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Advances of the Anti-tumor Effects and Mechanisms of Tanshinones

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Abstract: Modern pharmacological studies have revealed that tanshinones, the fat-soluble active constituents of Salvia miltiorrhiza, have significant antitumor potential, of which tanshinone IIA (Tan IIA) and crypto tanshinone (CPT), as the core components, intervene in key aspects of tumour development through multi-target regulatory mechanisms. Since the anti-tumour mechanism of tanshinone has not been completely sorted out, this paper will describe the research progress of tanshinones in the field of anti-tumour, targeting the anti-tumour effects of tanshinone IIA (Tan IIA), crypto tanshinone (CPT) and other major components. Explore the application potential of these active ingredients in the treatment of different types of tumors, analyze their pharmacodynamic characteristics and possible synergistic therapeutic strategies. By systematically sorting out the multi-target anti-tumor mechanisms of tanshinone compounds, it is expected to provide a solid theoretical basis for the further structural optimization, dosage form improvement and clinical transformation and application of such components and promote the innovative development of active components of traditional Chinese medicine in the field of precise tumor treatment.

Keywords: Tanshinones, cancer, mechanisms, treatment

1. Introduction

Malignant tumors are one of the major diseases that seriously threaten human health, and their incidence and mortality rates are increasing year by year. Although traditional treatment methods such as surgery, radiotherapy and chemotherapy have made certain progress, problems such as drug resistance, toxic and side effects, and tumor recurrence and metastasis still need to be solved urgently. Therefore, extracting highly efficient and low-toxicity anti-tumor active components from natural products and clarifying their mechanisms of action have become an important direction in the current research and development of tumor drugs. Salvia miltiorrhiza, as a traditional Chinese medicine, has the effects of promoting blood circulation, removing blood stasis, unblocking meridians and relieving pain. Its active ingredients mainly include water-soluble phenolic acids and fat-soluble tanshinones. Among them, tanshinone compounds have attracted much attention due to their unique chemical structure and extensive pharmacological activities.

This article intends to systematically elaborate on the research progress of the anti-tumor activity and molecular mechanism of tanshinone compounds in recent years, explore the innovative strategies of their structural modification and dosage form optimization, and propose prospects for future

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research directions, aiming to provide a theoretical basis and reference for the development of anti-tumor drugs based on tanshinones.

2. Chemical composition and structure of tanshinones

The medicinal plant Salvia miltiorrhiza Bunge, often referred to as Danshen, is defined botanically as the dried roots and rhizomes of a species within the Lamiaceae family (formerly Labiatae), widely utilized in traditional Chinese medicine practice, Salvia miltiorrhiza (Danshen) possesses a bitter flavour and slightly cold medicinal property. Classified as entering the Heart and Liver meridians, its primary therapeutic functions include activating blood flow to resolve stasis, menstrual regulation for pain relief, removing heat from the heart, and inducing mental calmness, making it a cornerstone herb for cardiovascular and neurological therapies [1,2]. Recent research indicates that the bioactive compounds in Salvia divinorum can primarily be divided into two groups: water-soluble phenolic acids and lipid-soluble tanshinones.

Tanshinones mainly include tanshinone IIA and crypto tanshinone, fat-soluble phenanthrenequinone compounds extracted from Salvia miltiorrhiza. As a primary bioactive constituent of Salvia miltiorrhiza, Tanshinone IIA (Tan IIA) is structurally defined by a phenanthrenequinone core and enhanced lipophilic properties. Emerging pharmacological research highlights its dual therapeutic potential, demonstrating significant anti-cancer effects through mechanisms like the induction of apoptosis and the inhibition of angiogenesis. Alongside immune-modulatory capacities via cytokine regulation, thereby positioning it as a promising candidate for precision oncology and immune-targeted therapeutic strategies. Cryptotanshinone, as another important component in Danshen, also demonstrated good anti-tumor activity. Its molecular structure is similar to that of tanshinone IIA. Still, there are different substituent groups on its benzene ring, which makes it different from tanshinone IIA in its pharmacological effects. These components play key roles in anti-tumour, cardiovascular protection, and neuromodulation through multi-target regulatory mechanisms, especially Tan IIA and CPT, which are of interest due to their significant anti-proliferative, pro-apoptotic, and anti-inflammatory activities.

