

The Application of Traditional Chinese Medicine-Derived Formulations in Cancer Immunotherapy: A Review

Yanyun Li¹, Changying Li², Junzi Fan³, Yutong Liu¹, Yincong Xu⁴, Guowei Pang¹

¹School of Acupuncture and Tuina, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China; ²School of Ophthalmology and optometry, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China; ³School of Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China; ⁴College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China

Correspondence: Yincong Xu; Guowei Pang, Email onion521@sina.com; pgw@sduetcm.edu.cn

Background: Cancer immunotherapy is an advanced therapeutic approach that harnesses the body's immune system to target and eliminate tumor cells. Traditional Chinese medicine (TCM), with a history rooted in centuries of clinical practice, plays a crucial role in enhancing immune responses, alleviating cancer-related symptoms, and reducing the risks of infections and complications in cancer patients.

Methodology: This review systematically examines the current literature on TCM-based formulations in cancer immunotherapy. It explores the mechanisms by which TCM augments immune responses, particularly focusing on how these formulations influence both innate and adaptive immunity. Various TCM herbs and compounds, their active ingredients, and their application in cancer prevention and treatment were analyzed through an integrated review of preclinical studies, clinical trials, and molecular mechanistic investigations.

Results: TCM formulations contribute to cancer therapy by modulating the body's internal environment to improve immune defense. They enhance the immune system's ability to detect and destroy cancer cells, promote apoptosis in tumor cells, inhibit tumor growth and metastasis, and augment the effectiveness of conventional cancer treatments. The review highlights specific TCM herbs and formulations that have demonstrated significant anti-cancer properties, including their ability to strengthen immune responses and provide synergistic effects with existing cancer therapies.

Conclusion: TCM-derived formulations represent a promising addition to cancer immunotherapy. The mechanisms through which these formulations enhance anti-tumor immunity are multifaceted, involving modulation of immune cell activity, apoptosis induction, and suppression of tumor progression. As cancer immunotherapy evolves, the integration of TCM into conventional treatment regimens may offer enhanced therapeutic efficacy, reduced side effects, and improved overall outcomes for cancer patients. Further clinical research is needed to fully elucidate the therapeutic potential and safety of TCM-based immunotherapeutic strategies in cancer care.

Keywords: traditional Chinese medicine, TCM, cancer, nanocarriers, immune ability, anti-tumor therapy, tumor microenvironment, drug delivery systems

Introduction

The phenomenon of tumor refers to the unchecked proliferation of cells, which, without intervention, may metastasize through the lymphatic system and bloodstream, posing significant life threats. The global incidence of malignant tumors, including early-onset cancers, is on the rise, necessitating a broadened approach to tumor treatment beyond conventional surgery, radiotherapy, and chemotherapy to include newer modalities such as immunotherapy and targeted therapy. These advancements have markedly enhanced the effectiveness and patient experience of tumor treatments.¹⁻³

Immunotherapy stands out as a notable advancement, offering substantial benefits in combating tumors. It operates on the principle of activating the body's immune system to target and eliminate cancer cells, and has shown promising outcomes across various cancer treatments, positioning it as a future mainstream tumor treatment method. Clinical

practices commonly employ tumor vaccines, adoptive cell therapy, and immune checkpoint inhibitors in immunotherapy regimens. Tumor vaccines, in particular, stimulate the body's immune response to fight tumors.^{4,5}

The effectiveness of traditional Western medicine in treating tumors is indispensable, such as radiotherapy and chemotherapy, surgical intervention, targeted therapy, and neoadjuvant chemotherapy. However, they also bring high recurrence rates and significant adverse reactions to patients, exacerbating their discomfort.⁶ Compared with them, the traditional Chinese medicine treatment has more obvious advantages.^{7,8} (1) Multi target and multi pathway effects: Traditional Chinese medicine has complex ingredients and often treats diseases through multiple targets and pathways. (2) Minor side effects: Traditional Chinese medicine treatment can reduce the adverse reactions and complications of radiotherapy and chemotherapy. (3) Adjusting and improving the body's immune function: Traditional Chinese medicine can not only directly combat tumor cells, but also enhance the body's immune system by regulating it, helping the body resist tumors. (4) Individualized treatment: Traditional Chinese medicine emphasizes on individuals, adheres to the principle of "treating the same disease differently", achieves personalized treatment, and thus improves the targeted and effective treatment. (5) Comprehensive regulation and improvement of quality of life: Traditional Chinese medicine treatment regulates the overall health status of patients, including improving fatigue, relieving pain, and increasing appetite, thereby improving their quality of life.

Traditional Chinese medicine (TCM) addresses some limitations of vaccine and other therapeutic approaches, including personalized treatment variations, pain management, and the regulation of the body's yin-yang balance.⁹⁻¹¹ TCM is characterized by minimal side effects and provides stage-specific, personalized treatments for cancer patients, enhancing treatment efficiency. Additionally, TCM plays a crucial role in managing pain, a common symptom among cancer patients. By harmonizing the flow of qi and blood and adjusting the yin-yang balance, TCM fortifies the body's defenses and offers immune system benefits. TCM's role in cancer immunotherapy is multifaceted. It directly suppresses or destroys tumor cells and mitigates immune evasion by modulating both innate and adaptive immunity. Moreover, it can improve cancer patients' quality of life by alleviating symptoms such as pain, nausea, and fatigue, through the regulation of qi and blood, and balancing yin and yang.^{12,13} The synergistic use of multiple TCM formulations can enhance therapeutic outcomes and minimize adverse effects.¹⁴ Nevertheless, safe medication practices must be observed, especially when using potent TCMs or combinations known for toxic side effects. While chemotherapy and radiotherapy can lead to side effects like nausea, vomiting, hair loss, and fatigue, Chinese herbal medicine is generally well-tolerated by patients.

Clinical observations indicate minimal adverse reactions with TCM, suggesting its potential to ease the treatment burden. TCM can holistically regulate the body, bolstering positive energy, and enhancing the immune response. However, challenges in TCM-based immunotherapy, such as dosage control, large-scale production of TCM nanoformulations, biocompatibility, and biosafety, remain. One potential solution is integrating multiple TCMs with small molecules or active components from conventional drugs, utilizing nanomaterials as carriers. This approach could enhance the anti-tumor efficacy and specificity while minimizing drug-related toxicities. By refining these strategies, the therapeutic potential of TCM-derived nanoformulations in cancer immunotherapy can be fully realized.

Traditional Chinese Medicine Enhances Cancer Immunotherapy

In China, traditional Chinese medicine (TCM) is utilized to treat approximately 70% of cancer patients, showcasing significant efficacy in augmenting the sensitivity of patients to chemotherapy and alleviating adverse effects associated with tumor therapy, such as fatigue and bone marrow suppression.^{15,16} TCM therapy spans a wide range of applications, including the use of TCM monomers, medicinal extracts, traditional compound formulas, approved compound medications, proprietary compound concoctions, and techniques like acupuncture and moxibustion. TCM's approach is holistic, targeting multiple components, targets, and pathways for a bidirectional and systemic treatment of tumors. Emphasizing tumors as systemic diseases, TCM advocates for comprehensive body treatment rather than focusing solely on localized symptoms.

TCM's philosophy aligns with the strategy of enhancing the body's immune system to combat tumors, echoing the TCM concept of "nourishing the positive to spontaneously expel cancer." TCM's mechanism in cancer treatment is distinguished by its ability to suppress tumor cell proliferation while simultaneously promoting the proliferation of

immune cells. It achieves tumor inhibition through the modulation of key signaling pathways, encouraging tumor cell apoptosis and autophagy, inducing cell cycle arrest, and suppressing tumor growth by targeting essential factors for tumor angiogenesis.^{17–19} Furthermore, TCM's active components fine-tune both the innate and adaptive immune systems, elevating the variety and efficacy of immune cells.^{20,21} This holistic approach aims to bolster the body's immune competence, thereby enhancing its defense against tumor invasion and metastasis while fostering lasting immune memory.

