Application of traditional Chinese medicine in inhibiting the PD-L1 pathway for gastric cancer and colon cancer treatment

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Research Article

Keywords: PD-L1, TCM, PD-1/PD-L1 axis, GC, CC

Posted Date: March 29th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2744681/v1

Abstract

Programmed death receptor-1 (PD-1) is a suppressor-like receptor located on T cells that interacts with programmed death ligand-1 (PD-L1) to suppress T cell expression, resulting in tumor immune escape. The way to achieve immunotherapy by inhibiting PD-1 and PD-L1 pathways and blocking PD-1 and PD-L1 binding, thereby achieving T-cell upregulation, has been validated by the FDA to enter clinical practice. To date, natural components from herbal medicine such as paclitaxel and camptothecin have been shown to play a role in oncological treatment either alone or in combination with currently known therapies. Meanwhile, many animal experimental studies have shown that natural ingredients from traditional Chinese medicine or traditional Chinese herbal compounds can play a positive role in gastric and colon cancer by inhibiting the PD-L1 pathway. This review focuses on the mechanism of PD-L1 and the modulation of PD-L1 pathway by some traditional Chinese medicines in two common types of digestive cancers, gastric cancer and rectal colon cancer, with the aim to open up new ideas for the development of novel drugs against digestive cancers.

1. Introduction

Tumor immune escape, phenomenon that tumors escape the recognition and attack immune system for growth and metastasis through various mechanisms, is one of the important elements of tumor survival and development[1]. Mechanisms of tumor immune escape include low immunogenicity of tumor cells, recognition of tumor-specific antibodies as autoantigens, tumor surface antigen regulation, and immunosuppression. Owing to its continuous clinical success, tumor immunotherapy is currently a promising tumor treatment[2]. Tumor-induced immunosuppression is currently the most widely studied area. Namely, tumor-induced immunosuppression consists of two main modalities. The first is to reduce the immune tolerance of tumor cells by inducing immunosuppressive cells to accumulate around the tumor and secrete immunosuppressive factors that inactivate cytolytic T lymphocytes. Programmed death ligand-1 (PD-1) and programmed death receptor ligand-1 (PD-L1) re known as immune checkpoints and can interact with each other to produce suppressive effects, thereby resulting in the inactivation of T lymphocytes and ultimately in tumor immune escape.

PD-1, which was first identified in 1992, is a member of the CD28 family[3][4]. Its structure consists of four parts, such as immunoglobulin variable region (Ig V), transmembrane region, immunoreceptor tyrosine-based inhibitory motifs (ITIM), and immunoreceptor tyrosine-based switch motifs (ITSM). PD-L1 is one of the two ligands of PD-1, and its structure consists of three parts, including IgV and IgC-like extracellular region, transmembrane region, and short cytoplasmic tail region. PD-L1 is expressed on antigen-presenting cells, non-lymphoid organs, and a variety of tumor cells[5][6]. PD-L1 is the most important ligand of PD-1. Although both PD-L1 and PD-L2 are ligands PD-1, PD-L2 is more narrowly expressed. After PD-1 binds to PD-L1, phosphorylation of tyrosine in ITSM occurs, thereby downregulating downstream pathways and causing inhibition of T-cell activation and induction of T-cell apoptosis[7][8][9][10].

PD-L1 is highly expressed in many tumors[11]. There are currently two hypotheses for the mechanism of its expression. The first includes intrinsic immune resistance regulated by oncogenes, which induces persistent PD-L1 protein expression in tumor cells, which does not correlate with the tumor microenvironment; the second involves adaptive immune resistance regulated by the tumor microenvironment, which induces non-persistent PD-L1 expression[12] [13].

Therefore, blocking the binding of PD-1 to PD-L1 can reverse the abovementioned immunosuppressive mechanism and help to improve the ability of the body's immune system to kill tumors, which provides a reliable theoretical basis for tumor immunotherapy based on blocking PD-1/PD-L1[14].

