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REVIEW

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Tailoring traditional Chinese medicine in cancer therapy

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Abstract

Cancer remains a formidable global health challenge, necessitating innovative therapeutic approaches to enhance treatment efficacy and reduce adverse effects. The traditional Chinese medicine (TCM), as an embodiment of ancient wisdom, has been validated to regulate the holistic human capacity against both internal and external "evils" in accordance with TCM principles. Therefore, it stands to reason to integrate TCM into current cancer therapy paradigms, such as chemotherapy, immunotherapy, and targeted therapy. This strategy conceptually intends to circumvent the inevitable side effects derived from present treatment, alleviate the discomfort, mollify the detrimental mood and synergize tumoricidal effects of distinct approaches. However, it is still vague whether TCM exert favorable function in cancer treatment. Therefore, it is imperative to retrieve and compile the existing literature on TCM in the realm of cancer, followed by a comprehensive recapitulation and synthesis of its core findings. Recently, with the advancement of contemporary biologic and medical theory and technology, it has become both feasible and imperative to elucidate the molecular signaling mechanisms and cellular biology underlying TCM. Specifically, leveraging TCM pharmaceutic components can not only directly impact tumor biology at the molecular level, but regulate the tumor immune environment through distinct pathways. Additionally, the administration of external TCM treatments such as acupuncture and moxibustion also demonstrates beneficial effects in cancer patients. Through comprehensive analysis, we demonstrated that TCM not only potentially increases the efficacy of conventional cancer treatments, but also significantly mitigates their toxic side effects, thereby prolonging patients' prognosis and improving their living quality. Furthermore, we have underscored the challenges and prospects associated with the integration of TCM into contemporary oncological practices, placing particular emphasis on the imperative for rigorous clinical trials and molecular investigations to substantiate the efficacy and safety of these combined therapeutic approaches. This synthesis aims to pave the way for a more integrated approach to cancer treatment rooted in both traditional wisdom and cutting-edge science.

Keywords Traditional Chinese medicine, Cancer, Herb, Acupuncture, Chemotherapy, Immunotherapy

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Introduction

Cancers are a broad range of diseases caused by uncontrolled cell growth and are characterized by the rapid emergence of aberrant cells that spread to other organs, infiltrate nearby tissues, and develop beyond their normal bounds. Invasion and metastasis are the primary reasons to instigate patients to succumb to cancers [1]. Approximately 20 million new cases of cancer and 9.7 million deaths from the disease were reported in 2022. The morbidity of cancer is predicted to reach 35 million by 2050 [2]. The limitation of conventional regimen, such as surgery, radiotherapy, and chemotherapy has been demonstrated as the high mortality rate of cancer. It is necessary to develop a practical and viable prevention countermeasure established in the foundation of screening and early diagnosis. In addition, the establishment and development of novel therapeutic strategies with new medicine and commitment to new targets are effective approaches to mitigate the threat of cancer. However, novel therapeutic strategies such as immunotherapy, targeted therapy, and gene treatment not only entail respectively inherent risks, including severe treatment-related adverse effects [3, 4], long-term carcinogenic effect [5], and medical ethical concerns [6, 7], but also impose a significant financial burden. Furthermore, demographic and geographic variations influence the accessibility and generalization of feasible cancer treatment agents and the propagation of novel oncologic guidelines, thereby producing considerable disparities in cancer quality and treatment capacity, including the availability of necessary services like surgery, chemotherapy, radiotherapy, and rehabilitation [8]. Studies have revealed that impoverished areas have a far greater percentage of premature cancer fatalities [9]. Consequently, affordable and effective medications have become an urgent need for society as a whole. Moreover, some cancer therapies, like radiation and targeted therapy, usually come with many side effects and can be too expensive to all patients, therefore more cost-effective treatments are urgently needed. Traditional Chinese medicine (TCM) plays a pivotal role in cancer treatment in China, owing to its well-documented efficacy rooted in ancient Chinese medical philosophy, cost-effectiveness, and widespread accessibility [10]. It has been reported to reduce the adverse effects caused by conventional regimen and increase the prognosis of patients with several cancers [11]. Numerous studies have indicated that the combination of TCM with other drugs or chemotherapy can enhance the survival rates of cancer patients, improve their quality of life, and stop the growth and spread of cancerous cells, such as hepatocellular carcinoma, cancer patients with comorbid depressive symptoms, and lung cancer [12–14]. TCM's anti-tumor treatment strategies include immune system control, stimulation of tumor cell death, prevention of tumor angiogenesis, and direct inhibition of tumor cell proliferation [15]. For example, artesunate therapy leads to mitochondrial malfunction in SW480 and HCT116 colorectal cancer (CRC) cells. This produces a significant increase in mitochondrial ROS generation, which in turn suppresses cell proliferation by triggering cell cycle arrest during the period known as G0/G1 and subsequent p16- and p21-mediated cell senescence [16]. According to earlier research, TCM was important for tumor immunotherapy, especially when it comes to controlling natural killer cells, dendritic cells, $CD8/CD4^+$ T cells, interleukin-2 (IL-2), M2 macrophages, IFN-γ, and tumor necrosis factor-α [15]. Ginsenoside Rh2 (G-Rh2), a monomeric compound extracted from ginseng, has been demonstrated to possess anti-tumor properties in lung cancer cells. G-Rh2 has demonstrated efficacy in reducing M2 macrophage markers, such as CD206 and VEGF in vivo, potentially changing the phenotype of tumor-associated macrophages (TAMs) from pro-tumor M2 to pro-inflammatory M1. This shift could impede lung cancer cell migration, indicating G-Rh2's therapeutic potential in lung cancer [17].

For thousands of years, TCM has been practiced in China, where it has developed into an extensive theoretical framework. It is used as a complementary and alternative medicine in the world. In terms of methodology, TCM is usually divided into internal treatment and external treatment. The internal treatment generally refers to the administration of Chinese herbal medicine, while the external treatment primarily encompasses non-pharmaceutical interventions such as acupuncture, massage, moxibustion, and other acupoint applications. This review focuses on the role of Chinese herbal medicine in oncology, alongside discussing the application of acupuncture, moxibustion, and massage as commonly employed external treatments within TCM.

Basic principles and mechanisms of TCM in cancer treatment

The main etiology of diseases in TCM lies in the imbalance between Yin and Yang, and the objective of TCM treatment is to restore the equilibrium of Yin and Yang. Cancer was first referred to as liu, tumor, and mass in TCM and was later fully elaborated in the Yellow Emperor's Inner Classic [18]. The occurrence of cancer is mainly due to the imbalance of Yin and Yang, Zhengqi deficiency, and Xieqi excess. The treatment principle, therefore, lies in the Fuzheng (harmonization) and Quxie (elimination of pathogenic factors), as well as the supplementation and facilitation of Yin-Yang rebalance (Table 1).

Zhengqi, also known as healthy qi, describes the actions of the body's regular function, such as the preservation

Table 1 The prevalent prescription and active ingredients of TCM, their application in various types of cancers, the underlying corresponding TCM-related theories, and the modern medical function

Compound/ single TCM/ extract	Cancer	Origin	TCM	Function	
Berberine	gastric cancer	coptis chinensis and berberis	QUXIE	inhibiting the proliferation of MKN-45 and HGC-27 cells, G0/G1 cell arrest	[19]
Andrographolide	colorectal cancer	Andrographis paniculata	QUXIE	reversing 5-FU resistance by elevating BAX expression	[20]
Triptolide	liver cancer	*Tripterygium wilfordii Hook. F*	QUXIE	activate the AKT pathway, G0/G1 cell arrest	[21]
Saikosaponin A	breast cancer	Radix Bupleuri	QUXIE	shifting Th1/Th2 balance toward Th1, upregulating the expression of IL-12 and IL-12 receptor	[22]
Baicalein	Lewis lung carcinoma	Scutellaria baicalensis Georgi (Scutellariae radix)	QUXIE	activation of AMPK pathway	[23]
(6)-Gingerol	colon cancer	*Zingiber officinale* Roscoe	QUXIE and FUZHENG	inhibiting MAPK/AP-1 signaling pathway	[24]
Astragaloside III	Not referred	*Astragalus mongholicus Bunge*	FUZHENG	inhibiting HIF-1α/PDHK-1 pathway	[25]
Zuojin Pill	pancreatic cancer	Huanglian and Wuzhuyu	QUXIE and FUZHENG	inhibiting PI3K/AKT/caspase pathway	[26]
Xiaochaihutang	colorectal cancer	Chaihu, Huangqin, and Renshen, etc	QUXIE and FUZHENG	downregulating TLR4/MyD88/NF-κB signaling	[13]
Wei-Tong-Xin	colorectal cancer	Dahuang, Muxiang, and Gancao, etc	QUXIE	inhibiting PI3K/AKT signaling pathway	[27]
Xiao-Ai-Ping injection	esophageal cancer	Marsdenia tenacissima	QUXIE	inhibiting ERK activation	[28]
Kangai injection	gastric cancer	astragalus, ginseng, and kurorinone	QUXIE	inhibiting IL-6/STAT3 Pathway	[29]

of the body's physiological function and the various abilities developed to preserve health. When the healthy qi is insufficient, the body will be too weak to resist evil, external evil will enter the void, and people will get sick, or the ability to regulate the functional activities of the viscera will decline, and it is easy to cause visceral function disorders and illness. Fuzheng is therefore a crucial component of disease treatment, it refers to promoting and maintaining the body's healthy qi so that it is adequate to eradicate harmful elements and restore health. It can be understood as enhancing immunity in tumor treatment.

Xieqi, also known as pathogenic qi, includes all kinds of disease-causing factors that exist in the outside world or are produced by the human body. When pathogenic qi invades the human body, it leads to physiological dysfunction, damage to the viscera, and a change in the individual's physical characteristics, which ultimately leads to illness. Quxie refers to the treatment principle of removing pathogenic factors to restore healthy qi and health, similar to killing tumor cells.

Direct role of Chinese medicine in tumors

The basic methods of treating tumors in Chinese medicine involve boosting immunity, preventing the growth of tumor cells directly, and repairing the body's natural Yin and Yang balance. Chinese medicines usually have a variety of components that function in multiple ways and targets (Fig. 1).

Cellular senescence marks a permanent state of growth arrest, in which cells enter an endless period of dormancy, losing the ability to divide further. Senescent cells have diverse properties, and they are biologically functional to fight the development of tumors and may contribute to tumor progression [30]. In the anti-tumor treatment, cellular senescence cannot be bypassed. TCM affects the development of malignant tumors in various ways, acting at different stages of the tumor, including promoting apoptosis, inhibiting angiogenesis, modulating oncogenes, inducing cycle blockade, promoting senescence, and interacting with multiple pathways [31]. Due to the wide range of anti-tumor effects of TCM with few side effects, the impact of TCM on cell senescence has also attracted attention. Many studies have found that the active components of traditional Chinese medicine can selectively eliminate senescent cells to play an anti-tumor role [32].

