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Traditional Chinese medicine enhances the effectiveness of immune checkpoint inhibitors in tumor treatment: A mechanism discussion

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ABSTRACT

Ethnopharmacological relevance: Immune checkpoint inhibitors (ICIs) have altered the landscape of tumor immunotherapy, offering novel therapeutic approaches alongside surgery, chemotherapy, and radiotherapy and significantly improving survival benefits. However, their clinical efficacy is limited in some patients, and their use may cause immune-related adverse events (irAEs). Integrating traditional Chinese medicine (TCM) with ICIs has demonstrated the potential to boost sensitization and reduce toxicity. Clinical trials and experimental explorations have confirmed that TCM and its active components synergistically enhance the effectiveness of ICIs.
Aims: This narrative review summarizes the TCM practices that enhance the clinical efficacy and reduce irAEs of ICIs. This paper also summarizes the mechanism of experimental studies on the synergies of Chinese herbal decoctions, Chinese herbal preparation, and Chinese herbal active ingredients. Most of the studies on TCM combined with ICIs are basic experiments. We discussed the mechanism of TCM enhanced ICIs to provide reference for the research and development of TCM adjuvant immunotherapy.
Methods: We conducted a literature search using PubMed and Chinese National Knowledge Infrastructure databases, with a focus on herbal decoction, Chinese medicine preparations, and active ingredients that boost the effectiveness of ICIs and reduce irAEs. The search keywords were "ICIs and traditional Chinese medicine", "PD-1 and traditional Chinese medicine", "PD-L1 and traditional Chinese medicine", "CTLA-4 and traditional Chinese medicine", "IDO1 and traditional Chinese medicine", "Tim-3 and traditional Chinese medicine", "TIGIT and traditional Chinese medicine", "irAEs and traditional Chinese medicine". The search period was from May 2014 to May 2024. Articles involving the use of TCM or its components in combination with ICIs and investigating the underlying mechanisms were screened. Finally, 30 Chinese medicines used in combination with ICIs were obtained to explore the mechanism. In the part of immune checkpoint molecules other than PD-1, there were few studies on the combined application of TCM, so studies involving the regulation of immune checkpoint molecules by TCM were included.
Results: TCM has been shown to boost the effectiveness of ICIs and reduce irAEs. Researchers indicate that TCM and its active components can work synergistically with ICIs by regulating immune checkpoints PD-1, PD-L1, CTLA-4, and IDO1, regulating intestinal flora, improving tumor microenvironment and more.
Conclusions: Combining TCM with ICIs can play a better anti-tumor role, but larger samples and high-quality clinical trials are necessary to confirm this. Many Chinese medicines and their ingredients have been shown to sensitize ICIs in experimental studies, which provides a rich choice for the subsequent development of ICI enhancers.

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Abbreviations

TCM	traditional Chinese medicine
ICIs	immune checkpoint inhibitors
HCC	hepatocellular carcinoma
NSCLC	non-small cell lung cancer
CRC	colorectal cancer
OS	overall survival
DFS	disease-free survival
TME	tumor microenvironment
APS	*Astragalus* polysaccharide
ICD	immunogenic cell death
MHC-I:	major histocompatibility complex I
CAG	cycloastragenol
Tregs	Regulatory cells
GZMB	granzyme B
MDSCs	myeloid-derived suppression cells
TGF-β:	growth factor-β
Neo	neobavaisoflavone
ROS	reactive oxygen species
AD	andrographolide
SMI	Shenmai injection
GQD	Gegen Qinlian decoction extract
JTT	Juzentaihoto
CWQ	Chang Wei Qing decoction
AKK	*Akkermansia*
QTN	The coformulation of ginsenoside Rg3 and quercetin
TNF	tumor necrosis factor
NF-κB	nuclear factor kappa-B
IFN-γ:	interferon gamma
IL-10	interleukin-10
EMT	epithelial-mesenchymal transition
AIL:	ailanthone
PZH	Pien Tze Huang
HXYQ	Huoxue Yiqi recipe
PTEN	phosphatase and tensin homolog
IDO1	Indoleamine-2,3-dioxygenase1
uLMS	antiuterine leiomyosarcoma
GGQL:	Gegen Qinlian decoction
QFTQ	Qingfei Tiaoqi decoction

1. Introduction

In 2022, the World Health Organization's International Agency for Research on Cancer reported nearly 9.7 million tumor deaths and 20 million new cases worldwide, underscoring the immense global economic and social burden of cancer. By 2050, there will be 35 million cancer cases, according to demographic projections (Bray et al., 2024). Therefore, successful cancer prevention and management are an urgent issue. The U.S. Food and Drug Administration's approval of ipilimumab for advanced melanoma signaled the onset of a transformative phase in cancer immunotherapy, particularly with immune checkpoint inhibitors (ICIs). Following this milestone, other ICIs, such as pembrolizumab, nivolumab, atezolizumab, and durvalumab, targeting PD-1 and PD-L1, have been authorized for other cancers, including breast cancer, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and hepatocellular carcinoma (HCC). ICIs provide new care strategies for patients ineligible for radical surgery or irresponsive to chemotherapy or targeted therapy. Whether used alone or together with other agents, ICIs have proven to enhance overall survival (OS) and remission rates (Bianco et al., 2018; J. K. H. Liu et al., 2021; Luo et al., 2021). Patients with metastatic or locally advanced NSCLC expressing PD-L1 show remarkably longer OS after pembrolizumab treatment than after chemotherapy (Mok et al., 2019). Pembrolizumab plus standard chemotherapy substantially prolongs progression-free survival in advanced endometrial tumor patients (Eskander et al., 2023). Similarly, atezolizumab plus bevacizumab offers superior OS and progression-free survival over sorafenib alone for HCC patients (Finn et al., 2020). Despite these groundbreaking advancements, not all patients benefit from ICIs (Morad et al., 2021). A biomarker analysis unveiled a connect of avelumab's survival benefits with the expression of genes linked to innate and adaptive immune activities, tumor mutational burden, APOBEC mutation signature, and PD-L1 level in tumors (Powles T., 2021). However, ICIs also trigger immune-related adverse events (irAEs) by inducing immune responses elsewhere, which may interrupt treatment and even cause death. As such, expanding the population responding to ICI treatment and reducing the irAEs induced by ICI treatment are urgent issues requiring resolution.

TCM is a multi-component, multitargeted medical system with a wide variety of monomers and herbal formulas (Zheng et al., 2023). The rational application of Chinese medicine is safe and affordable, and it has shown effectiveness in treating a wide range of illnesses when combined with Western therapy. Clinical research has demonstrated that TCM plus ICIs is more effective than ICIs alone (Y.-x. Yu et al., 2023). By controlling gut flora and altering the tumor microenvironment (TME), TCM can enhance antitumor immunity (Huang et al., 2020; Kong et al., 2021). Yet, TCM's broad use in cancer therapy has been hampered by the lack of clarity surrounding the active constituents of TCM and mechanisms of action when combined with ICIs (Li et al., 2019). Some studies have identified Chinese medicines that can sensitize PD-1 and PD-L1 inhibitors while reducing irAEs. Nevertheless, the underlying mechanisms have been inadequately explored. Recent research suggests that Chinese medicines can regulate other immune checkpoints, such as IDO1, Tim-3, and CTLA-4. This paper primarily summarizes the clinical efficacy of TCM in enhancing ICIs. It also explores the mechanisms underlying how Chinese medicines modulate immune checkpoints, specifically focusing on PD-1, PD-L1, IDO1, and CTLA-4, and discusses TCM approaches to reducing irAEs, providing a reference for developing TCM-based strategies to enhance ICI sensitivity and reduce toxicity in clinical settings. The Chinese medicine mentioned in this article have been checked with www.worldfloraonline.org.

2. Clinical efficacy of TCM in enhancing ICIs

A retrospective analysis of individuals with metastatic solid tumors receiving TCM plus PD-1/PD-L1 inhibitors found that those with prolonged TCM use experienced longer survival and improved prognosis. The study, which included lung, digestive system, gynecological and other tumors, revealed through Cox multivariate analysis that extended TCM use was an independent protective factor in immunotherapy (Wang, 2024). Another retrospective review of 90 patients with stage III–IV NSCLC indicated that TCM could reduce the side effects of ICIs (Lin Zhou, 2024). The combination of TCM and ICIs delayed tumor progression in advanced malignancies, with a lower incidence and toxicity grade of irAEs compared to reported averages, indicating that TCM may reduce irAEs, mitigate the severity of adverse reactions, and prolong treatment time, making it a valuable adjunct in clinical practice. Another study on 54 advanced cancer patients treated with both TCM and ICIs found that that those with an internal resistance to siltation type had the highest incidence of adverse reactions, suggesting TCM syndrome could be a potential predictor in guiding clinical practice (Chen, 2021).

