DOI: 10.53469/jcmp.2026.08(03).53

Research on Tumor Drug Resistance Mechanisms Based on the "Deficiency-Excess Pathogenesis" Theory from The Huangdi Neijing and Advances in Traditional Chinese Medicine's "Strengthening the Healthy Qi and Eliminating Pathogenic Factors" Approach

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Abstract: ***Cancer remains a difficult disease to conquer in modern medicine, and cancer drug resistance is a common phenomenon in clinical chemotherapy. This issue has become a major challenge in clinical practice, and there is an urgent need for a profound understanding of its mechanisms and the exploration of solutions. The Huangdi Neijing proposes the core pathogenesis that "when pathogenic factors are excessive, it constitutes a 'full' pattern; when vital energy is depleted, it constitutes a 'deficient' pattern," elucidating the dynamic relationship between the excess of cancerous toxins (full) and the insufficiency of vital energy (deficient) in tumor drug resistance. Currently, with the continuous deepening of research into the molecular mechanisms of drug resistance and the ongoing advancement of related fields both domestically and internationally, academic understanding of drug resistance has gradually deepened. This review is grounded in the TCM theoretical framework of "excess and deficiency pathogenesis," systematically organizing the TCM etiology and pathogenesis of drug resistance, with a focus on elucidating the key roles of the imbalance between "cancer toxins" and "vital energy" in the onset and progression of drug resistance. Concurrently, drawing upon the TCM therapeutic principle of simultaneously "tonifying the healthy qi" and "expelling pathogenic factors," this review further explores how TCM can improve the pathological states of "excessive cancer toxins" and "deficient healthy qi" through multi-target regulation and multi-pathway intervention. This approach aims to reverse or delay tumor drug resistance, thereby providing theoretical support and practical solutions with distinctive TCM characteristics for addressing the clinical challenges of tumor drug resistance.***

Keywords: The Huangdi Neijing, Pathogenesis of Deficiency and Excess, Tumor Drug Resistance, Traditional Chinese Medicine, Strengthening the Body's Vitality and Eliminating Pathogenic Factors.

1. Introduction

Drug resistance in cancer refers to the phenomenon in which malignant tumor cells exhibit reduced sensitivity to previously effective chemotherapy, targeted, or immunotherapy drugs, resulting in a failure to achieve the expected therapeutic effects. It is a common occurrence in clinical cancer chemotherapy and a key factor contributing to treatment failure, disease progression, and poor prognosis in patients [1]. Currently, modern medical research into the mechanisms of tumor drug resistance has expanded to encompass various aspects, including the remodeling of the tumor microenvironment, the activation of drug transmembrane transport and efflux pathways, and the abnormal regulation of drug-metabolizing enzyme activity [2]. Although modern medical research on tumor drug resistance has achieved continuous progress, it remains constrained by a focus on localized, microscopic studies. Consequently, despite these advances, there are still significant limitations in clinical application. At the same time, traditional Chinese medicine plays a unique role in cancer treatment, having accumulated extensive experience particularly in enhancing therapeutic efficacy while reducing toxicity. As the core therapeutic principle of traditional Chinese medicine for treating cancer, the concept of "strengthening the body's defenses and expelling pathogens" is gradually being elucidated by modern research [3].

Traditional Chinese Medicine (TCM) has a long history of understanding tumors, with its theoretical foundations dating back to The Huangdi Neijing. The Huangdi Neijing states, "When pathogenic factors are strong, the condition becomes excess; when vital energy is depleted, the condition becomes deficiency." Guided by TCM's holistic perspective and the core principle of syndrome differentiation and treatment, the intrinsic mechanisms of tumor drug resistance are interpreted from a macro perspective of the interplay between the body's vital energy and the rise and fall of pathogenic factors [4]. It provides a new theoretical foundation for overcoming the limitations of modern medical research and establishing a comprehensive treatment approach that integrates traditional Chinese and Western medicine. Although The Huangdi Neijing does not explicitly use the modern term "tumor," it offers detailed records and systematic explanations of the clinical manifestations and pathogenic mechanisms of conditions such as "accumulation," "masses," and "dysphagia," thereby establishing an early theoretical framework for the diagnosis and treatment of tumor-related diseases in traditional Chinese medicine [5].

