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Research Progress on Liuwei Dihuang Decoction Combined with Sijunzi Decoction plus Endocrine Therapy for Prostate Cancer with Spleen-Kidney Insufficiency Syndrome

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Abstract: ***Prostate cancer (PCa) is a common malignant tumor that seriously endangers the health of middle-aged and elderly men worldwide. In recent years, the incidence and mortality of prostate cancer in China have increased remarkably. Most patients are diagnosed at advanced stages and lose the opportunity for radical treatment. Androgen-deprivation therapy (ADT) serves as the standard foundational therapy for metastatic hormone-sensitive prostate cancer (mHSPC). While ADT brings survival benefits, it is accompanied by risks of progression to castration-resistant prostate cancer (CRPC) and a series of severe adverse events that impair patients' quality of life. Traditional Chinese medicine (TCM) exhibits unique advantages in the treatment of prostate cancer, especially in strengthening body resistance, attenuating toxic effects and enhancing therapeutic efficacy. Under the background of ADT, spleen-kidney insufficiency has become a common TCM syndrome among patients with hormone-sensitive prostate cancer receiving ADT. Liuwei Dihuang Decoction (LDD) and Sijunzi Decoction (SJD) are classical prescriptions for nourishing kidney-yin and tonifying qi to invigorate the spleen, respectively. The combination of the two prescriptions conforms to the therapeutic principle of simultaneous tonification of the spleen and kidney. This review systematically sorts out current status and challenges of western-medical treatment for prostate cancer, TCM understanding of its etiology and pathogenesis, as well as research advances in clinical application and underlying mechanisms of LDD and SJD in prostate cancer management. Furthermore, it demonstrates the theoretical basis, clinical potential and research value of LDD combined with SJD plus ADT for prostate cancer with spleen-kidney insufficiency syndrome.***

Keywords: Prostate cancer, Androgen-deprivation therapy, Spleen-kidney insufficiency, Liuwei Dihuang Decoction, Sijunzi Decoction, Integrated traditional Chinese and western medicine, Literature review.

1. Introduction

Prostate cancer is one of the most prevalent malignant tumors of the male genitourinary system. Its pathogenesis is closely associated with age, race, heredity and lifestyle. Prostate cancer has long ranked first in male malignant tumor incidence in European and American countries. Traditionally, China was regarded as a region with low PCa incidence [1]. Nevertheless, driven by population aging, westernized dietary patterns and popularization of prostate-specific antigen (PSA) screening, the age-standardized incidence of prostate cancer in China is growing rapidly at an annual rate of approximately 10%, constituting a major public-health concern that compromises the health and quality of life of middle-aged and elderly Chinese men [2-3]. Worse still, compared with European and American populations, Chinese PCa patients are diagnosed at relatively advanced clinical stages. Epidemiological data indicate that over 60% of Chinese patients present with locally advanced or metastatic lesions at initial diagnosis, and thereby miss the optimal window for radical prostatectomy or radical radiotherapy. Under such circumstances, endocrine therapy has become the primary therapeutic modality for advanced prostate cancer. As the cornerstone of mHSPC treatment, ADT reduces serum testosterone to castration levels via surgical or pharmacological interventions [4]. ADT can effectively suppress tumor progression and lower PSA levels in the initial treatment phase. However, its median duration of efficacy merely ranges from 18 to 24 months. The vast majority of patients eventually progress to CRPC, a disease state with limited therapeutic alternatives and dismal prognosis. Moreover, long-term ADT gives rise to multiple adverse reactions, including hot flashes, night sweats, fatigue, cognitive dysfunction, bone loss (elevated fracture risk), metabolic syndrome, increased cardiovascular risk and sarcopenia. These adverse events substantially undermine patients' physical function and quality of life.