However, challenges such as varying response rates to treatments and drug resistance persist, indicating areas for future enhancement and exploration. TCM's impact on the immune system is multifaceted, affecting different immune cells through a rich array of chemical constituents, including alkaloids, polysaccharides, flavonoids, and glycosides.²² These constituents exert diverse biological functions, broadly influencing both innate and adaptive immunity. Notably, TCM can modulate the immune response within the tumor microenvironment, potentially offering a pathway to up-regulate immune activity against cancer.^{23,24} Despite the benefits, ongoing issues like reaction variability and resistance to therapy underscore the need for continued research and methodological advancements.

Breast Cancer Immunotherapy & TCM

Breast cancer stands as the most prevalent malignancy affecting women globally, significantly impacting women's health. Addressing this challenge necessitates the discovery of innovative therapeutic targets to enhance treatment outcomes. The classification of breast cancer into Luminal A and B, HER-2 positive, and triple-negative types highlights the diversity in prognosis and treatment strategies. Specifically, HER-2 positive breast cancers, known for their aggressive nature, frequent recurrence, and challenging prognosis, constitute a significant portion (15–20%) of breast cancer cases, with recurrence and metastasis rates soaring up to 50%. Meanwhile, triple-negative breast cancer (TNBC), making up about 15–20% of breast cancer cases, is noted for its earlier onset, aggressive progression, and less favorable prognosis compared to its hormone receptor-positive or HER-2 positive counterparts.^{25–28}

Traditional Chinese medicine (TCM) offers a promising avenue for breast cancer treatment, grounded in a rich theoretical base and extensive clinical practice. TCM attributes crucial significance to blood stasis syndrome in the etiology and progression of breast cancer. Traditional Chinese medicine believes that excess milk stays in the breast and does not pass through the Ren and Chong meridians to the uterus on time every month, resulting in menstrual discharge. Over time, this leads to blocked blood vessels and blood stasis, resulting in breast cancer. Therefore, to cure breast cancer, it is necessary to promote blood circulation, promote qi circulation, and eliminate blood stasis and promote meridians. The Taohong Siwu Decoction (TSHWD), based on the foundational Siwu Decoction and revered as a quintessential gynecological remedy, is broadly utilized for treating various blood stasis and deficiency syndromes, especially in gynecology.^{29,30} Comprising six medicinal components such as Raw Rehmanniae Radix, Angelica Sinensis, Ligusticum Chuanxiong, Paeoniae Radix Alba, Peach Kernel, and Safflower, TSHWD markedly improves cancer tissue's microenvironment and microcirculation. Research by Professor Jiang suggests that TSHWD can curb the proliferation and metastasis of HER-2 positive breast cancer cells (SK-BR-3) by optimizing the tumor microenvironment, regulating tumor cells' EMT process, and thereby inhibiting their proliferation and spread.³¹ This mechanism mirrors the therapeutic effects of *Brucea Javanica* and its active compound Brucein D, renowned in TCM for antagonizing TNBC progression by modulating EMT and the PI3K/AKT pathways. Furthermore, Sanhuang Decoction (comprising Huangqin, Huanglian, and Huangbai) has been shown to induce apoptosis in tamoxifen-resistant BC cells by inhibiting NF- κ B signaling overactivation and enhancing EMT (Figure 1).³² Similarly, compounds like *Astragalus Membranaceus*, and formulations like Sanhuang Decoction and Gansui Banxia Decoction, demonstrate the potential of TCM in offering novel, effective strategies for managing breast cancer through immune modulation, promoting apoptosis, and inhibiting tumor growth and metastasis by regulating crucial signaling pathways such as NF- κ B, PI3K/AKT, and ERK mediated by CTGF.^{33,34} From this, it can be seen that Western medicine usually eliminates tumors through sectioning and surgery, which inevitably leads to the consequences of tumor spread. Traditional Chinese medicine emphasizes the integrity and connectivity of human organs and tissues, which are interdependent and inseparable. Traditional Chinese medicine can regulate qi and blood, unblock the Ren and Du meridians, unblock the meridians throughout the body, and examine diseases from a macro perspective, ultimately achieving therapeutic effects in treating and eradicating diseases.

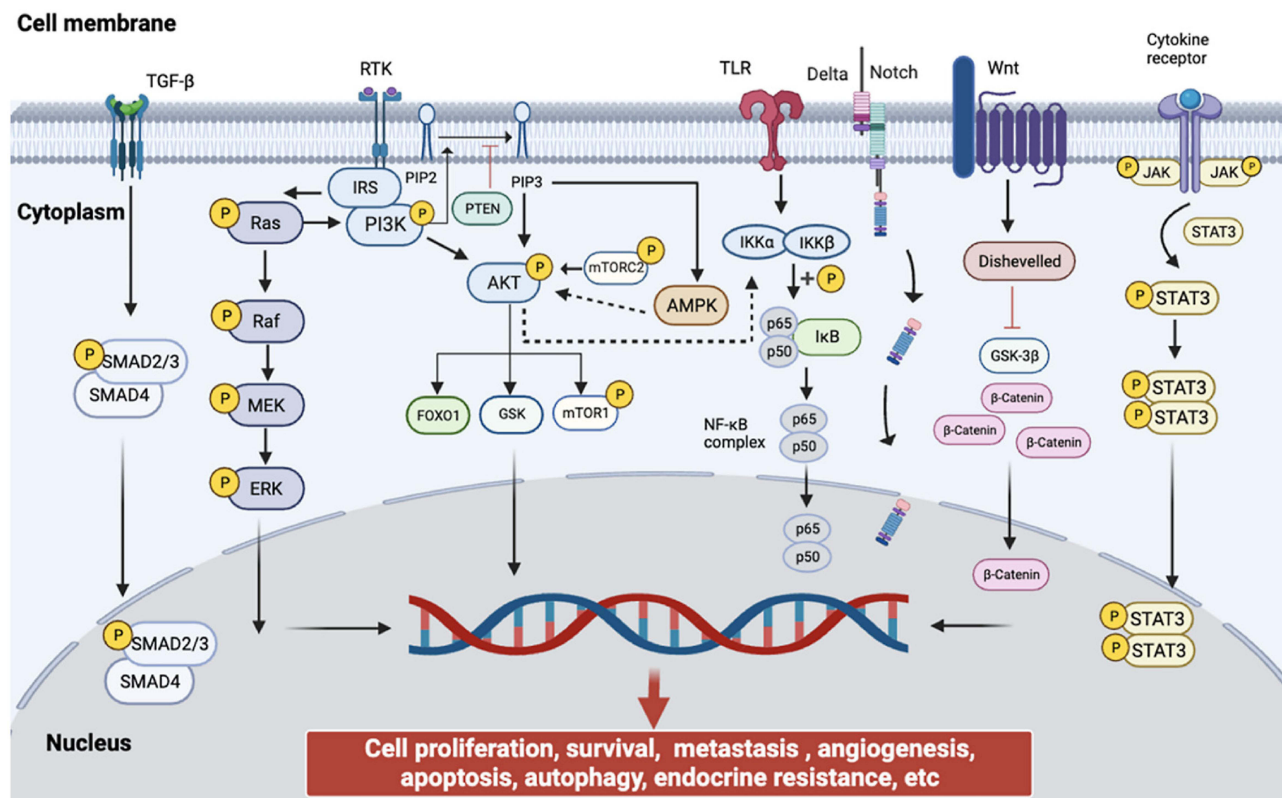


Figure 1 Chinese herbs/natural herbs or some of their components can interfere with BC cell proliferation and metastasis through the corresponding signaling pathways/targets.