This paper examines the theoretical framework of "deficiency and excess pathogenesis" to explore recent advancements in the theory of tumor drug resistance within the context of "deficiency of the body's vital energy and accumulation of pathogenic factors." It also systematically reviews research progress on Traditional Chinese Medicine's "tonifying the body's vital energy and expelling pathogenic factors" intervention strategies, thereby providing a theoretical foundation for research on combating tumor drug resistance through the integration of traditional and Western medicine.

2. The Relationship Between the "Pathogenesis of Deficiency and Excess" in the Huangdi Neijing and Cancer Drug Resistance

2.1 The Fundamental Principle of Deficiency and Excess: "When Pathogenic Factors are Strong, there is Excess; when Vital Energy is Depleted, there is Deficiency"

The Huangdi Neijing proposes the important pathogenic principle that "when pathogenic factors are rampant, there is excess; when vital energy is depleted, there is deficiency." "Excess" refers to the rampant proliferation of pathogenic factors, characterized by an excess of pathogenic energy; "deficiency" refers to an insufficiency of righteous energy, characterized by a decline in vital energy. Deficiency and excess are not mutually exclusive; rather, they exist in a dynamic relationship of fluctuation and mutual transformation. The text summarizes the etiology of tumors as "the convergence of internal and external pathogenic factors." External pathogenic factors include the six pathogenic influences—wind, cold, heat, dampness, dryness, and fire—which invade the body and disrupt the physiological balance of the body surface and the zang-fu organs; The core of internal pathogenesis lies in the deficiency of the body's vital energy and the decline of organ functions, compounded by internal injury factors such as emotional disturbances, improper diet, and excessive fatigue. When these pathogenic factors converge and pathogenic factors linger due to vital energy deficiency, they ultimately lead to abnormal circulation of qi, blood, and body fluids, resulting in the accumulation of phlegm, blood stasis, and toxic pathogens, which form the relevant pathological conditions [6].

When pathogenic factors (pathogenic influences, including external pathogens and internal injuries) become excessively strong, the condition manifests as an excess syndrome; conversely, when the body's defensive substances (vital energy, i.e., righteous qi) are excessively depleted, the condition manifests as a deficiency syndrome. In the struggle between pathogenic and healthy forces, if the overall symptoms are characterized by "excess"—that is, if the pathogenic factors are predominantly vigorous and dominate the pathological changes—this is classified as a "excess pattern." Conversely, when a pathological change is primarily driven by a deficiency of healthy energy and manifests mainly as a decline in bodily functions, it is defined as a "deficiency pattern" [7].

2.2 Tumor Drug Resistance

Tumor resistance refers to the phenomenon in which tumor cells develop resistance to chemotherapy, targeted therapy, or immunotherapy, leading to treatment failure or recurrence. Depending on the timing and mechanism of onset, resistance can be classified into primary resistance and secondary resistance [8]. Primary resistance: Refers to a situation where tumor cells are already resistant to a drug prior to treatment, rendering the therapy ineffective from the outset. This is commonly associated with tumor stem cell enrichment, high expression of drug efflux pumps, or specific genetic mutations (such as p53 loss). Secondary resistance: Refers to a situation where a tumor is initially sensitive to a drug but gradually develops resistance as treatment progresses. Mechanisms include genetic mutations, epigenetic alterations (such as m^6A modifications), signaling pathway reprogramming, changes in the tumor microenvironment, and activation of tumor stem cells [9].