Gegen Qinlian Decoction (GGQL), a traditional TCM from the *Treatise on Febrile Diseases* (Shang Han Lun), consists of *Coptis chinensis* Franch. (Huang lian), *Scutellaria baicalensis* Georgi (Huang qin), *Radix*

Pueraria DC. (Ge gen), and *Glycyrrhiza uralensis* Fisch. Ex DC. (Gan cao). It is commonly used for gastrointestinal diseases to clear gastrointestinal dampness and heat and has shown potential in maintaining intestinal flora diversity, lowering the Bacteroidetes/Firmicutes ratio, and upregulating Akkermansia abundance, thus improving the intestinal microenvironment in NSCLC patients. When combined with chemotherapy, GGQL may boost the clinical effectiveness of PD-1/PD-L1 blockers without significantly increasing irAEs. Bioinformatics analysis suggested that GGQL's effectiveness in enhancing PD-1 inhibitors involves key genes such as STAT3, NFKBIA, NFKB1, FOS, IL4, IL2, and EP300, with active components including quercetin, baicalein, beta-sitosterol, formononetin, kaempferol, and licochalcone A(Yu, 2023).

GO enrichment analysis highlighted its role in DNA-binding transcription factor binding, plasma membrane interactions, and mononuclear cell differentiation, while KEGG analysis points to the AGE-RAGE, T cell receptor, and IL-17 signaling pathways. Although these findings are promising, more large-scale clinical research is warranted to fully evaluate GGQL's role in conjunction with ICIs (Yu, 2023).

Table 1
Potential ICI sensitization mechanism of TCM.

TCM	Disease	Combination ICIs	Sensitization mechanism	Reference
Astragalus polysaccharide	Melanoma	PD-1	1. Induces tumor cellimmunogenic cell death (ICD) 2. Promotes the maturation of DC cells	Sha et al. (2022)
Cycloastragenol	Colorectal cancer (CRC)	PD-1	1. Boosts tumor antigenpresentation 2. Augments the killing ability of $CD8^+$ T cells	Deng et al. (2022)
Ginseng polysaccharides	Non-small cell lung cancer(NSCLC)	PD-1	1. Alters gut microbiota and its metabolites 2. Alters kynurenine: tryptophan ratio	Huang et al., 2022
Icaritin	Melanoma	PD-1	1. Reduces PD-L1 levels in myeloid-derived suppression cells (MDSCs) and neutrophils	Hao et al. (2019)
	CRC	CTLA-4	2. Increases $CD8^+$ T cell infiltration 3. Reduces MDSC infiltration	
Diosgenin	Melanoma	PD-1	1. Increases $CD8^+$ and $CD4^+$ T cell infiltration 2. Changes intestinal microbiota composition	Dong et al. (2018)
Bufalin	Hepatocellular carcinoma (HCC)	PD-1	1. Governs the conversion of M2 to M1 tumor-infiltrating macrophages 2. Inhibits p50 NF-κB factor overexpression	(Yu et al., 2022)
Apigenin and luteolin	NSCLC	PD-1	1. Inhibits lung cancer cell growth 2. Suppresses STAT3 phosphorylation	Jiang et al. (2021)
Evodiamine	NSCLC	PD-1	1. Induces tumor cell apoptosis by down-regulating MUC1-C/PD-L1 2. Elevates and activates $CD8^+$ T cells	Jiang et al. (2020)
Aqueous extract of Taxus chinensis var. mairei	NSCLC	PD-1	Promotes CD47 ubiquitin degradation and tumor cell phagocytosis	Dai et al. (2022)
Neobavaisoflavone	Breast cancer	PD-1	Targets STAT3 and reduces arginase-1 and reactive oxygen species to decrease MDSCs' immunosuppressive activity	Guo et al. (2022)
Andrographolide	NSCLC	PD-1	Reduces PD-L1 by binding to STAT3 and inducing autophagy	(Wang et al., 2022)
Sesquiterpene lactone-rich fraction of *I. helenium* L.	CRC	PD-1	Increases $CD8^+$ T cell and M1 macrophage infiltration in tumors	(Chun et al., 2023)
YIV-906	HCC	PD-1	1. Reduces PD-L1 and PD-1 levels 2. Potentiates M1-like macrophage polarization 3. Reduces immune tolerance by modulating IDO activity	Yang et al. (2021)
Shenmai injection	NSCLC	PD-1	1. Increases $GZMA^{high}$ and $XCL1^{high}$ NK cells	(Yu et al., 2023)
Gegen Qinlian decoction extract	CRC	PD-1	1. Augments antitumor immunity 2. Modulates gut microbiome composition 3. Influences glycerophospholipid and sphingolipid metabolism	Lv et al. (2019)
Juzentaihoto	Melanoma	PD-1	Activates NK cells and inhibits tumor cell metastasis	Ishikawa et al. (2017)
Chang Wei Qing decoction	CRC	PD-1	1. Augments $CD3^+$ and $CD8^+$ T cell infiltration in tumors 2. Modulates gut microbiota	Wang et al. (2023)
The coformulation of ginsenoside Rg3 and quercetin	CRC	PD-L1	1. Induces tumor cell apoptosis and ICD 2. Reprograms immunosuppressive TME	Sun et al. (2022)
Curcumin	Head and neck cancer	PD-L1	1. Modulates EMT-related tumor invasion 2. Enhances killing ability of $CD8^+$ T cells	(Liu et al., 2021)
Bilberry anthocyanin extracts	CRC	PD-L1, PD-1	Changes gut microbiota diversity and composition	(Xu et al., 2023; Wang et al., 2020)
Ailanthone	Melanoma	PD-L1	Promotes c-Jun degradation and reduces PD-L1	(Yu et al., 2022)
Oxymatrine	NSCLC	PD-L1	Augments $CD8^+$ T cell infiltration in the TME	Zheng et al. (2021)
Rhein	Breast cancer	PD-L1	1. Regulates cellular immunity 2. Causes tumor cell apoptosis	Shen et al. (2019)
Pien Tze Huang	CRC	PD-L1, PD-1	1. Inhibits Wnt/β-catenin signaling 2. Inhibits the IFNGR1/JAK1/STAT3/IRF1 signaling	Chen et al. (2022)
JieduSangen decoction	CRC	PD-L1	Inhibits PI3K/Akt-mediated EMT	Shan et al. (2020)
Huoxue Yiqi recipe	NSCLC	PD-L1	1. Reduces PD-L1 levels by inhibiting the PI3K/Akt signaling 2. Promotes polarization from M2 toward M1-like macrophages	Teng et al. (2020)
Lycorine	Renal cell carcinoma	CTLA-4	1. Suppresses renal cell migration and invasion 2. Suppresses Tregs and upregulates $CD8^+$ effector T cells	(Li X et al., 2017)
Cordycepin	CRC	CTLA-4	Bolsters CD8+T cell-modulated antitumor immunity	(Chen et al., 2023)
Benzosceptrin C	CRC	CTLA-4	1. Prevents PD-L1 palmitoylation by inhibiting DHHC3 enzymatic activity 2. Triggers the lysosome-mediated PD-L1 degradation	Wang et al. (2024)
Abrine	HCC	PD-1	1. Inhibits IDO1 activity 2. Reduces CD47 and promotes macrophage phagocytosis	Liang et al. (2023)

3. TCM for ICI sensitization

3.1. TCM and anti-PD-1 antibodies act synergistically against tumors

3.1.1. Active components of TCM sensitizing anti-PD-1 therapy

The active ingredients of *Astragalus mongholicus* Bunge (Huang qi) exhibit significant antitumor effects. In mice with breast cancer, *Astragalus* polysaccharide (APS) augmented anti-PD-1 antibody titer. A single-chain variable region segment of anti-PD-1 antibodies isolated from these mice blocked PD-L1-induced T-cell failure *in vitro* and attenuated tumor advancement and its associated macrophage abundance in vivo (Chang et al., 2020). APS also augmented DC cell maturation and activation *in vitro*, inducing immunogenic cell death (ICD) of cancer cells and improving antigen presentation. In a mouse xenograft melanoma model, APS plus anti-PD-1 therapy remarkably lowered tumor development compared to anti-PD-1 alone. Additionally, the proportions of $CD4^+$ and $CD8^+$ T cells increased in the spleens and cancer-draining lymph nodes (Pan et al., 2024; Sha et al., 2022).

