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Integrative Therapies of Traditional Chinese Medicine in Melanoma Treatment: Current Status, Mechanisms, and Prospects

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Abstract. Melanoma, a highly aggressive malignancy originating from melanocytes, poses significant therapeutic challenges due to its rapid progression and metastatic potential. While conventional treatments such as surgery, chemotherapy, and immunotherapy have improved outcomes, their limitations in efficacy and safety necessitate complementary approaches. Traditional Chinese Medicine (TCM), with its holistic philosophy and multi-targeted interventions, has demonstrated potential in enhancing therapeutic outcomes and mitigating adverse effects. This review synthesizes current evidence on TCM's role in melanoma management, focusing on its theoretical foundations, molecular mechanisms, and clinical applications. Key strategies including herbal formulations, acupuncture, and dietary interventions are analyzed, highlighting their synergistic effects when combined with conventional therapies. Challenges such as standardization of TCM protocols and mechanistic elucidation are discussed, with future directions emphasizing translational research and integrative treatment models. Clinical studies demonstrate that TCM combined with chemotherapy improves objective response rates by 16% (from 22% to 38%) while reducing myelosuppression incidence by 30%.

Keywords: Melanoma, Traditional Chinese Medicine, Integrative Oncology, Molecular Mechanisms, Herbal Therapy

1. Introduction

Melanoma, a highly malignant tumor, poses a serious threat to human health. Its incidence has risen globally, driven by genetic predisposition and environmental factors like UV radiation. Recent epidemiological data indicate a 3-5% annual increase in melanoma cases, with CDKN2A mutations and chronic immunosuppression identified as key risk factors [1]. Despite advances in targeted therapies (e.g., BRAF inhibitors) and immunotherapies (e.g., PD-1/PD-L1 blockade), resistance and recurrence remain prevalent. Approximately 50% of patients develop resistance to BRAF inhibitors within 12 months, often due to NRAS mutations or PTEN loss [2]. TCM, rooted in over two millennia of clinical practice, offers a complementary paradigm emphasizing "Yin-Yang balance" and "syndrome differentiation." For instance, the herbal formula Huai Jiao Wan inhibits VEGF expression in preclinical models, while Astragalus extracts enhance CD8+ T cell cytotoxicity [3-

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4]. This review explores TCM's multifaceted role in melanoma care, integrating classical theories with modern biomedical insights. However, challenges such as formulation variability and limited mechanistic evidence hinder broader clinical adoption.

Against this backdrop, TCM, with its unique theoretical system and rich practical experience, offers new opportunities for the treatment of melanoma. In-depth exploration of the mechanisms and efficacy of TCM in the treatment of melanoma is of great significance for improving patients' quality of life and prolonging their survival, and will also open up new ideas for the field of tumor treatment.

2. Melanoma pathophysiology and conventional therapies

2.1. Definition, classification, and molecular mechanisms

Melanoma is a highly malignant tumor originating from melanocytes—pigment-producing cells located in the skin, mucous membranes, uveal tract of the eye, and other tissues. Its pathogenesis involves a multifactorial interplay of genetic predisposition, environmental exposure (especially ultraviolet radiation), and immune system dysregulation. Once melanocytes undergo malignant transformation, they acquire the capacity for uncontrolled proliferation, invasion, and metastasis. The common classifications include cutaneous melanoma and mucosal melanoma. Cutaneous melanoma accounts for approximately 80% of the total number of melanomasand can be further subdivided as follows:

Superficial spreading melanoma (SSM) is primarily affects the trunk and extremities, particularly in young and middle-aged adults. It is manifested as a flat or slightly elevated patch with rich colors, irregular edges, and uneven pigmentation. It grows slowly in the early stage and can infiltrate deep tissues in the later stage. Nodular melanom (NM) has a high degree of malignancy and is commonly found in the head, neck, and trunk of older people. It presents as a rapidly growing nodule, mostly black or blue-black in color, hard in texture, prone to ulceration, bleeding, and metastasis. Lentigo maligna melanoma (LMM) is prone to occur in the sun-exposed areas of the elderly, such as the face and neck. Initially, it is a pigmented spot with unclear boundaries, grows slowly, and has a poor prognosis after invasive growth.

Acral lentiginous melanoma (ALM) is relatively common in Asian populations and mostly occurs in the acral parts such as the palms, soles, and subungual areas. It is manifested as a pigmented patch. Due to its rich blood supply and easy friction, it has high metastatic potential. Mucosal melanoma is rare, accounting for 5% - 10% of the total number of melanomas. It can occur in the mucous membranes of the oral cavity, nasal cavity, esophagus, vagina, rectum, etc. The symptoms vary in different parts. For example, oral mucosal melanoma is manifested as black or brown plaques, nodules, etc., often accompanied by symptoms such as ulcers. Due to its hidden onset and rich blood and lymph circulation, it is mostly in the middle-late stage at the time of diagnosis, with a poor prognosis.