2. Division

2.1 PD-L1 and digestive tract cancer

Emerging studies of immune checkpoint inhibition in gastrointestinal tumors are making promising progress. The PD-1/PD-L1 pathway is one of the most accepted immune checkpoint pathways today, and because of this, its inhibitors are most widely used. To date, a series of immune checkpoint inhibitors, represented by PD-1/PD-L1 inhibitors, have been approved for a variety of gastrointestinal cancer tract cancers, including gastric, rectal, and esophageal cancers[15]. So far, FDA-approved PD-L1 inhibitors such as pembrolumab and nabumab have entered the market one after another.

2.2 PD-L1 and gastric cancer

Gastric cancer is a significant factor associated with cancer deaths globally, and is now the second leading cause of cancer death worldwide[16]. It is now more widely accepted that gastric cancer evades recognition and killing by the immune system through the downregulation of immune expression, upregulation of immune checkpoints, inactivation of cytotoxic T cells, and alteration of the tumor microenvironment. Clinical studies have shown that the upregulation of PD-L1 in gastric cancer patients often predicts a poor prognosis[17][18][19][20][21]. PD-L1 is even a stimulator of tumor-associated fibroblasts (TAF) and directly stimulates the growth of gastric cancer cells. More importantly, PD-L1 knockdown slows down gastric cancer(GC) progression in vitro and inhibits tumorigenicity in vivo[22].KEYNOTE-012[23]—a multicenter, open, phase Ib clinical trial of pembrolizumab, an FDA-approved PD-L1 inhibitor, in advanced gastric/gastroesophageal junction cancer—suggests that the median survival achieved with pembrolumab is significantly longer than that achieved with single-agent chemotherapy, with manageable side effects. In combination with the results of KEYNOTE-012, a phase II clinical trial was designed (KEYNOTE-059[24][25][26]) and its results have shown that pembrolumab is effective and safe for advanced gastric cancer. In the quest for better therapeutic effects, in the combination of immune checkpoint inhibitors, cohort 2 and cohort 3 studies in KEYNOTE-059 demonstrated a controlled safety profile and promising antitumor activity of pembrolumab + 5-FU + cisplatin as a first-line agent in the treatment of advanced gastric/gastroesophageal junction cancer. There is growing body of evidence that

immune checkpoint inhibitors acting on PD-L1 may be an important tool for future anti-gastric cancer therapy.

2.3 PD-L1 and colorectal cancer

Rectal cancer is a common malignant tumor worldwide. It ranks the third and second among males and females, respectively[27]. It is a cancer of the digestive tract that seriously affects human survival. It can be treated with nivolumab(another FDA-approved PD-L1 inhibitor) in combination with pembrolizumab. The phase II clinical trial CheckMate142 for dMMR/MSI-H colorectal cancer showed excellent clinical results. On the combination of nivolumab, Overman, have shown controlled safety of the combination therapy, high disease control rates, and significant survival benefit. It has been confirmed that immune checkpoint inhibition therapy for rectal cancer provides good anticancer effects.

3 Role Of Traditional Chinese Medicine And Its Components In Gastric Cancer And Colon Cancer Through The Pd-1/pd-l1 Pathway

3.1 Effects of some natural products of traditional Chinese medicine and their derivatives on gastric cancer through the PD-L1 pathway

3.1.1 Berberine

Berberine (BBR), an alkaloid derived from *Brassica juncea*, has been used in the treatment of cancer, bacterial infections, diabetes, cardiovascular and inflammatory diseases[28][29][30]. Berberine has been shown to have minimal cytotoxic effects on healthy cells but antiproliferative effects on cancer cells (e.g., breast, liver, and colorectal cancer cells)[31][32].