Notes: Reproduced from Yu Q, Xu C, Song J, Jin Y, Gao X. Mechanisms of traditional Chinese medicine/natural medicine in HR-positive breast cancer: a comprehensive literature review. *J Ethnopharmacol.* 2024;319(Pt 3):117322. Copyright 2024, with permission from Elsevier.³²

Thyroid Cancer Immunotherapy & TCM

Thyroid cancer (TC), a significant endocrine malignancy, disproportionately affects women, representing about 3% of all cancer types. It typically presents as a painless neck mass or nodule, which may compress nearby structures like the esophagus and trachea. The primary therapeutic approach for TC includes surgical removal, complemented by post-surgical medication and localized radiation therapy. Although these treatments are generally effective, they are associated with a high recurrence rate and considerable adverse effects, exacerbating patient discomfort.^{6,35}

Papillary thyroid carcinoma (PTC) stands as the most prevalent form of thyroid cancer, accounting for 80–90% of cases, and is a major endocrine malignancy. Thyroid cancers are categorized into differentiated (DTC), undifferentiated (ATC), and medullary (MTC) types, with DTC being the most common. Treatment modalities typically involve surgery, radioactive iodine, hormone therapy, and molecular targeted therapies. Yet, about 30% of DTC cases may evolve into radioiodine-refractory differentiated thyroid cancer (RAIR-DTC), significantly diminishing the 10-year survival rate to below 10%.^{36–38}

Traditional Chinese medicine believes that there are two reasons behind thyroid diseases. Firstly, thyroid problems belong to liver and gallbladder problems, and the liver governs emotions. Therefore, people with emotional injuries are very prone to thyroid diseases. Women are prone to emotional trauma, so there are more women with thyroid diseases. The Small Bupleurum Decoction can enter the liver and gallbladder meridian and has the function of soothing the liver and relieving depression.

Traditional Chinese medicine (TCM) offers therapeutic alternatives, such as the Small Bupleurum Decoction, traditionally used for a range of conditions including colds, flu, and gastrointestinal disorders. This formula, containing ingredients like Pinellia, Bupleurum, Ginseng, Scutellaria, Ginger, Licorice, and Jujube, has demonstrated potential in reducing TC cell viability and promoting apoptosis through the caspase-3 pathway, alongside inducing autophagy via the PI3K-AKT pathway (Figure 2).³⁹ Similarly, *Dioscorea zingiberensis*, or yellow medicine seed, has been observed to

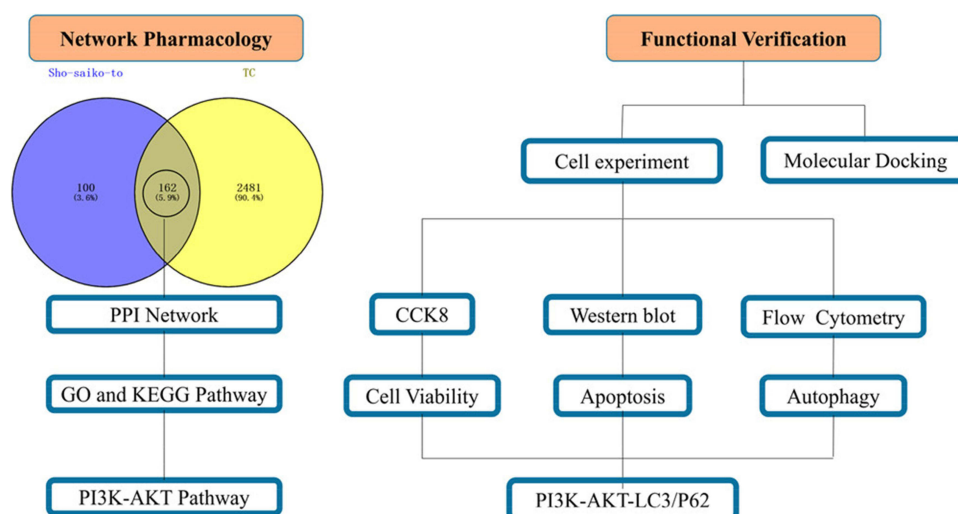


Figure 2 The main chemical components of Xiaochaihu Decoction could inhibit the viability and proliferation of TC cells, promote cell apoptosis through the caspase-3 pathway, and induce cell autophagy through the PI3K-AKT pathway.

Notes: Reproduced from Wang K, Qian R, Li H, Wang C, Ding Y, Gao Z. Interpreting the pharmacological mechanisms of sho-saiko-to on thyroid carcinoma through combining network pharmacology and experimental evaluation. *ACS Omega*. 2022;7(13):11166–11176. © 2022 The Authors. Published by American Chemical Society CC BY NC ND 4.0.³⁹

enhance clinical outcomes in TC patients and reduce tumor volumes, attributing its anti-TC effects to the modulation of the PI3K-Akt and focal adhesion pathways. Notably, it inhibits the migration and invasion of KMH-2 cells and promotes apoptosis by downregulating the activation of the PI3K-Akt pathway.⁴⁰

Secondly, the thyroid gland is located above, which is also caused by the disturbance of deficiency heat. The operation of the entire body should be intertwined, especially in the middle jiao, where the central axis operates together and heat and cold blend together. However, due to the gradual decline in spleen and stomach function, it can lead to the isolation of yin and yang, with heat moving upwards and cold moving downwards. The occurrence of a series of problems can be caused by the combination of upper heat and lower cold. And women are prone to lower body temperature and cold, so the deficiency heat in the upper body is also more severe, which explains why women are more prone to thyroid disease. *Sophora flavescens* can enter the liver meridian, nourish the qi of the liver and gallbladder, clear heat and dry dampness.

Moreover, Matrine, another TCM-derived compound, has shown promise in treating PTC in TPC-1 human cells. Research indicates that matrine's efficacy may be mediated through the miR-21/PTEN/Akt pathway, underscoring the potential of TCM in inducing apoptosis and halting the cell cycle in thyroid cancer cells.³⁸ This evidence highlights the value of integrating traditional Chinese medicine components into the therapeutic landscape for thyroid cancer, offering novel avenues for treatment and potentially improving patient outcomes.

Traditional Chinese medicine can classify the etiology and pathogenesis of thyroid gland. If the thyroid gland is caused by liver qi stagnation, use drugs that soothe the liver and relieve depression to regulate the whole body. If the liver qi of a female population is not smooth, combined with yin deficiency and heat deficiency, it can be treated with a combination of liver soothing medicine and heat clearing medicine. The above reflects the characteristics of personalized treatment in traditional Chinese medicine.

Osteosarcoma Immunotherapy & TCM

Osteosarcoma (OS), a leading bone tumor in pediatric populations, exhibits alarming rates of recurrence, disability, mortality, and metastasis, imposing severe economic and emotional strains on affected individuals and markedly degrading their life quality.⁴¹ The therapeutic arsenal against OS currently spans across radiotherapy, chemotherapy, surgical interventions, and the strategic use of neoadjuvant chemotherapy alongside limb salvage operations. Traditional Chinese medicine (TCM) interprets the etiology of osteosarcoma through the lens of the invasion or disturbance by the “six evils” that disrupt vital qi, leading to qi stagnation, blood stasis, and phlegm dampness, culminating in bone tumors.