Cycloastragenol (CAG), another active molecule of *Astragalus mongholicus* Bunge (Huang qi), inhibits tumor growth by blocking the cathepsin B (CTSB)-modulated major histocompatibility complex I (MHC-I) degradation in cell membranes. This action enhances MHC-I repolymerization in cell membranes, thereby improving the ability of $CD8^+$ T cells to identify and eradicate tumor antigens. Moreover, CAG reduces the levels of inhibitory receptors (Lag3, Tigit, and Havcr2) on $CD8^+$ T cells while increasing the levels of activation markers (Cd28, Cd69, Gzmk, Ccl5, and Pdcd1). CAG plus anti-PD-1 antibody shows a synergistic impact, demonstrating more robust antitumor responses than either treatment alone. This combination significantly boosts the tumor-destructive capacity of $CD8^+$ T cells and upregulates genes associated with antigen presentation, including tumor necrosis factor (TNF), interferon-gamma (IFN-γ), and human leukocyte antigen-A (HLA-A) in xenografted mice and CRC organoids (Deng et al., 2022).

In mice, *Panax ginseng* C.A.Mey. (Ren shen) polysaccharides (GPs) combined with anti-PD-1 antibodies augment mice's responsiveness to PD-1 blockage by lowering L-kynurenine and kynurenine: tryptophan ratio and elevating the microbial metabolite valeric acid. The treatment also remodels nonresponsive gut flora into more responsive flora, thereby making lung cancer mice sensitive to PD-1 inhibitors. Additionally, it reduces regulatory cells (Tregs) and boosts $CD8^+$ T cells that secret granzyme B (GZMB), TNF-α, and IFN-γ in both peripheral and tumors (Huang et al., 2022).

Icaritin, isolated from *Epimedium* L. (Yin yang huo), inhibits tumor metastasis and growth by activating p53 and SIRT6/NF-κB signaling pathways (Hao et al., 2019; Lei et al., 2020; Song et al., 2020; Tian et al., 2018). Currently, Icaritin is undergoing phase III clinical trials for advanced HCC (Bailly, 2020) and obtained approval from the China National Medical Products Administration in 2022 as an immunomodulatory drug for advanced HCC (Lu et al., 2022). Icaritin reduces tumor load in a T cell-dependent manner and lowers PD-L1 levels in myeloid-derived suppression cells (MDSCs) and neutrophils. It also reduces MDSC infiltration and increases $CD8^+$ T cells in the tumors of MC38 colon cancer and B16F10 melanoma mouse models. Furthermore, Icaritin remarkably enhances antitumor capacity when used alongside anti-PD-1/CTLA-4 (Hao et al., 2019).

Diosgenin, a steroidal saponin from *Dioscorea oppositifolia* L. (Shan yao), exerts antitumor effects by improving immune function and modulating gut flora. Diosgenin causes shrinkage and fragmentation of B16F10 melanoma cells *in vitro*, increases IFN-γ level in mouse tumors, promotes $CD8^+$ and $CD4^+$ T cell infiltration, modulates intestinal microbial composition, down-regulates *Bacteroidetes*; and upregulates *Clostridiales*, *Lactobacillus*, and *Sutterella*. Diosgenin plus PD-1 antibody significantly attenuates tumor weight and enhances antitumor immunity compared to either treatment alone (Dong et al., 2018).

Bufalin, the principal active ingredient of *Bufonidae* (Chan chu), modulates tumor-infiltrating macrophages (TIMs) by shifting a tumor-driving M2 phenotype to a tumor-mitigating M1 phenotype. This alteration enhances $CD8^+$ T cell-mediated cytotoxicity and stimulates $CD4^+$ T helper 1 cells, thereby promoting adaptive antitumor immunity. Bufalin also inhibits excessive expression of p50 nuclear factor kappa-B (NF-κB), facilitating the formation of p65-p50 heterodimers and activating the NF-κB signaling. This activation boosts immunostimulatory cytokine production and stimulates antitumor T-cell responses. Bufalin plus anti-PD-1 therapy significantly upregulates TNF-α and IFN-γ and inhibits interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), leading to synergistic suppression of HCC (Z. Yu et al., 2022). Furthermore, bufalin prevents gastric cancer development and spread by reversing BFAR-mediated PI3K/AKT/mTOR activation in vivo and *in vitro* (G. Chen et al., 2023).

Apigenin and luteolin markedly inhibit KRAS-mutant NSCLC cell augmentation *in vitro* and in vivo by blocking STAT3 phosphorylation and reducing IFN-γ-mediated PD-L1 production. In a Lewis lung cancer mice model, PD-1 antibody alone is ineffective at reducing tumor growth. However, when applied together with either luteolin or apigenin, the treatment considerably reduces tumor volume and weight, significantly augments $CD8^+$ T cell proportion and count, and increases GZMB, TNF-α, and IFN-γ production (Jiang et al., 2021).

Evodiamine, a natural alkaloidal compound extracted from the fruits of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley (Wu zhu yu), induces caspase-3/8-dependent tumor cell apoptosis and the arrest of G2/M cell cycle (Mohan et al., 2016; Ying Zhang, 2004). It reduces NSCLC cell growth by suppressing the MUC1-C/PD-L1 axis and increasing $CD8^+$ T cells and tumor cell apoptosis. In a Lewis lung cancer model, Evodiamine plus anti-PD-1 therapy effectively controls tumor enlargement compared to either treatment alone, increases $CD8^+$ T cells infiltrating and decreases Treg proportion in blood, tumors, and spleen, and promotes TNF-α, GZMB, and IFN-γ production, exhibiting a more potent antitumor response (Jiang et al., 2020).

The aqueous extract of *Taxus mairei* (Lemée & H.Lév.) S.Y.Hu (AETC) promotes phagocytosis of tumor cells by macrophages via enhancing ubiquitin-mediated CD47 degradation in lung adenocarcinoma cells, leading to increased $CD8^+$ T lymphocyte infiltration. Moreover, it also synergistically boosts the effect of anti-PD-1 treatment (Dai et al., 2022).

Neobavaisoflavone (Neo), an active ingredient in *Psoralea* L. (Bu gu zhi), enhances antitumor immunity against 4T1 tumors in mice by down-regulating arginase-1, reactive oxygen species (ROS), and STAT3 phosphorylation. Neo activates T cells and reduces MDSCs' immunosuppression. When applied together with anti-PD-1 antibody, Neo increases splenic IFN-γ+ $CD8^+$ and IFN-γ+ $CD4^+$ T cells and considerably enhances its efficacy against 4T1 tumors that are otherwise insensitive to PD-1 blockade treatment (Guo et al., 2022).

Andrographolide (AD), the principal active component of Neesfrom *Andrographis paniculata* (Burm.f.) (Chuan xin lian), and its derivatives demonstrate significant antitumor effects by inhibiting tumor cell proliferation and COX-2-mediated angiogenesis. AD markedly augments the effectiveness of PD-1 mAb treatment in a H1975 xenograft mouse model by reducing tumor size and weight without substantial toxicity. The combination treatment drastically decreases PD-L1 level, increases TNF-α, IFN-γ, and GZMB production, elevates f $CD8^+$ T cell infiltration, and reduces Treg proportion in the spleen, blood, and tumor. Mechanistically, AD inhibits PD-L1 expression by inducing P62-mediated selective cellular autophagy and directly binding to STAT3, thereby augmenting $CD8^+$ T cell function and infiltration (Li et al., 2020; Peng et al., 2018; Wang et al., 2022).

Sesquiterpene lactones, such as isoalantolactone and alantolactone from *Inula helenium* L. (Tu mu xiang), also show therapeutic promise for cancer. These compounds inhibit tumor growth by inhibiting proliferation, inducing cell cycle arrest, promoting cell apoptosis and pyroptosis (Hu et al., 2023; Li et al., 2022) and significantly enhance antitumor immunity when applied together with PD-1 mAb. The sesquiterpene lactone-rich fraction of *Inula helenium* L. (SFIH) promotes M1-like macrophages and $CD8^+$ T cell infiltration in the TME of MC38 CRC

mice. This combination treatment increases GZMB release, decreases TGF-β1 expression, and activates immune-related pathways in tumors, outperforming PD-1 mAb alone in enhancing antitumor immunity ("Chun et al., 2023. Enhances the Antitumor Effect of Anti-PD-1 Antibody in Colorectal Cancer: Integrative Phytochemical, Transcriptomic, and Experimental Analyses", 2023).

