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Treating Melanoma Based on the "Cancer Toxin Theory" from the Perspective of the Tumor Microenvironment

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Abstract: ***Melanoma is a malignant skin tumor originating from neural crest-derived melanocytes of the ectoderm. It has an insidious onset and a high mortality rate. The Cancer Toxin Theory is a traditional Chinese medicine (TCM) approach to tumor treatment proposed by Professor Cheng Haibo, based on the academic thought of Master of Chinese Medicine Zhou Zhongying. This theory posits that cancer toxin is the key factor in the occurrence and development of malignant tumors, with the pathogenesis characterized by the accumulation of pathogenic toxins and deficiency of healthy qi. The tumor microenvironment (TME) plays a crucial role in tumorigenesis and progression, and its formation and transformation align with the Cancer Toxin Theory. Guided by this theory, this article elaborates on the characteristics and correlations between the melanoma TME and the pathogenesis of cancer toxin, summarizes the syndrome differentiation-based treatment principles for melanoma under the Cancer Toxin Theory, and provides a reference for TCM treatment of melanoma.***

Keywords: Tumor microenvironment, Cancer Toxin Theory, Treatment, Melanoma**.**

1. Introduction

Melanoma is one of the most common malignant skin tumors, originating from melanocytes derived from the neural crest of the ectoderm. Clinically, it can be classified into cutaneous, acral, and mucosal types. Melanoma predominantly affects the elderly and adults over 30 years of age, with a high degree of malignancy. It results from a combination of genetic and environmental factors and is prone to early hematogenous and lymphatic metastasis. Due to patients' lack of awareness about melanoma, diagnosis is often delayed; thus, it is frequently detected at intermediate or advanced stages, with increasing mortality rates and poor treatment outcomes and prognosis.

The tumor microenvironment (TME) refers to the internal and external environment in which tumor cells undergo initiation, growth, and eventual metastasis. In simple terms, it is the ecological niche of tumor cells. In 1989, Paget proposed the "seed and soil" theory of tumor metastasis [1], suggesting that if tumor cells are viewed as "seeds," the TME is the "soil" that nurtures them. The TME not only encompasses the structure, function, and metabolism of the tissue where the tumor resides but also participates in the entire process of tumor occurrence, development, and metastasis. Its main components—tumor cells, stromal cells, and inflammatory cells—generate four distinct microenvironments (immune, acidic, hypoxic, and inflammatory) around the tumor under the influence of various factors, promoting tumor occurrence, development, invasion, and metastasis through different mechanisms [2].

Based on years of clinical experience, Master of Chinese Medicine Zhou Zhongying first proposed the concept of the "Cancer Toxin Theory," defining cancer toxin as a specific pathogenic factor induced by various internal and external factors on the basis of visceral dysfunction and *qi* and blood stasis. Cancer toxin is closely associated with the occurrence and development of malignant tumors.

1.1 Characteristics of the Melanoma Tumor Microenvironment

During melanoma progression, melanoma cells interact with stromal cells, T lymphocytes, B lymphocytes, natural killer (NK) cells, and related molecular substances to regulate the tumor stroma, ultimately forming the TME [3]. Modern research suggests that melanoma results from a combination of factors, including trauma, genetic factors, environmental factors, and immune factors. Immune factors are primarily manifested in individuals with immunodeficiency or impaired immune function, such as patients with hematologic malignancies, those receiving immunosuppressive therapy after organ transplantation, and patients with acquired immunodeficiency syndrome (AIDS). Additionally, dysregulation of signaling pathways such as MAPK and PI3K/AKT also contributes to melanoma development.

1.2 Characteristics of the Melanoma Immune Microenvironment

Among all mutation types in melanoma, BRAF V600E is the most common. Its primary mechanism involves affecting MAPK pathway activity and intracellular signal transduction, thereby enhancing cell proliferation and impairing upstream negative feedback regulation of the pathway, ultimately promoting tumor cell proliferation [4]. Furthermore, this mutation can inhibit the cytotoxic effects of T cells, enabling tumor cells to evade T cell immune surveillance and facilitating immune escape [5]. In advanced melanoma patients, the TME is typically in an immunosuppressive state. This occurs because the immune checkpoint receptor programmed death receptor-1 (PD-1) binds to its ligands PD-L1 and PD-L2, inhibiting T cell function. Once activated, PD-1 can also suppress relevant signaling pathways, thereby affecting T cell function and antitumor activity, allowing melanoma cells to escape [6]. Studies have shown [7] that regulating the expression of mTOR, a downstream molecule in the PD-1+ melanoma cell signaling pathway, can promote