A vast body of research underscores the potency of TCM-derived active ingredients in curtailing OS cell proliferation and differentiation, fostering apoptosis, and occasionally overturning chemotherapy resistance in OS cells.⁴²

Extracted from the *Isodon* genus (or dong ling grass) in 1970, Oridonin is celebrated for its analgesic, anti-inflammatory, and anticancer prowess. It champions anticancer activity by triggering mitochondria-mediated apoptosis, evidenced by the escalated Bax/Bcl-2 ratio, caspase-3 and -9 activation, alongside reactive oxygen species (ROS) generation. Moreover, Oridonin disrupts specific signal transduction pathways to encourage cancer cell apoptosis. For instance, in OS contexts, modulating the NF- κ B activation and JNK pathway inhibition plays a pivotal role in sustaining malignant cell viability, thus influencing therapeutic outcomes. Notably, Parthenolide has been documented to dose-dependently suppress NF- κ B activity while initiating JNK pathway activation, ensuing in caspase-independent death of bone cancer cells. Since ROS activity is intrinsically antitumoral, its accumulation within cancer cells emerges as a strategic therapeutic maneuver.⁴¹ Investigations led by Mickymaray et al revealed that Emodin significantly attenuates the PI3K/AKT/mTOR signaling cascade in MG-63 cells, leading to augmented ROS presence in the cytoplasm, diminished mitochondrial membrane potential, escalated nuclear damage, and an uptick in apoptotic events, positioning Emodin as a prospective osteosarcoma chemotherapeutic. Further, Professor Huang et al identified that Andrographolide inhibits the PI3K/AKT, Wnt/ β -catenin, and NF- κ B pathways in human OS cells, efficiently repressing cell proliferation, migration, and invasion (Figure 3).⁴² This underscores the therapeutic promise of leveraging TCM-derived compounds in osteosarcoma treatment strategies. The above content indicates that the various components contained in traditional Chinese medicine can treat bone cancer through multiple targets and pathways, making treatment more efficient.

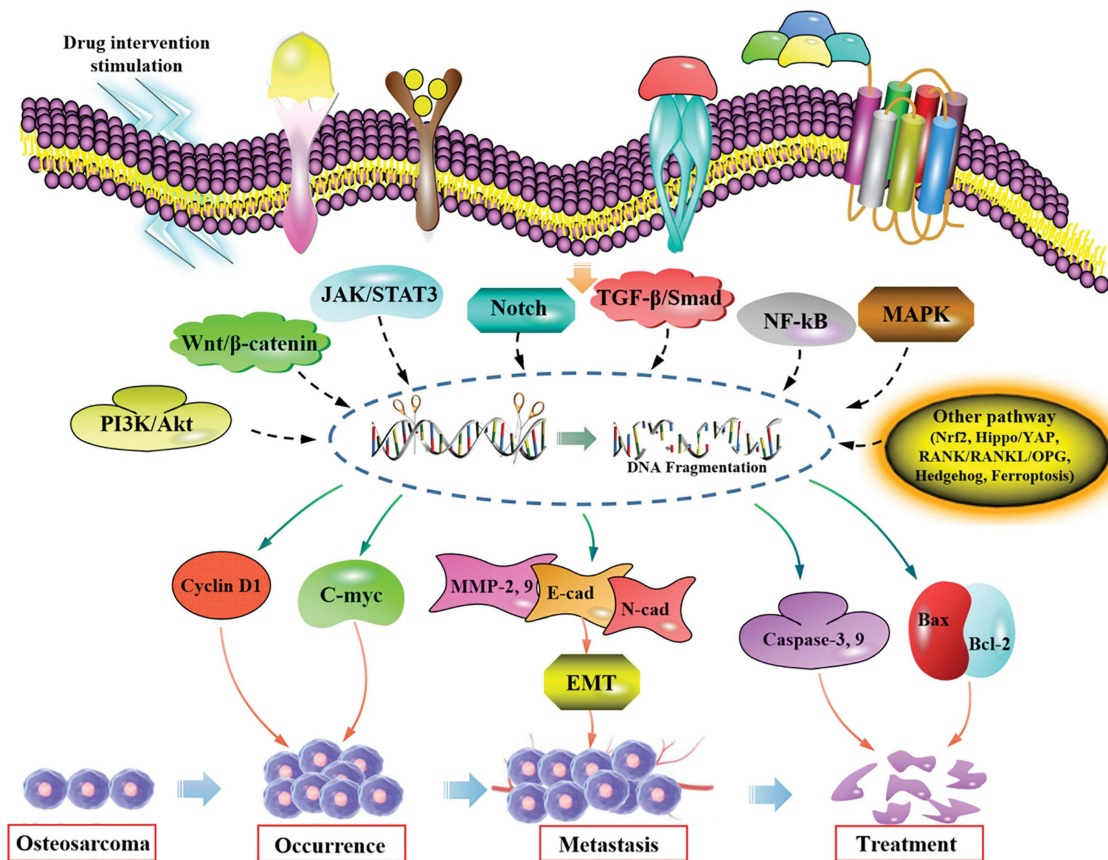


Figure 3 Traditional Chinese medicine can induce autophagic death, inhibit cell proliferation, differentiation and metastasis, promote cell apoptosis, and ultimately inhibit the development of OS from different signaling pathways.

Notes: Reproduced from . Liu Y, Jiang B, Li Y, et al. Effect of traditional Chinese medicine in osteosarcoma: cross-interference of signaling pathways and potential 410 therapeutic targets. *Medicine*. 2024;103(3):e36467. Copyright © 2024 the Author(s). Published by Wolters Kluwer Health, Inc. Creative Commons Attribution License 4.0 (CCBY).⁴²

Colorectal Cancer Immunotherapy & TCM

Colorectal cancer (CRC), a widespread gastrointestinal malignancy, is significantly influenced by the gut microbiome, which plays a crucial role in its development and progression. Characterized by low immunogenicity and microsatellite stability, CRC develops within a highly immunosuppressive tumor microenvironment (TME), rendering it resistant to many forms of immunotherapy (Figure 4). This underscores the critical need for novel therapeutic interventions aimed at enhancing drug sensitivity and reversing resistance to existing CRC treatments.^{43–45}

Amidst the conventional treatment modalities for CRC, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, enhancing patient survival and quality of life remains a paramount concern.⁴⁶ Traditional Chinese medicine (TCM) offers a unique approach, where the pharmacodynamics of TCM components is modulated by the liver, intestines, and stomach before systemic circulation. The gut microbiota plays a pivotal role in optimizing the bioavailability of these components, showcasing a symbiotic relationship between TCM and intestinal flora. This interaction aids in modifying the metabolism, absorption, and efficacy of TCM formulations, while various probiotics have shown promise in mitigating cancer-related inflammation through modulation of cellular activities and signaling pathways.

TCM has demonstrated effectiveness in the management of CRC by promoting apoptosis of cancer cells, hindering metastasis, and ameliorating drug resistance and adverse effects.⁴⁷ Notably, TCM sensitizers have the potential to reverse chemotherapy resistance in CRC by targeting and modulating traditional chemotherapy mechanisms, enhancing drug activation, and improving the TME. Pien Tze Huang (PZH), a distinguished TCM, has been noted for its broad biological activities including detoxification and anti-inflammation, showing potential in inhibiting CRC proliferation by modulating the Wnt/ β -catenin signaling pathway.⁴⁷