3.1.2. TCM preparations and compounds for sensitization to anti-PD-1 therapy

Huangqin Decoction originates from *Treatise on Febrile Diseases* (Shang Han Lun) and is made up of four herbs: *Paeonia lactiflora* Pall (Shao yao), *Glycyrrhiza uralensis* Fisch. Ex DC. (Gan cao), *Scutellaria baicalensis* Georgi (Huang qin), and *Ziziphus jujuba* Mill (Da zao). It is often used to treat gastrointestinal disorders. YIV-906, a standardized formulation of Huangqin decoction, improves the quality of life of cancer patients and enhances the antitumor activities of various anticancer drugs. When used with PD-1 antibody, YIV-906 decreases PD-L1 and PD-1 protein levels in Hepa 1–6 tumors, increases INF-γ expression, attenuates immunosuppression, and polarizes bone marrow-derived macrophages to M1-like macrophages. Furthermore, YIV-906 reduces MDSCs by regulating IDO activity, which can regulate Tregs expression, help recruit MDSCs into tumors, and induce immune tolerance (Yang et al., 2021).

Shenmai injection (SMI), consisting of *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Mai dong) and *Panax ginseng* C.A.Mey.(Hong shen), is a proprietary Chinese medicine. SMI combined with anti-PD-1 reduces tumor size and weight, considerably prolongs survival, and reduces irAEs in the Lewis lung cancer mice model and humanized squamous lung carcinoma mouse model. Moreover, this combination increases $GZMA^{high}$ and $XCL1^{high}$ NK cells in tumors, promotes GZMA and lymphotactin levels in NK cells, and enhances NK cell production of GZMA *in vitro* (D. Yu et al., 2023).

GGQL, a commonly applied formula for gastrointestinal disorders, was tested in CRC treatment using varying doses (300, 1500, and 7500 mg/kg) of Gegen Qinlian decoction extract (GQD) in conjunction with anti-PD-1 mAb in CT26 mice. The study found that 300 mg/kg GQD plus anti-PD-1 therapy produces the most tumor inhibition (70.526%) compared to only anti-PD-1 treatment. GQD enhances PD-1 mAb's antitumor activity by modulating intestinal microbiota, affecting glycophospholipid and sphingolipid metabolic signaling pathways, elevating IFN-γ and IL-2 levels in TME, increasing $CD8^+$ T cell proportion in tumor tissues and blood, and decreasing PD-1 levels (Lv et al., 2019).

Juzentaihoto (JTT), an herbal preparation named Shiquan Dabu decoction in China, contains 10 herbs, such as *Glycyrrhiza uralensis* Fisch. Ex DC. (Gan cao), *Panax ginseng* C.A.Mey. (Ren shen), and *Astragalus mongholicus* Bunge (Huang qi). JTT inhibits B16 melanoma cell metastasis in mice by stimulating NK cells, significantly increasing serum IFN-γ and IL-12 levels, and improving PD-1 mAb's inhibitory effects (Ishikawa et al., 2017).

Chang Wei Qing decoction (CWQ), a Chinese herbal formula consisting of *Astragalus mongholicus* Bunge (Huang qi), *Codonopsis pilosula* Nannf. (Dang shen) and other herbs, boosts anti-PD-1 therapy's anticancer ability. In mouse tumor models, CWQ intensifies $CD8^+$, $CD3^+$, and $CD8^+$ PD-1+ T cells by increasing PD-L1 protein level and correlates with heightened $CD3^+$, PD-1+ $CD8^+$, and $CD8^+$ T cell infiltration and *Akkermansia* (*AKK*) abundance (Wang et al., 2023). The presence of fecal AKK has been linked to augmented PD-1 blockade efficacy. Transplanting fecal microbiota from individuals responding to ICIs in germ-free mice enhances PD-1 blockade's anticancer effects (Routy et al., 2018). Interestingly, gavage with both exogenous and endogenous *AKK* markedly inhibits carcinogenesis in a Lewis lung cancer mouse model. Additionally, exogenous *Akk* migrates into tumors and affects the tumor microbiota profile (Zhu et al., 2023). Since gut microbiome composition affects the effects of ICIs, CWQ's ability to modify gut microbiota may boost the anticancer efficacy of PD-1 blockade. Furthermore, CWQ plus anti-PD-1 approach significantly lowers intestinal mucosal inflammatory response compared to anti-PD-1 alone, suggesting that CWQ may also help mitigate irAEs.

3.1.3. TCM simultaneously enhances sensitivity to chemotherapy and anti-PD-1 therapy

A commonly used clinical modality is chemotherapy with immunotherapy. Among the drugs discussed above, CAG, icaritin, diosgenin, and SMI have shown improved efficacy when combined with chemotherapy. CAG promotes apoptosis by activating anti-oncogene p53 and deactivating STAT3. The combination of CAG with 5-FU or paclitaxel enhances anticancer impacts and prevents drug unresponsiveness (Hwang et al., 2019; Park et al., 2022). Interestingly, similar to CAG, icaritin reduces cancer cell proliferation and metastasis by enhancing p53 activity (Tian et al., 2018). Thus, icaritin may sensitize chemotherapy and immune checkpoint blockade. Diosgenin promotes apoptosis in various cancers and counteracts chemotherapy resistance in cancer cells *in vitro* and in vivo (Sethi et al., 2018). SMI regulates tumor angiogenesis in patients with CRC. In combination with FOLFOX, SMI significantly down-regulates the proangiogenic factors plasminogen activator inhibitor-1 and fibroblast growth factor (FGF) at the transcriptional level, decreases the proangiogenic factors FGF and vascular endothelial growth factor, and increases antiangiogenic factor vasopressin. In a LoVo xenograft tumor mouse model, SMI enhances 5-FU's efficacy by increasing its intratumor concentration by 2.3-fold compared to 5-FU monotherapy (Cheng et al., 2021). Fig. 1 summarizes the main mechanism by which TCM boosts tumor responsiveness to anti-PD-1 treatment.

3.2. TCM combined with anti-PD-L1 antibodies acts synergistically against tumors

3.2.1. TCM and its active components exerts antitumor effects by reducing PD-L1 expression in tumors

Berberine influences metabolic diseases, cardiovascular diseases, neuropsychiatric disorders, and many other diseases (Och et al., 2020). It also exhibits anticancer properties and sensitization to chemotherapy by promoting apoptosis and hindering cell cycle in tumors. It enhances chemotherapy sensitivity by promoting PD-L1 ubiquitination and its degradation via inhibiting and binding to constitutive photomorphogenic-9 signalosome 5 (CSN5). This action stimulates tumor-infiltrating T cells, decreases PD-L1 levels in tumors, and increases T cell cytotoxicity against tumors (Liu et al., 2020).

APS remarkably impedes the growth of tumors formed by subcutaneous grafts in a mouse melanoma model by reducing PD-L2 and PD-L1 protein levels in tumors and increasing IFN-γ and IL-2 in peripheral blood (WANG Jie-ru, 2014).

Formononetin, a product extracted from *Astragalus mongholicus* Bunge (Huang qi), inhibits tumor cell survival and their resistance to chemotherapy by regulating growth factors, transcription factor, and their mediated oncogenic pathways (Ong et al., 2019). In HeLa cells, it inhibits PD-L1 synthesis and induces lysosomal biogenesis by modulating the RAS/ERK and JAK1/STAT3 signaling pathways and the communication of between STAT3 and MYC, degrading PD-L1 in a TFEB/tfe3 dependent manner. Formononetin also suppresses cancer cell proliferation, promotes apoptosis, and inhibits tubule formation and endothelial cell invasion and migration by reducing PD-L1 levels. In a mouse xenograft model, formononetin effectively inhibits cancer development and reduces vascular endothelial growth factor, MYC, p-STAT3, and PD-L1 levels and is more effective than 5-FU in inhibiting tumor growth at 75 mg/kg dose (Wang et al., 2022).

As the active ingredients of *Scutellaria baicalensis* Georgi (Huang qin), baicalein and its conjugate baicalin down-regulate IFN-γ-modulated PD-L1 by deactivating STAT3 in HCC and restoring T cell-modulated tumor destruction and reduce PD-L1 and $CD8^+$ cell proportions in tumor in a BALB/c H22 HCC mouse model (Ke et al., 2019).

Triptolide extracted from *Tripterygium wilfordii* Hook. f.(Lei gong

teng) has marked cytotoxicity against various tumor cells (Wei et al., 2019). In vitro, triptolide reduces tumor immune unresponsiveness by inhibiting IFN-γ-inducted PD-L1 in breast cancer (Liang et al., 2008).

BuFei decoction, a TCM recipe of *Codonopsis pilosula* Nannf. (Dang shen), *Morus alba* L. (Sang bai pi), *Aster* L. (Zi yuan), *Rehmannia glutinosa* (Gaertn.) DC. (Di huang), *Schisandra chinensis* (Turcz.) Baill. (Wu wei zi) and *Astragalus mongholicus* Bunge (Huang qi), inhibits PD-L1 and IL-10 expression *in vitro* and in NSCLC mice, disrupting the association between tumor cells and associated macrophages to exert anticancer effects (Pang et al., 2017).