tumor cell growth. Additionally, impaired interferon-gamma (IFN-γ) signaling reduces T cell infiltration in melanoma tissues, weakening the ability of T helper 1 (Th1) cells to suppress Th2 cells and leading to Th1/Th2 imbalance [7], which manifests as an immune microenvironment of healthy *qi* deficiency. Meanwhile, activated M2 macrophages—a phenotype of tumor-associated macrophages—can induce Th2-type immunity to support tumor growth and invasion. The substantial release of M2-type cells further promotes tumor cell formation. Currently, clinical use of ipilimumab (targeting CTLA-4) and nivolumab (targeting PD-1) has demonstrated favorable efficacy [8].

1.3 Characteristics of the Melanoma Inflammatory Microenvironment

Research has found that angiogenesis plays a significant role in melanoma development. Unlike normal blood vessels, newly formed tumor blood vessels are morphologically abnormal with disordered blood flow. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and interleukin-8 (IL-8) are closely associated with melanoma metastasis and prognosis. IL-8 induces PD-L1 expression in melanoma cells, mediating the PD-L1/PD-1 pathway to promote tumor proliferation. Additionally, trauma can trigger the release of angiogenesis-related factors, creating an inflammatory microenvironment conducive to melanoma cell growth [9]. Westphal et al. [10] further confirmed that VEGF, bFGF, IL-8, and PDGF-AB promote the proliferation and differentiation of melanocytes or tumor microvessels, thereby facilitating melanoma development.

1.4 Characteristics of the Melanoma Hypoxic Microenvironment

During melanoma progression, substantial oxygen consumption is required to meet energy demands, leading to the formation of a hypoxic microenvironment. Furthermore, treatments such as chemotherapy, radiotherapy, and immunotherapy can cause significant damage to *qi* and blood, resulting in anemia and reduced oxygen supply, thereby contributing to a hypoxic microenvironment. However, melanoma cells can utilize autophagy—a self-protective mechanism—to obtain sufficient nutrients, enabling survival under low-nutrient and hypoxic conditions [11].

1.5 Characteristics of the Melanoma Acidic Microenvironment

During rapid proliferation, melanoma cells metabolize glucose in the TME to synthesize substances required for tumor growth. The lactate accumulated during this process leads to the formation of an acidic microenvironment. Studies have found [12] that lactate accumulation in melanoma can impede the infiltration and function of CD8+ T cells and NK cells, promoting tumor progression.

2. Melanoma and the Cancer Toxin Theory

According to the Cancer Toxin Pathogenesis Theory, the basic pathogenesis of tumors is “accumulation of pathogenic toxins and deficiency of healthy qi” [13]. Cancer toxin arises from the deficiency of healthy *qi* in the body and is induced by various pathological factors. It is not only a pathogenic factor leading to tumor formation but also a pathological product formed during tumor development. In melanoma, on the basis of spleen *qi* deficiency, cancer toxin is generated under the combined influence of external factors, emotional factors, and dietary irregularities. It becomes entangled with pathological factors such as dampness, heat, and blood stasis in the skin or mucous membranes, forming tumors.

2.1 Healthy *qi* Deficiency as the Internal Basis of Melanoma Formation

In early-stage melanoma, local or systemic symptoms are often inconspicuous. At this stage, cancer toxin begins to develop within the body, healthy *qi* starts to decline, and an immunosuppressive microenvironment begins to form. The formation of the immunosuppressive microenvironment in melanoma is closely linked to healthy *qi* deficiency. In TCM, the spleen is considered the “acquired foundation,” responsible for absorbing food and transforming it into essential substances (*shuigu jingwei*) that are transported throughout the body to provide energy. If the spleen fails in its transport function, the middle *jiao* cannot function properly, leading to impaired fluid circulation and the condensation of fluids into dampness. Dampness obstructs local *qi* and blood circulation, causing stagnation that transforms into heat, thereby providing a foundation for the generation of cancer toxin.