Given the limitations of ADT, modern western medicine has evolved into the "ADT-plus" combined therapeutic paradigm, such as combining ADT with novel endocrine agents (abiraterone, enzalutamide, etc.) or chemotherapy (docetaxel). Although these regimens further prolong patient survival, they are associated with prohibitive medical costs, superimposed toxicities and inevitable drug resistance. Accordingly, exploring cost-effective combinatorial strategies with complementary mechanisms to enhance efficacy and mitigate adverse effects has become a priority in prostate cancer research. In this context, TCM provides novel insights and promising prospects for optimizing prostate cancer management owing to its holistic regulation and multi-target intervention characteristics based on the principle of strengthening body resistance and eliminating pathogenic factors [5].

Though there is no corresponding disease denomination of "prostate cancer" in TCM classics, its clinical manifestations fall under the categories of "abdominal mass", "stranguria", "dysuria", "lumbago" and "hematuria". Its pathogenesis is generally characterized by root deficiency and branch excess.

Deficiency of the spleen and kidney constitutes the core of root deficiency, whereas intermingled dampness, heat, blood stasis and toxin represent branch excess [6]. Pharmacological agents applied in ADT are regarded as pathogenically consuming in TCM theory, which tend to impair spleen qi, disrupt transportation and transformation functions, and result in insufficient generation of qi and blood. Clinical manifestations such as anorexia, abdominal distension, loose stools and lassitude are frequently observed. The spleen is the acquired foundation while the kidney is the innate foundation; the two organs mutually generate and nourish each other. Spleen deficiency fails to replenish innate essence, and kidney deficiency cannot warm the acquired origin, eventually leading to the pathological state of spleen-kidney insufficiency. Hence, the therapeutic principle of simultaneous tonification of the spleen and kidney should be adopted targeting this core pathogenesis. Liuwei Dihuang Decoction is a time-honored formula for nourishing kidney-yin, and Sijunzi Decoction serves as a basic prescription for tonifying qi and invigorating the spleen. Combined application of the two formulas can replenish innate essence as well as activate acquired qi. Theoretically, it can comprehensively strengthen body resistance to improve host anti-tumor capacity, retard disease progression, and specifically relieve ADT-related adverse events. This review elaborates the scientific connotation and application value of LDD combined with SJD plus ADT for prostate cancer with spleen-kidney insufficiency syndrome.

2. Current Status of Western-Medical Therapy for Hormone-Sensitive Prostate Cancer

2.1 Androgen-deprivation Therapy (ADT)

Since the pioneering work of Huggins and Hodges in the 1940s demonstrated the androgen dependence of prostate cancer, endocrine therapy has become the cornerstone for advanced prostate cancer. ADT suppresses androgen signaling pathways and induces apoptosis of androgen-dependent prostate cancer cells by lowering serum testosterone to castrate levels (<50 ng/dL or 1.7 nmol/L) using gonadotropin-releasing hormone agonists (GnRHa, e.g., goserelin, leuprorelin) or antagonists (e.g., degarelix). Nevertheless, monotherapy with ADT has two inherent drawbacks. First, limited therapeutic duration. Due to tumor heterogeneity and adaptive evolution, nearly all mHSPC patients progress to CRPC. Once CRPC develops, disease control becomes intractable, with median overall survival reduced to less than 2 years. Second, extensive and profound treatment-related adverse effects. Long-term hypoandrogenism induced by ADT triggers multiple complications: (1) Vasomotor symptoms: hot flashes and night sweats with an incidence up to 80% [7]; (2) Metabolic abnormalities: elevated risks of insulin resistance, dyslipidemia and cardiovascular diseases; (3) Body composition alternations: sarcopenia and increased fat mass; (4) Deteriorated bone health: accelerated bone loss and higher pathological fracture risk; (5) Neurocognitive and emotional disturbances: memory impairment, inattention and depressive mood. These adverse events not only severely compromise quality of life, but may also lead to treatment discontinuation and impaired anti-tumor efficacy.