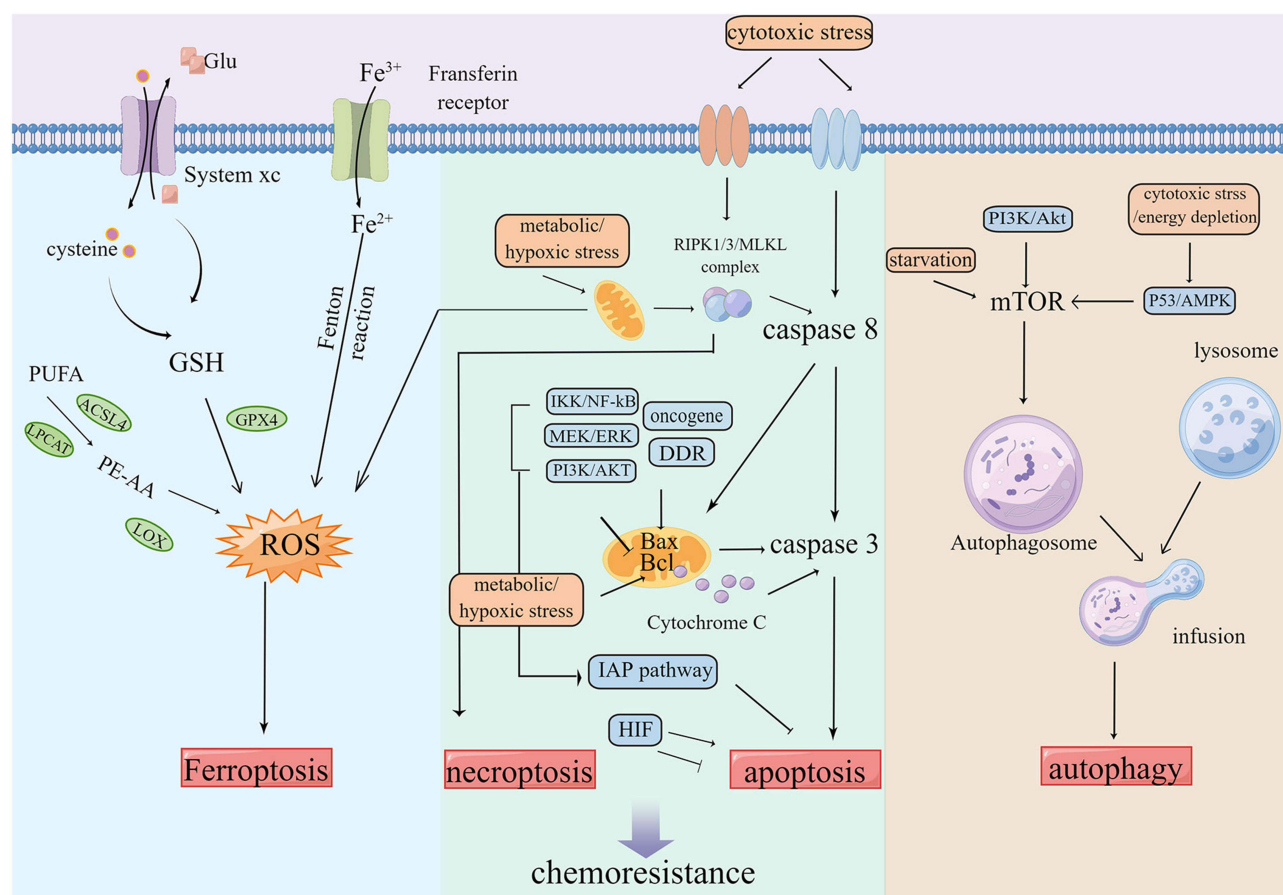


Figure 4 Tumors keep their sustained growth, metastasis and gain chemoresistance by escaping cell death such as ferroptosis, apoptosis and autophagy etc.

Notes: Reproduced from Lin X, Yang X, Yang Y, Zhang H, Huang X. Research progress of traditional Chinese medicine as sensitizer in reversing chemoresistance of colorectal cancer. *Front Oncol.* 2023;13:1132141. Copyright © 2023 Lin, Yang, Yang, Zhang and Huang. Creative Commons Attribution License (CC BY).⁴⁵

Moreover, the role of probiotics, such as *S. thermophilus* and *Clostridium butyricum*, in CRC treatment underscores the capacity of beneficial bacteria to regulate key signaling pathways and improve treatment outcomes. Investigations into the mechanisms of action of TCM and probiotics reveal their ability to influence DNA damage repair, ferroptosis, and inflammation-related pathways, enhancing the therapeutic efficacy against CRC.

In summary, the integration of TCM and probiotics into the treatment paradigm for CRC presents a promising avenue for overcoming the limitations of current therapeutic strategies, potentially leading to improved patient outcomes and a deeper understanding of the interplay between gut microbiota and cancer therapy. Traditional Chinese medicine can regulate and improve the tumor microenvironment in the colon and rectum, increase the types of immune cells, enhance the body's immune capacity, and be more conducive to combating cancer invasion.

Liver Cancer Immunotherapy & TCM

Liver cancer, marked as the sixth most diagnosed and the fourth leading cause of cancer-related deaths globally,⁴⁸ predominantly manifests through hepatocellular carcinoma (HCC), notorious for its high mortality rate. The median survival duration post-diagnosis scarcely exceeds a year,⁴⁹ underlining a grim prognosis for patients afflicted with this malignancy. The disease commonly occurs in individuals suffering from hepatitis B and cirrhosis, leading to a significant number of cancer fatalities.⁵⁰ The asymptomatic nature of early-stage primary HCC often results in late diagnoses, limiting the effectiveness of potential curative interventions such as liver transplantation, surgical resection, and radio-frequency ablation (RFA). Despite these treatments offering varying degrees of success, the 5-year survival rates ranging from 40% to 79% underscore the challenge of managing postoperative recurrence and enhancing patient prognosis.⁵¹

The arsenal against liver cancer encompasses a variety of treatments, each with distinct benefits and limitations. Preferred modalities like surgical resection and liver transplantation often grapple with challenges like local invasion and intrahepatic metastasis, which complicate postoperative outcomes and prognosis. Given the elusive early symptoms of HCC, many patients are diagnosed in advanced stages when curative treatments are no longer viable, rendering HCC among the most challenging malignancies to address at advanced stages. While chemotherapy offers another avenue for cancer treatment, its efficacy is marred by significant side effects targeting rapidly proliferating cancer cells.⁴⁹

In this complex treatment landscape, traditional Chinese medicine (TCM) emerges as a promising alternative, boasting high efficiency, effectiveness, and minimal adverse reactions.⁴⁹ TCM's holistic view of the human body emphasizes a balance between internal and external environments,⁴⁸ employing a multi-target and multi-pathway regulatory approach.⁵² It advocates for individualized treatment strategies based on a "component-target-pathway" model specific to diseases, aiming to modulate immunity, inflammation, and cell proliferation to decrease the recurrence rate among HCC patients. TCM underscores the enhancement of immune function in cancer patients as a cornerstone for improving outcomes.⁵¹

TCM prescriptions for liver cancer are characterized by a blend of cooling and warming properties, primarily employing cold bitter herbs. The treatment principles revolve around tonifying deficiencies, clearing heat, promoting blood circulation, removing stasis, and detoxification, showcasing a wide application in liver cancer management.⁵⁰ TCM interventions, including prescriptions and isolated compounds, counteract liver cancer by disrupting the tumor microenvironment (TME) and modulating exosome secretion and function. For instance, Jianpi-huayu decoction (JHD) effectively treats HCC by regulating epithelial-mesenchymal transition (EMT), immunity, the cell cycle, and apoptosis, specifically targeting the exosomal miR-23a-3p/Smad signaling pathway to inhibit EMT, migration, and invasion of HCC cells.⁵³

Moreover, TCM-derived alkaloids offer a broad spectrum of anti-liver cancer activities, including inhibiting cell proliferation and metastasis, promoting apoptosis, autophagy, cell cycle arrest, and modulating various cancer-related pathways such as the Mst1-JNK, ERK signaling, PINK1/Parkin axis, and PTEN/AKT pathways. Terpenoid alkaloids, for instance, manifest potent anti-hepatocellular carcinoma effects by modulating key proteins involved in DNA fragmentation, cell apoptosis, proliferation, and the cell cycle.⁴⁹