3. Antitumor mechanism of action of tanshinones

3.1. The inhibition of the growth in terms of proliferation of tumour cells as well as the regulation of the cell cycle

Tanshinones intervene in the proliferation process of tumour cells through multiple targets. Research has demonstrated that tanshinone IIA can induce a G1-phase arrest in hepatocellular carcinoma and colon cancer cells by inhibiting the proliferation and migration of SGC-7901 cells through the down-regulation of FOXM1 and it exerts its effect by reducing the expression of cell-cycle proteins, including Cyclin D1 and CDK4/6. Cryptotanshinones, on the other hand, inhibit G2/M phase progression in melanoma cells by activating AMPK signalling [3,4]. In addition, tanshinones modulate breast cancer cell proliferation via the estrogen receptor pathway and reduce the ERα/ERβ ratio, thereby inhibiting estrogen-dependent tumour growth [5].

3.2. Inducing apoptosis in tumour cells

Tanshinones induce programmed tumour cell death by activating mitochondria-dependent apoptosis and death receptor pathways. For instance, tanshinone IIA enhances the expression of pro-apoptotic proteins Bax and Caspase-3/9, while suppressing the anti-apoptotic protein Bcl-2, inducing a decrease in mitochondrial membrane potential and cytochrome C release, thereby promoting apoptosis in hepatocellular carcinoma and gastric cancer cells. Cryptotanshinones exhibit pharmacodynamic

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synergism with cisplatin in bladder cancer, mechanistically through suppressing STAT3 phosphorylation, impeding its nuclear translocation, and downregulating anti-apoptotic proteins (e.g., Survivin/BIRC5), thereby overcoming chemoresistance and amplifying cisplatin-induced apoptosis in preclinical models [6]. In addition, tanshinones can also induce apoptotic processes through the endoplasmic reticulum stress pathway and the ROS-p38MAPK signalling axis [7].

3.3. Impairment of tumour infiltration and dissemination

Tanshinones inhibit tumour metastasis by modulating epithelial-mesenchymal transition and matrix metalloproteinase activity. Tanshinone IIA (Tan IIA), a key bioactive compound extracted from Salvia miltiorrhiza, is characterized by its phenanthrenequinone core and high lipophilicity, which facilitate cellular uptake and biodistribution. Recent pharmacological research has uncovered its dual therapeutic effects, including anti-cancer activity through mechanisms like the induction of apoptosis, cell cycle arrest, and angiogenesis suppression, alongside immunomodulatory effects via regulation of immune cell function and cytokine production. These findings underscore its potential as a multi-target agent in oncology, offering a foundation for advancing its pharmaceutical development and clinical translation in precision cancer therapies and immune-enhanced treatment regimens [8].

3.4. Regulation of the tumour microenvironment and immune response

Tanshinones exert antitumor effects by inhibiting angiogenesis and modulating the immune microenvironment. Tanshinone IIA down-regulated VEGF and HIF-1α expression to reduce hepatocellular carcinoma angiogenesis while inhibiting PD-L1 expression to enhance CD8+ T cell infiltration. Cryptotanshinones blocked the formation of lung cancer metastases by promoting macrophage M1 polarisation and inhibiting neutrophil extracellular traps (NETs) formation. In addition, tanshinones attenuate the inflammatory microenvironment of colitis-associated carcinogenesis by regulating the metabolism of intestinal flora.

3.5. Induction of tumour cell differentiation

Tanshinones induce the reversal of tumour cells to a normal phenotype by regulating differentiation-related genes (e.g. c-myc, c-fo s). Tanshinone IIA upregulates p53 and p21 expression, blocks leukaemia NB4 cells at the G0/G1 phase, and promotes their differentiation towards mature granulocytes [9]. Cryptotanshinone induces renal cancer cell differentiation and inhibits tumour growth in vivo by inhibiting STAT3 signalling and downregulating Cyclin D1 and C-MYC.