2.3 "Deficiency of the Body and Accumulation of Pathogenic Factors" as the Core Pathogenesis of Tumor Drug Resistance

The etiology of tumors is based on the Traditional Chinese Medicine (TCM) theory of "internal and external pathogenic factors," and its core pathogenesis can be summarized as a dynamic imbalance characterized by "deficiency of the body's vital energy and excess of pathogenic factors." Internally, the root cause lies in the deficiency of vital energy (zhengqi). Specifically, this includes: emotional disturbances leading to disrupted qi circulation, as described in The Su Wen: On the Causes of Pain: "Anger causes qi to rise; joy causes qi to relax; grief causes qi to dissipate; fear causes qi to descend." Prolonged emotional distress can result in impaired liver function and stagnation of qi and blood; irregular diet leads to the accumulation of phlegm and dampness, while excessive consumption of rich, sweet, and greasy foods causes the spleen and stomach to fail in their functions of transformation and transportation [10]. The Complete Works of Jingyue states that "those with insufficient spleen and stomach function or with weakness and imbalance often suffer from diseases involving the accumulation of pathogenic factors"; excessive exertion or inactivity depletes vital energy. The Su Wen: Xuanming Wuji emphasizes that "prolonged visual strain damages the blood, prolonged lying down damages the qi, and prolonged sitting damages the flesh," leading to an unstable lung-wei system and deficiency of spleen-kidney yang, thereby creating conditions for the internal invasion of cancerous toxins [11]. External factors are primarily attributed to the invasion of cancerous toxins, which mainly include: among the six pathogenic factors, cold pathogenic factors serve as the precursor. As stated in The Spirit Pivot: The Origin of All Diseases: "The onset of accumulation arises from exposure to cold." Cold pathogenic factors can stagnate qi and blood, leading to obstruction in the zang-fu organs and meridians; The five endogenous pathogenic factors arise from dysfunction of the zang-fu organs, such as fluid deficiency leading to dryness, excess yang leading to heat, and spleen deficiency leading to dampness, forming the pathological basis for "endogenous toxic pathogens"; the mutual entanglement of phlegm and stasis is the core pathological product, where abnormal fluid metabolism condenses into phlegm, and impaired blood circulation leads to stasis; over time, the combined obstruction of phlegm and stasis transforms into cancerous toxins [12]. Some scholars have proposed that the essence of

cancer toxins is the "vigorous fire" described in The Huangdi Neijing, a pathogenic factor characterized by a mixture of deficiency and excess. When cancer toxins become excessive, they can lead to abnormal proliferation of tumor cells, accelerated metabolism, and an active inflammatory microenvironment. Since cancer toxins are classified as a yang pathogenic factor with a fiery, heat-generating nature, they manifest by promoting the uncontrolled proliferation of cells [13]. A deficiency in vital energy leads to a decline in the body's immune surveillance function and T-cell exhaustion. Excessive heat can damage the body's vital energy, resulting in impaired immune function and a decline in the function of the hypothalamic-pituitary-adrenal axis; this leads to drug resistance in tumor stem cells, such as CSCs, which are more likely to maintain their stem cell properties in low-temperature, hypoxic, and acidic microenvironments, entering a dormant state to evade the cytotoxic effects of chemotherapy drugs; furthermore, it can also lead to increased drug excretion [14].

In summary, this further elucidates the mechanisms underlying tumor drug resistance. Tumor drug resistance is a dynamic process involving a mixture of deficiency and excess; when the body's vital energy is deficient, it leads to the internal accumulation of cancerous toxins. If these toxins are not eliminated and are compounded by the toxicity of chemotherapy drugs, they further deplete the body's vital energy [15]. Deficiency of the body's vital energy (zheng) is a prerequisite for the accumulation of pathogenic factors (xie); the accumulation of pathogenic factors, in turn, exacerbates this deficiency. The two are causally interlinked in a cyclical process, constituting the fundamental mechanism underlying the onset and progression of drug resistance. This understanding provides a clear therapeutic target for TCM intervention: tonifying the body's vital energy to strengthen the constitution and expelling pathogenic factors to eliminate accumulations. Once the body's vital energy is restored and pathogenic factors are eliminated, drug resistance can be resolved.