According to an animal experimental study of gastric cancer by Yang Liu et al., PD-L1 is downregulated by BBR. BBR enhances the sensitivity of tumor cells to co-cultured T cells by reducing the level of PD-L1 in cancer cells. In addition, BBR exerts antitumor effects by enhancing tumor-infiltrating T-cell immunity and attenuating the activation of immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T-cell T-lymphocytes (Tregs). BBR also triggers PD-L1 degradation via a ubiquitin (Ub)/proteasome dependent pathway. Surprisingly, BBR was found to selectively bind to glutamate 76 of constitutive photomorphogenic-9 signalosome 5 (CSN5) and to inhibit the PD-1/PD-L1 axis through its deubiquitination activity, thereby leading to PD-L1 ubiquitination and degradation[33]. This experiment correlated the antitumor mechanism of BBR and synthetically confirmed that BBR is a small-molecule immune checkpoint inhibitor that can be used for cancer treatment, which is good news for the development of immune checkpoint inhibitors for GI cancers such as gastric cancer.

3.1.2 Quercetin

Quercetin is a natural flavonoid extracted from the traditional Chinese medicine rutin. It can be obtained from flowers, leaves, and fruits of many plants from a wide variety of sources. It has been shown that

quercetin can play an anticancer role in gastric and pancreatic cancers[34][35].

The study by Ling Li et al. identified potentially active compounds through network pharmacology, molecular docking, cellular studies, and enzyme activity analysis to screen for quercetin, the active ingredient in the Chinese medicine compound GuiQiBaizhu, which inhibits HER2 activity and acts on PD-L1 via the PI3K/AKT pathway. This study confirmed that quercetin can be used for gastric cancer treatment through the PD-L1 pathway. However, animal experiments and other experimental validation are lacking, and there are still gaps in the research on the effects of quercetin on PD-L1[36].

A number of scholars have conducted studies on quercetin GI cancers, especially gastric cancer, but there is still not sufficiently strong evidence to confirm whether quercetin can be applied as an immune checkpoint inhibitor in the future.

3.1.3 Astragaloside IV

Astragaloside IV (AS-IV) is one of the main compounds extracted from the traditional Chinese medicine Radix astragali (huang qi). It has been shown that astragalus has antitumor effects on gastrointestinal cancers such as rectal colorectal cancer(CRC) [37]. Specifically, AS-IV can prevent the onset of GC, which is preceded by a prolonged precancerous stage. AS-IV is a promising antitumor drug for GC through impeding the proliferative, migratory, and invasive capacities of GC-associated fibroblasts (inducers of tumor cell growth) [38]. This is important for the prevention of stomach cancer that occurs before the precancerous stage. An experimental study by Wei Liu et al. confirmed that AS-IV could exert inhibitory effects on epithelial mesenchymal transition (EMT) and angiopoietin in vitro by increasing the expression of miR-195-5p and inducing miR-195-5p to target negative regulation of PD-L1 expression, thereby producing a therapeutic effect in gastric cancer. AS-IV inhibited EMT and angiogenesis in GC, and downregulation of miR-195-5p or elevation of PD-L1 expression reversed the inhibitory effect of AS-IV on angiogenesis in EMT and GC cells.[39]

It has been shown that AS-IV, a substance from the Chinese traditional medicine Astragalus, may play a role in the growth, invasion, and migration of gastric cancer. Based on its significance in pancreatic, rectal, and gastric cancers, astragaloside may play an important role in the future development of anticancer drugs for gastrointestinal cancers.

3.1.4 Oleanolic acid

Oleanolic acid (OA) is a natural triterpenoid compound abundantly isolated from TCM nvzhenzi. The current literature shows that OA can effectively protect blood vessels, improve blood circulation, and play an anti-fatigue role, but it can also have a variety of anticancer effects[40].

Xilong Lu et al. found that OA blocked the IL-1β/NF-κB/TET3 axis in gastric cancer cells, leading to DNA hypomethylation and PD-L1 downregulation. OA is also used as an epigenetic modulator of immunotherapy or is involved in the adjuvant treatment of gastric cancer.OA IL-1β-stimulated PD-L1

expression and restores the sensitivity of gastric cancer cells to the killing effect of cytotoxic T lymphocytes[41]. Overall, OA has great potential as an immunomodulatory option to combat gastric cancer.