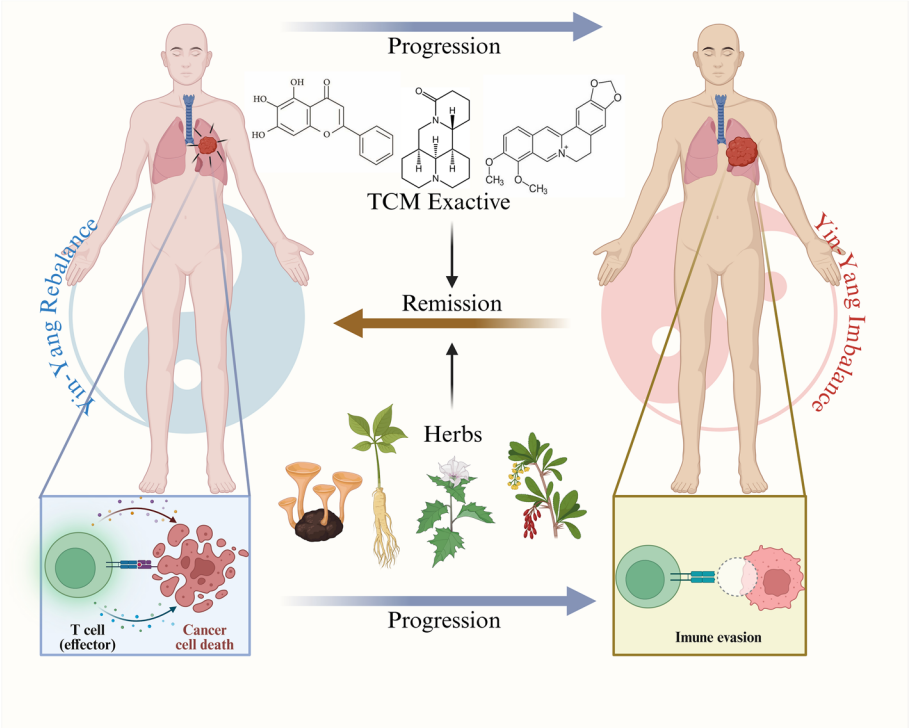

Fig. 1 Conceptual model of traditional chinese medicine (TCM) in cancer therapy. It's well established in traditional Chinese iatrology theories that cancer initiation and progression result from an imbalance of holistic and local Yin-Yang. Traditional Chinese Medicine (TCM) aims to rebalance individual holistic Yin and Yang, strengthen body resistance, eliminate pathogens, and activate T cells in the tumor microenvironment (TME), leading to targeted destruction of cancer cells and ultimately disease remission. The TME is primarily composed of various herbs and their extracts that invigorate immune responses, modulate bodily harmony, and restore balance

Alkaloids

Alkaloids are a class of nitrogen-containing organic compounds characterized by their cyclic structures and basic nitrogen constituents. Ubiquitously present across the natural world, they manifest as inherent secondary metabolites within the flora and fauna kingdoms [33]. Alkaloids are present in higher plants, including those in the Papaveraceae, Ranunculaceae, Menispermaceae, Loganiaceae, Amaryllidaceae, and Solanaceae families, even though they are mostly produced from amino acids [34].

Berberine, a bioactive isoquinoline alkaloid derived from traditional Chinese medicinal plants such as Coptis chinensis and various species of Berberis, exhibits a spectrum of therapeutic effects. It has been used to treat many illnesses, including cancer, as well as disorders of the digestive tract and metabolic, cardiovascular, and nervous systems. Berberine is most commonly used for the treatment of digestive disorders. It can protect the intestinal epithelial barrier from harm, reduce liver damage, and prevent toxins and bacteria [35]. Berberine has made significant progress in tumor therapy in recent years, particularly in the treatment of gastric cancer. Its method involves blocking the migration and invasion of gastric cancer cells, causing apoptosis and G0/G1 cell arrest, and impeding the proliferation of MKN-45 and HGC-27 cells in vitro [19].

Terpenoids

Terpenoids, also known as isoprenoids, constitute a vast group of natural compounds built from isoprene units, and play essential roles in the metabolic processes of every living organism. The diversity of terpenoid chemistry is particularly pronounced in plants, and many of these compounds are classified as secondary metabolites [36]. Andrographolide, a naturally occurring diterpenoid derived from Andrographis paniculata, possesses a range of beneficial properties including antibacterial, antiviral, and anti-inflammatory effects. Researchers have found that andrographolide can specifically bind to the BAX protein, inhibit its breakdown, and subsequently boost mitochondrion-driven apoptosis. This process is instrumental in countering the resistance to the chemotherapy drug 5-fluorouracil (5-FU) [20].

Triptolide (TPL), an abietane-type diterpenoid taken from the traditional Chinese herb (*Tripterygium wilfordii Hook. F.*) has a significant pharmacological activity for anti-tumor therapy [37]. TPL has been proposed by researchers to control the p53/p21 pathway, which might prevent HepG2 cell division, hasten cellular senescence and death, and stop cells in the G0/G1 phase. In addition, it has the ability to increase the levels of phosphorylated AKT and initiate the AKT pathway, which helps hasten the senescence of HepG2 cells and limit tumor development [21]. Radix Bupleuri's primary triterpenoid saponin component, saikosaponin A (SSA), has a range of pharmacological properties, including anti-inflammatory, anticancer, antioxidant, and hepatoprotective effects [38, 39]. In an animal experiment, by tipping the Th1/Th2 balance in favor of Th1, Zhao et al. discovered that SSA could stop the progression of breast cancer. The mechanism of action of SSA involves increased phosphorylation of STAT4 and overexpression of IL-12 and IL-12 receptor expression, both of which drive Th1 cell differentiation [22]. Moreover, SSA demonstrated the ability to stop Triple-Negative Breast Cancer cells from migrating and invading both in vitro and in vivo. The process by which SSA deactivated the Akt/mTOR signaling pathway, suppressed the expression of MMP-9 and MMP-2, and inhibited the expression of CXCR4 but not CXCR7 [40].

Flavonoids

A class of naturally occurring compounds called flavonoids is present in many different types of plants and has varied phenolic structures. It is frequently employed in the promotion of health and treatment of disease because of its antioxidant, anti-mutagenic, anti-inflammatory, and anti-carcinogenic qualities [41]. Baicalein, a principal flavonoid component, was discovered in the roots of Scutellaria baicalensis Georgi (Scutellariae radix), known in traditional Chinese medicine as Huangqin [42]. There is much evidence that baicalein has anti-cancer properties. When Deng et al. investigated the connection between mitochondrial fission and BA-induced apoptosis and autophagy, they found that in a Lewis lung carcinoma xenograft model, baicalein activated the AMPK/mitochondrial fission pathway, inhibiting tumor growth and inducing apoptosis and autophagy [23]. Moreover, baicalein reduces liver tissue damage and vacuolization by reducing the suppression of the AMPK/SIRT1/pGC-1α pathway brought on by CPF exposure [43].

Phenolics

Phenolic compounds are secondary metabolites that originate from plant shikimic acid and pentose phosphate through phenylpropanoid metabolism [44]. These compounds are prevalent in plants, are potentially significant components of the human diet, and have been demonstrated to be highly potent anti-oxidants, anti-genotoxic, and cytostatic activities in vitro [45, 46]. Ginger (*Zingiber officinale* Roscoe), a plant that contains phenols, has been used in a variety of fields. It is not only a popular food and spice, but is also used as a dietary supplement and flavor enhancer. Its widespread use in traditional medicine is attributed to its unique pungent flavor, aromatic properties, nutritional value, and pharmacological benefits [47]. Numerous studies have shown that ginger and ginger extracts have various effects, such as diabetes, metabolic syndrome, obesity, cancer, and inflammation [48]. (6)-Gingerol, a bioactive component derived from ginger, has been found to exhibit cytotoxic effects that are contingent upon the dosage administered. Specifically, it targets and damages colon cancer cells without adversely affecting the surrounding healthy intestinal epithelial cells. This selectivity is attributed to its ability to induce apoptosis in colon cancer cells, without affecting the viability of normal cells. Furthermore, in SW-480 colon cancer cells, (6)-gingerol inhibits the activation of MAPK, which is triggered by phorbol 12-myristate 13-acetate (PMA). To be more precise, (6)-gingerol suppresses PMA-induced activator protein-1 (AP-1) transcriptional binding activity while not affecting NF-κB. It is essential to inhibit AP-1 binding activity since it helps to prevent PMA-induced cell growth in SW-480 cells. The underlying mechanism involves the blockade of the c-Jun N-terminal kinase pathways and extracellular signal-regulated kinase 1/2, which are integral components of the MAPK signaling cascade. Collectively, this selective toxicity suggests that gingerol could potentially be utilized in targeted cancer therapies, offering a promising avenue for research into treatments that minimize harm to non-cancerous tissues [24].

Herbal preparations

Chinese herbal medicine refers to natural materials, such as plants, animals, and minerals that are used for the prevention, treatment, and diagnosis of diseases under the guidance of traditional Chinese medical theories. It has a long history and rich practical experience and is a precious cultural heritage of the Chinese nation. Zuojin Pill, a time-honored remedy in the annals of TCM, has been a staple for treating symptoms related to stomach disorders according to TCM principles by clearing liver fires and relieving pain in the stomach [49]. According to PPI analysis, Zuojin Pill (ZJP) demonstrated its anti-pancreatic cancer activity through a multifaceted approach, targeting key molecular nodes such as JUN, TP53, and MAPK1. The effects of this compound are orchestrated via several signaling pathways, with the PI3K/AKT pathway being particularly prominent owing to its high gene

enrichment. PI3K/AKT signaling is a common biochemical mechanism that promotes tumor growth and metastasis. PTEN gene is often activated in tumor cells due to PTEN deficiency, which leads to increased tumor cell viability and may cause tumor cells to acquire resistance to treatment [50]. It functions via a critical route that causes pancreatic cancer cells to undergo apoptosis in addition to suppressing cell cycle progression and proliferation. Additionally, KEGG analysis revealed that the effects of ZJP extended to other pathways, including the IL-17, HIF-1, TNF, and P53 signaling pathways, which collectively contribute to its comprehensive anti-cancer mechanism. The in vitro findings align with network pharmacological predictions, confirming the efficacy of ZJP in modulating these pathways to combat pancreatic cancer [26]. Xiaochaihutang (XCHT) inhibits tumor growth and extends patient survival time, with its antitumor effects primarily facilitated by the modulation of the gut microbiota, which plays a significant role in the therapeutic effects of XCHT. The mechanism is mainly through the downregulation of the TLR4/MyD88/NF-κB signaling pathway, a key mediator of immune responses and inflammation. As demonstrated in a clinical study by Shao et al., it was observed that XCHT could partially reverse the gut dysbiosis associated with cancer. This was particularly evident in the reduction of certain bacterial populations, such as Ruminococcaceae, Blautia, and Parabacteroides, which are often disrupted in cancer patients [13]. The restoration of a healthier gut microbiota balance through XCHT may contribute to its antitumor effects by regulating the immune response and potentially enhancing the body's ability to combat cancer cells. Drawing from the ancient Chinese herbal formula Wan-Ying-Yuan, Wei-Tong-Xin (WTX) has shown efficacy as a medicinal decoction for the treatment of various gastrointestinal disorders [51]. It is a compound herbal preparation consisting of five distinct medicinal herbs. Using a network pharmacological approach and in vitro tests, Lin et al. discovered that WTX contributes to cell cycle arrest in the G2/M phase, increases oxidative stress, and promotes apoptosis. Their research postulated and then verified that the primary method by which WTX impacted colorectal cancer cells was the control of the intrinsic apoptotic pathway through the PI3K/AKT signaling pathway. Further, in vivo investigations on animals provided additional evidence of WTX's potent anti-colon cancer properties [27] (Fig. 2).