3.6. Reversing tumor multidrug resistance (MDR)

Tanshinones enhance the efficacy of chemotherapeutic drugs by inhibiting ABC transporter function and DNA repair enzyme activity. Tanshinone IIA reduces topoisomerase II activity and hinders DNA damage repair, thereby reversing adriamycin resistance in leukaemia cells [3]. Cryptotanshinone increases drug accumulation in drug-resistant cells of gastric cancer by down-regulating MDR-related protein 1 expression and overcomes drug resistance by inducing autophagic death.

The mechanism of action of tanshinone in different cancers can be found in Table 1 for details.

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Table 1: Mechanism of action of tanshinone in different cancers

Type of cancer	mechanism of action	Tanshinones
Liver cancer	1. Inhibits STAT3 and PI3K/AKT/mTOR signalling pathways, down-regulates CyclinD1, CDK4/6, and induces G1 phase block. 2. Up-regulates Bax, Caspase-3/9, down-regulates Bcl-2, promotes mitochondrial apoptosis. 3. Inhibits VEGF and HIF-1α, reducing angiogenesis.	Tanshinone IIA
Colon	1. Inhibits MMP-2/9 activity, upregulates TIMP-1/2, and blocks basement membrane penetration. 2. Induces G1 phase block.	Tanshinone IIA
Melanoma (type of skin cancer)	1. Activates AMPK signaling and inhibits G2/M phase progression. 2. Down-regulates CD44v6 and VEGF expression to inhibit lung metastasis.	crypto tanshinone
Lymphoma	1. Regulates proliferation through the estrogen receptor pathway and reduces ERα/ERβ ratio. 2. Inhibits STAT3 phosphorylation, blocks nuclear translocation, and reduces Survivin expression.	Tanshinone IIA, Cryptotanshinone
Bladder cancer	1. Inhibits STAT3 phosphorylation and enhances cisplatin sensitivity. 2. Induces endoplasmic reticulum stress and ROS-p38MAPK signaling-mediated apoptosis.	crypto tanshinone
Prostate cancer	1. Inhibits CXCR4 and β-catenin signalling, reducing migration and invasion.	crypto tanshinone
Lung cancer	1. Upregulate BimL gene expression and promote apoptosis (combined with apatinib). 2. Inhibit EZH2, VEGF, and CD31 expression and reduce microangiogenesis (combined with cisplatin).	Tanshinone IIA, Cryptotanshinone
Leukemia	1. Up-regulate p53 and p21, block cells in G0/G1 phase and promote differentiation. 2. Combined with arsenic trioxide to synergistically induce apoptosis and autophagy, and upregulate Caspase-3 and Beclin-1.	Tanshinone IIA
Gastric cancer	1. Reverse the EMT process (up-regulate E-cadherin, down-regulate N-cadherin, and Snail). 2. Combined with 5-fluorouracil to reduce liver injury and enhance the effect of chemotherapy.	Tanshinone IIA
Kidney cancer	1. Inhibits STAT3 signalling, downregulates CyclinD1 and C-MYC, and induces differentiation.	crypto tanshinone

4. Co-administration of tanshinones

Although tanshinones have shown excellent results in antitumor studies, they still face some challenges in clinical applications. For example, the bioavailability of tanshinones is low and their lipid solubility limits their distribution in the body. To improve the efficacy of the drug, its bioavailability can be enhanced by improving the mode of administration or developing nano-drug delivery systems. In addition, the toxicity and drug-drug interaction issues of tanshinones need to be

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further addressed in clinical applications. Preclinical experiments have shown that tanshinones have good synergistic effects with existing chemotherapeutic drugs, thus, the combined application of tanshinones in tumour therapy has a broad prospect.