Ferroptosis, a regulatory cell death mechanism dependent on iron and lipotoxicity, represents a novel approach to inducing cancer cell apoptosis. Bicyclol, derived from *Schisandra chinensis*, exemplifies a pharmacologically versatile agent with potential benefits across a spectrum of liver pathologies, including its role in mediating the ferroptosis response and showcasing antiviral, anti-inflammatory, immunomodulatory, and anti-tumor properties (Figure 5).⁵⁴ TCM's multifaceted approach towards treating liver diseases, particularly through its impact on signal transduction

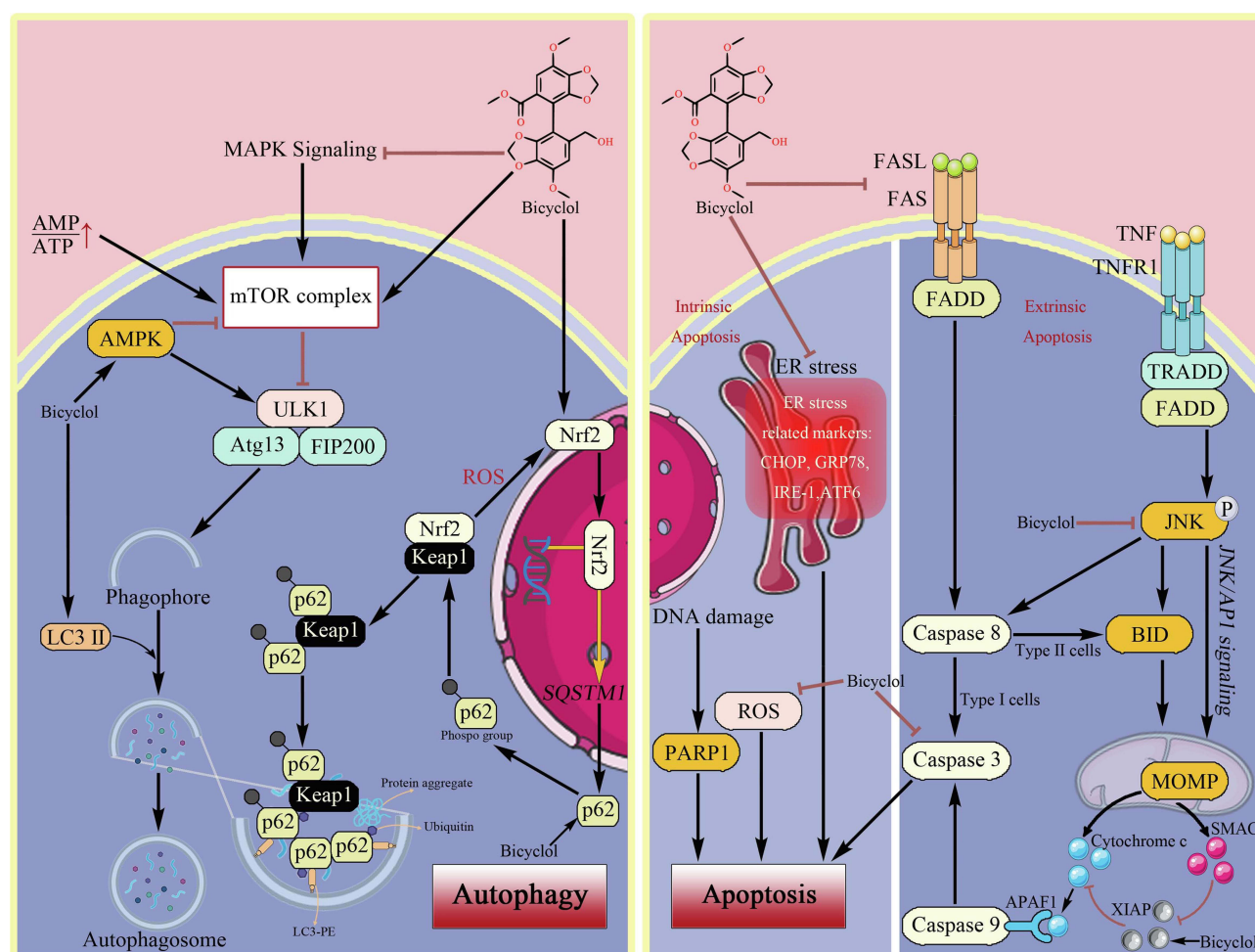


Figure 5 Regulation of cell death by bicyclol.

Notes: Reproduced from Zhao T, Mao L, Yu Z, et al. Therapeutic potential of bicyclol in liver diseases: lessons from a synthetic drug based on herbal derivative in traditional Chinese medicine. *Int Immunopharmacol.* 2021;91:107308. Copyright 2021, with permission from Elsevier.⁵⁴

and immune pathways, notably the PI3K-Akt pathway, signifies its integral role in managing liver cancer, advocating for a comprehensive strategy that encompasses immunity enhancement and inflammation inhibition.⁵⁰ Traditional Chinese medicine can damage the tumor microenvironment, inhibit the proliferation and metastasis of liver cancer cells, promote autophagy and apoptosis, and regulate various signaling pathways of liver cancer. The treatment of liver cancer focuses on nourishing qi and tonifying deficiency, clearing heat and detoxifying, promoting blood circulation and removing blood stasis, and achieving the advantages of “eliminating evil without damaging the body’s positive qi”, so the side effects are relatively small.

Discussion

While traditional Chinese medicine (TCM) holds promising anti-tumor capabilities, the clinical deployment of its active compounds is often hindered by less than optimal drug properties, including poor solubility, stability, limited bioavailability, and inadequate targeting and permeability. The integration of nanotechnology proposes a solution, potentially extending drug half-life, enhancing targeting precision, increasing permeability, and thus, amplifying the bioavailability of TCM active ingredients through improved solubility and stability. By encapsulating or binding TCM active compounds onto nanocarriers, it’s feasible to augment drug solubility while simultaneously shielding these compounds from premature receptor interaction. Such nanoformulations can prevent rapid clearance by the immune system, thereby prolonging the active compounds’ systemic circulation and half-life.

Nanomedicine delivery systems, such as polymer nanoparticles, liposomes, inorganic materials, and nanofibers, show exceptional clinical model targeting capabilities via controlled sizing. Essential to successful drug therapy is the sufficient accumulation of active compounds within target cells, a challenge compounded by the tumor microenvironment's dense extracellular matrix and interstitial pressure, which can impede the penetration of TCM active ingredients.

Nanoparticles are notably efficient at loading a wide range of hydrophobic drugs, capable of penetrating targeted sites without compromising their structural integrity. However, challenges such as nanoparticle instability and potential for drug leakage limit their practical application. Modifying nanoparticles with specific ligands can enhance the efficiency of oral nanocarriers in systemic delivery by navigating through the intestinal epithelium. Still, the effectiveness of these interactions can be diminished by the limited orientation, selectivity, or density of receptor bindings.⁵⁵

Sustained-release nanomaterials facilitate controlled and continuous drug delivery, characterized by high drug loading and encapsulation efficiency. Nano-controlled release technologies enable a more stable concentration of drugs within the body by shielding the drugs within nanoparticles, thereby prolonging their therapeutic effect. This approach has found widespread application in pharmaceutical formulations and the biomedical field, notably improving drug bioavailability and reducing adverse reactions. Despite these advancements, challenges in nanoparticle size control, stability, drug release rates, and biocompatibility remain areas for further exploration and improvement.

Integrating TCM with nano-preparations can significantly stimulate the body's immune response, actively targeting and removing cancer cells, thus offering a promising avenue for immunotherapy. This approach also aims to mitigate drug side effects, counteract drug resistance, and improve drug utilization efficiency. Despite the promise of combining TCM with nanotechnology, challenges such as adverse reactions from conventional therapies, multidrug resistance, and high rates of recurrence and metastasis call for innovative strategies to enhance treatment outcomes and patient quality of life.