2.2 “ADT-plus” Therapeutic Strategies

ADT combined with novel endocrine agents: Abiraterone (a CYP17A1 inhibitor) plus prednisone, enzalutamide (an androgen-receptor signaling inhibitor) and other agents [8] block androgen pathways more thoroughly. Large-scale phase-III clinical trials have validated their efficacy in prolonging overall survival (OS) and progression-free survival (PFS) in mHSPC patients, and these combinations have been recommended as first-line regimens by domestic and international guidelines. ADT combined with chemotherapy: For mHSPC patients with high tumor burden, ADT plus docetaxel chemotherapy yields definite survival benefits [9]. ADT combined with primary-site radiotherapy: Radiotherapy targeting the prostate primary lesion improves survival outcomes in mHSPC patients with low tumor burden [10]. Despite substantial prognostic improvements brought by “ADT-plus” strategies, unsolved challenges persist: (1) High costs of novel endocrine agents impose heavy burdens on patients and healthcare systems and restrict their widespread clinical utilization. (2) Combined regimens are associated with superimposed toxicities. For instance, abiraterone requires concomitant glucocorticoid administration which exacerbates metabolic disorders; enzalutamide is correlated with fatigue, fall risk and seizure events. (3) None of the “ADT-plus” regimens can cure prostate cancer. Tumors eventually acquire drug resistance via complex mechanisms and progress to refractory CRPC. Therefore, clinically accessible adjuvant strategies that synergize with standard therapies, alleviate toxicities and possess favorable cost-benefit profiles are urgently needed. TCM interventions emerge against such clinical demands.

3. TCM Understanding and Therapeutic Advantages for Prostate Cancer

No explicit nomenclature for PCa exists in TCM literature. Given its predominant urinary manifestations such as dysuria and thin urinary stream, PCa is categorized under “hematuria”, “dysuria”, “abdominal mass” and other TCM disease entities. mHSPC represents advanced-stage PCa with pre-existing metastasis. According to TCM visceral-manifestation theory, the kidney stores essence and governs growth, development and reproduction, and opens into the anterior and posterior orifices. The Spiritual Pivot · Treatise on the Liver Meridian records: “The liver foot-jueyin meridian passes through the external genitalia and reaches the lower abdomen”. Although the prostate gland is not described in TCM classics, it is inferred to be governed by the kidney, traversed by the liver meridian, and closely related to the spleen and stomach. From the TCM perspective, vital-qi deficiency constitutes the internal and primary cause of tumor onset and deterioration. Deficiency of healthy qi runs through the whole course of prostate cancer. When healthy qi is deficient and defensive function is compromised, external pathogenic factors invade, resulting in disturbance of body fluid and qi-blood transportation, phlegm stagnation, qi-blood stasis and mass formation. As documented in General Records of the Holy Benevolence: “When qi and blood circulation is obstructed, tumors arise under conditions of qi deficiency”. Jia Yingjie and colleagues proposed that “spleen deficiency-damp stagnation, qi deficiency-toxin-blood stasis” serves as the basic pathogenesis of PCa, which is closely linked to the

kidney, liver and spleen [11]. Accordingly, the TCM pathogenesis of mHSPC is summarized as root deficiency complicated by branch excess intermingled with dampness, phlegm, blood stasis and toxin. Therapeutic strategies for mHSPC prioritize tonifying the spleen and kidney, supplemented by detoxification and mass-resolving therapy targeting the innate kidney and acquired spleen [12]. Therapeutic objectives at this stage include improving quality of life, delaying the transition from hormone-sensitive status to castration resistance, stabilizing disease conditions and prolonging survival. Western-medical management for advanced PCa is based on ADT, combined with radiotherapy or chemotherapy when necessary. Guided by holistic concept and syndrome differentiation, TCM plays unique roles in advanced PCa treatment. Cumulative studies demonstrate that single herbal medicines, herbal extracts and compound prescriptions can ameliorate clinical conditions of PCa patients, suppress PSA elevation and improve quality of life for patients with tumor-bearing survival [13-15]. Furthermore, herbal interventions enhance clinical efficacy and relieve ADT-related adverse events. Zhang Xiaoqing et al. established mouse models of advanced PCa with bone metastasis. Animals were randomly divided into control group, LDD plus Sansan Decoction group and combined-treatment group. After 14-day intragastric administration, hepatic function and alkaline phosphatase were detected. The results revealed that the medication groups exhibited superior performance in improving hepatic function, reducing alkaline phosphatase and elevating serum P63 levels, as well as restraining tumor progression compared with model animals [16]. In another clinical investigation, 39 patients with advanced PCa were randomized into treatment group and control group. Patients in the control group received conventional ADT, while the treatment group was additionally administered Qianfu Yinfang. Urinary-symptom improvement and quality-of-life changes were dynamically observed. Clinical efficacy was significantly higher in the treatment group ($P < 0.05$), indicating the clinical value of Qianfu Yinfang for advanced prostate cancer [17].