3.2.2. Active components of TCM for sensitization to anti-PD-L1 treatment

Quercetin, a flavonoid largely presents in fruits and vegetables, binds to PD-L1 and PD-1, activating T cells and inhibiting cancer growth (Jing et al., 2021). Ginsenoside Rg3 enhances the cytotoxic effects on lung tumors by restoring $CD8^+$ T cell cytotoxicity and inhibiting the Akt and NF-κB pathways while also blocking PD-L1 up-regulation in lung cancer during chemotherapy resistance (Jiang et al., 2017). The coformulation of ginsenoside Rg3 and quercetin (QTN) shows excellent antitumor effects on CRC. Ginsenoside Rg3 enhances high-mobility group protein 1 (HMGB1) release, ATP secretion, and calreticulin (CRT) exposure in CRC cells, all of which are hallmarks of activated ICD. QTN further amplifies the ability of Ginsenoside Rg3 to induce ICD by promoting reactive oxygen species formation, inhibiting proliferation, and inducing apoptosis of CRC cells. QTN exhibits superior antitumor effects in an orthotopic CT26-Luc-derived CRC mouse model compared to anti-PD-L1 treatment. Additionally, QTN plus anti-PD-L1 remarkably promotes tumor cell apoptosis, reprograms TME, activates DC cells, $CD4^+$ T cells, and $CD8^+$ T cells in tumors, and down-regulates M2 macrophages, MDSCs, and Tregs. These changes are associated with elevated IFN-g, IL-12, CXCL9, and CXCL10 levels and reduced IL-10, IL-6, and IL-4. Additionally, quercetin promotes cell cycle arrest, cell apoptosis and necrosis, and inhibits genes associated with inflammation, proliferation, and angiogenesis in HCC. The combination of quercetin and sorafenib can improve liver injury and play a good anti-tumor role (Abdu et al., 2022a). This treatment offers a promising tumor treatment strategy (Sun et al., 2022).

Curcumin, a polyphenol isolated from rhizomes of *Curcuma longa* L. (Jiang huang), modulates epithelial-mesenchymal transition (EMT)-related tumor invasion in head and neck squamous cell tumor by reducing the levels of immune checkpoint ligands Galectin-9, PD-L2, and PD-L1 (L. Liu et al., 2021). The decrease in PD-L1 is likely linked to curcumin's ability to inhibit the JAK2/STAT3 pathway and reduce NF-κB level. Curcumin plus anti-PD-L1 antibody therapy boosts IFN-γ and GZMB production and $CD8^+$ T cell-mediated cancer death. Additionally, curcumin modulates TIM-3 and PD-1 expression in $CD8^+$ and $CD4^+$ T cells and in $CD4^+$CD25+FoxP3+ Tregs, thereby restoring the action of effector T cells in the 4-NQO oral carcinoma model (Giordano et al., 2019).

Bilberry anthocyanin extracts increase the abundance of gut flora Clostridia, thereby improving the effectiveness of anti-PD-L1 therapy in colon tumor mice (Wang et al., 2020). *Clostridium butyricum*, a Gram-positive anaerobic bacterium in class Clostridia, produces acetate, butyrate, and other short-chain fatty acids by consuming dietary fiber. By influencing Wnt signaling and microbiota, *C. butyricum* inhibits intestinal tumor growth (D. Chen et al., 2020). Moreover, it enhances anti-PD-1 immunotherapy and attenuates MYC-mediated 5-FU resistance by enhancing proteasome-mediated ubiquitination in CRC cells, leading to MYC degradation (Xu et al., 2023). *C. butyricum* coupled with anti-PD-1 therapy significantly augments GZMB, CD8, and CD4 levels in tumors.

Ailanthone (AIL), derived from the bark of *Ailanthus altissima* (Mill.) Swingle (Chou chun), is a c-Jun protein inhibitor. It can directly target c-Jun to promote its degradation and prevent c-Jun from attaching to the PD-L1 promoter, thus inhibiting Treg differentiation, promoting T cell cytotoxicity, and reducing PD-L1 levels. These effects significantly improve anti-PD-L1 therapy for melanoma (P. Yu et al., 2022).

Oxymatrine, isolated from the root of *Sophora flavescens* Aiton (Ku shen), significantly enhances anti-PD-L1 therapeutic effects and $CD8^+$ T cell infiltration in TME in a mouse lung adenocarcinoma model (Zheng et al., 2021). It remarkably suppresses IFN-γ-enhanced PD-L1 protein and mRNA contents and inhibits CRC cell viability *in vitro* (Hua et al., 2020).

Rhein, an anthraquinone extracted from *Rheum* L. (Da huang), has shown synergistic effects with atezolizumab, an anti-PD-L1 antibody for treating malignancies such as NSCLC, HCC, and melanoma. This combination substantially increases $CD8^+$ T cell proportion in tumors and the spleen of 4T1 breast tumor mice, elevates serum IL-6 and TNF-α levels, and upregulates mRNA contents of apoptotic factors such as Bax/Bcl-2 and caspases 3/8/9 in tumors (Shen et al., 2019).

3.2.3. TCM preparations and compounds for sensitization to anti-PD-L1 therapy

Pien Tze Huang (PZH), a proprietary TCM composed of *Calculus bovis* (Niu huang), *Snake Gall* (She dan), *Moschus* (She xiang), and *Panax notoginseng* (Burkill) F.H.Chen (San qi), inhibits CRC proliferation by down-regulating the production of cyclin D1 and proliferating cell nuclear antigen through blocking the Wnt/β-catenin signaling. Additionally, PZH reduces PD-L1 levels and inhibits immune escape from CRC by inhibiting the IFNGR1/JAK1/STAT3/IRF1 signaling. In anti-PD-L1/PD-1 immunotherapy, PZH elevates GZMB and IFN-γ mRNA levels and promotes $CD3^+$ and $CD8^+$ T cell infiltration and effector functions in tumors relative to monotherapy (Chen et al., 2022).

JieduSangen decoction, consisting of *Polygonum cuspidatum* Willd. ex Spreng. (Hu zhang), *Adina rubella* Hance (Shui yang mei gen) roots, and *Actinidia chinensis* Planch (Teng li gen), suppresses the PI3K/AKT pathway and reverses EMT when combined with a PD-L1 inhibitor, thereby inhibiting colon cancer cell invasion and migration in mice. EMT is featured by the existence of mesenchymal markers such as N-cadherin and Vimentin, along with the loss of E-cadherin. This combination upregulates E-cadherin levels while attenuating Vimentin and N-cadherin levels (Serrano-Gomez et al., 2016; Shan et al., 2020).

Huoxue Yiqi recipe (HXYQ) comprises *Glycyrrhiza uralensis Fisch. Ex DC.* (Gan cao), *Panax ginseng* C.A.Mey. (Ren shen), and *Salvia miltiorrhiza* Bunge (Dan shen). Teng discovered that the targets of the active ingredient of HXYQ were significantly enriched in signaling pathways that are connected to PD-L1 and NSCLC. The tumor weight and volume are reduced significantly in xenograft mice treated with HXYQ, and PD-L1 expression is reduced in vivo and *in vitro*. This reduction might be connected to HXYQ's capability to block the PI3K/Akt signaling. Additionally, HXYQ remarkably augments mouse intestinal *Akk* levels, facilitates M2 macrophages converting into M1 macrophages, and improves anti-PD-L1 therapeutic effect (Teng et al., 2020). Fig. 2 summarizes the main mechanism by which TCM sensitizes tumors to anti-PD-L1 treatments.