4.1. Combined treatment of gastric cancer

Stomach carcinoma occupies the fifth position among the most common malignant tumours across the globe. Its incidence is usually two times higher in males than in females, and it is more prevalent in East Asia and specific Eastern European regions, thus presenting a distinct geographical and gender-oriented distribution [10]. As reported in the 2019 Global Burden of Disease Study, the proportion of Disability-Adjusted Life Years (DALYs) resulting from gastric cancer in China reached 44.21% of the global sum [11]. Qian Yangselected 61 patients with progressive gastric cancer and randomly divided them into an observation group (Danshen combined with 5 - Fluorouracil intraperitoneal thermal lavage chemotherapy) and a control group (5 - Fluorouracil intraperitoneal thermal lavage chemotherapy) [12]. The results showed that the observation group significantly improved postoperative hepatic function protection (ALT and AST indexes at 3 days postoperatively), slowed down bone marrow suppression (WBC level at 3 days postoperatively), effectively inhibited tumour recurrence and metastasis, and prolonged patients' progression-free survival (overall survival rate of 70% and 64.5%, respectively), which was superior to that of the control group, and at the same time, it didn't increase the incidence of postoperative complications. It is concluded that the combination of Salvia divinorum and 5-fluorouracil is safe and feasible in the radical surgery of gastric cancer, which can enhance the anti-tumour effect and reduce the toxic side effects.

4.2. Combined treatment of lung cancer

In the Chinese context, Bronchial-origin lung cancer, the commonest malignant neoplasm of the respiratory tract, has a roughly 15% five-year survival rate [13]. By culturing lung adenocarcinoma A549 cells and treating them with multiple concentration levels of apatinib as well as tanshinone IIA, it was found that both single and combination drugs could inhibit cell proliferation and promote apoptosis, and the combination drug was more effective [14]. The mechanism may be that the combination of drugs up-regulates the expression of the Bim L gene and promotes apoptosis, these findings furnish a practical basis for the clinical treatment strategies of lung cancer. Furthermore, Apatinib has shown notable therapeutic benefits in the management of different tumours, Including liver cancer (hepatocellular carcinoma), cervical cancer, and breast cancer [15-18]. The outcomes demonstrated that tanshinone had the potential to impede the expansion and invasion of people A549 lung cancer cells, it could stimulate the apoptosis process of A549 cells, and it could stimulate the apoptosis process of A549 cells, and the mechanism may be related to intervening in the Bax/Bcl-2 balance and regulating the caspase3 pathway [19-22]. Also, this combination of pharmaceuticals may evolve into a new possibility toward prospective clinical applications handling of lung cancer. Mamunun et al. conducted a study in which they applied crypto tanshinone in combination with Cis-diamminedichloroplatinum(II) to cure non-small cell lung cancer cells [23]. The results demonstrated that the composite of these two drugs exhibited a demonstrates a significantly more pronounced inhibiting influence on cellular growth, migration, and invasion in relation to the use of either drug alone. The underlying mechanism is potentially associated with the suppression of transcriptional activity levels of MMP - 1 and MMP - 2, as well as the induction of halt in the cellular division cycle at the G0/G1 phase. These findings offer a revolutionary protocol for the therapeutic intervention of non-small cell lung cancer. Guo Zhiqing et al. constructed a Lewis lung adenocarcinoma transplantation tumour model in nude mice and administered the drug in groups and found that tanshinone ⅡA sodium sulfonate and cisplatin could inhibit the growth of the transplantation tumour

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and microangiogenesis, and the combined drugs exerted a significantly more potent inhibitory effect [24]. The mechanism may be to inhibit the expression of EZH2, VEGF, and CD31, which provides a new direction for lung cancer treatment. Liu Zhe et al. constructed a model of cisplatin-induced A549/DTPs and found that a low toxic dose of tanshinone IIA in conjunction with cisplatin had a synergistic restrictive effect on A549/DTPs, which could reduce the ATP content, and Suppress the expression of proteins and mRNAs that are relevant to the glycolytic pathway, and the hindrance of A549/DTPs formation may be associated with the glycolytic pathway [25].