4. Research Progress of Liuwei Dihuang Decoction in Prostate Cancer Treatment

4.1 Origin and Composition of the Prescription

Liuwei Dihuang Decoction was originally recorded in Key to Therapeutics of Children's Diseases compiled by Qian Yi in the Song Dynasty. It consists of Rehmanniae Radix Preparata, Corni Fructus, Dioscoreae Rhizoma, Alismatis Rhizoma, Moutan Cortex and Poria Cocos. Its sophisticated compatibility embodies the principle of "three-tonifying herbs and three-draining herbs". Rehmanniae Radix Preparata nourishes kidney-yin; Corni Fructus tonifies liver and kidney; Dioscoreae Rhizoma invigorates spleen and consolidates essence, constituting the "three tonics". Alismatis Rhizoma purges kidney turbidity; Moutan Cortex clears deficient heat; Poria Cocos percolates spleen dampness, forming the "three purgatives". The whole formula balances tonification and purgation, with tonification as priority. It nourishes yin without causing greasiness, and is recognized as the representative basic prescription for kidney-yin nourishment.

4.2 Clinical Application Studies

Multiple clinical trials have explored the value of LDD and its modified formulas in prostate cancer therapy, mainly focusing on combination with endocrine therapy. One clinical observation reported that modified LDD plus bicalutamide achieved superior PSA response rate and clinical benefit rate compared with bicalutamide monotherapy for advanced prostate cancer. Longer median survival time and time to PSA progression (TTPP) were observed in the combined-treatment group [18]. Another study demonstrated that modified LDD combined with endocrine therapy markedly ameliorated TCM symptoms such as soreness and weakness of lumbar and knee joints, dizziness, tinnitus, hot flashes and night sweats, accompanied by elevated FACT-P scores, confirming its benefits for quality-of-life improvement. Early clinical practices also suggested that combination of LDD with endocrine therapy prolonged overall survival and PSA-progression-free survival in advanced PCa patients versus endocrine monotherapy [19]. Existing clinical evidence preliminarily indicates that LDD combined with endocrine therapy may exert synergistic effects in tumor control, disease-progression delay and symptom relief.

4.3 Mechanism Research

Modern pharmacological studies, especially network pharmacology and in-vitro experiments, have uncovered potential molecular mechanisms of LDD against prostate cancer. Direct anti-tumor effects: In-vitro cellular experiments confirm that drug-containing serum or bioactive components of LDD can inhibit proliferation, migration and invasion of androgen-independent prostate cancer cell lines (PC-3, DU145) and induce cell apoptosis. Regulation of key signaling pathways: The PI3K/Akt signaling pathway, which is critically involved in the development of prostate cancer particularly CRPC, has been identified as one core target of LDD. LDD down-regulates protein expression of PI3K and phosphorylated Akt (p-Akt), thereby suppressing abnormal activation of this pathway and exerting anti-tumor activities. Moreover, network-pharmacology analyses predict that LDD modulates MAPK, p53, HIF-1 and other pathways associated with cell cycle, apoptosis and angiogenesis, forming a multi-pathway synergistic regulatory network. Multi-component and multi-target characteristics: Bioactive ingredients including quercetin, kaempferol and β-sitosterol in LDD target core prostate-cancer-related molecules such as AKT1, TP53, MAPK1, MYC and TNF, reflecting the holistic regulatory features of TCM compound prescriptions.