3.1.5 Paclitaxel

Paclitaxel, a diterpenoid alkaloid, is one of the most efficacious antitumor natural products. It was first obtained by American scientists Wani and Wall in 1967 from the bark of Pacific yew, *Taxus brevifolia* Nutt. [42] Since their discovery, paclitaxel analogues have emerged as a variety of clinically marketed drugs such as albumin paclitaxel and polyene paclitaxel. Paclitaxel has been

sed in prostate cancer, advanced breast cancer, pancreatic cancer[43], melanoma[44], non-small cell lung cancer, gastric adenocarcinoma, and many other cancers.[45]

There are no studies investigating the direct action of paclitaxel on PD-L1, but a study by JinLing Yu et al. found that PD-L1 monoclonal antibody-modified nanoliposomes containing a combination of paclitaxel and a P-gp transporter inhibitor were therapeutically effective in multidrug-resistant gastric cancer[46].

In addition, a clinical study by Sasaki et al. showed that receiving anti-PD-1 therapy first may improve tumor response to paclitaxel plus RAM, thereby improving the survival cycle of patients with advanced gastric cancer[47].As an antitumor natural product with more research and better efficacy, paclitaxel has various antitumor effects. At present, there is direct evidence that paclitaxel can act through the PD-1/PD-L1 pathway in gastric cancer, and there is an enhanced effect of PD-L1 inhibition in gastric cancer through the combined drug mode, but he mechanism of action is not yet clear and further research is needed.

3.1.6 Bu-zhong-yi-qi decoction

Bu-zhong-yi-qi decoction (BYD) comes from the “Treatise on Spleen and Stomach” written by Dong-Yuan Li, a member of the ‘four great doctors of the Jin and Yuan period’ (1271–1368, B.C.). It is composed of Radix astragali (huang qi), Radix codonopsis pilosulae (dangshen), Radix angelicae sinensis (danggui), Radix glycyrrhizae (gancao), Cimicifugae rhizoma (shengma), Radix bupleuri (chaihu), Atractylodes macrocephala (baizhu), Pericarpium citri reticulatae (chenpi), Rhizoma Sparganii (sanleng), and Rhizoma Curcumae (erzhu). BYD has a wide range of applications in the field of digestion, and previous studies have suggested its role in irritable bowel syndrome, diarrhea, gastroenteritis, and rectal colon cancer.

A study by Ruihan XU et al. showed that BYD could inhibit PD-L1 expression in gastric cancer through the PI3K/AKT pathway while directly promoting the value and activation of T lymphocytes. In addition, tonic Chinese Yi Qi Tang was shown to reduce the proportion of PD-1+ Treg cells and repair the already damaged immune system to some extent[48]. Comprehensive studies have shown that BYD can be effective in gastric cancer treatment by inhibiting the immune escape pathway. At the same time, the prospect of research and development is very promising for the post-chemotherapy treatment of gastric

cancer, metastasis and recurrence of gastric cancer after chemotherapy, and improving the quality of survival. However, as it is a Chinese medicine formula, it has more compound components, the mechanism of action and pathways are not clear, and further verification of its specific active ingredients and mechanism of action is needed.

3.1.7 Banxia xiexin decoction

Banxia xiexin decoction (BXXX) is a traditional Chinese medicine formula. Pharmacological studies have shown that BXXX contains a variety of active ingredients, including ketones, alkaloids and saponins[49]. The prescription is composed of pinellia, skullcap, dried ginger, ginseng, coptis, licorice, and jujube. BXXX can achieve the desired effect in gastroenteritis, diarrhea, and ulcerative colitis, and there are also studies that support the role of BXXX in lung and rectal cancers[50][51].

