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Synergistic Potential of Traditional Chinese Medicine and CART Cell Therapy: Immunoenhancement and Persistence Regulation Strategies

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Abstract: CAR-T cell therapy demonstrates tremendous potential for tumor treatment, yet faces challenges in solid tumor therapy due to immune suppression, T-cell exhaustion, and cytokine release syndrome (CRS) induced by the tumor microenvironment (TME). Traditional Chinese medicine (TCM) holds substantial potential to enhance CAR-T efficacy and mitigate adverse reactions due to its multi-targeted advantages. TCM active ingredients and formulations can synergistically amplify CAR-T anti-tumor effects while reducing adverse events through multiple mechanisms, including reversing T-cell exhaustion, prolonging CAR-T cell persistence, improving TME hypoxia and fibrosis, modulating gut microbiota, and suppressing CRS. This benefits patient treatment and recovery. Combining TCM with CAR-T therapy can increase objective response rates, prolong cell persistence, and reduce CRS incidence. Future efforts will focus on exploring the precise mechanisms and standardized protocols for TCM-enhanced CAR-T treatment through high-quality clinical trials and multi-omics technologies, driving its clinical translation and application.

Keywords: Traditional Chinese Medicine; CAR-T cell therapy; Tumor microenvironment; T cell exhaustion; Cytokine storm

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1. Introduction

CAR-T cell therapy is a cancer immunotherapy that genetically engineers T cells to express chimeric antigen receptors (CARs), enabling them to precisely recognize and eliminate tumor cells. This approach has significantly improved overall survival rates and quality of life for patients with malignant hematologic malignancies and is now widely adopted in clinical practice. However, its application in solid tumor treatment remains challenging, primarily due to the immunosuppressive properties of the tumor microenvironment (TME).

Within the TME, T cells highly express inhibitory receptors such as PD-1 and CTLA-4. These molecules suppress the PI3K/AKT signaling pathway, leading to T cell exhaustion and diminishing the therapeutic efficacy of CAR-T cells. Hypoxic conditions and tissue fibrosis within the TME further hinder effective CAR-T cell infiltration, limiting treatment outcomes. Conversely, CAR-T therapy may also trigger severe adverse reactions such as cytokine release syndrome (CRS), compromising patient safety and recovery outcomes.

Traditional Chinese medicine shows promising applications in synergizing CAR-T therapy, particularly in addressing some limitations of CAR-T in treating solid tumors. Leveraging their multi-component, multi-targeted properties, certain TCM formulas that fortify the body's foundation can enhance overall immune status through mechanisms like replenishing qi and nourishing blood, or tonifying yin and warming yang. These formulas suppress excessive inflammatory responses, regulate fibrosis and abnormal angiogenesis within the tumor microenvironment (TME), thereby promoting CAR-T cell infiltration and cytotoxicity. The World Health Organization (WHO) has incorporated traditional Chinese medicine into its cancer supportive care framework. Emphasizing holistic concepts and syndrome differentiation, TCM reduces healthcare costs while prioritizing mind-body integrated rehabilitation models, offering unique Eastern wisdom and solutions for global cancer prevention and treatment.

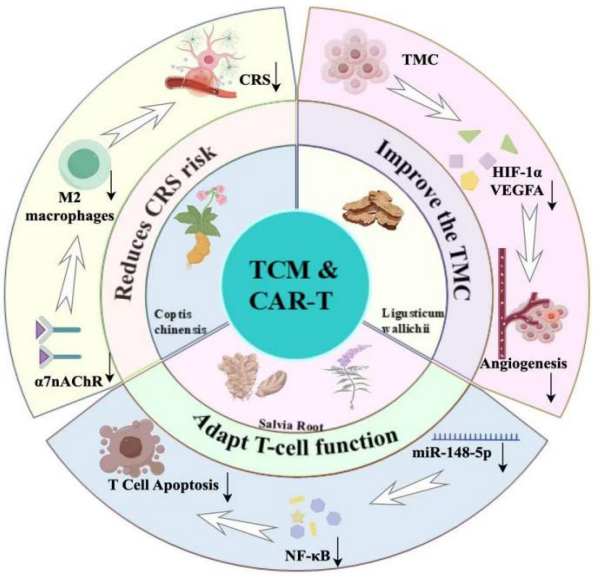

Figure 1. Traditional Chinese medicinal materials and CAR-T.