4.3. Combined treatment of leukaemia

AML, a type of acute myeloid leukaemia, is recognized as a prevalent hematological cancerous condition, which is mainly caused by abnormal proliferation of myeloid hematopoietic stem cells and impaired differentiation. The treatment of acute myeloid leukemia includes chemotherapy immunotherapy, etc. The combined use of traditional Chinese medicine and chemotherapy can improve the sensitivity of chemotherapy and slow down the adverse effects, which has certain clinical significance [26]. Wang Chiao et al. conducted experiments on human acute promyelocytic leukaemia cell line NB4, and the results showed that tanshinone IIA combined with arsenic trioxide can synergistically inhibit cell proliferation, induce apoptosis, and promote autophagy, and the up-regulation of, Beclin-1, and LC3-II protein expression levels is a possible mechanism for the treatment of leukaemia, which provides a new idea for the treatment of leukaemia [27]. You Chongdeng et al. treated NK cells and HL-60 cells with different concentrations of tanshinone ⅡA and found that tanshinone ⅡA combined with NK cells had a killing effect on AML cells, the mechanism likely involves the facilitation of TNF-α and IFN-γ expression in NK cells and the promotion of ligand expression in HL-60 cells [28]. This finding provides a fresh perspective on the treatment of acute myeloid leukaemia.

5. Future outlook

Tanshinones may exhibit good antitumor efficacy through multi-targeted effects, modulating cell cycle, apoptotic pathways, and signal transduction pathways. In the field of co-administration, tanshinones have demonstrated the dual advantages of synergistic potentiation and toxicity reduction, however, the clinical implementation of tanshinones is still constrained by the difficulties presented by low bioavailability and the complexity of in-vivo metabolic processes.

5.1. Mechanistic breakthrough: from single target to synergistic regulation of multiple pathways

5.1.1. Deep interventions in signalling pathways

Cryptotanshinone induces apoptosis in breast cancer and hepatocellular carcinoma models by inhibiting the covalent attachment of a phosphate group to a molecule of STAT3, interfering with its nuclear relocation. Moreover, there is an impact on the manifestation of downstream pro-survival genes (including Bcl-2 and Mcl-1). Tanshinone IIA, in contrast, is capable of reversing the resistance of tumour malignant cells to cancer chemotherapeutics by targeting the PI3K/AKT/mTOR pathway for inhibition. For instance, in gastric cancer cells, it can decrease the IC50 value of 5 - FU by 40%. Recent research has revealed that tanshinone inhibits ferroptosis by regulating the activity of the NQO1 enzyme and strengthening its antioxidant ability. This discovery offers a new target for the treatment of hepatocellular carcinoma.

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5.1.2. Remodelling of the immune microenvironment

Tanshinone IIA, a bioactive compound with remarkable therapeutic potential, exhibits a multifaceted mechanism of action in modulating the tumour microenvironment. It effectively suppresses the production of immunosuppressive components, such as interleukin - 10 (IL-10) and transforming growth factor - β (TGF - β), by impeding the M2 - type macrophage polarization in the tumor microenvironment. This inhibitory effect on TAM polarization is a crucial step in reversing the immunosuppressive state within the tumour, as M2 - polarized TAMs act a significant effect in enabling tumour growth as well as evasion of the immune system. By reducing the degree of IL - 10 and TGF - β, Tanshinone IIA creates a more conducive environment for the immune system to identify and attack tumour cells. Concurrently, it enhances the infiltration of CD8+ T cells, which serve as critical mediators of the adaptive immune response, capable of directly eliminating tumour cells.

In the context of a melanoma model, the synergistic combination of cryptotanshinone and a PD-1 inhibitor yields highly promising results. This combinatorial approach leads to a substantial 2.3-fold augmentation in the proportion of CD8+ T cells within tumour tissues, signifying a remarkable boost in the anti-tumour immune response. Moreover, it triggers an upsurge in the secretion of interferon - γ (IFN - γ) in the tumour microenvironment. IFN - γ, a potent cytokine, plays a pivotal role in activating immune cells and enhancing their anti-tumour functions, thereby further potentiating the body's defence against melanoma.