3.3. TCM regulates other immune checkpoints to exert antitumor efficacy

3.3.1. TCM regulates CTLA-4 and induces sensitization to CTLA-4 inhibitors

In a mouse HCC model, PD-1, AKT, CTLA-4, and phosphatase and tensin homolog (PTEN) levels are upregulated in exosomes, with CTLA-4 promoting tumor metastasis and invasion by modulating the PTEN/CD44 signaling (Wang et al., 2021). Among luminal B $HER2^-$ breast cancer patients, CTLA-4+ patients had shorter disease-free survival, indicating a poor prognosis associated with CTLA-4 expression (Lan et al., 2018). In NSCLC, modulating serum CTLA-4 levels may be a mechanism in maintenance treatment with herbal medicine. In patients with advanced NSCLC, serum CTLA-4 concentration is markedly lower after two cycles of maintenance therapy with TCM than before treatment. Multivariate analysis showed that sCTLA-4 levels and treatment regimen were independent prognostic factors for time to progression

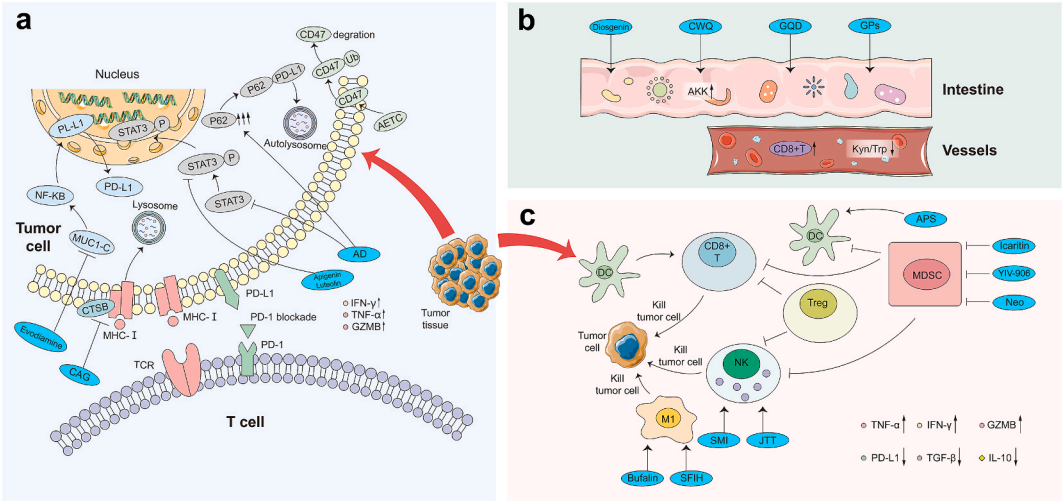

Fig. 1. Main mechanism by which TCM boosts tumor responsiveness to anti-PD-1 treatment. a: Evodiamine suppresses the MUC1-C/PD-L1 axis. Cycloastragenol (CAG) inhibits cathepsin B (CTSB)-mediated MHC-I degradation and promotes tumor antigen presentation. Apigenin and luteolin down-regulate PD-L1 levels by inhibiting STAT3 phosphorylation. Andrographolide (AD) reduces PD-L1 levels by binding to STAT3 and inducing P62-mediated autophagy. The water-soluble extract of Taxus chinensis var. mairei(AETC) promotes ubiquitination-mediated CD47 degradation and tumor cell phagocytosis. b: Diosgenin regulates intestinal microbial composition. Chang Wei Qing decoction (CWQ) increases the abundance of intestinal *Akkermansia* (*AKK*). Gegen Qinlian decoction extract (GQD) regulates the intestinal microbiota and increases circulating CD8+T cells. Ginseng polysaccharides (GPs) remodel intestinal flora and improve responsiveness to PD-1 blockade by lowering kynurenine:tryptophan (Kyn:Trp) ratio. c: Bufalin and sesquiterpene lactone-rich fraction of *I. helenium* L. (SFIH) increase M1-like macrophages, enhancing antitumor immunity. Shenmai injection (SMI) and Juzentaihoto (JTT) promote NK cells to enhance antitumor immunity. *Astragalus* polysaccharide (APS) improves the antigen-presenting function of DC cells and promotes their activation and maturation. Icaritin and YIV-906 reduce the invasion of myeloid-derived suppression cells (MDSCs) into cancer tissues. Neobavaisoflavone (Neo) decreases MDSCs' immunosuppression ability. In tumor microenvironment (TME), TNF-α, IFN-γ, and GZMB increase, whereas PD-L1, TGF-β, and IL-10 decrease.

(Weijie, 2016). An extensive body of evidence supports the therapeutic utility of *Artemisia capillaris* Thunb. (YinChen) in HCC. Network pharmacological analyses suggest that YinChen may activate immune cells by inhibiting BIRC5-targeted immune checkpoints (CTLA4 and LAG3) (Mo et al., 2020). Lycorine, an alkaloid extracted from Amaryllidaceae time- and dose-dependently inhibits renal cancer cell viability, migration, and invasiveness. Treatment with lycorine plus anti-CTLA-4 antibody synergistically reduces Tregs in peripheral blood while upregulating $CD8^+$ effector T cells in renal cancer mice, exerting strong antitumor effects (Li X, 2017). Cordycepin, an adenosine derivative, shows promising antitumor effects when used in combination with CTLA-4 blockers. In MC38 and CT26 tumor mouse models, anti-CTLA-4 plus cordycepin significantly impedes tumor development and increases OS. This combination alters the exhaustion and effector status of $CD8^+$ T cells, reducing $CD8^+$ T cell exhaustion, increasing effector $CD8^+$ T cells, and enhancing $CD8^+$ T cell-modulated antitumor immunity within the TME (L. Chen et al., 2023). DHHC3, a palmitoyl acyltransferase, alters the binding of peripheral membrane proteins to the cell membrane through posttranslational modifications (e.g., *S*-palmitoylation) (Solis et al., 2022). DHHC3 stabilizes PD-L1 by modifying it in the cytoplasm and blocking its ubiquitination, thereby hindering PD-L1 lysosomal degradation (Yao et al., 2019). Immunohistochemical analysis unveiled a positive connection between PD-L1 and DHHC3 levels in tumor tissues of CRC patients. Benzosceptrin C, a marine natural compound, down-regulates PD-L1 levels in CRC cells to augment T cell cytotoxicity to CRC and blocks PD-L1 palmitoylation through inhibiting DHHC3 activity, facilitating the lysosomal-mediated PD-L1 degradation and triggering antitumor immunity. Moreover, in MC38 mice, anti-CTLA-4 plus Benzosceptrin C therapy effectively augments antitumor T cell immunity, comparable to anti-CTLA-4 plus anti-PD-L1 remedy. This combination increases $CD8^+$ T cells in tumor-infiltrating lymphocytes, elevates GZMB levels, and drastically reduces MDSC and Treg infiltration compared to monotherapy group (Wang et al., 2024).

3.3.2. *TCM regulates indoleamine-2,3-dioxygenase 1 to exert antitumor effectiveness*

Indoleamine-2,3-dioxygenase 1 (IDO1) is an emerging potent antitumor target due to its functions in the immune escape mechanism. As a tryptophan-degrading enzyme, IDO1 serves as the initial rate-limiting step in tryptophan catabolism, with its metabolites promoting tumor cell metastasis and motility. Although IDO1 is lowly expressed in normal tissues, its high level in tumors is strongly linked to poor prognosis (Platten et al., 2019).

Curdione, an active ingredients of *Curcuma zedoaria* (Christm.) Roscoe (E zhu), exerts antiuterine leiomyosarcoma (uLMS) effects *in vitro* and in vivo. Curdione reduces uLMS cell viability and proliferative capacity while time- and concentration-dependently elevating apoptosis and autophagic death by targeting IDO1 *in vitro*. In a mouse xenograft tumor model, curdione reduces tumor weight and volume and down-regulates IDO1 and ki67 in tumors (Wei et al., 2021).

Astragaloside IV (AS-IV) exhibits a similar mechanism. AS-IV encourages uLMS autophagy and apoptosis by triggering the PTEN/PI3K/AKT signaling via inhibiting IDO1 and effectively suppresses uLMS growth in vivo (Qiu et al., 2022). High doses of AS-IV decrease B7-H3 protein and mRNA levels, blocking NSCLC cell growth and improving its sensitivity to cisplatin chemotherapy (He et al., 2016). PD-1, PD-L1, and CTLA-4 blockers induced the increased IDO1 levels and metabolic activity, implying that combining IDO1 inhibitors with other ICIs improves clinical outcomes (Fujiwara et al., 2022).