2. Traditional Chinese medicine modulates T cell function: Alleviating exhaustion and prolonging survival

2.1. Reversal of T-cell exhaustion by traditional Chinese medicine components

T cell exhaustion is one of the core mechanisms underlying immune dysfunction in chronic infections and the tumor microenvironment (TME). Its occurrence is closely associated with the presence of immunosuppressive cells in the TME, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages, as well as the cytokines they release, including transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10). This state is primarily characterized by sustained high expression of inhibitory receptors

(such as PD-1 and CTLA-4), metabolic abnormalities including mitochondrial dysfunction, and epigenetic alterations. It represents an adaptive response of T cells to prolonged antigenic stimulation. While T cell exhaustion provides some protective effect in suppressing autoimmune reactions, it also significantly impairs T cell tumor clearance capacity, limiting the efficacy of immunotherapies such as CAR-T cell therapy.

Recent studies have demonstrated that multiple active components of traditional Chinese medicine exhibit potential to reverse T cell exhaustion in in vivo experiments and animal models. The underlying mechanisms involve multiple pathways, including regulating key inhibitory receptors, improving T cell metabolic dysfunction, modulating exhaustion-associated transcription factors, and reshaping the tumor microenvironment. Shi *et al.* [1] discovered in a systemic candidiasis infection model that paeoniflorin promotes memory T cell formation by upregulating SOCS1/SOCS3 expression, thereby inhibiting excessive activation of the cytokine/JAK/STAT pathway. Yu *et al.* [2] confirmed in a Hepa1-6 subcutaneous tumor-bearing mouse model that combined treatment with bufadienolide and either pyruvate (PA) or oxalic acid (OX) suppressed lactate dehydrogenase A (LDHA) expression, enhanced the activity and stability of NK1.1 and NKG2D receptors in NK cells, and elevated serum levels of perforin, TNF-α, and IFN-γ, ultimately significantly inhibiting tumor growth. Zhang *et al.* [3] discovered in a cardiomyocyte injury model that Tanshinone IIA (TIIA) inhibits NF-κB pathway activation by regulating miR-148-5p, thereby reducing T cell apoptosis. These studies suggest that active components of traditional Chinese medicine can reverse T cell exhaustion through multiple pathways, providing theoretical support for combining traditional Chinese medicine with immune-targeted therapies to enhance tumor treatment efficacy.

2.2. Traditional Chinese Medicine Enhances CAR T-Cell Persistence

Insufficient CAR-T cell persistence is a key limiting factor affecting the long-term efficacy of this therapy, primarily associated with mechanisms such as T cell exhaustion, immune desertification, and metabolic dysregulation, which reduce tumor clearance capacity and limit treatment outcomes. Recent studies have revealed that multiple classical Chinese herbal formulas can optimize CAR-T cell function through multiple mechanisms, prolonging their survival in vivo and enhancing antitumor activity. Gao *et al.* [4] demonstrated in an IL-6-induced HCCLM3 hepatocellular carcinoma epithelial-mesenchymal transition (EMT) model and H22 tumor-bearing mouse model that Biejia Jianwan promotes $CD8^+$ T cell infiltration into the tumor microenvironment by upregulating CCL5 chemokine expression [5]. simultaneously modulating the CCL5–CCR5 axis to enhance T-cell chemotaxis, suppressing PD-L1 expression to alleviate immunosuppressive microenvironments, and downregulating the EMT-related transcription factor TWIST via the JAK/STAT3 signaling pathway to sustain T-cell activity. Zhang *et al.* [6,7] discovered in a total parenteral nutrition (TPN)-induced intestinal mucosal immune injury model that Yupingfeng Powder modulates gut microbiota in Peyer's patches (PPs), enhances antigen-presenting cell function, and subsequently activates naive T cells via MHC-antigen peptide complexes and co-stimulatory signals (CD28-B7). This promotes cytokine secretion (e.g., IL-2), induces T cell clonal expansion, and increases the proportion of central memory T cell precursors ($CD62L^+CD127^+$). This formula also significantly reduces apoptosis rates in activated T cells (from 13.1% in the model group to 6.2% in the Yupingfeng group), promoting cell survival by regulating Bcl-2/Bax expression, enhancing CCR9/α4β7-mediated migration and retention of memory T cells in the small intestinal lamina propria, and maintaining levels of key survival factors like IL-7 and IL-15. This multifaceted approach supports the long-term persistence of Tcm cells.The synergistic multi-component, multi-target regulatory mechanism of

traditional Chinese medicine offers a unique approach to enhancing CAR-T therapy persistence. Its integration with modern immunotherapy holds promise as a novel strategy to overcome tumor resistance and recurrence.