At the molecular level, melanoma development is driven by several signaling pathways. Approximately 50% of cutaneous melanomas harbor activating mutations in the BRAF gene (e.g., V600E), leading to constitutive activation of the MAPK/ERK pathway, which promotes uncontrolled proliferation and survival of melanocytes [1]. Concurrently, hyperactivation of the PI3K/AKT/mTOR pathway enhances tumor cell survival and metastasis by inhibiting apoptosis and facilitating angiogenesis [2].

Immune evasion is another hallmark of melanoma. Tumor cells often upregulate PD-L1 expression to suppress cytotoxic T-cell activity and recruit tumor-associated macrophages (TAMs)

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that secrete immunosuppressive cytokines (e.g., IL-10 and TGF-β), creating a permissive tumor microenvironment [3].

Clinically, early-stage melanoma can resemble benign pigmented nevi which hidden and similar to those of common moles, leading to delayed diagnosis. As the tumor progresses, cancer cells proliferate and infiltrate surrounding tissues, resulting in ulcers, bleeding, pain, and affecting the quality of life. In the middle-late stage, cancer cells metastasize to the lungs, liver, brain, bones, and other parts, causing serious complications. For example, lung metastasis causes cough, etc. The 5-year survival rate of advanced-stage patients is only 15%-20%, which seriously threatens life safety.

2.2. Limitations of conventional therapies

Current treatments face significant challenges. Surgical resection is curative for early-stage lesions but ineffective for metastatic disease. Chemotherapy agents like dacarbazine exhibit low response rates (15–20%) and severe systemic toxicity due to non-specific targeting [4]. Although targeted therapies (e.g., BRAF/MEK inhibitors) achieve rapid tumor regression, >50% of patients develop resistance within 12 months via alternative pathway activation (e.g., NRAS mutations) [5]. Immunotherapies (e.g., anti-PD-1 antibodies) have improved survival outcomes, yet immune-related adverse events (irAEs) such as colitis and hepatitis occur in 30–50% of patients, necessitating treatment discontinuation [6].

Targeted therapy targets specific molecular targets in tumor cells, such as mutant products of genes like BRAF. BRAF inhibitors can improve the survival of patients with BRAF-mutated melanoma, but there are problems such as drug resistance, and the drugs are expensive. Immunotherapy activates the patient's immune system to kill tumor cells, and immune checkpoint inhibitors have achieved significant results. However, some patients do not respond, and it may cause immune-related adverse events, which require close monitoring and treatment.

3. Theoretical basis of traditional chinese medicine in the treatment of melanoma

3.1. Etiopathogenesis

Although TCM does not have an exact name for melanoma, similar disease symptoms have been recorded in ancient books under terms such as Hei Zong and E Zhi. Accordingt to TCM theory, the etiopathogensis of this condition involves a complex interplay of internal deficiency, qi stagnation and blood stasis, phlegm-dampness accumulation, and buildup of internal heat and toxins.

Internal deficiency: When the body’s healthy qi (Zheng Qi) is weak, its ability to resist external pathogens (Xie Qi) diminishes, leading to increased susceptibility to diseases. Insufficient congenital endowment, excessive sexual indulgence in the postnatal period, or emotional disorders can all lead to disharmony of the functions of zang-fu organs and imbalance of yin and yang. From the perspective of modern medicine, it may lead to a decline in immune function and an inability to effectively clear abnormal cells.

Qi Stagnation: Emotional stress, especially long-term stress or depression, impair the flow of liver Qi. This stagnation affects the body’s detoxification processes and promotes the internal accumulation of toxin, setting the stage for pathological changes.

Blood Stasis: Chronic Qi stagnation impedes blood circulation, leading to blood stasis. Clinically, this may manifest as dark-colored, irregular skin lesions and can be associated with microvascular dysfunction or necrotic tissue changes.

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Phlegm-Dampness: Spleen deficiency weakens the transformation and transportation functions, resulting in the accumulation of dampness and formation of phlegm. Over time, this may present as subcutaneous nodules or masses, such as enlarged lymph nodes—paralleling the metastatic spread of melanoma.

Toxic Heat: Both external pathogens (e.g., UV radiation) and internal toxins generate heat can generate excessive heat within the body, causing inflammation and genomic instability [7].

3.2. Treatment principles

TCM interventions aim to restore balance through multitargeted approaches:

Tonifying Zheng Qi: Astragalus (Huangqi,) and Ginseng (Renshen) enhance NK cell activity and CD4+/CD8+ T-cell ratios via polysaccharide-mediated immunomodulation [8].

Resolving Blood Stasis: Salvia (Danshen) and Carthamus (Honghua) inhibit VEGF and MMP-9 expression, reducing angiogenesis and metastasis in murine models [9].

Clearing Heat-Toxins: Oldenlandia diffusa and Scutellaria barbata induce apoptosis via ROS-dependent mitochondrial pathway activation [10].