Abrine, a specific IDO inhibitor derived from *Abrus cantoniensis* Hance (Ji gu cao), inhibits the IFN-γ-mediated IDO1/JAK1/STAT1 signaling by targeting IDO1 in HepG2 cells. It also reduces PD-L1 levels in IDO1-overexpressing cancer tissues and cells. Additionally, IDOI increases CD47 expression, which impairs macrophages-mediated phagocytose of tumor cells. Abrine reverses this phenomenon, enhancing macrophage recruitment to cancer cells and preventing tumor cell immune escape. In a Hepa1-6 xenograft mouse model, abrine plus anti-PD-1 antibody down-regulates Foxp3+ Tregs, upregulates $CD8^+$ T cells in tumors, inhibits IDO1, PD-L1, and CD47 expression, and

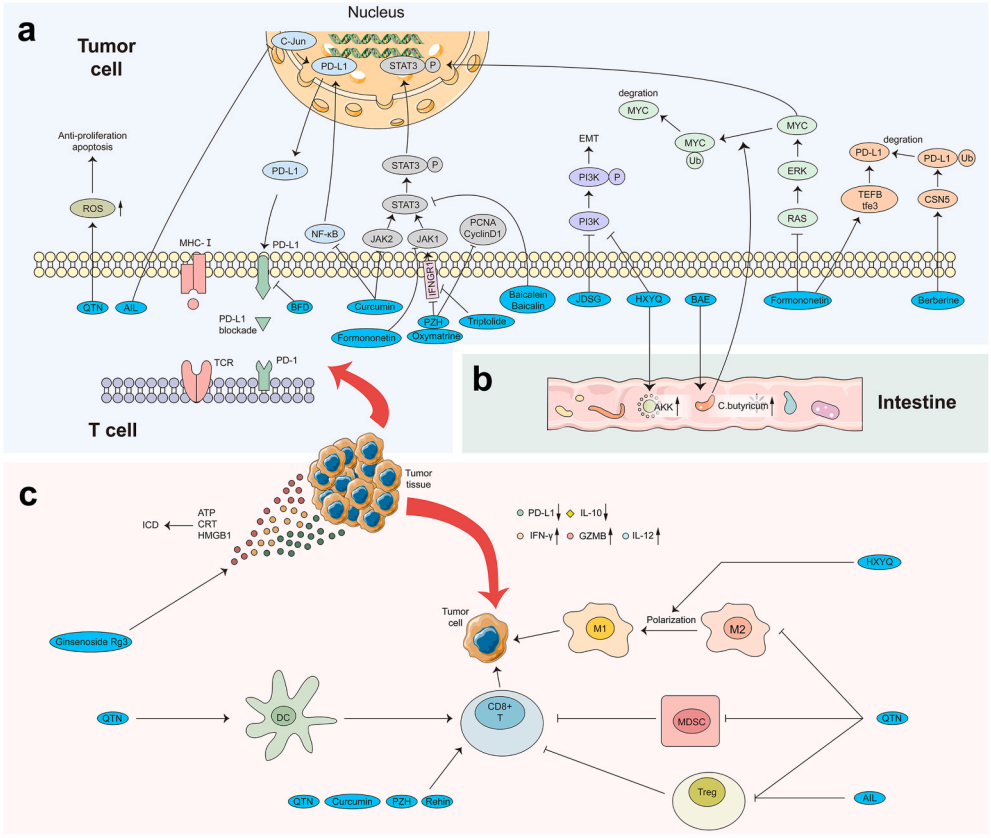

Fig. 2. The main mechanism through which TCM sensitizes tumors to anti-PD-1 treatments. a: The coformulation of ginsenoside Rg3 and quercetin (QTN) induces reactive oxygen species (ROS) formation and exerts antiproliferation and apoptosis effects. Ailanthone (AIL) targets c-Jun to promote its degradation and prevent c-Jun from attaching to the PD-L1 promoter, thus reducing PD-L1 levels. BuFei decoction (BFD) and oxymatrine decrease PD-L1 levels. Curcumin decreases PD-L1 levels by inactivating JAK2/STAT3 signaling and down-regulating NF-κB. Formononetin decreases PD-L1 levels by inactivating the RAS/ERK and JAK1/STAT3 pathways and blocking communication between STAT3 and MYC, initiating TFEB/TFE3-dependent PD-L1 degradation. Pien Tze Huang (PZH) reduces PD-L1 levels by diminishing the IFNGR1/JAK1/STAT3 pathway. Triptolide attenuates IFN-γ-augmented PD-L1 levels and reduces tumor immune resistance. Baicalein and baicalin down-regulate IFN-γ-augmented PD-L1 level through inactivating STAT3. JieduSangen decoction (JDSG) inhibits tumor cell invasion and migration by impeding the PI3K signaling and reversing epithelial-mesenchymal transition (EMT). Berberine binds to CSN5 and causes PD-L1 degradation. b: Huoxue Yiqi recipe (HXYQ) inhibits PI3K and increases *Akkermansia muciniphila* level in the intestine. Bilberry anthocyanin extracts (BAE) improve the effectiveness of anti-PD-L1 antibodies by increasing the abundance of intestinal Clostridia, whereas *C. butyricum* degrades MYC by enhancing proteasome-mediated ubiquitination. c: Ginsenoside Rg3 increases high-mobility group protein 1 (HMGB1) and ATP release and calreticulin (CRT) exposure and induces immunogenic tumor cell death. QTN down-regulates M2-like macrophages, MDSCs, and Tregs and upregulates CD8 + T and DC cells in tumors. Curcumin augments tumor eliminating via $CD8^+$ T cells. PZH promotes the effector function and infiltration of $CD8^+$ T cells in tumors. Rhein increases CD8+T cell proportion in tumors. AIL inhibits Treg differentiation. HXYQ promotes M2-like to M1-like macrophage transformation. PD-L1 and IL-10 decrease, whereas IFN-γ, GZMB and IL-12 increase. in tumor microenvironment (TME).

synergistically suppresses tumor growth, while showing no toxicity to the heart, lungs, kidneys, liver, spleen, and brain (Liang et al., 2023).

3.3.3. *TCM modulates the levels of other immune checkpoints*

Yangyin Fuzheng Jiedu prescription reduces Tim-3, TIGIT, and PD-1 expression in $CD8^+$ T cells, increases effector factors IFN-γ and TNF-α in tumor and serum, and effectively blocks tumor growth in a mouse HCC model (Xie et al., 2022; Yan et al., 2021). In a cohort study, high HHLA2 levels are linked to prolonged disease-free survival in lung adenocarcinoma patients. The median IHC scores for HHLA2 and B7-H4 are dramatically augmented in patients with EGFR-mutant lung adenocarcinoma compared to patients with wild-type EGFR, suggesting that HHLA2 and B7-H4 are potential immune targets for treating EGFR-mutated lung adenocarcinoma (Chen et al., 2020). TCM shows a good sensitizing effect on anti-PD-1, PD-L1, and CTLA-4 remedies. Focusing on TCM's sensitizing effects in developing immune checkpoint-related drugs may enhance therapeutic efficacy.(see Table 1)

4. TCM reduces irAEs

4.1. *Manifestations of irAEs and implications for immunotherapy*

The widespread use of ICIs in cancer treatment has brought increased attention to irAEs they can induce. These irAEs are often characterized by a delayed onset and prolonged duration, occurring at any point during treatment or even after it has concluded. They can affect numerous organs, including the lungs, cardiovascular system, gastrointestinal tract, liver, skin, and kidney (Brahmer et al., 2018). PD-1, PD-L1, and CTLA-4 are the most common targets in immune checkpoint blockade. Among patients with various cancer, irAEs occur mostly in the gastrointestinal tract, skin, and endocrine system, with an incidence of 40%–60% in those receiving anti-PD-L1 or PD-1 antibodies (Das et al., 2019). In a randomized, double-blind phase III trial on ipilimumab for melanoma treatment (NCT00094653), the incidence of irAEs is ~60%, with cutaneous and gastrointestinal reactions being the most frequent (Hodi et al., 2010). Severe cases of irAEs can even be fatal (Eggermont et al., 2015). Cutaneous and gastrointestinal adverse reactions typically manifest as pruritus, rashes, diarrhea, and colitis (Puzanov et al., 2017). These reactions not only affect the efficacy of

immunotherapy but also significantly reduce patients' quality of life. Per the Common Terminology Criteria for Adverse Events Version 5.0 (SERVICES, 2017), adverse events are ranked as mild, moderate, severe, life-threatening, or fatal (SERVICES, 2017). Patients with mild irAEs can continue ICI treatment under close monitoring, whereas those with moderate to severe irAEs require specialist intervention, which may include discontinuing ICIs or administrating immunomodulatory agents, such as glucocorticoids (Bagchi et al., 2021). However, stopping treatment or using glucocorticoid can negatively impact ICI therapy. High-dose glucocorticoid therapy for ipilimumab-triggered hypophysis is linked to poor survival in melanoma patients (Faje et al., 2018). Additionally, while prednisolone prevents inflammatory adverse events, it may also diminish the antitumor effects of ICIs (Bobé et al., 2021). Therefore, managing irAEs requires early detection and proper management (Brahmer et al., 2018). Moreover, new strategies must be developed to ensure the continuation of ICI therapy and to improve clinical outcomes for patients.