Through cellular and animal experiments, Xuan Feng et al. demonstrated that BXXX exerted antitumor effects by decreasing IL-6/JAK/STAT3-mediated PD-L1 activity and improved drug sensitivity in gastric cancer cells by regulating the expression of 6-O-methylguanine-DNA methyltrans-ferase(MGMT)[52]. In another study by Xuan Feng, network tool analysis and experimental validation led to the conclusion that key molecules such as PD-L1, HIF-1, EFGR, IFNGR, and TLR4 in each pathway of the BXXX regulatory network have targeting effects, which was verified by cellular and animal experiments, finally confirming the mechanism of BXXX's multi-target and multi-pathway effects on gastric cancer[53]. As an ancient formula in Chinese medicine, BXXX is still used for digestive system diseases, but its composition is complex and pharmacological research is still inadequate. Further studies on its pharmacological composition and mechanism of action are needed, which may be helpful in the future for gastric cancer treatment, adjuvant therapy, and post-chemotherapy treatment.

The mechanisms of action of the abovementioned traditional Chinese medicine ingredients and compound medicines are listed in Table1 and Table 2.

Table 2

Traditional Chinese	Composition	Target	References
Bu-zhong-yi-qi decoction	Tragali, Codonopsis pilosulae, Angelicae sinensis, glycyrrhizae, Cimicifugae rhizoma, bupleuri, Atractylodes macrocephala, Pericarpium citri reticulatae, Rhizoma Sparganii, Rhizoma Curcumae	PI3K/AKT PD-1^{+} Treg↓	48
Banxia xiexin decoction	*Pinellia, skullcap, dried ginger, ginseng, coptis, licorice and jujube*	IL-6/JAK/STAT3	53

4 Effects Of Some Natural Products Of Traditional Chinese Medicine And Their Derivatives On Colorectal Cancer Via The Pd-l1 Pathway.

4.1 Camptothecin

Camptothecin was first discovered and extracted by Wall et al. in 1966. Its source is the Chinese endemic plant Camptothecin[54]. Since its discovery, camptothecin has attracted much attention worldwide for its unique anticancer mechanism. Camptothecin has been shown to be effective against a variety of cancers such as stomach, rectal, esophageal, and breast cancers[55][56]. Many scholars have structurally modified camptothecin and synthesized a variety of active derivatives, some of which have entered clinical applications. For example, irinotecan and topotecan have entered clinical applications in Japan and the United States, respectively.

In a study by Deepa Bedi et al., it was proposed that Camptothecin acts on the NF-kB signaling pathway to upregulate the expression of PD-L1 [57]. That study analyzed the anticancer mechanism and stoichiometric concentrations of camptothecin, which may be useful for the clinical application of camptothecin and camptothecin derivatives.

4.2 Salvia plebeia R.Br

Salvia (*Salvia plebeia* R.Br, SP) comes from traditional Chinese medicine and exhibits better anti-inflammatory and antiviral properties[58][59][60]. SP is a traditional Chinese herb that has been proven to treat common cold, diarrhea, and hepatitis[61].

Jang-Gi Choi et al. demonstrated that Salvia plebeia R. Br. Extract (SPE), a component from Salvia, blocked PD-1/PD-L1 interaction and enhanced T-cell-mediated antitumor activity in a concentration-dependent manner. In addition, cosmosiin in SP has a strong effect on blocking PD-1/PD-L1[62]. The study by Jang-Gi Choi et al. was the first to investigate the role of SPE through immunotherapy targeting the PD-1/PD-L1 pathway, which provided more clarity regarding the anticancer mechanism of action for *Salvia miltiorrhiza*, a traditional Chinese medicine, and contributed to the development of novel potent anticancer drugs targeting immune checkpoint inhibitors of the PD-1/PD-L1 pathway.

4.3 *A. membranaceus*

Astragalus membranaceus is a classical traditional Chinese medicine that is widely used in the treatment of inflammatory diseases, tumors, and various cardiovascular diseases. It also has free radical scavenger activity and neuroprotective activity. PG2 is a natural product extracted from the traditional Chinese medicine *Astragalus membranaceus*[63]. Hsu-Liang Chang et al. found that PG2 extracted from *Astragalus membranaceus* could downregulate PD-L1 expression through the protein kinase B (Akt)/mammalian target of rapamycin (mTOR)/ribosomal protein S6 kinase beta-1 (p70S6K) pathway, thereby exerting an antitumor effect[64]. This study provides a rationale for combining PG2 with other treatments against PD-L1 and provides a rationale for future anti-PD-L1 therapy combinations.