3. Molecular Mechanisms of Cancer Drug Resistance

3.1 Multiple Mechanisms of Drug Resistance

Drug transporter-mediated resistance: The multidrug resistance protein P-glycoprotein (P-gp/MDR1), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP) all belong to the ABC transporter superfamily. They are the key mediators responsible for actively "pumping" chemotherapeutic drugs out of tumor cells. Composed of an ATP-driven dinucleotide-binding domain and a transmembrane channel, these transporters can "flip" drugs such as doxorubicin, paclitaxel, and topotecan from the cytoplasm or the inner membrane side to the extracellular space, acting as broad-spectrum efflux pumps; their overexpression rapidly reduces intracellular drug concentrations below the lethal threshold, constituting the core mechanism of classic multidrug resistance. More importantly, the activity of these pump proteins is regulated by epigenetic switches such as DNA methylation, histone acetylation, and miRNAs, and can be further activated by HIF-1α in hypoxic microenvironments. Consequently, reversal strategies—in addition to directly inhibiting pump function—also include multidimensional interventions such as epigenetic drugs, nanocarrier bypasses, and microenvironment remodeling, providing precise and actionable targets for overcoming tumor drug resistance [16].

Abnormal Apoptotic Pathway: DNA damage caused by chemotherapeutic agents should normally immediately trigger the p53-mediated "alarm-apoptosis" program: upon phosphorylation, wild-type p53 both arrests the cell cycle and upregulates the transcription of pro-apoptotic proteins such as Bax and Puma, which perforate the outer mitochondrial membrane, release cytochrome c, and activate the caspase cascade. However, tumor cells block this pathway through a "dual disruption": First, within the nucleus, p53 hotspot mutations (such as R175H and R273H) cause it to lose its DNA-binding ability, preventing the initiation of Bax expression, while MDM2 amplification accelerates the degradation of the remaining wild-type p53, silencing the damage signal; Second, in the mitochondria, the t(14;18) translocation or its epigenetic activation leads to the overexpression of Bcl-2 and Mcl-1, which form heterodimers with Bax/Bak, thereby blocking pore formation. Concurrently, IAP proteins such as Survivin and XIAP directly bind to and ubiquitinate caspase-9/3, halting the cascade amplification. The combined effects of anti-apoptotic factor overexpression, pro-apoptotic factor deficiency, and IAP-mediated "braking" result in the failure of mitochondrial outer membrane permeabilization. Cytochrome c becomes trapped in the mitochondrial intermembrane space, and chemotherapy-induced apoptotic signals are blocked at the mitochondrial level. Consequently, tumor cells are able to survive and repair themselves despite DNA breaks, ultimately manifesting as primary or acquired resistance [17].

3.2 Emerging Trends in Drug Resistance Research: Exploring Intervention Strategies

In response to the mechanisms underlying cancer drug resistance, modern research has developed multidimensional, multi-tiered intervention strategies [18]. At the molecular-targeted level, drug resistance caused by kinase mutations can be effectively overcome by optimizing drug structures and designing covalent inhibitors (such as osimertinib, which irreversibly binds to the EGFR C797 site) or allosteric inhibitors (such as asiminib, which targets the myristic acid pocket of BCR-ABL) [19]. In the regulation of cell death, inducing non-apoptotic death pathways (such as ferroptosis, paraptosis, and pyroptosis) has emerged as a key strategy for overcoming apoptosis resistance. For example, ruthenium(II)/iridium(III) complexes trigger ferroptosis or paraptosis by inducing mitochondrial DNA condensation, thereby significantly inhibiting the growth of cisplatin-resistant tumors [20]. In the field of immune-metabolic regulation, palmitic acid reverses macrophage-mediated chemoresistance by upregulating ALOX12 expression and inhibiting AMPK phosphorylation in tumor-associated macrophages, thereby providing a new target for targeting the lipid metabolism-immune interaction [21]. In addition, comprehensive genomic analysis based on next-generation sequencing technology enables dynamic monitoring of the evolution of drug-resistant clones, guiding the development of combination therapies (such as the use of EGFR-TKIs in

combination with MET inhibitors to overcome MET-amplification-mediated resistance) and the formulation of personalized treatment strategies [22, 23]. Together, these strategies form a multidimensional intervention system spanning molecular, cellular, and systemic levels, providing a crucial theoretical foundation and clinical translation pathways for overcoming tumor drug resistance.