Conclusion

Traditional Chinese medicine (TCM) has been utilized for centuries in the prevention and treatment of various ailments, gaining global recognition for its efficacy. TCM has the potential to modulate the tumor microenvironment, enhancing the body's anti-tumor immune responses, alleviating tumor-related symptoms, and potentially inducing tumor remission. However, the clinical application of TCM is often hindered by the poor solubility and low bioavailability of its natural active compounds. The integration of TCM with nanocapsules offers a promising solution, providing an eco-friendly, biodegradable, and biocompatible approach. Nevertheless, this strategy faces challenges, including the instability of nanoparticles and the risk of drug leakage. Therefore, there is an urgent need to accelerate the development and optimization of self-assembling nanoformulations derived from TCM. Moreover, while TCM shows promise in cancer therapy, identifying the specific TCM components responsible for its therapeutic effects remains a challenge. This highlights the need for further identification and investigation of TCM's active components with anti-tumor properties, as well as elucidating their mechanisms of action. Such efforts are essential for expanding the clinical applicability of TCM in cancer treatment.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors appreciate financial support from Shandong Provincial Natural Science Foundation of China under grant no. ZR2022LZY016 and National Natural Science Foundation of China under grant no. 81673843.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- Church SE, Galon J. Tumor microenvironment and immunotherapy: the whole picture is better than a glimpse. *Immunity*. 2015;43(4):631–633. doi:10.1016/j.immuni.2015.10.004
- Tang H, Qiao J, Fu YX. Immunotherapy and tumor microenvironment. *Cancer Lett*. 2016;370(1):85–90. doi:10.1016/j.canlet.2015.10.009
- Curran MA, Fox BA, Redmond WL. Editorial: advances in combination tumor immunotherapy. *Front Oncol*. 2015;5:198. doi:10.3389/fonc.2015.00198
- Tan Y, Chen H, Gou X, Fan Q, Chen J. Tumor vaccines: toward multidimensional anti-tumor therapies. *Hum Vaccin Immunother*. 2023;19(3):2271334.
- Huang J, Li M, Mei B, et al. Whole-cell tumor vaccines desialylated to uncover tumor antigenic Gal/GalNAc epitopes elicit anti-tumor immunity. *J Transl Med*. 2022;20(1):496. doi:10.1186/s12967-022-03714-y
- Ozgen Kiratli P, Volkan-Salanci B. Current approach to pediatric differentiated thyroid cancer. *Q J Nucl Med Mol Imaging*. 2024;68:1. doi:10.23736/S1824-4785.24.03551-9
- Edo GI, Nwachukwu SC, Makia RS, et al. Unveiling the Chinese or red date (*Ziziphus jujuba*); its phytochemical, botanical, industrial and pharmacological properties: a review. *Phytochem Rev*. 2024;1–34.
- Umar H, Aliyu MR, Usman AG, Ghali UM, Abba SI, Ozsahin DU. Prediction of cell migration potential on human breast cancer cells treated with *Albizia lebbek* ethanolic extract using extreme machine learning. *Sci Rep*. 2023;13(1):22242. doi:10.1038/s41598-023-49363-z
- Wang ZR. Review on experimental studies on Yin-yang theory of traditional Chinese medicine. *Zhonghua Yi Shi Za Zhi*. 2005;35(1):22–24.
- Patrick H. Traditional Chinese medicine and public health: the Yin and the Yang. *J R Soc Med*. 1995;88(9):485–486.
- Fu R, Li J, Yu H, Zhang Y, Xu Z, Martin C. The Yin and Yang of traditional Chinese and Western medicine. *Med Res Rev*. 2021;41(6):3182–3200. doi:10.1002/med.21793
- Xie J, Huang H, Li X, et al. The role of traditional Chinese medicine in cancer immunotherapy: current status and future directions. *Am J Chin Med*. 2023;51(7):1627–1651. doi:10.1142/S0192415X2350074X
- Feng X, Li Z, Guo W, Hu Y. The effects of traditional Chinese medicine and dietary compounds on digestive cancer immunotherapy and gut microbiota modulation: a review. *Front Immunol*. 2023;14:1087755. doi:10.3389/fimmu.2023.1087755
- Zhou Y, Zuo P, Zhang S, Luo B. Immunotherapy combined with Bianzheng traditional Chinese medicine for advanced lung cancer: a preliminary experience. *Asian J Surg*. 2023;46(12):5807–5808. doi:10.1016/j.asjsur.2023.08.148
- Xu W, Towers AD, Li P, Collet JP. Traditional Chinese medicine in cancer care: perspectives and experiences of patients and professionals in China. *Eur J Cancer Care*. 2006;15(4):397–403. doi:10.1111/j.1365-2354.2006.00685.x
- Liu L, Wei Y, Teng Y, Yan J, Li F, Chen Y. Health-related quality of life and utility scores of lung cancer patients treated with traditional Chinese medicine in China. *Patient Prefer Adherence*. 2022;16:297–306. doi:10.2147/PPA.S344622
- Wu Z, Zhu Q, Zhang Y, et al. EGFR-associated pathways involved in traditional Chinese medicine (TCM)-1-induced cell growth inhibition, autophagy and apoptosis in prostate cancer. *Mol Med Rep*. 2018;17(6):7875–7885. doi:10.3892/mmr.2018.8818
- Hsu YL, Kuo PL, Tzeng TF, et al. Huang-lian-jie-du-tang, a traditional Chinese medicine prescription, induces cell-cycle arrest and apoptosis in human liver cancer cells in vitro and in vivo. *J Gastroenterol Hepatol*. 2008;23(7 Pt 2):e290–9. doi:10.1111/j.1440-1746.2008.05390.x
- Gao X, Wang Y, Li Y, et al. Hupanpian, a traditional Chinese medicine, inhibits liver cancer growth in vitro and in vivo by inducing autophagy and cell cycle arrest. *Biomed Pharmacother*. 2019;120:109469. doi:10.1016/j.biopha.2019.109469
- Zhang J, Gao J, Cui J, et al. Tumor-associated macrophages in tumor progression and the role of traditional Chinese medicine in regulating TAMs to enhance antitumor effects. *Front Immunol*. 2022;13:1026898. doi:10.3389/fimmu.2022.1026898
- Zhang K, Peng Y, Wang Q, et al. Crosstalk between lung cancer cells and macrophages contributes to traditional Chinese medicine feiyanning-induced anti-tumor activities by suppressing M2 macrophage polarization. *Acta Biochim Biophys Sin*. 2023;55(10):1681–1684. doi:10.3724/abbs.2023221
- Yang C, Li D, Ko CN, Wang K, Wang H. Active ingredients of traditional Chinese medicine for enhancing the effect of tumor immunotherapy. *Front Immunol*. 2023;14:1133050. doi:10.3389/fimmu.2023.1133050
- He J, Yin P, Xu K. Effect and molecular mechanisms of traditional Chinese medicine on tumor targeting tumor-associated macrophages. *Drug Des Devel Ther*. 2020;14:907–919. doi:10.2147/DDDT.S223646
- Wang YP, Fu XQ, Yin CL, et al. A traditional Chinese medicine formula inhibits tumor growth in mice and regulates the miR-34b/c-Met/beta-catenin pathway. *J Ethnopharmacol*. 2020;260:113065. doi:10.1016/j.jep.2020.113065
- Marin-Aguilera M, Jares P, Sanfeliu E, et al. Analytical validation of HER2DX genomic test for early-stage HER2-positive breast cancer. *ESMO Open*. 2024;9(3):102903. doi:10.1016/j.esmoop.2024.102903
- Chen S, Navickas A, Goodarzi H. Translational adaptation in breast cancer metastasis and emerging therapeutic opportunities. *Trends Pharmacol Sci*. 2024;45:304–318. doi:10.1016/j.tips.2024.02.002
- Song F, Tarantino P, Garrido-Castro A, Lynce F, Tolane SM, Schlam I. Immunotherapy for early-stage triple negative breast cancer: is earlier better? *Curr Oncol Rep*. 2024;26(1):21–33. doi:10.1007/s11912-023-01487-1
- Bezerra de Mello RA, Perez KR, Vazquez TP. Current and future trends in neoadjuvant immunotherapy for the treatment of triple-negative breast cancer. *Immunotherapy*. 2024;16(4):257–266. doi:10.2217/imt-2022-0277
- Yang Y, Zhu Y, Liu C, Cheng J, He F. Taohong Siwu decoction reduces acute myocardial ischemia-reperfusion injury by promoting autophagy to inhibit pyroptosis. *J Ethnopharmacol*. 2024;321:117515. doi:10.1016/j.jep.2023.117515
- Fengjin C, Peng Z, Guoying LI, et al. Taohong Siwu decoction ameliorates atherosclerosis in rats possibly through toll-like receptor 4/myeloid differentiation primary response protein 88/nuclear factor-kappaB signal pathway. *J Tradit Chin Med*. 2024;44(1):103–112. doi:10.19852/j.cnki.jtcm.20231215.003