2.2 Dampness-Heat-Stasis-Toxin as Key Conditions for Melanoma Development

During melanoma progression, factors such as trauma, environmental changes, and genetic mutations alter the internal environment. Meanwhile, the substantial release of VEGF and IL-8 from melanoma cells accelerates tumor microvessel formation and promotes cell proliferation, further depleting healthy qi. As the body becomes unable to overcome the pathogenic factors, cancer toxin accumulates, causing visceral dysfunction. Blood stasis and phlegm turbidity congeal to form masses, and the conflict between healthy *qi* and pathogenic factors manifests as inflammatory pathological features such as local redness, swelling, heat, and pain.

Thus, the pathogenesis of melanoma is characterized by root deficiency and branch excess. Dampness-heat-stasis-toxin is the key factor in disease onset, while healthy *qi* deficiency underlies the condition. Dampness and heat arise internally, *qi* and blood circulation become obstructed, and dampness-heat-stasis-toxin stagnates in the skin or mucous membranes. Over time, cancer toxin is generated, and the tumor gradually forms.

3. Exploring the Modern Scientific Connotation of the Cancer Toxin Theory from the Tumor Microenvironment Perspective

Through continuous research on the TME in relation to the Cancer Toxin Theory, Professor Cheng Haibo’s team has

concluded that the Cancer Toxin Theory is inseparable from the TME [14]. The Cancer Toxin Pathogenesis Theory proposes that healthy *qi* deficiency is the fundamental condition for cancer toxin generation. Deficient *qi* lacks the power to propel the circulation of fluids and blood, leading to the production of pathological products such as phlegm and stasis. Cancer toxin arises on the basis of healthy *qi* deficiency and visceral dysfunction, induced by various factors, and subsequently becomes entangled with heat, phlegm, and blood stasis to form masses. This further disrupts the balance of qi, blood, *yin*, and *yang*, creating an internal environment conducive to tumor development. This perspective closely parallels the modern medical understanding of the TME [14].

3.1 Immune Microenvironment and Cancer Toxin

"When healthy *qi* is present within, pathogenic factors cannot invade." Healthy *qi* can be regarded as the body's immune capacity. When healthy *qi* is insufficient, immune cells may be inadequate, or tumor cells may undergo immune escape, leading to tumor dissemination and metastasis [15]. As immune cells, T cells can specifically kill tumor cells and are crucial in the body's defense against tumors. The Cancer Toxin Pathogenesis Theory holds that healthy *qi* deficiency impedes the transportation and transformation of fluids and blood, generating pathological factors such as phlegm and stasis, which form the basis of tumor formation. These pathological factors interact with cancer toxin, consuming healthy *qi* and resulting in a deficiency of T cells in the TME, leading to a state of healthy *qi* deficiency and latent pathogenic factors [16].

3.2 Acidic Microenvironment and Cancer Toxin

TCM holds that *qi* deficiency impairs the propulsion of fluid circulation, leading to the internal generation of phlegm turbidity. Phlegm turbidity accumulates and obstructs local *qi* and blood circulation, affecting the spleen's transport function. Spleen deficiency impairs its ability to transform and transport water-dampness, further reducing metabolic capacity and energy production. When the spleen is deficient and fails to properly transform food, the body resorts to glycolysis for energy, creating a local acidic microenvironment. Under ideal conditions, normal cells metabolize glucose primarily through aerobic oxidation and anaerobic glycolysis. However, studies have found that tumor cells, whether under aerobic or anaerobic conditions, preferentially utilize aerobic glycolysis in mitochondria or reduce oxidative phosphorylation—or even bypass it entirely—to obtain energy, producing lactate in the process. This phenomenon is known as the "Warburg effect" [17]. During this process, substantial lactate accumulation leads to the formation of an acidic microenvironment, promoting tumor cell invasion. In addition to lactate, CO_2 under hypoxic conditions is converted into HCO_3^- and H^+ through various pathways. Bicarbonate transporters return HCO_3^- into tumor cells, while extracellular H^+ concentration increases, contributing to the formation of an acidic microenvironment [18].