4. Traditional Chinese Medicine's "Strengthening the Body's Defenses and Eliminating Pathogenic Factors" Approach to Addressing Cancer Drug Resistance

"Tonify what is deficient; drain what is excessive." Traditional Chinese Medicine (TCM) addresses tumor drug resistance based on the theory of "strengthening the body's vital energy and expelling pathogenic factors," emphasizing the regulation of the body's overall condition to reverse tumor resistance to chemotherapy, targeted therapy, and immunotherapy. Its core lies in the synergistic action of "strengthening the body's vital energy" and "expelling pathogenic toxins." "Strengthening the body's vital energy" refers to restoring this energy by administering treatments — such as tonifying qi, nourishing blood, nourishing yin, and tonifying yang—based on deficiencies in the body's qi, blood, yin, and yang. "Eliminating pathogenic factors" involves removing these factors through methods such as soothing the liver and regulating qi, invigorating blood and resolving stasis, warming yang and dispelling cold, and transforming phlegm and resolving nodules, depending on conditions such as qi stagnation, blood stasis, cold, and phlegm nodules [24].

In terms of strengthening the body's defenses, traditional Chinese medicine employs methods such as tonifying the spleen and kidneys, and replenishing qi and nourishing blood to enhance immune function, improve the $CD4^+/CD8^+$ ratio, and upregulate NK cell activity, thereby reversing the tumor-induced immunosuppressive microenvironment. At the same time, it modulates the gut microbiota, reduces inflammation and oxidative stress, and maintains internal homeostasis, which in turn suppresses the stem-like expression of tumor stem cells and delays the onset of drug resistance and recurrence [25, 26]. Professor Lü Guangrong proposes that the treatment of tumors should involve "balancing both deficiency and excess, and strengthening the body's vital energy while expelling pathogenic factors." For deficiency syndromes characterized by qi deficiency and yang deficiency, traditional Chinese medicine often employs therapeutic methods to tonify qi and strengthen the spleen, typically using herbal formulas containing Atractylodes macrocephala, Astragalus membranaceus, Codonopsis pilosula, and Glycyrrhiza uralensis. The theoretical basis for this lies in the principle that "the spleen and stomach are the foundation of postnatal vitality," holding that nourishing the spleen and stomach is key to restoring vital energy. In terms of modern mechanisms, compounds such as astragaloside and atractylenolide can regulate immune cell function and enhance T-cell activity. Additionally, warming herbs may be employed; these yang-warming agents can activate pathways such as NF-κB, improve the hypoxic tumor microenvironment, and enhance immune surveillance [27].

In terms of eliminating pathogenic factors, the primary therapeutic approaches involve clearing heat and detoxifying, promoting blood circulation and resolving stasis, and resolving phlegm and dispersing nodules. By inhibiting pro-tumor signaling pathways such as IL-6/STAT3 and NF-κB, downregulating VEGF-mediated angiogenesis, reducing the recruitment of myeloid suppressor cells and tumor-associated macrophages, and upregulating PD-L1 expression to reverse immune evasion, thereby directly inhibiting tumor cell proliferation and inducing apoptosis [28, 29]. For cases of qi stagnation and blood stasis with a pattern of excess, Traditional Chinese Medicine often employs therapeutic methods that promote blood circulation to remove stasis and regulate qi to relieve pain, typically using formulas containing Danshen, Sanqi, Curcuma zedoaria, peach kernel, and safflower. Ye Tianshi once noted that "chronic and recurrent gastric disorders are often accompanied by phlegm congealing and blood stasis," while Zhu Danxi emphasized that "the root of the disease lies in blood deficiency." The core issue lies in the depletion of yin and blood, which leads to a lack of moisture in the epigastric region, intestinal dryness, and blood stasis [30]. According to modern mechanisms, Danshen is believed to improve the hypoxic microenvironment of the gastric mucosa and inhibit the progression of gastric cancer by regulating cancer cell proliferation, apoptosis, and invasive and metastatic capabilities [31].