Others

TCM extracts are a special way to extract active ingredients from Chinese herbs and are used to treat various diseases. Injections of Xiao-Ai-Ping, an extract from *Marsdenia tenacissima*, are frequently used to cure cancer. Xiao Aiping injection modifies the cell cycle, MAPK signaling pathway, and regulatory proteins to prevent the growth of human esophageal cancer cells. This effect

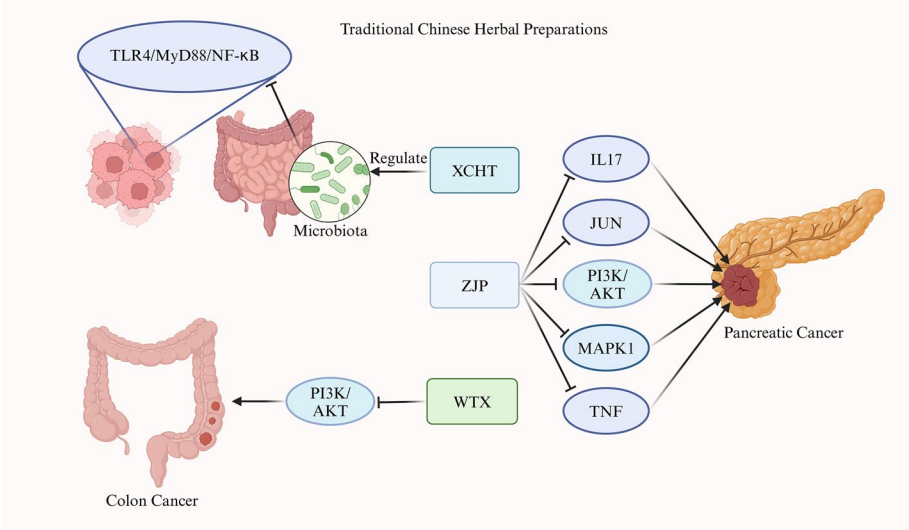

Fig. 2 Impact of traditional Chinese herbal preparations on cancer pathways. This diagram illustrates the molecular mechanisms through which different TCM formulations—Xiaochaihutang (XCHT), Zuojin Pill (ZJP), and Wei-Tong-Xin (WTX)—modulate signaling pathways in cancer therapy. XCHT is shown to regulate the microbiota, influencing the TLR4/MyD88/NF-κB pathway, which is critical in immune response modulation in colon cancer. ZJP targets multiple signaling molecules including IL17, JUN, PI3K/AKT, MAPK1, and TNF, intersecting at various nodes to suppress tumor growth and proliferation in pancreatic cancer. WTX directly affects the PI3K/AKT pathway in colon cancer, highlighting its role in cellular processes such as growth and survival. The interplay of these herbal preparations illustrates a complex network of biochemical modulation that supports their use in complementary cancer therapy

may be mediated by the reduction of ERK activation [28]. Kangai injection (KAI) is a TCM mixture prepared using modern technology with *Astragalus*, ginseng, and kurorinone as the main extracts and has been widely used in the treatment of lung cancer [52], gastric cancer [53], and liver cancer [54]. In vitro tests were done by Zhang et al. to study the mechanism by which KAI reduces the proliferation of gastric cancer cells. The results showed that KAI decreased the growth of BGC823 and MGC803 cells depending on dosage and time. Human gastric cancer cells treated with KAI for 48 h showed a significant decrease in STAT3 phosphorylation, suppression of IL-6 mRNA and protein production, and activation of G1 phase arrest, all of which had an anti-proliferative impact [29]. Moreover, in an in vivo animal study, Astragaloside IV, an extract of *Astragalus*, inhibited CRC metastasis by down-regulating the expression of nSMase2 and Rab27a to inhibit the production and secretion of tumor-derived extracellular vesicles (TEVs) and the activation of M2-type TAMs in CRC cells [55]. *Astragalus*, as one of the effective components of KAI, has been confirmed to have anti-tumor effects [56, 57], which also provides strong evidence for the application of KAI.

Although Chinese medicinal preparations have been proven effective in treating diseases, the specific components that work have not yet been effectively identified, which is a direction we need to continue exploring and conducting in-depth research in the future.

Combination of herbal medicines with chemotherapy

Although the listing of various anti-tumor drugs, such as targeted drugs, has brought new choices for tumor patients, post-surgery chemotherapy still has an irreplaceable position. Chemotherapy, a widely used method for cancer treatment, focuses on employing specific chemical agents to inhibit the growth and division of cancer cells, thereby aiming to control and treat malignancy. These chemical drugs operate through various mechanisms: some can cause DNA to act as a danger signal, are released from tumor cells after chemotherapy, and play a role in boosting anti-cancer immunity. These chemical agents release and extricate the episomal DNA by destroying the tumor cells and facilitating chromosome fragmentation, resulting in its recognition by antigen-presenting cells through the GAMP-cGAS-STING-IFN pathway, akin to the process of tumor-associated antigen identification [58]. However, the efficiency of specific chemotherapy is usually unsatisfactory due to the inevitable resistance of the tumor, especially in the advanced stages of cancer. Concomitantly, dose escalation can overcome this limitation. However, it aggravates systemic dose-associated side effects. Researchers generally agree that increasing the dose of chemotherapy drugs or adding other chemotherapy drugs to achieve better treatment results in a higher cumulative dose and overall burden as well as a higher toxicity burden [59]. However, chemotherapeutic drugs, while achieving a certain degree of therapeutic efficacy, also carry the risks of high toxicity and side effects as well as heavy adverse reactions. In the face of these disadvantages, TCM can play a complementary role, improving the efficacy of chemotherapy, reducing its toxic side effects, and improving safety [11].

Enhance the efficacy of chemotherapy

The efficacy of chemotherapy is affected by many factors such as tumor stage [60], age [61], and changes in the tumor microenvironment [62]. The combined application of TCM and chemotherapy has achieved good results in reducing the influence of other factors on the efficacy of chemotherapy. Hyperactivation of YAP1 is closely associated with tumor growth, and cisplatin has been shown to reduce its expression [63]. Studies have indicated that ginsenoside compound K, an active ingredient derived from babaodan, can inhibit the growth of cholangiocarcinoma cells (CCAs) by modulating the phosphorylation status of YAP1. This mechanism not only reveals the potential of Babaodan in suppressing tumors but also suggests that it may enhance chemotherapeutic efficacy by increasing the sensitivity of cancer cells to cisplatin [64]. Xu et al. discovered that the 5-FU plus Bu-zhong-yi-qi decoction (mBYD) group had a lower percentage of $CD8^{+}PD\text{-}1^{+}$ T cells. Additionally, this treatment mitigated suppressive T cell signals and bolstered T cell proliferation and their effector functions in gastric cancer [65]. Vincristine is extracted from the periwinkle plant and consists of two multiline units, indoline, and catarrhorethine, which have been applied to several types of cancer. Vincristine was first studied for its potential hypoglycemic effects, but its true value was not realized until its antitumor and immunosuppressive properties were confirmed in 1959. It targets tubulin during cell division, resulting in mitotic arrest and cell death [66]. Zhang et al. developed a novel co-delivery nanoparticle system, S-D1@L-D2 NP, capable of encapsulating two distinct anticancer drugs, DOX and VCR. The system featured smaller DOX-loaded nanoparticles encapsulated within larger VCR-loaded nanoparticles, creating a dual-layered structure. Tumor cell pH influences drug delivery, enhancing the therapeutic efficacy and cytotoxicity of combined treatments both in vivo and in vitro, while minimizing side effects [67].

Reduce pharmic toxic side effects

Chemotherapy-induced nausea and vomiting are the most common adverse reactions in treating cancer patients [68], and other adverse reactions include

cardiotoxicity [69], nephrotoxicity [70], hair loss [71], and skin side effects [72]. With the increasing application of Chinese medicine to tumors, the combination of Chinese medicine with chemotherapy to reduce side effects has become a routine treatment. Intestinal mucositis is a common complication of cyclophosphamide treatment and is characterized by intestinal cell deficiency, barrier dysfunction, epithelial damage, and villous atrophy. Ginsenosides have been found to improve anti-tumor immunity by maintaining gut microbiota and modulating related immune cytokines, which activate Nrf2 and inhibit the NF-κB pathway to alleviate cyclophosphamide-induced intestinal mucositis, including decreased intestinal permeability, reduced diarrhea and epithelial damage, and increased tight junction proteins, thereby reducing the adverse effects of cyclophosphamide [73]. In a randomized phase II study involving patients with stage III or high-risk stage II resected CRC, it was discovered that Huachansu (HCS), a *Bufo gargarizans* extract, combined with adjuvant chemotherapy did not enhance the OS of patients at 3 years but mitigated chemotherapy-induced diarrhea in comparison with the absence of HCS [74].

Oridonin is a diterpenoid compound derived from '*Rabdosia rubescens*' (Donglingcao). These organic materials have a range of biological properties, such as anticancer, antibacterial, and anti-inflammatory properties. Oriolinin especially has been demonstrated to dramatically reduce the growth of tumor cells, cause cell cycle arrest, and promote cell death [75]. In an in vivo tumor xenograft mouse model, it was found that the combination of Ori and doxorubicin (Dox) prevented the weight loss caused by Dox application and reversed the Dox-induced alterations in the Bcl-2 and Bax concentrations in cardiac tissue, alleviating Dox-induced cardiotoxicity [69]. As a major obstacle in the anti-tumor effect of Dox, cardiotoxicity has always been one of the difficult problems that we want to solve. In contrast to the more conventional cell death mechanisms of apoptosis, necrosis, and autophagy, ferroptosis is a new process of cell death brought on by the peroxidation of phospholipids in the cell membrane [76]. A large number of studies have shown that ferroptosis is associated with cardiovascular diseases, including Dox-induced cardiotoxicity [77]. Protosappanin A (PrA), a *Caesalpinia sappan* extract, has medicinal properties of antioxidant, anti-inflammatory, and anticancer [78]. In an in vitro and in vivo study, Cui J et al. discovered that PrA could directly bind to the ferroptosis-related proteins ACSL4 and FTH1, inhibiting ACSL4 phosphorylation, preventing FTH1 autophagic degradation, and reducing ferrous ion (Fe^{2+}) release, all of which reduced cardiomyocyte ferroptosis and ultimately improving Dox-induced cardiotoxicity [79].

Polysaccharides are important components of higher plants, membranes of animal cells, and cell walls of microbes, and play an essential role in the growth and development of organisms. This compound exhibits multiple biological functions, allowing it to be used for various medicinal applications. It enhances the immune response, inhibits the proliferation of cancer cells, fights against viral agents, counters oxidative damage [80], and helps lower blood glucose levels [81]. *Astragalus* is a widely used herbal medicine in TCM, and its extract *Astragalus* polysaccharides (APS) has attracted the attention of researchers. Pharmacologically, APS contains anti-inflammatory, anti-tumor, and immunomodulatory properties. Inducing tumor cell death, suppressing tumor cell growth, halting invasion and metastasis, increasing tumor susceptibility to anticancer medications, and controlling the immune system are the key ways in which it has an anti-tumor effect [82]. In the experiment of adriamycin-resistant gastric cancer cells, it was discovered that APS could enhance the proapoptotic effect of adriamycin on gastric cancer cells and exert its role by regulating the expression of the tumor suppressor gene and the multidrug resistance gene. This indicates that APS might be utilized as a chemotherapy sensitizer to enhance the sensitivity of gastric cancer cells to adriamycin [83]. Furthermore, in a randomized, placebo-controlled phase II clinical study, Shen WC et al. found that premenopausal breast cancer patients treated with pg2 (high-purity *Astragalus* polysaccharide) had significantly better improvements in chemotherapy side effects such as fatigue and insomnia than the control group [84] (Fig. 3).