31. Jiang H, Li M, Du K, et al. Traditional Chinese Medicine for adjuvant treatment of breast cancer: taohong siwu decoction. *Chin Med*. 2021;16(1):129. doi:10.1186/s13020-021-00539-7
32. Yu Q, Xu C, Song J, Jin Y, Gao X. Mechanisms of traditional Chinese medicine/natural medicine in HR-positive breast cancer: a comprehensive literature review. *J Ethnopharmacol*. 2024;319(Pt 3):117322. doi:10.1016/j.jep.2023.117322
33. Yang Z, Zhang Q, Yu L, Zhu J, Cao Y, Gao X. The signaling pathways and targets of traditional Chinese medicine and natural medicine in triple-negative breast cancer. *J Ethnopharmacol*. 2021;264:113249.
34. Liu YT, Hsiao CH, Tzang BS, Hsu TC. In vitro and in vivo effects of traditional Chinese medicine formula T33 in human breast cancer cells. *BMC Complement Altern Med*. 2019;19(1):211. doi:10.1186/s12906-019-2630-5
35. Yun KM, Cohen EW. An era of advances in systemic therapies for advanced thyroid cancer. *JCO Oncol Pract*. 2024;OP2300747.
36. Kong H, Chen J, Tang SC. Synchronous papillary thyroid carcinoma and breast ductal carcinoma. *J Int Med Res*. 2020;48(8):300060520948710. doi:10.1177/0300060520948710
37. Feng JW, Qu Z, Qin AC, Pan H, Ye J, Jiang Y. Significance of multifocality in papillary thyroid carcinoma. *Eur J Surg Oncol*. 2020;46(10 Pt A):1820–1828. doi:10.1016/j.ejso.2020.06.015
38. Zhao L, Zhang X, Cui S. Matrine inhibits TPC-1 human thyroid cancer cells via the miR-21/PTEN/Akt pathway. *Oncol Lett*. 2018;16(3):2965–2970. doi:10.3892/ol.2018.9006
39. Wang K, Qian R, Li H, Wang C, Ding Y, Gao Z. Interpreting the pharmacological mechanisms of sho-saiko-to on thyroid carcinoma through combining network pharmacology and experimental evaluation. *ACS Omega*. 2022;7(13):11166–11176. doi:10.1021/acsomega.1c07335
40. Liu Z, Zhong L, Wang L, Li M, Chen C. Integrating network pharmacology and experimental studies for uncovering the molecular mechanisms of *Dioscorea bulbifera* L. in the treatment of thyroid cancer. *Heliyon*. 2023;9(8):e18886. doi:10.1016/j.heliyon.2023.e18886
41. Kazantseva L, Becerra J, Santos-Ruiz L. traditional medicinal plants as a source of inspiration for osteosarcoma therapy. *Molecules*. 2022;27:15. doi:10.3390/molecules27155008
42. Liu Y, Jiang B, Li Y, et al. Effect of traditional Chinese medicine in osteosarcoma: cross-interference of signaling pathways and potential therapeutic targets. *Medicine*. 2024;103(3):e36467. doi:10.1097/MD.00000000000036467
43. Wan X, Tou F, Zeng J, et al. Integrative analysis and identification of key elements and pathways regulated by traditional Chinese medicine (Yiqi Sanjie formula) in colorectal cancer. *Front Pharmacol*. 2022;13:1090599. doi:10.3389/fphar.2022.1090599
44. Mao Q, Min J, Zeng R, et al. Self-assembled traditional Chinese nanomedicine modulating tumor immunosuppressive microenvironment for colorectal cancer immunotherapy. *Theranostics*. 2022;12(14):6088–6105. doi:10.7150/thno.72509
45. Lin X, Yang X, Yang Y, Zhang H, Huang X. Research progress of traditional Chinese medicine as sensitizer in reversing chemoresistance of colorectal cancer. *Front Oncol*. 2023;13:1132141. doi:10.3389/fonc.2023.1132141
46. Chen JF, Wu SW, Shi ZM, Hu B. Traditional Chinese medicine for colorectal cancer treatment: potential targets and mechanisms of action. *Chin Med*. 2023;18(1):14. doi:10.1186/s13020-023-00719-7
47. Zou Y, Wang S, Zhang H, et al. The triangular relationship between traditional Chinese medicines, intestinal flora, and colorectal cancer. *Med Res Rev*. 2024;44(2):539–567. doi:10.1002/med.21989
48. Liao X, Bu Y, Jia Q. Traditional Chinese medicine as supportive care for the management of liver cancer: past, present, and future. *Genes Dis*. 2020;7(3):370–379. doi:10.1016/j.gendis.2019.10.016
49. Liu C, Yang S, Wang K, et al. Alkaloids from traditional Chinese medicine against hepatocellular carcinoma. *Biomed Pharmacother*. 2019;120:109543. doi:10.1016/j.biopha.2019.109543
50. Wang Z, Zhang Y, Zhang Q, et al. On the core prescriptions and their mechanisms of traditional Chinese medicine in hepatitis b, liver cirrhosis, and liver cancer treatment. *J Oncol*. 2022;2022:5300523. doi:10.1155/2022/5300523
51. Peng Y, Wu X, Zhang Y, et al. An overview of traditional Chinese medicine in the treatment after radical resection of hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2023;10:2305–2321. doi:10.2147/JHC.S413996
52. Li H. Advances in anti hepatic fibrotic therapy with traditional Chinese medicine herbal formula. *J Ethnopharmacol*. 2020;251:112442. doi:10.1016/j.jep.2019.112442
53. Yao M, Liang S, Cheng B. Role of exosomes in hepatocellular carcinoma and the regulation of traditional Chinese medicine. *Front Pharmacol*. 2023;14:1110922. doi:10.3389/fphar.2023.1110922
54. Zhao T, Mao L, Yu Z, et al. Therapeutic potential of bicyclol in liver diseases: lessons from a synthetic drug based on herbal derivative in traditional Chinese medicine. *Int Immunopharmacol*. 2021;91:107308. doi:10.1016/j.intimp.2020.107308
55. Abbasi M, Sohail M, Minhas MU, et al. Folic acid-decorated alginate nanoparticles loaded hydrogel for the oral delivery of diferourylmethane in colorectal cancer. *Int J Biol Macromol*. 2023;233:123585. doi:10.1016/j.ijbiomac.2023.123585

Cancer Management and Research

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>

Dovepress
Taylor & Francis Group