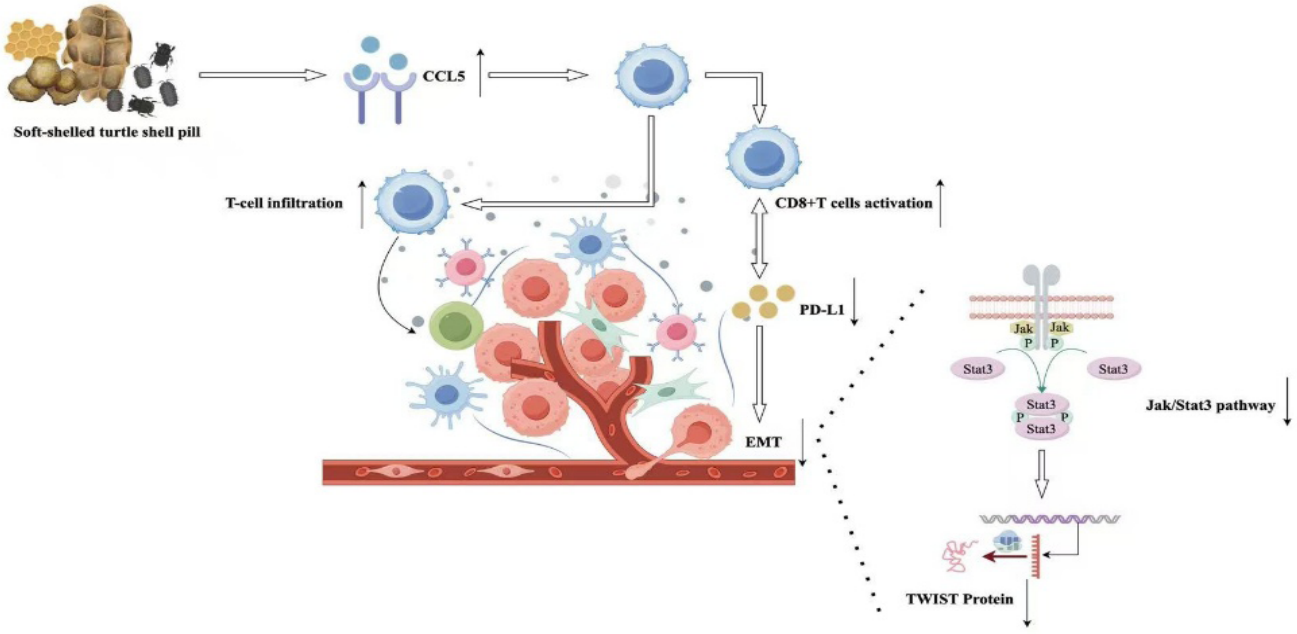

Figure 2. Biejia Jianwan suppresses TME to maintain T cell activity.

3. Traditional Chinese medicine improves tumor microenvironment: Targeted intervention in hypoxia and fibrosis

3.1. Blood-activating and stasis-resolving herbs alleviate hypoxia

Hypoxia within the tumor microenvironment (TME) is a key factor contributing to radiation resistance, chemotherapy resistance, and immunosuppression. Its mechanism is primarily associated with the sustained activation of hypoxia-inducible factor-1α (HIF-1α), which not only promotes tumor cell invasion and metastasis but also creates an immunosuppressive microenvironment by recruiting myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), thereby diminishing the efficacy of immunotherapies such as CAR-T cells and NK cells. Traditional Chinese medicines that promote blood circulation and resolve stasis offer a potential strategy to alleviate tumor hypoxia through their multi-targeted mechanism of action," improving microcirculation–modulating immunity–reprogramming metabolism" [8]. Among these, chuanxiongzine and tanshinone IIA provide novel insights for reversing TME immunosuppression by enhancing tumor blood flow perfusion and inhibiting hypoxia-related signaling pathways through distinct mechanisms.

