AR) in LNCaP cells [13]. In addition, nano-curcumin preparations exert anti-inflammatory and antioxidant effects through the NF- κ B signaling pathway, demonstrating potential application value in preventing radiotherapy-induced rectal toxicity in patients with advanced PCa. However, the existing clinical evidence still has limitations such as limited sample size and insufficient follow-up time. Its exact efficacy and safety still need to be further verified through extensive Phase III clinical investigations conducted across diverse medical centers [14]. In order to overturn the challenges of curcumin's low water solubility, rapid metabolism and low bioavailability, it is clinically combined with phospholipids for the treatment of benign prostatic hyperplasia (BPH). After 24 weeks of clinical efficacy comparison, the curcumin and phospholipid conjugate known as Meriva was indeed able to alleviate the signs and symptoms of BPH patients, and no side effects were found [15].

Combination therapy shows that curcumin and ursolic acid (UA) inhibit the formation of prostate intraepithelial neoplasia (PIN) and delay the progression of PCa by synergistically targeting NF- κ B, Akt, androgen receptors and the apoptotic pathway [16]. In addition, curcumin can also be used in combination with other effective components of TCM. Clinical trials have shown that the role of COX-2 in human carcinogenesis is attributed to its overexpression in PCa tissues. Zyflamend (A compound herbal formulated from dozens of TCM) prevents PCa by inhibiting COX activity and preventing the increase of PSA [17].

5. Discussion

Although there are no exact prescriptions for treating PCa recorded in ancient medical books, from the perspective of etiology and pathogenesis, this disease can be classified into categories such as "urinary syndrome" and "retention of urine". According to the views of TCM, tumors are caused by external pathogenic factors. They develop over time due to local stagnation of qi, phlegm coagulation, blood stasis, dampness accumulation, and the interplay of heat and toxins that block the meridians. The main cause of tumors is the dysfunction of internal organs and the disharmony of qi and blood caused by the invasion of external pathogenic factors. Promoting blood circulation and removing blood stasis, as well as eliminating phlegm and dampness, are the main treatment methods for tumors. Modern research has found that *Ganoderma lucidum* extract, ginsenosides, matrine, quercetin, curcumin, tetrandrine, *Tripterygium wilfordii* extract, etc. are all effective in the prevention and treatment of PCa to varying degrees [18]. Curcumin is regarded as a highly promising anti-cancer lead compound due to its low toxicity, mild side effects, and exerted dual anti-tumor effects by constraining cell growth and triggering apoptosis. However, its poor water solubility and low bioavailability, as well as other pharmacokinetic defects, limit the clinical application effect. In response to these issues, future research should focus on making breakthroughs in the following aspects. Firstly, the development of novel drug delivery systems to enhance their

bioavailability, such as nanoformulations, including polymer nanoparticles, liposomes, micelles and nanoemulsions, combined with peptides and drugs, can better target tumor cells. Nanocurcumin, especially formulations with polylactic acid-glycolic acid copolymer (PLGA), have been proven to help improve solubility, stability and targeted delivery. At the same time, it reduces the side effects caused by traditional chemotherapy [19]. Secondly, the optimal dosage for treating PCa is determined through systematic animal experiments to achieve the highest therapeutic effect while reducing the side effects it brings. Finally, it is necessary to conduct multi-center clinical research trials on curcumin for patients at different stages, evaluate its therapeutic effect on PCa at different stages through data, and explore its synergistic mechanism as an adjuvant drug with traditional chemotherapy drugs. Through elucidating molecular mechanisms and therapeutic potential of curcumin, the data from these studies will facilitate its future clinical development.

6. Conclusion

The pathogenesis of PCa has different mechanisms, including genetic variation, hormonal signal imbalance, microenvironment interaction and metabolic adaptation, etc. The regulation of AR pathways and immune microenvironments should be the focus of current research. The anti-inflammatory and antioxidant properties of curcumin affect the signaling pathways of cells and regulate autophagy and apoptosis of cancer cells. It can be used to treat various diseases (neurodegenerative, cardiovascular, inflammatory, cancer), and has a good effect on the treatment of PCa. Its disease resistance mechanism and pharmacological properties can expand the path for future research on its treatment of other diseases. This article does not fully discuss the clinical application of curcumin. It is still necessary to achieve translational medical confirmation of the clinical benefit and risk-benefit ratio through prospective multi-center studies and long-term follow-up, so as to increase people's usage. Future research should first enrich its drug delivery system and focus on addressing the issue of its low bioavailability. Secondly, more research should be conducted on the active ingredients of TCM. Experience should be drawn from ancient prescriptions, and modern technology should be applied to clarify the active ingredients of drugs, so as to enhance the therapeutic effect of single drugs in treating diseases.

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