3.3 Hypoxic Microenvironment and Cancer Toxin

TCM holds that blood transports the clear *qi* inhaled by the lungs and the essential substances produced by the spleen throughout the body, and also carries metabolic wastes from organs and tissues for excretion. Normal blood circulation is a prerequisite for orderly metabolism. "Qi moves blood." When *qi* movement is obstructed or *qi* deficiency fails to propel blood circulation, blood stasis develops. Blood stasis, in turn, impedes the circulation of clear *qi* inhaled by the lungs, leading to hypoxia. Modern medicine recognizes that tumor patients commonly have hypercoagulability. The essence of "blood stasis" is impaired oxygen supply, accompanied by extensive angiogenesis in the microenvironment [19]. In the hypoxic microenvironment, tumor cells enhance their adaptability through invasion and metastasis. Thus, the formation of a hypoxic microenvironment increases the difficulty of tumor treatment [20].

3.4 Inflammatory Microenvironment and Cancer Toxin

According to the Cancer Toxin Pathogenesis Theory, cancer toxin affects *qi* movement and becomes entangled with pathological factors such as phlegm and blood stasis. The conflict between healthy *qi* and pathogenic factors, along with the stagnation of pathogenic heat, can cause local redness, swelling, heat, and pain—typical inflammatory manifestations. Modern medicine holds that the tumor inflammatory microenvironment results from the induction of local angiogenesis by inflammatory factors and inflammatory cells [21]. Unlike normal blood vessels, newly formed tumor blood vessels are tortuous and exhibit increased permeability, thereby promoting tumor growth and metastasis. If tumor development lacks the warming effect of *yang qi* and the nourishment of essential substances, it will spontaneously decay—what Western medicine refers to as inflammation.

4. TCM Understanding of Melanoma

Currently, melanoma treatment primarily includes surgical resection, targeted therapy, immunotherapy, and biotherapy. Although these approaches are effective, their associated adverse effects impose a burden on patients. As an adjunctive therapy, TCM can effectively alleviate treatment-related adverse reactions and improve patients' quality of life. Although the concept of "melanoma" was not explicitly mentioned in ancient TCM classics, records of related clinical manifestations and symptoms exist, describing conditions similar to "malignant sore," "black mole," "black boil," and "gangrene of the digit." For instance, *Zhubing Yuanhou Lun* (Treatise on the Origins and Manifestations of Various Diseases) in the chapter on "Black Mole" states: "When a person has black moles, wind pathogens attack the blood and qi, causing transformation and generation. When one's blood and *qi* are abundant, the skin is moist and smooth, without blemishes. If deficiency and impairment occur, black moles may transform and change." This suggests that in individuals with black moles, once the body is invaded by wind pathogens, the moles may undergo pathological changes. When blood and *qi* are abundant, the skin remains moist and smooth, preventing such occurrences. Conversely, when the body is weakened, malignant transformation—i.e., melanoma—may develop. The "Consolidating the Foundation and Clearing the Source" theory posits that the etiology of tumors lies in constitutional insufficiency, invasion by external pathogens, internal damage from the seven emotions, and improper diet

and overexertion, all of which lead to qi, blood, *yin*, and *yang* imbalance in the viscera. This imbalance generates pathological products such as *qi* stagnation, phlegm-dampness, blood stasis, and heat toxin, which become entangled and accumulate over time to form cancer.

5. Treating Melanoma Based on the "Cancer Toxin Theory"

Surgery, targeted therapy, and immunotherapy are the preferred modalities for melanoma treatment in modern medicine. However, the emergence of drug resistance and adverse effects has limited the progress of Western medical treatment. Practice has demonstrated that focusing solely on the tumor itself is insufficient. TCM treatment, guided by the "holistic concept," emphasizes improving the internal environment, demonstrating unique advantages in the treatment of malignant tumors. Building upon the understanding of melanoma by physicians throughout history, Professor Cheng Haibo's team proposed the Cancer Toxin Pathogenesis Theory. Under this guidance, Professor Cheng Haibo identified "accumulation of pathogenic toxins and deficiency of healthy qi" as the basic pathogenesis and adopted the treatment principle of "eliminating pathogenic factors and detoxifying, supporting healthy *qi* and consolidating the foundation" for the prevention and treatment of malignant tumors based on the Cancer Toxin Theory [2].