Reversal of chemoresistance

Chemotherapy, one of the most commonly used means of cancer treatment, is prone to come up in drug resistance when used for a long time. Multidrug resistance (MDR) is a complex phenomenon in which cancer cells develop diminished sensitivity to various anticancer drugs, regardless of their chemical structures or the way they function. This resistance is a significant contributor to the ineffectiveness of chemotherapy [85]. Numerous studies have shown that the MDR of cancer cells during chemotherapy is associated with multiple mechanisms, including enhanced drug efflux, genetic factors, growth factors, enhanced DNA repair, and enhanced xenobiotic metabolism [86].

Breast cancer is the most common cancer in women and the second most common disease globally [2]. Ursolic acid (UA), a pentacyclic triterpene, has been identified and extracted from a wide array of plant sources including vegetables, fruits, and traditional medicinal plants. Over the past 20 years, the potential medicinal uses of

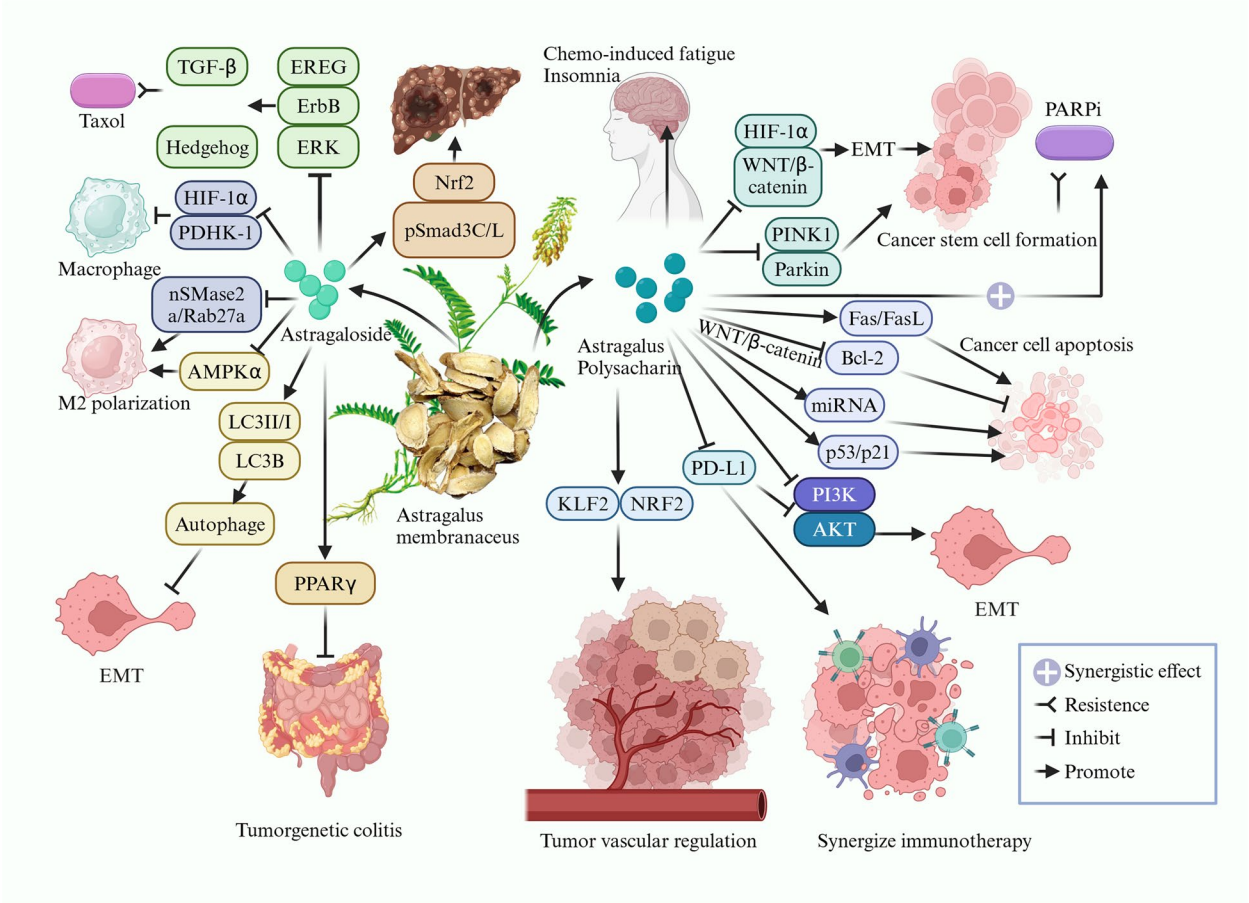

Fig. 3 Mechanism of Astragalus-mediated inhibition of tumor growth. The anti-tumor active ingredients of Astragalus are Astragalus Polysacharin and Astragaloside. They exert a diverse range of anti-tumor effects by directly targeting tumor signaling pathways, such as HIF-1α, Nrf2, or modulating the surrounding components, including immune cells and vascular growth. Moreover, Astragalus polysacharin regulate central nerve system to mitigate chemotherapy induced fatigue and insomnia

UA have garnered considerable attention. UA has been demonstrated in numerous research to possess antioxidant, antiproliferative, antibacterial, and anti-inflammatory properties [87]. Zong et al. discovered that in a breast cancer model with multidrug resistance, MCF-7/ADR cells treated with both UA and Dox had increased nuclear Dox levels compared to Dox alone. Their study indicated that UA notably improved Dox's effectiveness in these resistant cells. The efflux of chemotherapeutic agents is associated with the transporter protein P-glycoprotein (P-gp), and UA acts as a substrate for P-gp, which can in turn inhibit the function of P-gp [88].

Dehydrobruceine B (DHB) is a compound isolated from *Brucea javanica*. In China, *Brucea javanica* is widely used for anti-tumor treatment. DHB has been shown to reduce cell viability, cause apoptosis through a mitochondria-dependent pathway, and obstruct the cell cycle in the S-phase [89]. DHB and cisplatin (CDDP) have a synergistic effect on the cytotoxicity and apoptosis of lung cancer A549 cells, and CDDP plus DHB treatment significantly reduced mitochondrial membrane potential, increasing the Bax/Bcl-2 ratio, and released mitochondrial cytochrome c, thereby enhancing the efficacy of CDDP. In conclusion, CDDP combined with DHB therapy effectively alleviated the problem of drug resistance caused by CDDP alone [90].

Astragaloside IV (ASIV) facilitated the K48-linked polyubiquitination of EREG, resulting in the degradation of the EREG protein. This, in turn, suppressed the EREG/ErbB/ERK signaling pathway, and inhibition of this signaling pathway decreased the signaling activity of TGFβ and Hedgehog. Eventually, the expression of stem cell-related genes in non-small cell lung cancer (NSCLC) was lowered, and the resistance of cancer cells to paclitaxel was reversed, enabling the resistant cancer cells to regain sensitivity to chemotherapy drugs [91].

Combination of herbal medicines with targeted therapy and immunotherapy

Targeted therapy, as the name suggests, aims to deliver drugs to specific target organs through specific guidance mechanisms to achieve precise treatment. Immunotherapy uses the body's immune system to identify, control, and eliminate cancer cells. Both have made a significant contribution to the field of tumor immunology as a new oncological treatment option. Targeted therapy and immunotherapy are inseparable, and these two treatment methods are dependent on the tumor microenvironment. Throughout the current large number of anti-tumor therapy research, targeted therapy and immunotherapy always cooperate to resist tumors [92–94]. In clinical practice, cancer immunotherapies like as immune checkpoint inhibitors (ICIs), cytokine treatments, cancer vaccines, adoptive cell metastases, and oncolytic viral therapies have shown promise [95]. The combination of targeted therapy and ICIs represents the most prevalent combined therapy.

For example, VEGF-A, as an important member of the VEGF (vascular endothelial growth factor) family, plays a crucial role in regulating angiogenesis and affecting the tumor microenvironment. Therefore, antibody agents inhibiting VEGF-A also possess significant efficacy in tumor therapy [96]. Bevacizumab, an anti-VEGFA drug, is the first human anti-angiogenic antibody approved to treat CRC. A randomized phase II trial discovered that the combination of PD-1 antibody, histone deacetylase inhibitor (HDACi), and VEGF antibody bevacizumab could be a potential therapy option for advanced colorectal cancer patients with MSS/pMMR. The combination of their medications has a greater therapeutic effect than the combination of PD-1 antibody and HDACi, possibly due to increased $CD8^+$ T cell infiltration, resulting in a more immunologically active tumor microenvironment [97]. Similarly, bufalin, an extract of venom of toad, has been proven to enhance the anti-tumor activity of the anti-PD-1 antibody through activating the anti-tumor T cell immune response by indirectly activating NF-κB signaling [98]. It is clear that TCM has an immune-enhancing role in this, and the molecular mechanism and tumor microenvironment serve as a bridge for various therapies to communicate effectively.

Harnessing TCM to optimize cancer targeted therapy

It is worth noting that the use of multiple TCM targeting different pathways has demonstrated improved tumor treatment success compared to single-target treatments in recent years [99]. These targeted agents have stronger pharmacological effects on target tissues, regulated drug release, and fewer systemic side effects [100]. Liu et al. prepared nanoliposomes that were co-loaded with adriamycin and baicalin. Nanoliposomes co-loaded with adriamycin and baicalein showed a stronger inhibitory effect than adriamycin alone on the expansion of cells resistant to breast cancer in humans [101]. To improve curcumin's (CUR) anticancer activity, Yu designed a multistage drug delivery system, in which CUR can intelligently alter its size and surface charge following extended circulation and emission from vascular leakage arteries at the tumor site [102]. Low-density lipoproteins (LDL) are endogenous NP that are biocompatible, biodegradable, and immunogenic. It is not recognized or removed by the endogenous reticuloendothelial system in vivo. It follows that the perfect ligand for targeting tumors is LDL [103]. Tumor cells express receptors that specifically bind to hyaluronic acid (HA). Using hyaluronic acid/chitosan (HA/CS) as a water-insoluble curcumin carrier, Yang et al. created curcumin-loaded hyaluronic acid/chitosan nanoparticles (Cur-PENPs). Compared to the free curcumin solution, Cur-PENPs demonstrated increased absorption efficiency in C6 cells and enhanced dose-dependent cytotoxicity against C6 glioma cells [104]. Zhang W et al. created a cell membrane camouflaged and BA-loaded nanoparticles (CBAP) and discovered that it could directly target the NOD2 protein, inhibit NF-κB expression, and subsequently decrease the expression of ABC transporters (like ABCB1 and ABCG2), decrease chemotherapy drug efflux, and increase the sensitivity of pancreatic cancer cells to chemotherapy drugs like gemcitabine and 5-fluorouracil. In addition, limiting the autophagic flux can lessen the cardiotoxicity of bufalin, increase the effectiveness of chemotherapy, and increase treatment safety by controlling the expression of the transporter CFTR [105].

Herbal formulas and targeted therapies exhibit synergistic effects. For example, Complex Ku Shen Injection (CKI) is used in the clinical treatment of a variety of solid tumors, including lung, gastric, liver, CRC, and other cancer types [106, 107]. CKI was used in conjunction with sorafenib, an inhibitor of several tyrosine kinases, by Yang et al. to treat hepatocellular cancer. As demonstrated by their research, sorafenib directly targeted tumor cells, but CKI functioned on $CD8^+$ T cells and macrophages to alter the immunological microenvironment. The effectiveness of low-dose sorafenib as a therapeutic agent was enhanced when combined with CKI at subclinical dosages, since it successfully suppressed cancer development and recurrence without causing considerable damage [108].