4.2. TCM improves irAEs

Existing studies have shown that TCM combined with ICIs can reduce the incidence of irAEs, alleviate irAE symptoms, and advance the quality of life for tumor patients. A review of 160 advanced solid tumor individuals receiving PD-1/PD-L1 blockers plus TCM found that the incidence of irAEs is only 35.62%, with grade 3–4 irAEs occurring in just 10% of cases (Chai X et al., 2023). TCM plus PD-1/PD-L1 inhibitor treatment lowers the occurrence and severity of adverse reactions compared to ICIs alone. A study showed that TCM plus PD-1 inhibitors dramatically attenuate ALT and AST levels and alleviate fatigue of patients with intermediate and advanced HCC after three treatment cycles compared to the control, suggesting that combining TCM with anti-PD-1 treatment can mitigate treatment-related adverse events and augment the quality of life for HCC patients (Zhang, 2023).

Herbal topical irrigation may be effective in preventing cutaneous irAEs induced by immunotherapy. A retrospective cohort study of 358 cancer patients showed 72.3% experience at least one cutaneous AE before the occurrence of irAEs, suggesting that the prevention of cutaneous-related adverse reactions may reduce the occurrence of other systemic toxicities (Thompson et al., 2021). Prophylactic skin rubbing with an aqueous decoction of *Cnidium monnieri* Cusson (She chuang zi), *Sophora flavescens* Aiton (Ku shen), *Scutellaria baicalensis* Georgi (Huang qin), *Kochia scoparia* (L.) Schrad. (Di fu zi), and *Glycyrrhiza uralensis* Fisch. Ex DC. (Gan cao) reduces anti-PD-1 antibody-induced cutaneous irAEs from 58.33% to 29.17% (Qi, 2022). In one case report, treatment with a Chinese herbal decoction considerably alleviated G3 immune-related bullous dermatitis that did not respond to glucocorticoid therapy (Wang et al., 2022a).

Qingfei Tiaoqi decoction (QFTQ), which consists of 13 herbs such as *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Mai dong), *Glehnia littoralis* F. Schmidt (Bei sha shen), *Astragalus mongholicus Bunge* (Huang qi), *Codonopsis pilosula* Nannf. (Dang shen), *Polygonum cuspidatum* Willd. ex Spreng. (Hu zhang), and *Atractylodes macrocephala* Koidz. (Bai zhu), nourishes Yin, strengthens the spleen, and clears the lungs. In Wang's study, 29 patients with advanced NSCLC treated with QFTQ had significantly lower irAEs than the 30 patients treated with ICIs alone. QFTQ can effectively reduce irAEs in NSCLC patients by regulating intestinal flora structure (Xiao Wang, 2024).

Yanghe decoction, a surgical formula in TCM, consists of *Rehmannia glutinosa* (Gaertn.) DC (Di huang), *Cinnamomum cassia* (L.). J.Presl (Rou gui), Colla Cornus Cervi(Lu jiao jiao), *Ephedra sinica* Stapf (Ma huang), *Sinapis alba var. mairei* (H.Lindb.) B.Bock (Bai jie zi), *Glycyrrhiza uralensis* Fisch. Ex DC. (Gan cao), and *Zingiber officinale* Roscoe (Pao jiang). In postoperative patients with endometrial cancer, Yanghe decoction combined with radiotherapy can effectively improve discomfort and further enhance therapeutic efficacy (Wang G, 2023). Yang observed two cases of immune-associated pneumonia, two cases of liver function impairment, and one case of renal function impairment in 28 NSCLC patients receiving anti-PD-1. By contrast, none of the 30 individuals receiving anti-PD-1 antibody plus Yanghe decoction experiences any relevant adverse events (Hang, 2023). Yanghe decoction inhibits breast tumor metastasis and growth by decreasing MDSCs in the TME and regulating JAK2/STAT3 and HIF-1α signaling pathways (LIU Yang-jing, 2023; Mao et al., 2018; You et al., 2023). Additionally, HIF-1α inhibitors plus anti-CTLA-4 antibodies exert antitumor impacts similar to anti-CTLA-4 plus anti-PD-1 antibodies while also increasing PD-L1 levels in normal tissues to reduce irAEs (Bailey CM, 2022). Therefore, Yanghe decoction has the potential to increase sensitivity and reduce toxicity in immune checkpoint blockade therapy. Shengyang Yiwei San, an herbal formula for the treatment of gastrointestinal diseases, effectively improves immune-related diarrhea symptoms in patients with malignant tumors when combined with conventional Western medicine. 28 patients treated with Shengyang Yiwei San have considerably augmented Karnofsky scores and reduced incidence of other adverse events compared to the 28 patients in the conventional group. Three rash cases are identified in the conventional group, whereas none occurs in the Shengyang Yiwei San group (Han, 2024). TCM not only improves a single symptom of irAEs but also prevents the simultaneous occurrence of multiple irAEs.

5. Conclusion and outlook

Effective treatment of malignant tumors requires well-coordinated and comprehensive multidisciplinary strategies (Zhang et al., 2021). TCM offers active components and compounds that not only promote tumor cell death but also synergize ICIs. Moreover, they have the potential to alleviate adverse symptoms and reduce the occurrence of irAEs. By promoting cell cycle arrest, apoptosis and necrosis, regulating intestinal flora, inhibiting immune checkpoint molecules and changing TME, TCM inhibits tumor growth and sensitizes ICIs. It can be seen that the mechanisms by which TCM exerts anti-tumor and sensitizes ICIs are diverse. Since each study involves different directions of mechanisms, depth of study, and tumor type, one study cannot fully illustrate the effect and mechanism of a Chinese medicine when combined with ICIs. A single Chinese medicine may have multiple pathways to sensitize ICIs and show different suppressing effects in different cancer types. On the other hand, Chinese medicine is rich in many anti-cancer active ingredients, and its ingredients or extracts cannot be equivalent to Chinese medicine itself(Abdalla et al., 2022; Abdu et al., 2022b). It is also necessary to further study whether there is interaction between various components in the application of Herbal composition.

The side effects of TCM also need to be studied and explored. In the studies discussed in this paper, TCM generally did not have liver and kidney toxicity and was relatively safe. Although the rational application of TCM is safe and effective, the quality, dosage and dosage form will affect the toxicity and effect of TCM. For example, although GGQL has the potential to sensitize ICIs, it also aggravates nausea and vomiting in NSCLC patients (Yu, 2023). Therefore, in drug development and clinical application, the quality, dosage and drug dosage form are the key points that researchers should pay attention to.

Chinese medicine is a huge treasure house. Many anti-cancer TCM extracts, components, combinations and extraction methods have been patented, such as icaritin, bufalin, AD, curcumin, AIL and cordycepin (Patent number: 20080214844, 9814734, 20230165832, 9447050,20180125814, 20240116976). Herbal composition (Patent number: 20140106013) inhibits the growth of cancer cells and cancer stem cells. It contains *Coptis chinensis* Franch. (Huang lian), *Scutellaria baicalensis* Georgi (Huang qin), *Atractylodes macrocephala* Koidz. (Bai zhu), *Glycyrrhiza uralensis* Fisch. Ex DC. (Gan cao), and other herbs. In the previous chapters, the ingredients or herbal combinations involved in these herbs play an anti-tumor role. Herbal composition (Patent number: 8858953) can be used for the treatment of lung cancer and improve the life quality of patients, and no serious adverse reactions

have been observed. Crocin and Safranal derived from Saffron can be used for prevention and treatment of liver cancer (Patent number: 10933076, 10912741, 10568873). The antitumor effect of safranal is related to protein instability induced by oxidative stress(Abdalla et al., 2022; Nelson et al., 2022). Crocin can enhance the anti-proliferative, anti-inflammatory and apoptosis-promoting effects of sorafenib in HCC, and reduce the formation of undesirable nodules(Awad et al., 2023). Combinations of TCM and immunotherapy have also been patented, such as YIV-906 and quercetin sensitizing immunotherapy (Patent number: 20220339233, 20190336473).

However, clinical studies using TCM to prevent and treat irAEs remain scarce. Further exploration is necessary to explore the sensitizing and detoxifying effects of TCM plus ICIs, both at the mechanistic and clinical levels. The drug proportion, dosage, drug cycle and administration mode of combination drug need further detailed study. This paper provides a summary of the role of TCM in ICI sensitization and irAE reduction, along with related mechanisms, to serve as a reference for optimizing combination treatment strategies and expanding the benefits of ICI treatment to a broader patient population.

CRediT authorship contribution statement

Manting Wang: Writing – review & editing, Writing – original draft, Visualization, Investigation. **Fan Yang:** Writing – review & editing, Visualization, Investigation. **Jingwei Kong:** Writing – review & editing, Visualization, Investigation. **Yuhan Zong:** Writing – review & editing, Visualization, Investigation. **Qin Li:** Writing – review & editing, Conceptualization. **Bin Shao:** Writing – review & editing, Conceptualization. **Ji Wang:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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Data availability

No data was used for the research described in the article.

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