5.1 Supporting Healthy *qi* and Consolidating the Foundation

The Cancer Toxin Pathogenesis Theory holds that healthy *qi* deficiency is a prerequisite for cancer toxin formation. As stated in *Suwen* (Plain Questions), "Where pathogenic factors converge, *qi* must be deficient" [22]. Under the condition of healthy *qi* deficiency, pathological factors such as phlegm and blood stasis emerge. Cancer toxin then becomes entangled with phlegm and blood stasis, settling in areas of greatest deficiency and creating a vicious cycle. Supporting healthy *qi* aims to regulate the stability of qi, blood, *yin*, *yang*, meridians, and viscera, thereby enhancing the body's ability to resist external pathogenic invasion. Based on the understanding of the Cancer Toxin Pathogenesis Theory, clinical treatment can employ TCM herbs such as those that nourish *yin* and supplement *qi* to consolidate the foundation, enhance immune cell activity, and improve the body's antitumor function.

Studies have found that herbs such as *Renshen* (Ginseng) and *Huangqi* (Astragalus) enhance immunity by regulating the expression of tumor necrosis factor-alpha (TNF-α) and IL-6 [23]. Astragalus polysaccharides (APS), an active component of *Huangqi*, possess important pharmacological activities including antitumor and immunomodulatory effects. APS can regulate the microenvironment of various solid tumors, improve the immunosuppressive state, inhibit PD-L1 expression, and block the interaction between PD-1 and PD-L1 [24], thereby suppressing tumor growth. Research has shown that APS can inhibit tumor growth in tumor-bearing mice, reduce the proportion of regulatory T cells in the spleen, and decrease IL-10 expression [25]. Hwang et al. [26] demonstrated in a study on the effects of APS on pulmonary metastatic melanoma in mice that APS can activate dendritic cells (DCs), thereby stimulating NK cells and T cells, and enhancing T cell function in the tumor microenvironment. They also found that the combination of APS and anti-PD-L1 antibodies inhibited lung infiltration by melanoma cells. Additionally, studies have found [27] that *Shenqi Fuzheng Injection* combined with PD-L1 antibodies can exert a synergistic anti-melanoma effect, possibly by enhancing DC cell infiltration and promoting T cell activation.

5.2 Resolving Phlegm and Dissipating Masses

Under the condition of healthy *qi* deficiency, the spleen is deficient and unable to transport and transform fluids, leading to the condensation of fluids into phlegm, which accumulates internally to form masses.

Modern pharmacology has found that the TCM herb *Sanleng* (Sparganium) has antiplatelet aggregation, analgesic, and anticancer effects. Its active component, formononetin, can inhibit the viability of human melanoma A375 cells and induce apoptosis, and can also inhibit pyruvate kinase activity [28] while reducing the expression level of pyruvate dehydrogenase. Furthermore, *Manjingzi* (Vitex) can reduce the expression of matrix metalloproteinase-2 to weaken tumor cell migration and invasion, thereby treating melanoma [29]. Lactate accumulation in melanoma prevents CD8+ T lymphocytes from functioning normally. Research has found [30] that andrographolide, the main component of *Chuanxinlian* (Andrographis), can increase CD8+ T lymphocyte infiltration and induce tumor cell apoptosis. Additionally, it can increase tumor-suppressive cytokines such as IFN-γ and perforin, exerting antitumor effects.

5.3 Activating Blood Circulation and Resolving Stasis

The Cancer Toxin Pathogenesis Theory holds that *qi* deficiency leads to blood stagnation, which condenses into stasis. Modern medicine suggests that aerobic glycolysis promotes angiogenesis, which is necessary for tumor growth and metastasis. Blood-activating and stasis-breaking herbs can interfere with the microenvironment and inhibit angiogenesis, suppressing tumor development by affecting aerobic glycolysis in tumor cells [31]. For tumor treatment, activating blood circulation and resolving stasis should be the therapeutic principle. Compared with other blood-activating and stasis-resolving herbs, those that break blood stasis and eliminate masses have a stronger inhibitory effect on tumor metastasis.

5.4 Clearing Heat and Detoxifying

TCM holds that cancer toxin, combined with various pathological factors such as phlegm and blood stasis, generates fire over time. Modern medicine suggests that inflammatory factors can cause local redness, swelling, heat, and pain—inflammatory reactions that further promote tumor dissemination. Therefore, clearing heat and detoxifying should be the primary therapeutic approach. Heat-clearing and detoxifying herbs can directly induce tumor cell apoptosis, reduce inflammatory factor levels, and inhibit tumor angiogenesis, thereby effectively improving the tumor inflammatory microenvironment [32]. Local angiogenesis is a key factor in the inflammatory microenvironment. Studies

have found that ginsenoside Rg3 can reduce the number of tumor blood vessels by modulating the interaction between endothelial cells and VEGF, leading to tumor ischemia and necrosis [29].