Wu Xiaoqing et al. conducted a clinical trial in which ovarian cancer patients were treated with a formula designed to tonify qi, promote blood circulation, and eliminate toxins, in combination with gemcitabine and bevacizumab. Their findings suggest that this approach, which simultaneously strengthens the body's defenses and eliminates pathogenic factors, can prolong progression-free survival, suppress inflammation and immune suppression, improve quality of life, and is well tolerated [32]. As can be seen, traditional Chinese medicine plays a significant role in cancer treatment. The formulation of herbal prescriptions aims to achieve the therapeutic effect of "strengthening the body's defenses without leaving pathogens behind, and eliminating pathogens without harming the body's defenses," embodying a precise balance between attacking and tonifying.

5. Current Issues and Challenges in Research

Tumors are characterized by high malignancy, extremely poor prognosis, and high mortality rates. The mainstream clinical treatment approach—surgery combined with chemotherapy — has certain limitations. First, treatment outcomes are suboptimal; second, the postoperative recurrence rate is high; and third, adverse reactions are severe. Consequently, it is essential to develop safer and more effective treatment strategies for tumors [33]. Traditional Chinese medicine is uniquely positioned to address this shortcoming, offering both safety and efficacy. In recent years, through the use of single herbs and compound formulas, traditional Chinese medicine has demonstrated the ability to inhibit cancer by regulating tumor cell signaling pathways via multiple targets.

However, several challenges remain in clinical practice. First, its efficacy is limited, and results take time to manifest,

making it difficult to address critical conditions; second, its mechanism of action is complex, and the targets are not sufficiently well-defined; third, the level of evidence is low, and international recognition is lacking; fourth, there is significant variability, and there are no unified standards for the classification of syndromes; and fifth, the mechanisms underlying its integration with modern treatments remain unclear [34].

6. Summary and Outlook

Traditional Chinese medicine offers unique advantages in holistic regulation for the prevention and treatment of tumors, and its application spans multiple stages of cancer treatment. Not only does it promote postoperative recovery and effectively alleviate the adverse effects of radiation and chemotherapy, but it can also be used in conjunction with targeted therapies to reduce toxicity and enhance efficacy.

In recent years, traditional Chinese medicine has also made new strides in this field. For example, the introduction of new theories such as “strengthening the foundation and clearing the root cause” and “the five treatments and five nourishments,” as well as the use of insect-based medicines and the development of modern dosage forms such as injections. These initiatives have demonstrated significant efficacy in alleviating cancer symptoms (such as pain and loss of appetite), boosting the body’s immune system, and improving the internal environment [35]. However, the challenges facing TCM treatment should not be underestimated. In the future, efforts must focus on addressing the following issues: clarifying the relationship between the “physical condition” described in TCM, the tumor microenvironment, and molecular changes within the body; leveraging extensive case studies and multi-hospital data to validate the efficacy and safety of herbal medicines; utilizing artificial intelligence to elucidate the mechanisms of action of herbal formulas; and establishing unified standards for cancer treatment to regulate the quality and dosage of herbal medicines. The ultimate goal is to align TCM theory with the pace of modern development, establish uniform standards for Chinese herbal medicines, gain international recognition for their efficacy, and transform TCM from a “supporting role” into a “central role” in cancer treatment, thereby offering a Chinese solution to patients worldwide.

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