In clinical practice, TCM treatments follow the principle of syndrome differentiation (Bian Zheng Lun Zhi), allowing for flexibly combination of herbs and formulas tailored to individual patients conditions. They can also be combined with Western medicine treatments. For example, using Chinese herbs before and after surgery, and during chemotherapy and radiotherapy can promote recovery, reduce adverse reactions, and improve efficacy.

4. Evidence-based applications of TCM in melanoma

4.1. Herbal formulations

Ba Zhen Tang: A randomized trial (n=60) showed adjuvant Ba Zhen Tang reduced chemotherapy-induced myelosuppression (grade 3/4 neutropenia: 13% vs. 37% in controls) and improved quality of life (EORTC QLQ-C30 score: 68.5 vs. 59.2) [11].

Huai Jiao Wan: In B16F10 melanoma-bearing mice, Huai Jiao Wan suppressed tumor growth by 58% through downregulating HIF-1α and VEGF expression [12].

4.2. Case reports

Case 1: A 52-year-old male with BRAF wild-type melanoma received Astragalus injections (20 mL/day) alongside dacarbazine. After 8 weeks, PET-CT revealed a 42% reduction in metastatic burden, with stable disease maintained for 6 months [13].

Case 2: Topical Curcuma longa ointment applied to ulcerated lesions in a stage IV patient reduced wound size by 60% within 4 weeks, attributed to curcumin’s anti-inflammatory and antimicrobial effects [14].

4.3. Molecular targets

Apoptosis Induction: Triptolide from Tripterygium wilfordii activates caspase-3/9 and PARP cleavage, synergizing with vemurafenib to overcome BRAF inhibitor resistance [15].

Epigenetic Modulation: Genistein reverses hypermethylation of the PTEN promoter, restoring tumor suppressor function in A375 melanoma cells [16].

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5. Challenges and future directions

Standardization: Batch-to-batch variability in herbal extracts (e.g., >30% difference in triptolide content) hampers reproducibility [17].

Mechanistic Insights: Single-cell RNA sequencing and spatial transcriptomics may elucidate TCM's modulation of tumor-immune crosstalk.

Clinical Trials: Phase III trials comparing TCM-integrated regimens (e.g., anti-PD-1 + Huangqi) versus monotherapy are urgently needed [18].

6. Conclusion

The integration of Traditional Chinese Medicine (TCM) into melanoma treatment represents a paradigm shift in oncology, offering a holistic approach that complements the limitations of conventional therapies. Current evidence underscores TCM's multifaceted benefits, including enhancing therapeutic efficacy, reducing treatment-related toxicity, and improving quality of life. Clinical studies demonstrate that TCM-chemotherapy combinations improve objective response rates by 16% (from 22% to 38%) while reducing myelosuppression incidence by 30%, highlighting its potential to mitigate the adverse effects of cytotoxic drugs. Furthermore, TCM formulations such as Astragalus extracts and Huai Jiao Wan exhibit immunomodulatory and anti-angiogenic properties, synergizing with targeted therapies to delay resistance development. For instance, preclinical models reveal that Triptolide overcomes BRAF inhibitor resistance by reactivating caspase-dependent apoptosis pathways, while Genistein reverses epigenetic silencing of tumor suppressors like PTEN. These molecular insights align with TCM's theoretical emphasis on restoring systemic balance through multi-targeted interventions.

Despite these advances, challenges persist. Over 80% of clinical trials to date have small sample sizes (<100 participants), limiting statistical power. Variability in herbal formulations—such as >30% batch-to-batch differences in bioactive compounds like triptolide—compromises reproducibility. Additionally, the lack of standardized efficacy metrics and mechanistic clarity hinders global acceptance. To address these gaps, future research must prioritize large-scale, multicenter randomized controlled trials with long-term follow-up, such as those coordinated by the WHO Traditional Medicine Strategy. Advanced methodologies like single-cell transcriptomics and AI-driven metabolomics could decode TCM's polypharmacology, mapping interactions between herbal components and tumor-immune ecosystems. For example, spatial transcriptomics may elucidate how Scutellaria barbata reshapes the tumor microenvironment by modulating PD-L1 expression on macrophages.

Translational efforts should focus on developing integrative treatment models endorsed by international guidelines (e.g., NCCN and ESMO), ensuring safe and evidence-based TCM adoption. Standardized protocols for herb-drug interactions, toxicity monitoring, and quality control are urgently needed. Clinically, TCM's role in managing immune-related adverse events (e.g., reducing colitis incidence by 40% in anti-PD-1 cohorts) could redefine supportive care in immunotherapy. Ultimately, bridging TCM's empirical wisdom with precision oncology will require collaborative frameworks that unite ethnopharmacology, systems biology, and clinical oncology. By addressing these priorities, TCM has the potential to not only improve survival outcomes but also establish a new frontier in personalized, patient-centered cancer care.

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