Liu *et al.* [9] discovered in an in vitro model of A549 lung cancer stem-like cells (CSLCs) that chuanxiongzine significantly suppressed the expression of the vascular mimicry (VM)-associated protein EphA2 ($P < 0.05$) and downregulated the protein levels of hypoxia-inducible factor HIF-1α and vascular endothelial growth factor VEGFA ($P < 0.01$). suggesting that chuanxiongzine may exert anti-angiogenic effects by modulating the hypoxia-angiogenesis signaling axis in the tumor microenvironment (TME). Ren *et al.* [10] similarly demonstrated in the A549 CSLCs model that Tanshinone IIA significantly suppressed VEGF expression under both normoxic and hypoxic conditions (48.6% reduction in normoxia, 62.3% reduction in hypoxia) by

modulating the VE-cadherin/MMP-9/Integrinβ1 signaling cascade to remodel the tumor microenvironment. The combination of blood-activating and stasis-resolving Chinese herbal medicines with anti-angiogenic drugs (e.g., bevacizumab) holds potential for synergistic inhibition of tumor neovascularization. However, caution is warranted to avoid the risk of "vascular pruning" caused by excessive vascular normalization. Currently, Salvia and Ligusticum Injection is widely used as an adjunctive therapy for cardiovascular and cerebrovascular diseases. Future research may explore its potential value as an adjunct to tumor chemotherapy and immunotherapy, a translational direction warranting further investigation.

3.2. Anti-fibrotic effects promote CAR T-cell infiltration

In solid tumor therapy, the physical and biochemical barriers formed by tumor tissue fibrosis severely impede CAR-T cell infiltration and function. Overactivated cancer-associated fibroblasts (CAFs) form physical barriers by secreting abundant extracellular matrix (ECM) proteins such as collagen I/III and fibronectin [11], impeding CAR-T cell infiltration while inducing immunosuppression through factors like TGF-β and IL-6. Research indicates that targeting the fibrotic tumor microenvironment significantly enhances CAR-T cell penetration and activity. Traditional Chinese medicine components like crocin and notoginsenosides offer novel strategies for improving CAR-T cell infiltration through their anti-inflammatory, anti-fibrotic, and ECM remodeling effects. Crocin, the core active component of safflower, serves as the primary active ingredient in this blood-activating and stasis-resolving agent. Zheng *et al.* [12] investigated the safflower pigment through a PI3K/AKT/mTOR signaling pathway model. They discovered that safflower pigment exerts anti-inflammatory effects by inhibiting the PI3K/AKT signaling pathway (downregulating p-PI3K, PI3K, AKT, and p-AKT protein expression), reducing the secretion of pro-inflammatory factors such as VEGF, and modulating the ratio of apoptosis-related proteins Bcl-2/Bax. Concurrently, Cheng *et al.* [13] observed in tumor microenvironment studies that Notoginsenoside R1 reduces ECM stiffness by inhibiting the release of matrix metalloproteinases (MMPs) associated with NETs formation, thereby promoting CD8+ T cell infiltration. Furthermore, notoginsenosides may also mitigate ECM degradation via the TNF-α/MMP-2 axis with a certain probability [14].

Traditional Chinese medicine exhibits a certain degree of alleviating effect on fibrosis within the TME. Future approaches could combine traditional Chinese medicine with CAR-T targeting the TME to dissolve barriers formed by tumor fibrosis, thereby promoting CAR-T infiltration.

4. Immunomodulatory strategies of traditional Chinese medicine to reduce CRS risk

4.1. Intervention in cytokine storms

Cytokine release syndrome (CRS) is the most common and potentially life-threatening complication in CAR-T cell therapy, severely limiting its clinical application and adoption. Its pathogenesis involves an overactivated immune system triggering explosive release of inflammatory factors such as IL-6, IFN-γ, and TNF-α, leading to systemic inflammatory responses and multi-organ dysfunction. Current clinical interventions primarily rely on monoclonal antibodies, which face limitations such as single-target specificity and difficulty in blocking upstream signaling pathways. Consequently, traditional Chinese medicine (TCM) formulas demonstrate unique advantages in CRS prevention and treatment through multi-targeted interventions. Their strategy primarily focuses on inhibiting key inflammatory cytokines, modulating core inflammatory signaling pathways,

stabilizing immune cell function to suppress excessive activation, protecting endothelial cells, and reducing vascular leakage, critical steps in CRS development, thereby inhibiting CRS progression at multiple levels.