5.5 "Chuangyu Formula" Inhibits Melanoma Progression

Lingshu (Spiritual Pivot) records in the chapter on "Abscesses and Ulcers": "When it occurs on the side of the foot, it is called Li Ju... It should be treated urgently, removing the blackened part. If not eliminated, it will enlarge; if untreated, death occurs within one hundred days. When it occurs on the toes, it is called Tuo Ju..." Physicians throughout history have believed that if a patient has constitutional insufficiency, prolonged deficiency of *qi* and blood, coupled with internal damage from the seven emotions, visceral deficiency and impairment, and invasion by toxic pathogens, the pathogenic factors will prevail while healthy *qi* declines. Heat toxin attacks the blood and qi, causing blood coagulation and *qi* stagnation, which become entangled in the skin, leading to malignant disease. Additionally, dietary irregularities—such as a preference for greasy, fatty, sweet, and spicy foods—can generate dampness-heat that brews into heat toxin over time, causing pre-existing black moles to ulcerate and suppurate, developing into melanoma. Guided by this concept, Chief Physician Ma Shuanquan—a renowned TCM physician in Shaanxi Province, a mentor for the fourth and fifth batches of senior TCM experts' academic inheritors, and a member of the Dermatology Department at the Affiliated Hospital of Shaanxi University of Chinese Medicine—summarized years of clinical experience and led his team to successfully develop the "Chuangyu Formula." This formula is widely used to treat superficial abscesses and swellings, including melanoma. It consists of ten TCM herbs: *Huangqi* (Astragalus), *Huanglian* (Coptis), *Huzhang* (Polygonum cuspidatum), *Zhebeimu* (Fritillaria thunbergii), *Xiakucao* (Prunella), *Baihuasheshecao* (Hedyotis diffusa), *Diyu* (Sanguisorba), *Danshen* (Salvia), *Baizhu* (Atractylodes), and *Rendongteng* (Lonicera japonica). The formula is modified according to clinical syndrome differentiation and has been used for many years with confirmed efficacy.

In this formula, *Huangqi* serves as the sovereign herb, leveraging its effects of supplementing *qi* and raising yang, promoting movement and unblocking impediments, drawing out toxins and expelling pus, and healing sores and generating tissue. It also enhances immune function, promotes *qi* and blood generation, strengthens healthy qi, and expels toxins externally, facilitating the resolution of abscesses and swellings. *Baizhu*, sweet, warm, bitter, and dry, supplements *qi* and strengthens the spleen, dries dampness and promotes diuresis, preventing cold and cool herbs from causing stasis and protecting the spleen and stomach from damage by cold-natured drugs. *Huanglian*, bitter and cold, is adept at clearing middle *jiao* dampness-heat. *Huzhang*, bitter and slightly cold, clears heat, detoxifies, activates blood circulation, and dissipates stasis. The combination of *Huanglian* and *Huzhang* enhances the heat-clearing and detoxifying effect. *Zhebeimu*, bitter and cold, has strong detoxifying, dissipating, and swelling-reducing properties. *Xiakucao*, pungent, bitter, and cold, dissipates masses and reduces swelling. *Baihuasheshecao*, bitter, sweet, and cold, has heat-clearing and detoxifying effects. These herbs together serve as ministers, enhancing the effects of clearing heat, detoxifying, resolving phlegm, and dissipating masses to resolve superficial abscesses and swellings. *Diyu*, bitter, sour, and cold, detoxifies and astringes sores. *Danshen*, bitter and slightly cold, activates blood circulation, resolves stasis, cools blood, and eliminates abscesses. The combination of *Diyu* and *Danshen* activates blood circulation, resolves stasis, unblocks collaterals, and alleviates pain, improving local blood circulation, preventing blood stasis, and reducing pain. *Rendongteng*, pungent and dispersing, clears heat, detoxifies, unblocks collaterals, and alleviates pain, serving as an envoy herb to guide the other herbs to the affected site. The combination of these herbs achieves the effects of clearing heat, detoxifying, dissipating stasis, alleviating pain, resolving phlegm, and dissipating masses.