4.4 Licochalcone

Lichalcone is an ancient herb with powerful pharmacological activities, including anticancer, anti-inflammatory, and antioxidant activities, according to modern pharmacological studies. The medicinal value of licorice is attributed to the flavonoid and triterpenoid saponin bioactive components of licorice[65]. Licochalcone A (LCA) is a novel flavonoid isolated from licorice root[66]. Current studies have shown that LCA acts on different types of tumors by different mechanisms.

Experiments by XueShuang Liu et al. verified that LCA inhibited PD-L1 expression in colon cancer by suppressing the interaction between p65 and Ras. It also enhanced the activity of cytotoxic T lymphocytes and restored the ability to kill tumor cells. LCA also inhibits cell proliferation and promotes apoptosis by targeting PD-L1[67]. The study by Liu et al. confirmed the pharmacological mechanism and principle of action of LCA, which serves as a good reference in the development of targeted immunosuppressive checkpoint drugs against PD-L1 in colon cancer.

4.5 Curcumin

Curcumin is an extract from the rhizome of turmeric, which is used in Chinese medicine for pain relief and other applications. Modern research has found that curcumin has a variety of biological activities such as antioxidant, anti-inflammatory, and antitumor[68]. There are also more studies showing the effectiveness and safety of curcumin in the prevention and treatment of various human diseases[69]. Paul Dent et al. validated (curcumin + sildenafil) the enhanced efficacy of 5-fluorouracil in CT26 colorectal tumors. In the experiment, it was found that prior exposure of established CT26 tumors to curcumin + sildenafil significantly enhanced the efficacy of the subsequently administered anti-PD-1 antibody. Overall, the combination curcumin + sildenafil is promising and has the potential to be an effective neoadjuvant therapy for colon cancer. As a food-derived drug, curcumin has a high safety profile with few adverse effects. However, the available experimental sample size is small; the mechanism of action and pathway studies have not been perfected; and more in-depth studies on curcumin + sildenafil are needed to fill in the many gaps in this field.

4.6 Ziziphus jujuba Mill.

Ziziphus jujuba Mill., a herbal medicine from natural fruits, has high nutritional and medicinal value. An animal study by Jing et al. showed that oral administration of ultrafine septoria powder was able to improve the gastrointestinal microbiota of mice through enriched populations of Trichoderma spp. and Flavobacterium tumefaciens, enhance the production of short-chain fatty acids(SCFAs), and improve tumor immune infiltration and systemic immunity, which together contributed to the antitumor efficiency of αPD-L1 in vivo. The study by Nan Jing et al.[70] contributed to the development of dietary interventions for cancer immunotherapy using natural nutrients, and it is worth trying to see whether combining nutritional interventions during anti-PD-L1 can be effective in improving antitumor effects.

4.7 Actinidia eriantha

The root of *Actinidia eriantha* is a traditional Chinese medicine (TCM) and has been widely used in treating various malignant tumors. *A. eriantha* polysaccharide (AEPS) is the active component of *A. eriantha* and has been reported to have antitumor effects[71]. JinXia Liu et al. studied the efficacy and mechanism of introducing anti-PD-1 therapy combined with AEPS therapy into rectal cancer–xenograft mice. Through experiments, the authors found that the combined therapy inhibited tumor growth and prolonged the survival rate of the mice. At the same time, the immunoregulatory cytokines TNFα and IFNγ were significantly increased[72]. That experiment explored AEPS combined with anti-PD-1 therapy, which may provide a reference for the future AEPS combined therapy as adjuvant therapy.