Xin *et al.* [15] found that berberine inhibits the anti-inflammatory function of M2 macrophages and reduces IL-10 secretion by activating α7 nicotinic acetylcholine receptors (α7nAChR). This mechanism may involve α7nAChR-mediated inhibition of the JAK2-STAT3 signaling pathway or downregulation of NF-κB activity through cholinergic anti-inflammatory pathways, thereby suppressing IL-10 transcription and release. This action helps reverse immunosuppressive microenvironments and restore pro-inflammatory/anti-inflammatory balance, demonstrating potential value in infection- or tumor-associated immune regulation. Hao *et al.* [16] demonstrated that Gansui Banxia Tang inhibits excessive neutrophil recruitment by targeting the CXCL2/CXCR2 pathway. During CRS, activated macrophages massively secrete CXCL2, which binds to CXCR2 on neutrophil surfaces to promote their infiltration into inflammatory sites. This activates NF-κB and MAPK pathways, further amplifying the release of inflammatory mediators like IL-1β and IL-8. The terpenoid esters in Gan Sui directly inhibit CXCL2 transcription, while Pinellia alkaloids downregulate CXCR2 expression, thereby blocking this positive feedback loop through dual-targeted inhibition.

Traditional Chinese medicine (TCM) offers a holistic regulatory strategy for CRS prevention and treatment distinct from monoclonal antibody drugs, operating through a multidimensional synergistic mechanism: "antagonizing cytokines, inhibiting signaling pathways, stabilizing immune cells, protecting target organs." Current evidence primarily stems from basic research and small-scale clinical observations. The precise targets, pharmacokinetic properties, and synergistic effects with conventional anti-CRS drugs require validation through high-quality randomized controlled trials (RCTs) and in-depth mechanistic studies. Integrating TCM into CRS prevention and control systems holds promise for effectively managing toxicity while maximizing the antitumor efficacy of CAR-T cells, thereby broadening the therapeutic window.

4.2. Gut microbiota modulation of CRS association

In recent years, the role of gut microbiota in immune regulation has garnered increasing attention, with its association with cytokine release syndrome (CRS) emerging as a research hotspot. Studies indicate that dysbiosis of the gut microbiota compromises intestinal barrier function, allowing harmful bacteria and their metabolites to enter the systemic circulation. This activates inflammatory signaling pathways, promotes the release of pro-inflammatory cytokines (such as IL-6 and TNF-α), and ultimately triggers a cytokine storm. During CAR-T therapy, pre-treatment chemotherapy-induced gut microbiota disruption exacerbates CRS severity, providing theoretical support for traditional Chinese medicine (TCM)-based microbiota modulation as a CRS intervention [17]. Intervention strategies, exemplified by TCM formulas improving microbiota composition and rhubarb restructuring the intestinal microenvironment, demonstrate significant CRS mitigation effects by multi-target regulation of the microbiota-immune interaction network.

TCM formulas regulating microbiota structure offer unique advantages in CRS prevention and treatment. Liu *et al.* [18] found that spleen-tonifying formulas like Sijunzi Tang increase the abundance of probiotics (e.g., bifidobacteria, lactobacilli), promote short-chain fatty acid (SCFA) production, thereby enhancing regulatory T cell (Treg) function and suppressing excessive inflammatory responses. Zhang *et al.* [19] discovered that rhubarb and its active components exert CRS intervention by restructuring the intestinal microenvironment. Anthraquinone components of rhubarb (e.g., emodin, aloe-emodin) downregulate the TLR4/NF-κB pathway to reduce intestinal macrophage activation while promoting tight junction protein expression (occludin, ZO-1) to

repair chemotherapy-damaged intestinal barriers.

Current individual variations hinder the establishment of standardized treatment protocols, and the interaction mechanisms among herbal components, microbiota, and hosts require further elucidation. Future research integrating metagenomic sequencing and metabolomics could establish predictive models for "Chinese herbal medicine-microbiota-CRS" interactions. Exploring combined regimens of Chinese herbal medicine and probiotics may achieve synergistic effects in CRS prevention and treatment.