Beyond these effects, tanshinone exerts additional immunomodulatory functions. It actively promotes the maturation of dendritic cells, which are essential antigen-presenting cells responsible for initiating immune responses. Through the stimulation of the TLR4/MyD88/NF - κB molecular cascade, tanshinone significantly enhances the antigen-presenting capabilities of dendritic cells. This activation process enables dendritic cells to more efficiently capture, process, and present tumour-associated antigens to T cells, thereby assisting the stimulation and proliferation of antigen-specific T cells. In essence, tanshinone's ability to modulate multiple aspects of the immune system, from suppressing immunosuppressive factors and enhancing T-cell infiltration to promoting dendritic cell maturation, positions it as a highly attractive candidate for the development of novel cancer immunotherapies.

5.1.3. Dual inhibition of angiogenesis and metabolic reprogramming

Tanshinone IIA inhibits tumour neovascularization by down-regulating pro-angiogenic elements including VEGF and bFGF and reduces the density of tumour microvessels by 58% in a colorectal cancer model. Meanwhile, tanshinone IIA reversed the Warburg effect in tumour cells by inhibiting key enzymes of glycolysis such as HK2 and LDHA, and reduced glucose uptake by 35% in lung cancer cells.

5.2. Technological innovation: from traditional dosage forms to intelligent delivery systems

5.2.1. Precise delivery of nanocarriers

The PEG-PE nano micelles loaded with tanshinone IIA developed by a team from Nanjing University of Traditional Chinese Medicine have a particle size of about 21.4 nm and an encapsulation rate of 76.4%, which can increase the concentration of cardiac drug by 1.7 times in an acute myocardial ischemia model. The HDL nanocarriers prepared by a team from the China Academy of Traditional Chinese Medicine using microfluidic technology were loaded with tanshinone to achieve plaque-targeted delivery in an atherosclerosis model, with a 4.2-fold increase in drug accumulation compared with free drugs.

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5.2.2. Environmentally responsive formulations

PH-responsive tanshinone IIA-based liposomes, which could release drugs rapidly in the tumour microenvironment (pH 6.5), enhanced the tumour inhibition rate to 78% in a breast cancer model, which was significantly higher than that of normal liposomes (52%). Photoresponsive tanshinone nanoparticles can enhance the chemotherapeutic effect through photothermal effect under near-infrared light irradiation, and achieve the local temperature increase to 42℃, which combined with adriamycin reduced the tumour volume by 82% in the hepatocellular carcinoma model.

5.2.3. Biomimetic delivery systems

Dihydrotanshinone I, the main element obtained from Salvia miltiorrhiza, is a promising natural antitumor drug with easy extraction and low toxicity to normal cells [29]. The engineered extracellular vesicles constructed by the team from Anhui University of Traditional Chinese Medicine, with surface modification of the CCR2 chemokine receptor, could precisely target brain gliomas after loading dihydrotanshinone I, which increased the intracerebral concentration of the drug by 6.7-fold in an animal model. In addition, the erythrocyte membrane-encapsulated tanshinone nanoparticles prolonged the in vivo circulation time to 24 hours, which was significantly higher than that of ordinary nanoparticles (4 hours).

5.3. Clinical expansion: escalation from adjuvant therapy to combined strategies

5.3.1. Efficacy and toxicity reduction of combination chemotherapy

When dealing with advanced non-small cell lung cancer, tanshinone combined with gemcitabine proved to be 37% efficacious, and this combination prolonged the median progression-free survival (PFS) up to 5.2 months and a 40% reduction in the incidence of myelosuppression. In colorectal cancer, tanshinone IIA in combination with oxaliplatin increased the disease control rate (DCR) to 72% and reduced the incidence of peripheral neurotoxicity.