Resveratrol is mainly derived from the rhizome extract of the Chinese herbal medicine *Reynoutria japonica* Houtt. Resveratrol has some other biological activities such as anti-aging, antibacterial, antioxidant, immunomodulatory. Piceatannol is a compound with a chemical structure similar to resveratrol, which helps prevent cancer, heart disease, and neurological disorders. In a pilot study, Justin Lucas et al. demonstrated that resveratrol and leucovorin could regulate PD-L1 expression in breast and colorectal cancer cells. When resveratrol was used in combination with leucovorin, it caused synergistic upregulation of PD-L1 in some cell lines. PD-L1 was most clearly induced in Cal51 triple-negative breast cancer (TNBC) and SW620 colon cancer cells by the combination of drugs, and this was mediated by NF-κB transcription[73]. This approach, by causing upregulation of PD-L1, can sensitize such cells, which are originally insensitive to PD-L1, to PD-L1 inhibitors and develop new therapeutic modalities.

4.8 Pien Tze Huang

Pientzehuang (PZH) is a famous traditional Chinese medicine. It is composed of *Panax ginseng*, niuhuang, musk, snake bile, and other ingredients. It has the functions of clearing heat and relieving pain, detoxifying and anti-inflammatory effects, and obvious liver-protecting effect[74]. So far, although PZH has not entered extensive clinical oncology treatment, many scholars have already conducted research on its antitumor mechanism. Qiang Chen et al. confirmed that the role of PZH in mediating immune escape and synergistically enhancing anti-PD-1/PD-L1 immunotherapy in rectal colon cancer is mediated through the IFNGR1–JAK1–STAT3–IRF1 pathway to attenuate PD-L1 expression, weaken the immune escape ability of rectal colon cancer cells, and reactivate CD8+ cells to exert antitumor ability[75].

The study by Huang et al. [76] confirmed that the deterioration rate of PZH combined with conventional radiotherapy in patients with primary or advanced liver cancer was reduced. This has paved the way for the wide application of PZH in the future. As a traditional precious Chinese medicine, PZH uses many rare animal herbs (snake bile, cowry, musk, etc.), and it is still questionable whether it can pass the ethical approval at present when the environment and animal protection are getting better and better.

4.9 Jiedu Sangen decoction, JSD

Jiedu Sangen decoction (JSD) is a herbal medicine developed from the team of FeiYu Shan et al. It contains three herbs, including vine plum root (kiwi root), salicornia root (peppermint leaf herb root), and

thuja root (tiger stick). This herbal mixture is known to contain ursolic acid, 12-en-28-oic acids of oleananetype (from Radix Actinidiae chinensis), and emodin (from Polygoni Cuspidati Radix). It has been shown that the combination of detoxifying Sanguine Tang and PD-L1 inhibitor inhibited the migration, invasive ability, and EMT of CT-26 cells, and significantly reversed EMT and metastasis in vivo. The combination reversed EMT through the PI3K/AKT signaling pathway, thereby inhibiting migration and invasion of rectal colon cancer cells. The reported effects of the combination of herbal prescriptions and PD-L1 inhibitors on the PI3K/AKT pathway[77] provide a reference for the application of herbal formulas or natural ingredients in immune checkpoint inhibition. TCM has multi-target and multi-pathway effects, and many natural ingredients from TCM may be useful in the combination of drugs.

4.10 Gegen Qinlian decoction

Gegen Qinlian decoction is a common prescription in traditional Chinese medicine and consists of four traditional Chinese herbs, including gegen, scutellaria, scutellaria, and licorice. GQD has remarkable efficacy in the field of digestion, especially damp-heat diarrhea. In addition, modern studies have shown that Ge Gen Scutellaria Tang is effective in type 2 diabetes[78] and ulcerative colitis[79].

Experimental animal studies by Ji Lv et al. showed that the antitumor effect of the combination therapy of GQD and anti-mouse PD-1 was greater than that of monotherapy, which was related to the dose of GQD[80]. However, given that GQD has four herbs in combination with complex compound components, which may involve multiple complex mechanisms of action including PD-1/PD-L1, the combined mechanism of action of Ge Gen Scutellaria Tang in anti-PD-1/PD-L1 needs to be further explored.