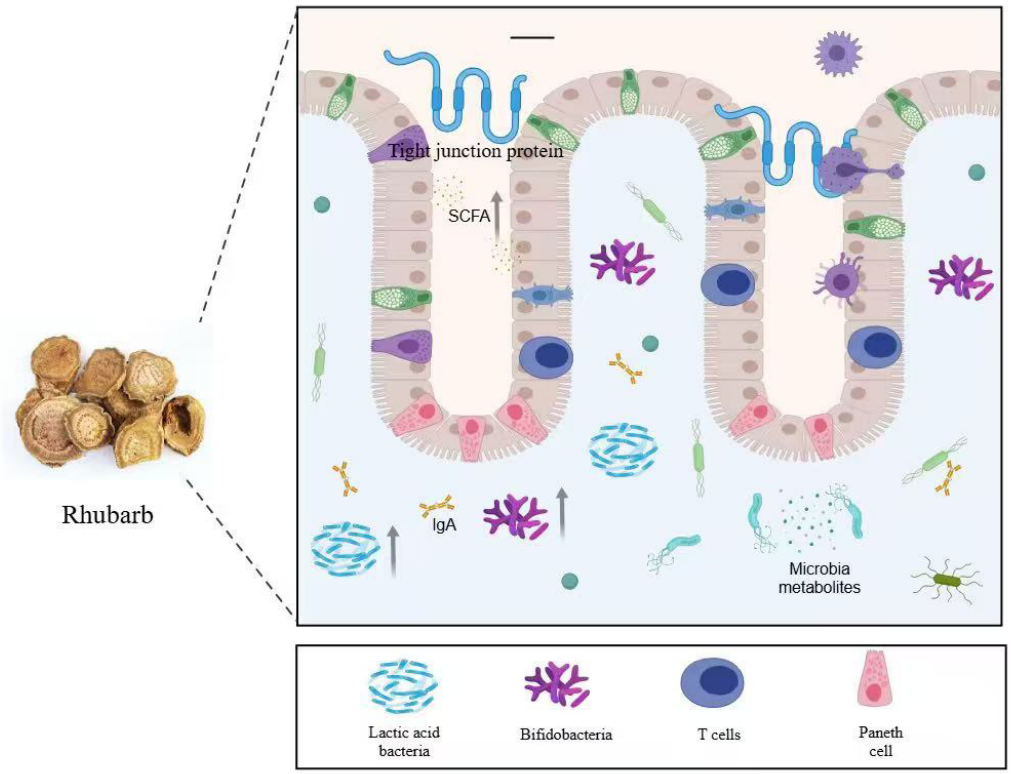

Figure 3. Rhubarb acts on the gut microenvironment to inhibit CRS occurrence.

5. Clinical Translation Pathways for Combination Therapy

5.1. Current Clinical Evidence

As applied research continues to advance, multiple clinical observations and prospective studies have preliminarily demonstrated the feasibility and clinical value of combining traditional Chinese medicine with CAR-T therapy in treating malignant tumors. Notably, studies on Salvia miltiorrhiza combined with CAR-T therapy for B-cell lymphoma and Yu Pingfeng San pre-treatment to reduce cytokine release syndrome (CRS) incidence provide crucial practical evidence for optimizing cell immunotherapy through integrated Chinese and Western medicine. These clinical data not only validate the potential of TCM in enhancing therapeutic efficacy and mitigating adverse effects but also guide the design of subsequent large-scale clinical trials.

A clinical study by Xiao *et al.* [20] demonstrated that co-administering Danshen significantly optimized CAR-T therapy outcomes in B-cell lymphoma patients. The objective response rate in the Danshen group increased to 85% (vs. 67% in the control group), with CAR-T cell expansion peaks averaging 1.5 times higher

and persistence extending beyond 28 days. Regarding safety, the incidence of grade 3 or higher CRS in the Danshen group decreased to 14%, significantly lower than the 31% in the control group. This effect may be related to Danshen's inhibition of the IL-6/JAK/STAT3 signaling pathway. The results indicate that Danshen can optimize CAR-T therapy through a dual mechanism of "enhancing efficacy and reducing toxicity." Shuai *et al.* [21] found that pre-treatment with Yupingfeng Powder significantly reduced the CRS incidence to 25.6% compared to 46.5% in the control group ($p = 0.032$). Mechanistic studies revealed that serum IL-6 and IFN-γ peak levels decreased by 30%–40% in the pretreated group, while the proportion of CD4+CD25+Foxp3+ Treg cells increased twofold. This aligns with the role of astragaloside IV in Yupingfeng San, which modulates Th17/Treg balance. Long-term follow-up data revealed no significant difference in progression-free survival (PFS) between groups, indicating that Yupingfeng San reduced toxicity without compromising antitumor efficacy.