In short, TCM formulations play a crucial role in evaluating the efficiency of targeted therapies [109], increased drug susceptibility [110], overcoming drug

resistance and toxicity [111], decreasing recurrence or metastasis rates in cancer patients, increasing cancer patient survival rates [112], and enhancing their prognosis [113].

Exploiting TCM for cancer immunotherapy

The role of TME in cancer immunotherapy

The purpose of immunotherapy is to restore the tumor-killing effect of anti-tumor immune cells, especially T cells, which are the main executors of the anti-tumor immune response [114]. TME significantly influences tumor initiation, progression, and invasion, making it crucial for developing effective anti-tumor immunotherapies [115].

TME is a complex network of nonmalignant cells and molecules within tumor tissue, including fibroblasts, endothelial cells, immune cells, and stromal cells that closely interact with cancer cells [116]. The cells and molecules in the tumor microenvironment not only affect the growth and survival of cancer cells, but also promote the invasion and metastasis of tumors by secreting various signaling molecules such as cytokines, growth factors, and chemokines. Moreover, the TME can influence the sensitivity of tumors to therapeutic drugs, thereby having a significant impact on treatment outcomes. Therefore, in-depth research on the mechanisms of action of the TME is of great significance for the progression of new cancer treatment strategies [117]. Therein, especially, T cells are especially essential to the TME, where they recognize tumor cells and initiate immune responses to combat cancer. Their antitumor activity is determined by their unique T-cell receptors (TCRs), which recognize specific antigens present in human leukocyte antigen (HLA) molecules [118]. As mentioned in the tumor immune surveillance hypothesis, host lymphocytes (T cells, etc.) can recognize and destroy tumor cells, because of the complexity of the TME and the existence of various negative regulatory mechanisms, cancer cells can evade immune system monitoring and attack in a variety of ways [119]. The two most prevalent subtypes of T cells and the most researched therapeutic targets are cytotoxic T cells ($CD8^+$ T cells) and T helper cells ($CD4^+$ T cells) [120]. Chinese herbal medicines can exert a significant supportive role in tumor treatment by influencing various T cells, including pro-T cells, $CD8^+$ T cells, Tregs, $CD4^+$ T cells, and NK cells [121].

TCM regulates the holistic immune cells and cytokines

Bufalin is a toadstool diene lactone that can be found in many plant and animal species, but its main source is the skin and parotid gland secretions of *Bufo gargarizans* [122]. Chemically, it is a cardiotonic steroid whose structure consists of a steroidal backbone and lactone cycle, a structure that provides unique chemical and biological properties. The fundamental pharmacological mechanism of action is predicated on the inhibition of the membranal sodium potassium ATPase [123]. In virtue of this, bufalin can induce Ca^{2+} overload, and further trigger pyroptosis, thereby synergizing PD-1 antibody [124]. Yu et al. found that bufalin activates NF-κB signaling by curbing the overexpression of p50 NF-κB, recruiting macrophages to the tumor site, and controlling their polarization from M2 to M1 phenotypes, thereby activating anti-tumor T-cell immune responses in a macrophage-dependent manner and ultimately inducing Hepatocellular carcinoma (HCC) inhibition [98]. A possible adjuvant for cancer immunotherapy is *polyriboinosinic-polyribocytidylic* acid (Poly (I:C)), a Toll-like receptor 3 (TLR3) agonist that, depending on the dose, exhibits entirely distinct effects on HCC cells. According to Feng et al., bufalin can prevent TBK1 from being activated, which prevents HCC cells from migrating, invading, and metastasizing when these cells are triggered by Poly (I:C) [125]. 2,4-dienoyl-CoA reductase (DECR1), an auxiliary component of β-oxidation, can facilitate the proliferation of breast cancer cells, whereas bufalin could markedly inhibit its expression. In vivo experiment has demonstrated that bufalin regulated solute carrier family 7 member 11 (SLC7A11) by reducing DECR1 levels, augmented intracellular reactive oxygen species (ROS) and $Fe2^+$ levels, and triggered lipid peroxidation. Eventually leads to ferroptosis in breast cancer cells, especially MDA-MB-231 cells [126]. Although bufalin has a promising role in the treatment of many different types of tumors, it also faces some challenges such as toxic effects, cytoprotective effects, and limited structure–activity relationship (SAR) information [127] (Fig. 4).

PLP-2, a polysaccharide isolated from *Plantaginaceae* seeds with a purity of > 99.8%, boosted intracellular interleukin (IL)-12 levels, lowered DC endocytosis, and enhanced maturation marker expression on DCs. In an activation model of syngeneic T cells, Huang et al. found that DCs given PLP-2 treatment were more effective in presenting ovalbumin antigen to T cells, which was evidenced by a higher rate of T cell expansion. This result might be because PLP-2 activates DCs through TLR4 receptors, promoting their phenotypic maturation and cytokine secretion, thereby regulating T cell-mediated immune responses [128]. It's also a polysaccharide, by activating the STAT5 signaling pathway, APS promotes the formation and persistence of $CD122^+$/$CXCR3^+$/$PD\text{-}1^-$ memory T cells and enhances the proliferation, migration, and chemotactic ability of these cells, thereby enhancing the anti-tumor effect of CAR-T cells on liver cancer in vitro and in vivo models [129]. In addition, a dosage form of Radix *Astragalus* combined with honey

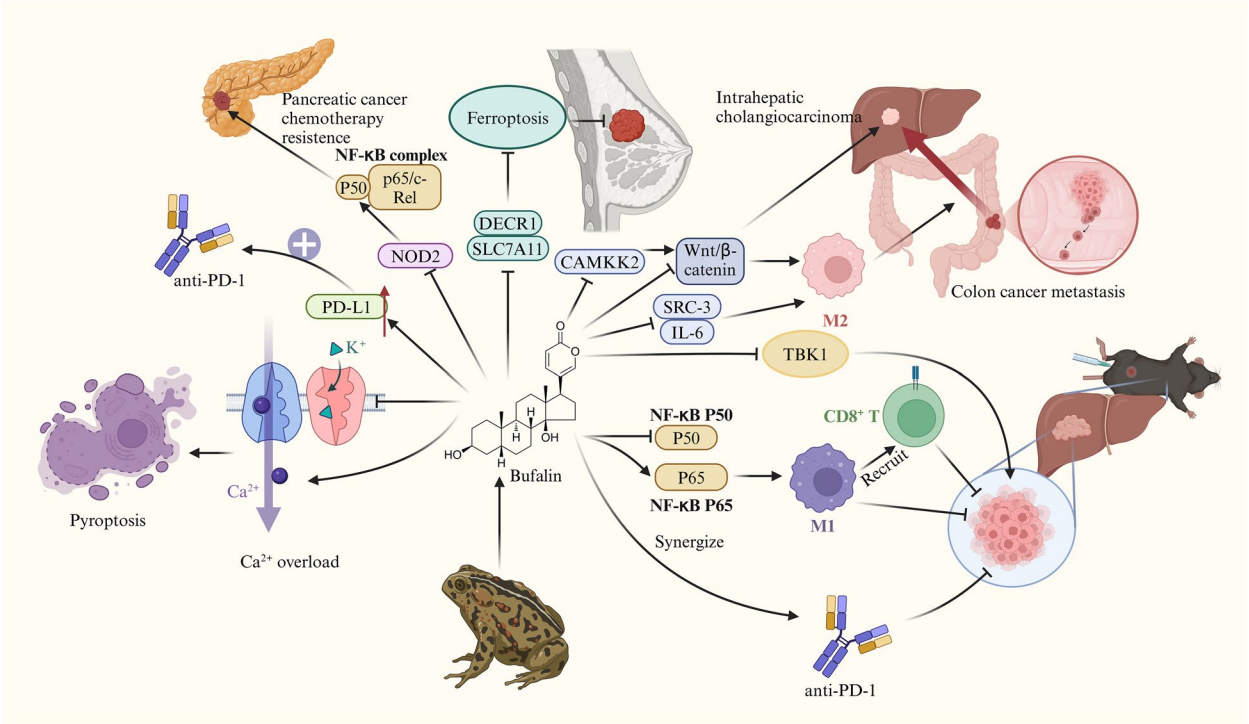

Fig. 4 Modulation of immune responses by bufalin in cancer therapy. Basically, bufalin, a compound derived from the venom of the toad, inhibit ATP dependent Na^+-K^+ ion channel to induce Ca^{2+} overload, ulteriorly spur tumor pyroptosis. In liver cancer, bufalin influences the NF-κB signaling pathway by interacting with components such as NF-κB p50 and p65, which are crucial for the transcriptional regulation of immune response genes. This interaction reprograms macrophages from an M2-like phenotype, which promotes tumor growth, to an M1-like phenotype, which is tumoricidal. Additionally, bufalin enhances the recruitment and polarization of CD8 + T cells, critical effectors in anti-tumor immunity. Bufalin could synergize with anti-PD-1 therapy to potentiate the anti-cancer immune response in a preclinical model. Additionally, bufalin suppresses intrahepatic cholangiocarcinoma and colon cancer liver metastasis through CAMKK2/Wnt/β-catenin, and SRC-3/IL-6 signaling. In pancreatic cancer, bufalin inhibits the NOD2-driven NF-κB signaling to overcome chemotherapy resistance

called honey-processed *Astragalus* polysaccharide (HP-APS) increases the death of tumor cells by causing them to proliferate less rapidly and enter the G1-S phase. The upregulation of CRT, MHC-I, HSP70, CD86, other markers, and immunogenic death could be linked to this apoptosis. Moreover, HP-APS therapy boosted the percentage of $CD8^+$ T cells and greatly decreased tumor size in melanoma-affected animals. In addition, a further slowdown in the rate of tumor growth was observed when HP-APS was combined with PD-1 mAb therapy, suggesting a potential beneficial outcome [130].

TCM regulates the immune checkpoints

Immune checkpoints (ICs) comprise inhibitory receptors on T cell surfaces, including lymphocyte activation gene 3 (LAG3), T-cell immunoglobulin mucin 3 (Tim3), programmed death receptor 1 (PD-1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), which interacts with their respective ligands on antigen-presenting cells or other tissues to affect immune responses [131]. Tumor cells can be recognized and eliminated by the immune system but are inhibited by inhibitory receptors and ligands, which tumor cells can always use to evade immune destruction [132]. In a study utilizing a Lewis lung carcinoma mouse model, Zhang et al. found that a high-dose of Qiyusanlong decoction effectively suppressed tumor progression by downregulating the PD-L1 and PD-1 expression at the mRNA and protein levels within the tumor tissue [133]. Han et al. found that polysaccharides extracted from Atractylodis macrocephalae rhizoma (PAMR) have the potential to inhibit the proliferation of esophageal cancer cells that highly express PD-L1. This inhibitory effect is achieved through the upregulation of microRNA-34a (miR-34a), which subsequently modulates the expression of its downstream target genes, thereby interfering with the cancer cell's ability to evade immune detection [134]. Coincidentally, in a study involving Lewis tumor xenograft mice, it was discovered that BBR induced the degradation of PD-L1, which was accomplished by means of the ubiquitin/proteasome system. By lowering the levels of PD-L1, BBR enhanced the capability of T cells to infiltrate and assault

tumors. Additionally, the antitumor activity of BBR was ascribed to its capacity to enhance the immune response through increasing the presence and activity of tumor-infiltrating T cells. Concurrently, it reduced the activation of myeloid-derived suppressor cells (MDSC) and regulatory T cells (Tregs), which are recognized for suppressing immune responses against tumors. This study sheds light on the mechanism of anti-tumor action that BBR has never been recognized [135].