5. Research Progress of Sijunzi Decoction in Prostate Cancer Treatment

5.1 Origin and Composition of the Prescription

Sijunzi Decoction derives from Peaceful Benevolent Dispensatory of the Song Dynasty, composed of Ginseng Radix et Rhizoma (replaced by Codonopsis Radix in most clinical practices), Atractylodis Macrocephalae Rhizoma, Poria Cocos and Glycyrrhizae Radix et Rhizoma Preparata cum Melle. As the monarch herb, Codonopsis Radix tonifies qi and nourishes the spleen-stomach. Atractylodis Macrocephalae Rhizoma serves as the minister herb to invigorate the spleen and dry dampness. Poria Cocos acts as

the adjuvant herb to percolate dampness and strengthen the spleen. Glycyrrhizae Radix et Rhizoma Preparata cum Melle, the envoy herb, harmonizes the whole formula. With mild properties, the formula tonifies qi without generating dryness-heat, and reinforces healthy qi without causing excessive tonicity. It is honored as the premier qi-tonifying prescription.

5.2 Clinical Application Studies

As a representative formula for strengthening body resistance, Sijunzi Decoction is widely applied in adjuvant tumor therapy, mainly for managing treatment-related toxicities and improving general physical status. One study on CRPC patients revealed that SJD plus docetaxel chemotherapy yielded higher disease-control rate and overall response rate compared with chemotherapy monotherapy [20]. Meanwhile, SJD alleviated chemotherapy-induced myelosuppression (leukopenia, thrombocytopenia) and gastrointestinal adverse reactions (nausea, vomiting), and improved treatment tolerance. In maintenance therapy for advanced prostate cancer, spleen-tonifying and qi-replenishing therapies represented by SJD ameliorated fatigue, appetite and physical performance, and elevated Karnofsky performance status (KPS) and quality-of-life scale scores [21]. These findings highlight the irreplaceable role of SJD in reinforcing healthy qi and host defense capacity.

5.3 Mechanism Research

Preliminary achievements have been obtained regarding anti-tumor and adjuvant-treatment mechanisms of SJD. Immunomodulatory effects: SJD mitigates tumor- or treatment-induced immunosuppression. It elevates proportions of T-lymphocyte subsets ($CD3^+$, $CD4^+$), $CD4^+/CD8^+$ ratio and natural-killer-cell (NK-cell) activity, enhancing cellular immune function [22]. Tumor-growth inhibition and apoptosis induction: Experimental studies demonstrate that SJD extracts induce tumor-cell apoptosis via mitochondrial and death-receptor pathways and suppress tumor angiogenesis. Gastrointestinal protection: SJD modulates gastrointestinal-hormone secretion, promotes intestinal-epithelial repair and preserves intestinal-barrier function, which explains its efficacy against gastrointestinal injuries induced by chemotherapy, radiotherapy and targeted agents [23]. Network-pharmacology exploration: Network-pharmacology-based investigations on SJD for prostate cancer postulate that SJD may target key genes such as PTGS2 (COX-2) and AKT1 to regulate inflammatory responses and cell proliferation, so as to restrain tumor progression [24].