Modern research has also shown that APS from *Huangqi* can regulate the microenvironment of various solid tumors and improve the immunosuppressive state [24]. Berberine, an active component of *Huanglian*, can reduce the expression levels of related mRNA, thereby inhibiting the proliferation of human melanoma A375 cells. *Zhebeimu* alkaloids can reverse tumor cell drug resistance and synergize with other antitumor drugs [33]. Ursolic acid, the main component of *Baihuasheshecao*, can inhibit tumor cell proliferation, induce apoptosis, and suppress tumor angiogenesis [34]. The active components of *Xiakucao* can exert antitumor effects by regulating miRNA and signaling pathways such as PI3K/Akt and Nrf2 [35]. Ellagic acid from *Diyu* has an inhibitory effect on B16F10 melanoma cells, and its combination with cisplatin effectively induces melanoma cell death [36]. Through years of refinement and summarization, this formula has been ultimately applied to treat superficial abscesses and swellings, including melanoma, with remarkable efficacy.

Meanwhile, preliminary experimental studies have found that this formula can inhibit melanoma cell progression. The PI3K/AKT signaling pathway converts phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-triphosphate (PIP3). Overactivation of this pathway promotes cell cycle progression, leading to continuous tumor cell proliferation. MicroRNA-21 (miR-21) plays a key role in regulating tumor oncogenes and tumor suppressor genes. It possesses oncogenic activity and can promote the invasion and migration of various tumors, serving as a major regulator of malignant tumor behavior and being highly expressed in various malignant solid tumors. Phosphatase and tensin homolog (PTEN), a tumor suppressor protein, dephosphorylates PIP3 back to PIP2, thereby inhibiting the activation of the PI3K/AKT signaling pathway. In tumor cells, mutation, deletion, or downregulation of PTEN leads to overactivation of the PI3K/AKT signaling pathway, promoting tumor cell proliferation, survival, invasion, and metastasis. MiR-21 can regulate tumor proliferation, invasion, and metastasis by directly targeting PTEN or tropomyosin 1. Experimental studies have found that the Chuangyu Formula can inhibit the release of miR-21 in melanoma cells, activate PTEN, thereby inhibiting PI3K/AKT pathway activation, and suppress M2 macrophage polarization, further inhibiting melanoma cell development. Additionally, studies have found that miR-34a can inhibit tumor cell proliferation and migration and promote apoptosis by regulating the TGF-β/Smad4 signaling pathway, thereby suppressing tumor growth.

It can also affect immune cell function in the tumor microenvironment by regulating immune responses, influencing tumor immune escape.

6. Conclusion

Melanoma is a malignant tumor of the skin and mucous membranes with an insidious onset, making it difficult to detect in a timely manner. TCM records related to melanoma include terms such as “black mole” and “black nevus.” Based on its clinical manifestations and characteristics in advanced stages, it can also be classified under the category of “accumulations and gatherings.” The Cancer Toxin Pathogenesis Theory holds that the treatment of accumulations should be based on the pathogenesis of “accumulation of pathogenic toxins and deficiency of healthy qi,” following the treatment principle of “eliminating pathogenic factors and detoxifying, supporting healthy *qi* and consolidating the foundation,” and providing symptomatic treatment according to different manifestations at different stages. The melanoma TME is characterized by low pH, hypoxia, high tissue pressure, and chronic inflammatory reactions, which are key factors in abnormal tumor cell proliferation, invasion, metastasis, and angiogenesis. This aligns with the Cancer Toxin Pathogenesis Theory. In treatment, guided by the Cancer Toxin Pathogenesis Theory and based on the different clinical manifestations of the melanoma TME at various stages, different formulas are employed to treat melanoma. In advanced melanoma, heat, phlegm, stasis, and deficiency run through the entire disease course. Therefore, anticancer detoxification is the key to treatment, while supporting healthy *qi* and eliminating pathogenic factors constitute the fundamental approach. Treating melanoma based on the Cancer Toxin Theory can effectively reduce the side effects and adverse reactions of Western medical treatment, improve patients’ quality of life, alleviate clinical symptoms, and enhance their well-being.

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