TCM regulates the intestinal microbiota

TCM has both positive and potentially negative effects on the intestinal microbiota. They are mutually complementary and closely interrelated, offering enormous promise for the healing and prevention of numerous illnesses [136]. The gut microbiota stimulates the intestinal immune response via its metabolites and pathogen-associated molecular patterns (PAMPs). It is essential for the maturation of the intestinal immune system in the early years, especially around birth, and proper colonization of the intestinal microbiota can promote the maturation of intestinal mucosa-associated lymphoid tissues [137, 138]. The intestinal microbiota is closely related to the development of the human enteric nervous system and the expression level of innate genes. In the early stages of embryonic development, the enteric nervous system (ENS) begins to form and has a certain electrical activity, which might have an impact on the establishment and maturation of the early intestinal microbiota [139]. The gut microbiota modulates the immune system within TME, affecting DC development and T-cell stimulation. In addition, the loss of the therapeutic effect of CTLA4 blockade in sterile environments or broad-spectrum antibiotic-treated mice suggests that the efficacy of immune checkpoint blockers is strongly dependent on the intestinal microbiota [140]. Boosting immune responses to PD-1/PD-L1 checkpoint inhibitors can be achieved through two strategies: increasing the abundance of beneficial microorganisms and reducing the effects of harmful microorganisms. This effect might result from increased infiltration of effector T cells or remission of immunosuppressive conditions in the tumor microenvironment, which in turn increases the effectiveness of anti-PD-1/PD-L1 therapies or overcomes drug resistance [141]. A large number of studies have found that the gut microbiota interacts with both innate and adaptive immune cells, strengthening the former's effectiveness while greatly boosting the latter's capacity to fight tumors. Additionally, this interaction promotes immune recognition of tumor cells, thereby optimizing the immune response within TME, which is of great significance for improving the effectiveness of ICI [142].

In vivo, Wang et al. discovered that the Chang Wei Qing Decoction (CWQ) in conjunction with anti-PD-1 antibody decreased the inflammatory response to the intestinal mucosa induced by anti-PD-1 antibody alone, upregulated PD-L1 protein, and decreased the amount of Bacteroides in the gut microbiota while increasing the amount of Firmicutes, Actinobacteria, and Akkermansia. In addition, they discovered that CWQ intensified $CD8^+$ and $PD\text{-}1^+$ $CD8^+$ T cell infiltration, amplifying the anticancer effects of the anti-PD-1 antibody [143]. In a xenograft model, analysis of the intestinal microbiota revealed that B. acidifaciens was significantly enhanced when Gegen Qinlian decoction (GQD) and anti-mouse PD-1 were combined. In addition, the combination treatment also boosted IFN-γ expression, downregulated PD-1, raised IL-2 levels, and enhanced the percentage of $CD8^+$ T cells in the tumor tissues and peripheral blood. These results suggest that GQD combined with PD-1 blockade immunotherapy may be a new therapeutic strategy for treating colorectal cancer [144]. Using the 16S RDNA analysis in a clinical study, it was discovered that GQD increased the relative abundance of Akkermansia, Bacteroides, and Prevotella and decreased the relative abundance of Veillonella and Megamonas. Additionally, following GQD treatment, patients with colorectal cancer had a much higher proportion of $CD4^+$ T cells and NKT cells than they had before treatment, and the treatment group's tumor tissues had significantly lower levels of TNF-α and NF-κB expression [145] (Fig. 5).

Molecular mechanisms of TCM in cancer treatment

In the above content, we have presented the indispensable roles of TCM in cancer treatment either alone or in combination with existing anti-cancer therapies. Contemporarily, the progression of molecular biology, cell biology, and other disciplines has driven the development of modern medicine, which has played a significant role in understanding how drugs' ingredients work and how they affect the body. Therefore, in addition to traditional methods of treatment by virtue of differential symptoms and thereby empirical drug use, exploration and exploitation TCM can also be implemented through proof-of-concept of drug discovery and targeting in cancer treatment hinged on scrutiny of their pharmacology and subsequently instigating signaling pathways variations. TCM exerts its anti-tumor effects through various mechanisms, the most common of which are molecular mechanisms, including AKT, NF-κB, MAPK, and JAK-STAT signaling pathways. These mechanisms are closely related to the occurrence, development, and invasion of tumors.

The PI3K-AKT pathway controls important metabolic functions in response to cytokines, growth factors, and insulin under physiological settings. By increasing the

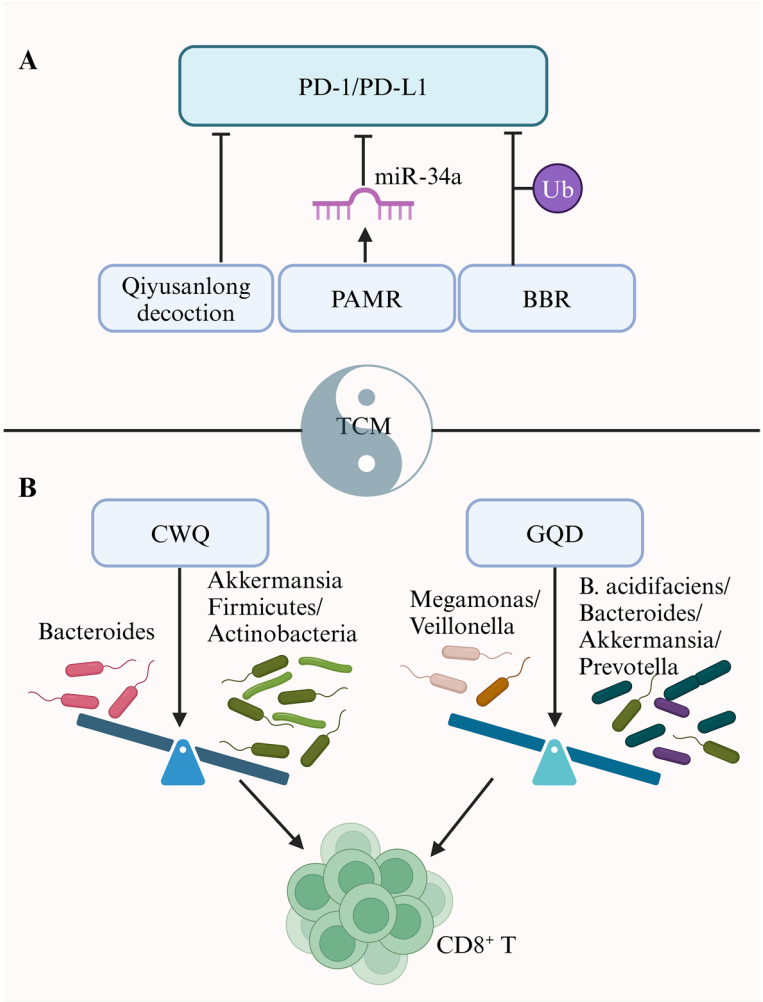

Fig. 5 Modulation of Immune Checkpoints and Gut Microbiota by Traditional Chinese Medicine Formulations. **A** The regulation of the PD-1/PD-L1 pathway by different TCM formulations. Qiyusanlong decoction and PAMR (Polysaccharide of Atractylodis Macrocephalae Rhizoma) influence PD-1/PD-L1 interactions indirectly through the modulation of miR-34a, which plays a role in the ubiquitination (Ub) of PD-L1, reducing its expression. Berberine (BBR) is also shown to engage in this pathway, suggesting a mechanism by which these TCM agents might enhance immune response against tumors by reducing immune checkpoint activity. **B** The effects of Chang Wei Qing (CWQ) and Gegen Qinlian Decoction (GQD) on the gut microbiota and their subsequent impact on $CD8^+$ T cell modulation. CWQ is associated with shifting the gut microbiota towards a composition rich in Akkermansia, Firmicutes, and Actinobacteria, known to enhance immune responses. GQD modifies the gut microbiota by increasing levels of Bacteroides, Akkermansia, and Prevotella, while decreasing Megamonas and Veillonella, thereby potentially enhancing $CD8^+$ T cell function and the overall anti-tumor immune response. These changes in microbiota composition are critical for the modulation of systemic immune responses, particularly in enhancing the efficacy of immunotherapies

activity of metabolic enzymes and nutrient transporters, the PI3K-AKT pathway causes cellular metabolic reprogramming in cancer cells, supporting the synthetic demands of abnormally growing cells [146]. Emodin is an anthraquinone derivative extracted from *Polygonum multiflorum* and *Rheum palmatum.* It has a wide range of pharmacological effects, including antiviral [147], antibacterial [148], lipid-regulating [149], and anti-tumor [150]. Using the normal human hepatocyte line L02, Zheng et al. investigated the effect and mechanism of emodin on hepatocytes. They discovered that emodin did not affect the total protein expression levels of PI3K, AKT, and mTOR, but it significantly decreased the expression levels of p-AKT (phosphorylated AKT), p-mTOR (phosphorylated mTOR), and p-PI3K (phosphorylated PI3K) in L02 cells in a dose-dependent manner [151]. This implies that by either directly or indirectly altering the phosphorylation state of these important proteins, emodin may suppress the PI3K/AKT/mTOR signaling pathway. In the bone cancer pain (BCP) rat

model, it was found that EA could reduce the increased phosphorylation levels of mTOR and its complex markers S6K and AKT in BCP rats, which may contribute to the alleviation of mechanical hyperalgesia induced by BCP. This study also found that the inhibitor of mTOR signaling pathway could further reduce hyperalgesia in BCP rats, while the agonist of mTOR could weaken the analgesic effect of EA, which also indirectly indicates that EA improves BCP by regulating mTOR signaling pathway [152].

NF-κB plays a key role in cell differentiation, inflammation, stress response, and cell death. A complex network of signaling pathways and a wide range of stimuli can activate it, and these pathways can also influence each other. In addition, it regulates multiple target genes and generates complex feedback loops [153]. Curcumin is a polyphenolic molecule that was extracted from *Curcuma longa* and has been shown to have antioxidant, anti-inflammatory, anti-cancer, and anti-aging properties [154]. In a mouse model of IL-10 knockout, Larmonier CB et al. discovered that curcumin's effect was limited and NF-κB activity was unaffected. In vitro, however, curcumin was able to reduce inflammation by inhibiting the activation of NF-κB, and it had a synergistic effect with IL-10 to enhance the anti-inflammatory effects of IL-10 [155].

The mitogen-activated protein kinase (MAPK) signaling pathway controls important cellular processes such as senescence, differentiation, migration, and proliferation. Its dysfunction or mutation is the cause of most cancers [156]. Jing M et al. discovered that the andrographolide derivative AL-1 inhibited LPS-induced phosphorylation levels of JNK, p38, and ERK in RAW 264.7 cells, preventing the activation of the MAPK signaling pathway in both in vitro and in vivo experiments [157]. Through observation in human peripheral blood samples, acupuncture treatment was found to mitigate fatigue after breast cancer chemotherapy through suppressing the Leptin/AMPK signaling pathway. In addition, acupuncture can improve the immune status of T lymphocyte subsets in the peripheral blood of breast cancer patients, and reduce the mitochondrial DNA mutation rate in WBCs [158].