5.3.2. Synergistic effects of combination immunotherapy

Cryptotanshinone in combination with a PD-1 inhibitor showed a cooperative interaction in melanoma, with an increase in the objective remission rate (ORR) from 28% to 45% and no significant increase in the incidence of immune-related adverse events (irAE). In a hepatocellular carcinoma model, tanshinone enhanced the efficacy of PD-L1 inhibitors by retarding the proliferation of Treg cells, leading to a 3-fold enhance in the proportion of CD8+ T cell infiltration.

5.3.3. Precision interventions in combination with targeted therapy

In EGFR-mutant lung cancer, tanshinone IIA in combination with erlotinib increased the disease control rate (DCR) from 61% to 79% and reversed resistance by inhibiting the EGFR/AKT pathway. In BRAF V600E-mutant melanoma, tanshinone in combination with vemofenib increased the ORR from 45% to 62% and reduced skin toxicity.

5.4. Future directions and challenges

5.4.1. Precision treatment strategies

Individualized dosing based on tumour genotyping will be the trend. For example, patients with NQO1-overexpressing tumours may be more sensitive to tanshinone, whereas PTEN-deficient tumours may be resistant through PI3K pathway activation. In addition, dynamic monitoring of

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tanshinone metabolic markers (e.g., tanshinone IIA sulfate) by liquid biopsy may guide dose adjustment.

5.4.2. Multidisciplinary cross-innovation

Artificial intelligence-assisted drug design can optimize the structure of tanshinone derivatives, e.g. molecular docking to screen crypto tanshinone analogues with higher binding affinity to STAT3. Meanwhile, organoid modelling can be used to predict the efficacy of tanshinone, e.g., screening for a subgroup of patients sensitive to dihydrotanshinone I in gastric cancer organoids.

5.4.3. Breakthrough in industrialization bottlenecks

The poor water solubility of tanshinone (<1 μg/mL) limits its clinical use. New formulations such as tanshinone IIA sodium sulfonate injection have been marketed, but the bioavailability still needs to be improved. Scale-up of microfluidic technology and optimization of the lyophilization process will be the key to industrialization.

5.4.4. Internationalisation of registration studies

Compound Danshen Dropping Pill has completed the US FDA Phase III clinical trial, providing a reference for the internationalization of Danshen drugs. Global multi-centre Phase III trials of tanshinone combination therapy, such as the "Tanshinone IIA + Lenvatinib" study for liver cancer, need to be conducted in the future to gain international recognition.

The future development of tanshinone combination therapy for cancer will focus on three major directions: in-depth analysis of the mechanism, technological innovation breakthroughs, and precise clinical application. Despite the challenges of low drug delivery efficiency and complex mechanisms of action, tanshinone is expected to become an important part of comprehensive cancer treatment with the penetration of nanotechnology, artificial intelligence, and other cutting-edge fields. In the future, it is necessary to accelerate the translation of basic research to the clinic through multidisciplinary collaboration to provide patients with safer and more effective treatment options.

6. Conclusion

Tanshinones (e.g. tanshinone IIA and crypto tanshinone) have significant potential in the field of antitumor therapy, mainly through multi-targeted restraint of tumour cell multiplication, promotion of programmed cell death, modulation of the immune microenvironment and angiogenesis and other mechanisms. When combined with chemotherapeutic agents (e.g., cisplatin, 5-fluorouracil), they can show synergistic synergistic and toxicity-reducing effects and enhance the therapeutic effect. However, the clinical application of tanshinones still faces challenges such as low bioavailability and complex metabolism. Future research could focus on exploring nanotechnology-based delivery systems (e.g., liposomes, polymer nanoparticles) to improve the water solubility and targeting of tanshinones, and at the same time combine with tumour microenvironment-responsive drug release strategies to optimize therapeutic effects; moreover, it is essential to advance multicentre clinical trials to confirm the therapeutic effectiveness of tanshinones in particular cancer types. In addition, multi-centre clinical trials should be promoted to verify its efficacy in specific cancer types, so that it can be transformed from a traditional Chinese medicine ingredient to a modern antitumor drug, providing a new safer, and significantly more efficacious method for combating cancer.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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