In summary, the combination of TCM and CAR-T therapy shows great promise in improving treatment outcomes and quality of life for patients with malignant tumors. However, current studies remain limited by small sample sizes and insufficient standardization. Future efforts should focus on conducting larger-scale phase III randomized controlled trials (RCTs) and deepening the exploration of its mechanisms of action. This will facilitate the transition of TCM from empirical use to evidence-based medical practice in the field of cellular immunotherapy, ultimately achieving precise synergy between TCM and CAR-T therapy.

5.2. Future research directions

Current preclinical and preliminary clinical studies combining traditional Chinese medicine with CAR-T cell therapy have demonstrated promising results, though their mechanisms of action and efficacy remain unclear, posing challenges for widespread adoption. Moving forward, traditional Chinese medicine will integrate more closely with other fields. For instance, a dynamic monitoring system based on immune cell subset analysis could establish a ternary model linking "TCM components-immune subsets-therapeutic efficacy prediction." Single-cell sequencing technology could be employed to dynamically track changes in the immune microenvironment during treatment, enabling precise evaluation and personalized dosing for combined TCM-CAR-T therapy. For instance, astragaloside IV reduces the proportion of PD-1+ exhausted T cells, enhancing CAR-T persistence [22]. Concurrently, nanogel technology offers novel approaches for the targeted delivery of TCM bioactive components. This system protects small-molecule TCM components from rapid clearance and enables their enrichment at tumor sites via the EPR effect or active targeting. It may even enable controlled release of TCM immunomodulators for synergistic action with CAR-T cells. For instance, pH-responsive nanogels loaded with *Tripterygium wilfordii homoside* selectively suppress tumor-associated macrophages (TAMs) in the tumor microenvironment, enhancing CAR-T infiltration [23]. Future developments may include dual-drug delivery systems simultaneously transporting CAR-T cells and TCM immunomodulators.

This technological breakthrough transforms traditional empirical knowledge into digital standards, propelling TCM from "vague experience" toward "precision medicine." Ultimately, it enables personalized prevention and treatment of chronic and complex diseases (such as fibrosis and tumors), positioning TCM as a vital complement to global healthcare systems.

6. Conclusion

Theoretically, the synergistic therapy combining traditional Chinese medicine (TCM) with CAR-T cells

demonstrates unique comprehensive advantages. Through its multi-component, multi-target holistic regulatory mechanism, it overcomes the limitations of existing monotherapy across multiple dimensions. On one hand, TCM effectively modulates the tumor immune microenvironment by suppressing cancer-associated fibroblast activation and extracellular matrix deposition, thereby enhancing CAR-T cell infiltration into tumor sites. On the other hand, TCM components regulate T cell differentiation states, inhibit the expression of T cell exhaustion-related molecules, and promote the formation of central memory T cell subsets, ultimately prolonging CAR-T cell persistence in vivo. Regarding toxicity management, TCM formulas with heat-clearing, blood-cooling, detoxifying, and stasis-resolving effects significantly inhibit the activation of inflammatory signaling pathways like NF-κB and reduce levels of key inflammatory cytokines such as IL-6 and TNF-α. This mitigates the severity and duration of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). This dual-regulatory effect of "reducing toxicity while enhancing efficacy" embodies a therapeutic philosophy integrating holistic perspectives with precision medicine, aligning with contemporary trends in personalized healthcare.

Practical application in this field still faces several challenges. The complexity and standardization of TCM components pose difficulties, as existing formulations lack unified quality control standards. Significant variations in active ingredient content make it challenging to ensure consistent and reproducible therapeutic outcomes. Second, although basic research suggests multiple potential mechanisms of action, a translation gap persists between laboratory evidence and clinical validation. Rigorous large-scale, multicenter randomized controlled trials (RCTs) are urgently needed to clarify the actual clinical benefits and safety of TCM synergistic therapy. Furthermore, the specific molecular targets of TCM-CAR-T cell interactions, pharmacokinetic characteristics, and optimal timing and protocols for combination therapy lack an established evidence-based medical framework. High-quality research is required to advance these areas, thereby promoting the standardization and internationalization of integrated Chinese-Western medicine approaches in tumor immunotherapy.

Disclosure statement

The author declares no conflict of interest.

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