The Janus kinase/signal transduction and activator of transcription (JAK-STAT) signaling pathway is mainly composed of transmembrane receptors, receptor-associated cytosolic tyrosine kinases (JAK protein), and signal transducers and activators of transcription (STAT protein). Although the pathway is relatively easy to deliver, it is crucial for several vital physiological functions, such as hematopoiesis, differentiation, metabolism, and immune regulation. This suggests that the pathway is deeply linked to inflammation and autoimmune diseases [159–161]. To reduce the toxicity of triptolide and maintain pharmacological efficacy, the researchers introduced a furan pyrimidine fragment at the 14-position of the triptolide core and extracted ZT01 [162]. In a mouse model of DSS-induced acute colitis, ZT01 treatment significantly reduced the expression of p-STAT1 and p-STAT3, as well as the phosphorylation levels of upstream molecules p-JAK1 and p-JAK2. This helped to regulate the JAK-STAT signaling pathway [163].

TCM plays a crucial role in the treatment of tumors, but the complexity and diversity of its mechanism restrict its widespread application. Currently, a considerable number of scholars are exploring the anti-tumor mechanism of TCM to furnish strong evidence for its better utilization in the future (Table 2).

Utilizing non-pharmaceutical TCM practices for cancer treatment optimization

When tumor patients fail to respond to conventional anti-tumor treatment or seek more efficacious therapeutic options, they often turn their attention towards complementary and alternative non- pharmaceutical interventions, such as acupuncture, massage, and moxibustion. These modalities are characterized by their cost-effectiveness, minimal adverse effects, and high acceptability among patients [182]. Acupuncture also has a complex theory, but it is also inseparable from TCM. In short, acupuncture can stimulate particular body acupoints, regulate blood and Qi, stimulate meridians, and restore the body's Yin and Yang balance, so as to achieve the purpose of treating diseases [183] (Fig. 6). Massage and moxibustion share a similar theory (Table 3).

Acupuncture can reduce cancer-related pain and side effects after chemotherapy and radiotherapy, including nausea and vomiting, xerostomia, fatigue, nervousness, and insomnia [193]. There are now two types of acupuncture: electroacupuncture (EA) and manual acupuncture (MA). EA, which combines electrical acupoint stimulation with MA [194], is now the most researched therapeutic approach and is usually thought to have a better curative impact than traditional acupuncture. In the mouse model of CRC, EA stimulates the acupoints of ST36 and ST40, activating the SIRT1 protein, inhibiting the expression of miR-215, and promoting the expression of Atg14 protein, thereby suppressing the inflammatory response and enhancing autophagy activity and consequently improving the condition of AOM/DSS-induced mice CRC [195]. In a breast cancer mouse model, moxibustion can improve the anti-tumor effect of paclitaxel by reducing the total number of WBCs, and overcome the tumor immune escape by inhibiting the PD-1 and PD-L1 signaling pathways, so as to enhance the chemotherapy effect of paclitaxel [196].

Table 2 The formulae and herbs of TCM and their anti-tumor effects in various cancers

Disease	Formulae and herbs	Main component	Signaling pathways	Influence mode	reference
colon cancer	Liquidambar formosana	liquidambaric acid (LDA)	Wnt/β-catenin signaling	LDA inhibits oncogenic Wnt/β-catenin signaling in vitro and in vivo through its direct target tumor necrosis factor receptor-associated factor 2 (TRAF2)	[164]
esophageal cancer	Garcinia bracteata C. Y. Wu ex Y. H. Li	beobractatin (NBT)	TOM20/BAX signaling pathway	NBT increases mitochondrial ROS level, which then active TOM20/BAX signaling pathway	[165]
colon adenocarcinoma	Babao Dan (BBD)	bezoar, snake gall, antelope horn, pearl, panax, musk	IL-6/STAT3 signaling pathway	BBD inhibits IL-6 expression and STAT3 phosphorylation	[166]
gastric cancer	*Celastrus orbiculatus* Thunb	*Celastrus orbiculatus* extract (COE)	TGF-β/Smad signaling pathway	COE directly blocks the TGF-β/Smad signaling pathway and decreases the expression of associated proteins	[167]
pancreatic cancer	Qingyihuaji Formula (QYHJ)	*Scutellaria barbata*, *Scleromitrion diffusum*, *Arisaema erubescens*, Schott, *Gynostemma pentaphyllum* Makino, and *Myristica fragrans* Houtt	MAPK/ERK and PI3K/Akt/mTOR signaling pathways	QYHJ down-regulates the activities of p-ERK1/2, p-PI3K, p-Akt, and p-mTOR, thereby indirectly inhibiting the MAPK/ERK and PI3K/Akt/mTOR signaling pathways	[168]
ovarian cancer	Fraxetin (FXT)	Fraxetin	TLR4/STAT3 signaling pathway	FXT inhibits the expression of TLR4, reduces the level of P-STAT3, and affects the downstream target protein of STAT3	[169]
cervical cancer	Baicalein	baicalein	NF-κB signaling pathway	Baicalein directly inhibits the activity of the NF-κB signaling pathway or affects the NF-κB signaling pathway by reducing nuclear translocation of NF-κB p65 and regulating the expression of related genes and proteins	[170]
lung cancer	*Selaginella doederleinii*	Delicaflav-one	Akt/mTOR/p70S6K signaling pathway	Delicaflavone downregulates the expression of p-Akt, p-mTOR, and p-p70S6K in a time- and dose-dependent manner	[171]
glioma	*Tripterygium wilfordii*	Celastrol	ROS/JNK and Akt/mTOR signaling pathways	Celastrol induces JNK activation and ROS production and inhibits the activities of Akt and mTOR kinases	[172]
hepatocellular carcinoma	*Lobelia chinensis* Lour. (LCL)	*Lobelia chinensis* Lour	PTEN/AKT signaling pathway	LCL increases the expression level of tumor suppressor gene PTEN and inhibits p-AKT1	[173]
non-small-cell lung cancer	*Proralea corylifolia* L	Bavachinin	p38/p21$^{Waf1/Cip1}$-Dependent Signaling Pathway	After Bavachinin inhibits p38 MAPK activation, bavachinin-induced p21$^{Waf1/Cip1}$ expression is repressed	[174]

Table 2 (continued)

Disease	Formulae and herbs	Main component	Signaling pathways	Influence mode	reference
colon cancer liver metastasis	*Bufo gargarizans*	Bufalin	SRC-3/IL-6 signaling pathway	Bufalin inhibits colon cancer liver metastasis by inhibiting the SRC-3/IL-6 pathway and reducing the M2-type polarization of Kupffer cells (KCs)	[175]
Intrahepatic cholangiocarcinoma (ICC)	*Bufo gargarizans*	Bufalin	Wnt/β-catenin signaling pathway	Bufalin affects the level of $Ca2^{+}$ and the expression of ANXA2 by targeting CAMKK2, thereby inhibiting Wnt/β-catenin signaling pathway	[176]
breast cancer	*Cnidium monnieri*	Osthole	ITGα3/ITGβ5 signaling pathway	Osthole directly inhibits the expression of ITGα3 and ITGβ5 and affects their downstream signaling pathways	[177]
oral cancer	*Astragalus*	*Astragaloside* IV (AS-IV)	AMPK and AKT/mTOR pathways	AS-IV triggers the AMPK pathway and retards the AKT/mTOR pathway	[178]
colorectal cancer (CRC)	Astragali Radix-Curcumae Rhizoma (AC)	Astragali Radix, Curcumae Rhizoma	HIF-2α/β-catenin pathway	AC inhibits CRC growth and cell stemness by down-regulating HIF-2α signaling and WNT/β-catenin signaling pathway	[179]
Hepatocarcinogenesis	*Astragalus*	AS-IV	pSmad3C/3 L and Nrf2/HO-1 signaling pathway	AS-IV exerts its anti-HCC effect through the bidirectional crosstalk pSmad3C/3 L and Nrf2/HO-1, especially Nrf2/HO-1 signaling	[180]
colitis-associated tumorigenesis	*Astragalus*	AS-IV	PPARγ signaling pathway	AS-IV can activate PPARγ signaling in intestinal epithelial cells and reduces DNA damage caused by intestinal inflammation, thereby inhibiting colon tumorigenesis	[181]

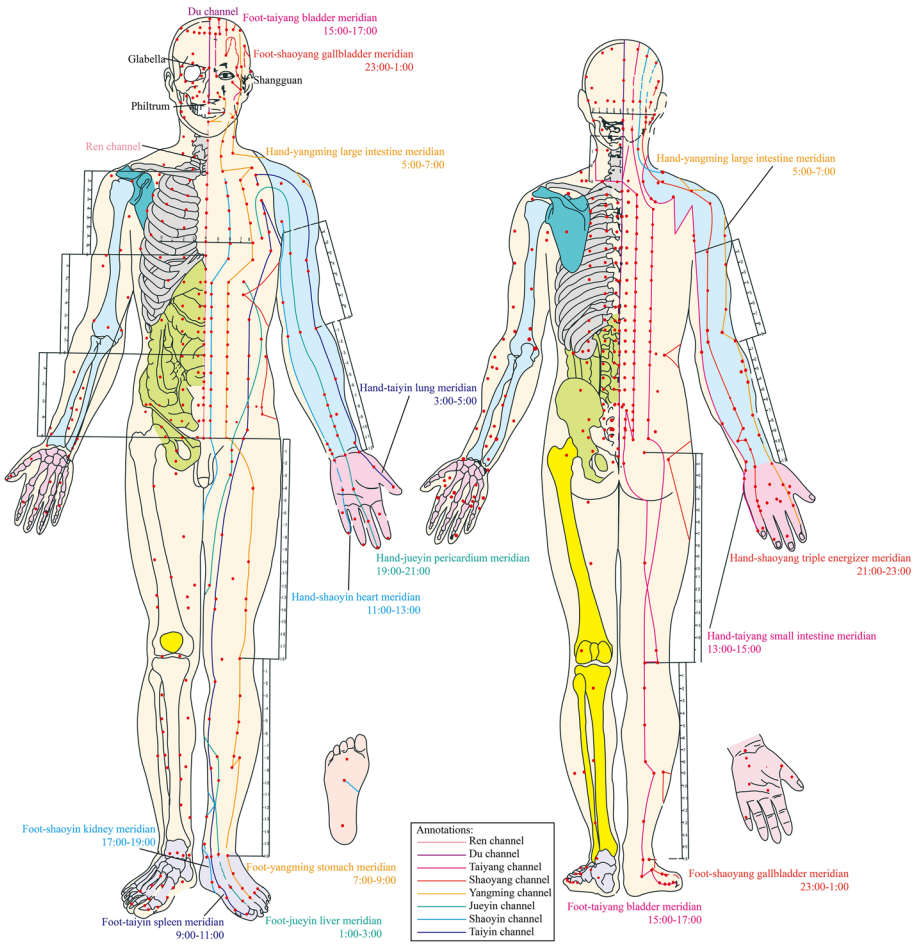

Fig. 6 Meridian and acupoint of human body. The acupoints refer to specific locations on the body that are interconnected with the meridian system, and can be effectively stimulated through acupuncture or massage techniques in order to enhance physical well-being and address a wide range of ailments. The principles of TCM posit a close correlation between the physiological activities of the human body and natural fluctuations, particularly those associated with the passage of time. In ancient Chinese medicine, a 24-h day was divided into twelve intervals, each corresponding to a specific meridian within the human body

Mao JJ et al. conducted a study of the PEACE randomized clinical trial in 360 cancer survivors to compare the effectiveness of electroacupuncture and auricular acupuncture with usual care in relieving chronic musculoskeletal pain among cancer survivors. Both EA and auricular acupuncture were found to significantly reduce pain compared with usual care, and auricular acupuncture did not show noninferiority to EA, but auricular acupuncture was less well tolerated. This trial highlights the potential value of EA as pain management in cancer survivors, while pointing out the relative worse adherence when conducting auricular acupuncture [197]. Zhang J et al. conducted a double-blind randomized controlled trial to evaluate the efficacy and safety of acupuncture for chemotherapy-related insomnia in breast cancer patients. They found no significant difference in reducing the insomnia severity index, but showed better short-term and long-term effects in improving sleep latency, total sleep time, sleep efficiency, anxiety, depression, and quality of life compared with sham acupuncture controls. In addition, the real acupuncture group had a greater effect on reducing or discontinuing the use of sleep medications, and treatment-related adverse events were mild, with no participants discontinuing treatment because of adverse events. The study concluded that acupuncture is an effective option for the management of chemotherapy-related insomnia, and may be used as a way to reduce or replace sleep medications [198]. In a clinical trial of moxibustion in improving cancer-related fatigue (CRF), moxibustion was found to be more effective in reducing fatigue and improving quality of life, and the improvement in the moxibustion group was sustained during the 4-week follow-up period after the end of treatment [199].