6. Theoretical Conception and Research Prospects of Combined Liuwei Dihuang Decoction and Sijunzi Decoction

6.1 Scientific Connotation of the Simultaneous Spleen-Kidney-Tonification Conception

Based on the core TCM pathogenesis of spleen-kidney insufficiency in prostate cancer and pre-clinical pharmacological evidence for LDD and SJD, combined administration of the two formulas constitutes an optimized therapeutic strategy characterized by simultaneous tonification of the spleen and kidney, as well as combined reinforcement and elimination. Its theoretical advantages and scientific connotation are interpreted as follows: Comprehensive strengthening of healthy qi and synergistic efficacy: LDD specializes in nourishing kidney-yin to replenish the innate foundation; SJD focuses on tonifying qi and invigorating the spleen to reinforce the acquired foundation. Combined application enables mutual promotion between innate essence and acquired qi, achieving more comprehensive and stable reinforcement of host healthy qi. Such holistic reinforcement may enhance anti-tumor immunity and form favorable complementarity with the anti-pathogenic effect of ADT (androgen inhibition), generating synergistic effects beyond simple superposition. Targeted alleviation of ADT-related adverse events: ADT-induced hot flashes, night sweats and xerostomia correspond to TCM manifestations of yin-deficiency internal heat, which can be addressed by the yin-nourishing and heat-clearing effects of LDD. Meanwhile, severe fatigue, anorexia, sarcopenia and weight loss secondary to ADT are typical manifestations of spleen-qi deficiency, the primary indication of SJD. Therefore, the combined formula may relieve multiple ADT-related adverse events from the pathogenic origin via multi-target interventions, and remarkably improve patients' quality of life. Potential to delay CRPC onset: Persistent activation of PI3K/Akt/mTOR and other signaling pathways is a crucial driver for the transition from mHSPC to CRPC. LDD has been verified to inhibit the PI3K/Akt pathway. Meanwhile, SJD stabilizes the internal milieu by improving systemic immunity, which may reshape the tumor microenvironment unfavorable for adaptive drug resistance. Combined usage may intervene in both tumor-cell intrinsic properties and host microenvironment, prolonging the therapeutic window of ADT and deferring CRPC occurrence.

6.2 Future Research Prospects

Notwithstanding solid theoretical foundations and promising prospects for LDD combined with SJD plus ADT for prostate cancer with spleen-kidney insufficiency, high-level evidence from standardized studies is still required. Multicenter, large-sample randomized controlled trials (RCTs) should be carried out. Further large-scale multicenter RCTs are needed to confirm its benefits in hard endpoints including OS, PFS and PSA90 response rate. Mechanism studies should be deepened. Modern molecular-biological techniques should be adopted to elucidate how the combined formula modulates androgen receptors and their variants, immune-cell infiltration in tumor microenvironment, as well as the balance between autophagy and apoptosis. Distinctions between simple additive effects and genuine synergistic targets of the combined prescription deserve further clarification. Standardized research on formula-syndrome correspondence: Standardized and objectified diagnostic criteria for spleen-kidney insufficiency syndrome need to be established to realize precise application and reproducible research findings. Exploration of optimal intervention timing and treatment duration: Clinical studies are required to identify optimal therapeutic time windows (e.g., at ADT initiation or after adverse-event onset) and appropriate treatment courses to maximize clinical benefits.

7. Conclusion

In summary, bottlenecks of ADT-based prostate-cancer management call for more humanistic and holistic comprehensive therapeutic strategies. Rooted in TCM cognition of spleen-kidney-insufficiency pathogenesis, the therapeutic principle of simultaneous spleen-kidney tonification provides unique solutions for such clinical challenges. As classical prescriptions for kidney tonification and spleen invigoration respectively, LDD and SJD are supported by abundant clinical practices and modern pharmacological data, verifying their potential in anti-tumor activity, immunoregulation, efficacy enhancement and toxicity attenuation. The combined prescription theoretically achieves multiple goals including comprehensive reinforcement of healthy qi, synergistic anti-tumor effects and targeted toxicity reduction. It may serve as an effective integrated traditional-Chinese-and-western-medicine regimen for optimizing clinical outcomes of mHSPC patients. Future research should validate its therapeutic efficacy through rigorous clinical trials and further explore molecular mechanisms, so as to promote the scientific application of this classical formula combination in modern prostate-cancer management and benefit more patients.

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