Table 3 Undergoing clinical trials on TCM employed in cancer regimen

Types	Interventions	Acupoints/Position	Outcomes	Clinical Trial/Reference
Cancer pain	Electroacupuncture (EA) and Message	The most painful part	Both treatments improved fatigue, insomnia, and quality of life, and there were no significant differences between the two groups	NCT04095234/ [184]
Chemotherapy-induced peripheral neuropathy (CIPN)	EA	Yin Tang, LI 11, TW 5, Baxie, SP 9, ST 36, SP 6, K 3, LR 3, Qiduan	Breast cancer survivors treated with chemotherapy showed significant improvement in neuropathy symptoms after 8 weeks of acupuncture	NCT02129686/ [185]
Radiation-induced xerostomia in Head and Neck Cancer	True acupuncture (TA), sham acupuncture (SA), and standard oral hygiene (SOH)	Auricular point: Shenmen, point 0, and salivary gland 2-prime. Others: CV 24, LU 7, LI-1-prime, K 6	TA is more effective than SA or SOH in the treatment of chronic RIX in patients with head and neck cancer after radiotherapy	NCT02589938/ [186]
Opioid-induced constipation (OIC) in patients with cancer	EA	ST 25, SP 14, ST 37,	Eight weeks of EA treatment can increase weekly spontaneous bowel movements with good safety and improve the quality of life of OIC patients	NCT03797586/ [187]
Fatigue after chemotherapy in gastrointestinal cancer patients	Massage	Foot	The fatigue score of foot massage was gradually reduced immediately after chemotherapy and 24 h later	[188]
Sleep quality in patients with Leukemia	Acupressure, reflexology	SP 6, foot	The sleep quality of the acupressure and foot reflexology group was significantly improved	[189]
Severe radiotherapy-induced oral mucositis (SRTOM) and lipid metabolite changes in nasopharyngeal carcinoma (NPC)	Massage	Maxillofacial and oral	Maxillofacial and oral massage significantly reduced the incidence of SRTOM in NPC patients and boosted anti-inflammatory lipid metabolites	[190]
Cancer-related fatigue in breast cancer	Infrared laser moxibustion (ILM)	ST 36, CV 4, CV 6	ILM could significantly reduce fatigue in breast cancer patients and is safe	NCT04144309/ [191]
Paclitaxel-induced peripheral neuropathy	EA	LI11, TE5, LI 4, ST 36, GB 34	EA is effective in treating paclitaxel-induced peripheral neuropathy, especially 2 Hz/100 Hz electroacupuncture	[192]

Although TCM external treatment usually plays an auxiliary role in the treatment of tumors, including enhancing immunity, reducing the side effects of radiotherapy and chemotherapy, and improving the quality of life of patients, with the development of modernization, it is believed that TCM external treatment will be more widely used in oncology in the future, and may even become an irreplaceable scheme for the treatment of tumors.

Conclusions and perspectives

With the aggravation of global cancer burden and relative sluggish progression of research and development of anti-tumor drugs, TCM have garnered tremendous attention, which exerts tumoricidal effects both in direct and adjuvant approaches. It overcomes the limitations of simple radiotherapy, chemotherapy, and targeted therapy, enhancing antitumor efficacy, diminishing side effects, and reversing drug resistance. That is derived from them exhibiting multifaceted anti-tumor mechanisms. However, as the saying goes, "no remedy is without risk." The natural form of TCM, in particular, can induce adverse effects in clinic, even drug-associated toxicity. For example, The co-administration of Coptis with gliclazide is associated with an increased susceptibility to hypoglycemia, while the concurrent use of polygonum multiflorum exacerbates acetaminophen-induced liver damage [200, 201]. Moreover, it should be noted that the active ingredients extracted also possess inherent side effects. For example, bufalin, as mentioned earlier, sporadically exhibits cardiotoxicity, limiting its widespread use in cancer treatment [122]. Solutions to this drawback include prodrug strategies, optimized drug formulations, repeated low-dose drug administration, active targeted drug delivery systems, and nanocarriers [202]. That is because that the chemical composition of TCM is complex, leading to many challenges in clinical applications [203]. First, since TCM is generally a single or multiple herbs used to treat diseases, the main substance and mechanism of action are not clear. Second, the sources of TCM are diverse, and the variability in planting, harvesting, and processing may lead to inconsistencies in the quality of TCM, which makes it difficult to ensure the efficacy and safety of Chinese medicinal herbs. Third, although TCM has a long history and traditional experience, many of them lack large-scale, randomized controlled clinical trials to verify their efficacy and safety. Moreover, a challenge in the clinical application of TCM also involves inappropriate combinations, which can arise from factors like improper formulation, excessive dosage, or drug interactions. Given the complex composition of TCM, the pharmacokinetics and drug-drug interactions often remain underexplored, amplifying safety concerns. Although some clinical studies have reported the benefits of TCM combinations, comprehensive safety evaluations and mechanistic studies are still lacking. Therefore, establishing a standardized safety evaluation system for TCM combination therapy is crucial for ensuring patient safety and optimizing treatment outcomes in clinical practice.

In fact, the majority of TCM compound preparations are derived from renowned ancient prescriptions or formulations developed by medical institutions, which are supported by TCM theory and extensive clinical experience. In comparison to chemical drugs and biological drugs, TCM compound preparations possess distinct advantages and characteristics, enabling the rational utilization of existing real-world data or evidence. This provides essential support for determining the safety profile during the clinical study of combined use in Chinese medicine. It is necessary to evaluate the safety risks associated with combined drug use for TCM compound preparations that have been clinically used in humans before deciding whether they can proceed directly to phase II clinical trials for combined drug use. If both the proposed combination drug and the observed TCM demonstrate clinical safety when used together, if single-drug toxicology results indicate relative safety during combined use, if literature reports on similar varieties corroborate these findings, and if non-clinical pharmacological data supports their combination, then it may not be necessary to conduct non-clinical safety experiments for the combined drug. In such cases, the recommended dosage of the observed traditional Chinese medicine can be directly utilized in a phase II clinical trial involving its combination with the proposed combination drug. However, if there is a high risk associated with TCM compound preparations (such as toxic medicinal materials or previous studies indicating significant safety concerns), it is advisable to conduct non-clinical safety studies prior to human trials. These studies will provide crucial data support for subsequent research design and usage methods regarding combined drug use in future clinical trials while also serving as a basis for managing potential safety.

Moreover, the safety of TCM combined drug use is influenced by various factors. Nowadays, however, there is still a lack of systematic and complementary research systems such as pharmacy, non-clinical trials, registered clinical trials, post-marketing clinical trials, and adverse drug reaction monitoring to evaluate its safety. Therefore, the combined use of TCM should be researched and developed from an early stage and undergo the entire life cycle of new drugs from clinical trials to post-marketing evaluation. To ensure safety evaluation, it is crucial to prioritize research design and risk–benefit assessment while establishing a dynamic research model that includes

research design-monitoring and evaluation-analysis-prediction-risk management. Additionally, it's necessary to explore safety evaluation methods for combined drug use that align with TCM characteristics while continuously analyzing safety research results through scientific measurement. A multidisciplinary comprehensive evaluation system for clinical medicine, evidence-based medicine, pharmacy pharmacology toxicology clinical pharmacology statistics etc., must be established regularly along with implementing a risk assessment mechanism to guarantee better service in meeting clinical needs.

In the exploration of TCM practically utilized in tumor clinic, CRISPR-Cas9, as the most widely used gene editing technology, prompts the progression [204, 205]. The versatility of CRISPR/Cas9 extends from revealing fundamental biological mechanisms to pioneering therapeutic interventions for cancer, and a large number of scholars have made CRISPR/Cas9 beyond the limitations of previous technologies through continuous exploration and research. Furthermore, it also serves as a powerful tool for screening susceptible genes, making it possible to intervene before tumor initiation or progression [206]. The lack of genetic and genomic information, high natural heterozygosity, and the absence of advanced genetic transformation technology in Chinese herbal plants may be the reasons for the lack of functional genomics research. This shortage severely limits the identification and genetic enhancement of functional genes in medicinal plants, which hinders the development of the TCM industry [207]. The utilization of CRISPR/Cas9 technology in the future could enable precise genetic editing to achieve optimal combination effects, addressing the limitations posed by single Chinese herbal remedies that may contain ineffective components or be accompanied by significant side effects during application.

In summary, TCM, especially internal treatment has a variety of mechanisms of action in tumor treatment, including direct inhibition of tumor cell growth, furtherance of tumor cell apoptosis, suppression of tumor angiogenesis, and regulation of the immune system. The combination of Chinese herbal medicines with chemotherapy, targeted therapy, and immunotherapy has greater advantages in terms of enhancing efficacy, reducing toxic side effects, and potentially reversing drug resistance. However, there is still a lack of a substantial amount of animal experiments and clinical studies to determine the efficacy of TCM combination therapies. Nevertheless, we predict that TCM and its extracts will bring more surprises to the field of anti-tumor treatment in the future. This has a profound impact on cancer treatment and human health.

Abbreviations

TCM	Traditional Chinese Medicine
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeat
Cas	CRISPR-associated protein
OV	Oncolytic virus
IL	Interleukin
G-Rh2	Ginsenoside Rh2
TAM	Tumor-associated macrophage
NF-κB	Nuclear factor-κB
BBR	Berberine
5-FU	5-Fluorouracil
TPL	Triptolide
SSA	Saikosaponin A
MAPK	Mitogen-activated protein kinases
ERK	Extracellular signal-regulated kinase
AP-1	Activator protein-1
PPI	Protein–protein interaction
ZJP	Zuojin pill
XCHT	Xiaochaihutang
WTX	Wei-Tong-Xin
KAI	Kangai injection
CWQ	Chang Wei Qing decoction
GQD	Gegen Qinlian decoction
TNF	Tumor necrosis factor
TLR	Toll-like receptor
TBK	Tank-binding kinase
MDR	Multidrug resistance
CKI	Complex Ku Shen Injection
NP	Nanoparticle
DC	Dendritic cell
MDSC	Myeloid-derived suppressor cell
Treg	Regulatory T cell
ICI	Immune checkpoint inhibitor

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Authors' contributions
SL and XC performed literature selection, drafted the manuscript, and prepared the figures. HS drafted partial sections of this manuscript, collected related references, and participated in the discussion. TL, BX, and MY designed the study and revised the manuscript. All authors contributed to the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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