The mechanism of action of the abovementioned traditional Chinese medicine ingredients and compound medicines is listed in Tables 3 and 4.

Table 4

Traditional Chinese	Composition	Target	References
Pien Tze Huang	*Panax ginseng, niuhuang, musk, snake bile, etc.*	IFNGR1-JAK1-STAT3-IRF1	77
Jiedu Sangen decoction	*Teng Li Gen, Shui Yang Mei, GenHu Zhang Gen*	PI3K/AKT	81
Gegen Qinlian decoction	*Pueraria, Scutellaria, Coptidis, Licorice*		

5. Conclusion And Outlook

Immune checkpoint PD-1/PD-L1 induces the expression of immunosuppressive molecules and their receptors, inhibits the activation of T lymphocytes, and is an important part of tumor immune escape. In recent years, immune checkpoint–oriented inhibitors have become an important direction in antitumor therapy. At present, the way to achieve immunotherapy by inhibiting PD-1 and PD-L1 pathways and blocking PD-1 and PD-L1 binding so as to achieve T-cell upregulation has been validated by FDA to enter the clinical practice. Although there are currently five classes of PD-L1 blockers entering the clinic, this is not enough. More immune checkpoint inhibitors are urgently needed to be discovered and used.

Although TCM is a valuable research hotspot in the field of adjuvant therapy and drug sensitivity in oncology, a lot of preclinical and clinical research still needs to be done to study and develop effective therapeutic agents before they can be introduced into clinical use. First, although the development of herbal anticancer drugs has played an important role in the effective treatment of cancer patients[81][82] and has been used by Chinese herbalists for a long time, their toxicity and safety evaluations are still inadequate, and studies on their toxicity, safe dosage, and safety evaluation are urgently needed[83]. Second, especially in recent years, as more and more attention is paid to natural products of Chinese medicine and their derivatives, pharmacokinetic and pharmacodynamic studies are becoming more and more important. The application prospect of a drug, especially the market prospect, is judged not simply by its strong efficacy and low toxic side effects, but also by good pharmacokinetic properties[84]. Third, the development of many antitumor drugs is still at the in vitro stage, validating their mechanisms of action and pathways in cellular and animal experiments. In the future, more efficient and sophisticated clinical trials are needed to further validate the anticancer effects of TCM and its natural products. Fourth, some Chinese medicines, such as Xi Shu Lin, come from the unique Chinese plant Kong Dong tree, and mass collection for pharmaceuticals will inevitably have irreparable impact on ecological environment. As Pientzehuang comes from rare animals, its collection may damage ecological environment; thus, whether mass production can be conducted through artificial synthesis is important in terms of both ethics and ecological environment in today's increasingly perfect animal and environmental protection. Fifth, diet is an important aspect for GI cancer patients. Many herbs derived from fruits and grains have been shown to have a role in regulating intestinal flora, and how nutritional interventions can play a role in anti-PD-L1 therapy seems to be a boon for GI cancer patients at this point in time. Finally, many herbal medicines and their derivatives play a unique role in the treatment of digestive tumors, and the mechanisms regarding their correlation with PD-L1 have not yet been explored, which requires additional research efforts.

In conclusion, we hope that this review will provide some insights into the mode of action and pathways of PD-L1, the role of traditional Chinese medicine and its natural products in gastric and rectal cancers, and their pharmacological mechanisms. At present, traditional Chinese medicine and its natural products have unique advantages as immune checkpoint inhibitors in the PD-L1 pathway. In this regard, we hope that more researchers and doctors will devote attention to this, conduct more studies and trials, and do more in-depth research.

Declarations

The authors have declared that no competing interest exists.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

All authors contributed substantially to the article. CSC conceived and designed this paper. XHZ, LX, DMC, and TRZ summarized and analyzed the data. XHZ, MRZ, and ZCF drafted, revised, and edited the paper.

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Tables

Table 1 and 3 are available in the Supplementary Files section.

Figures

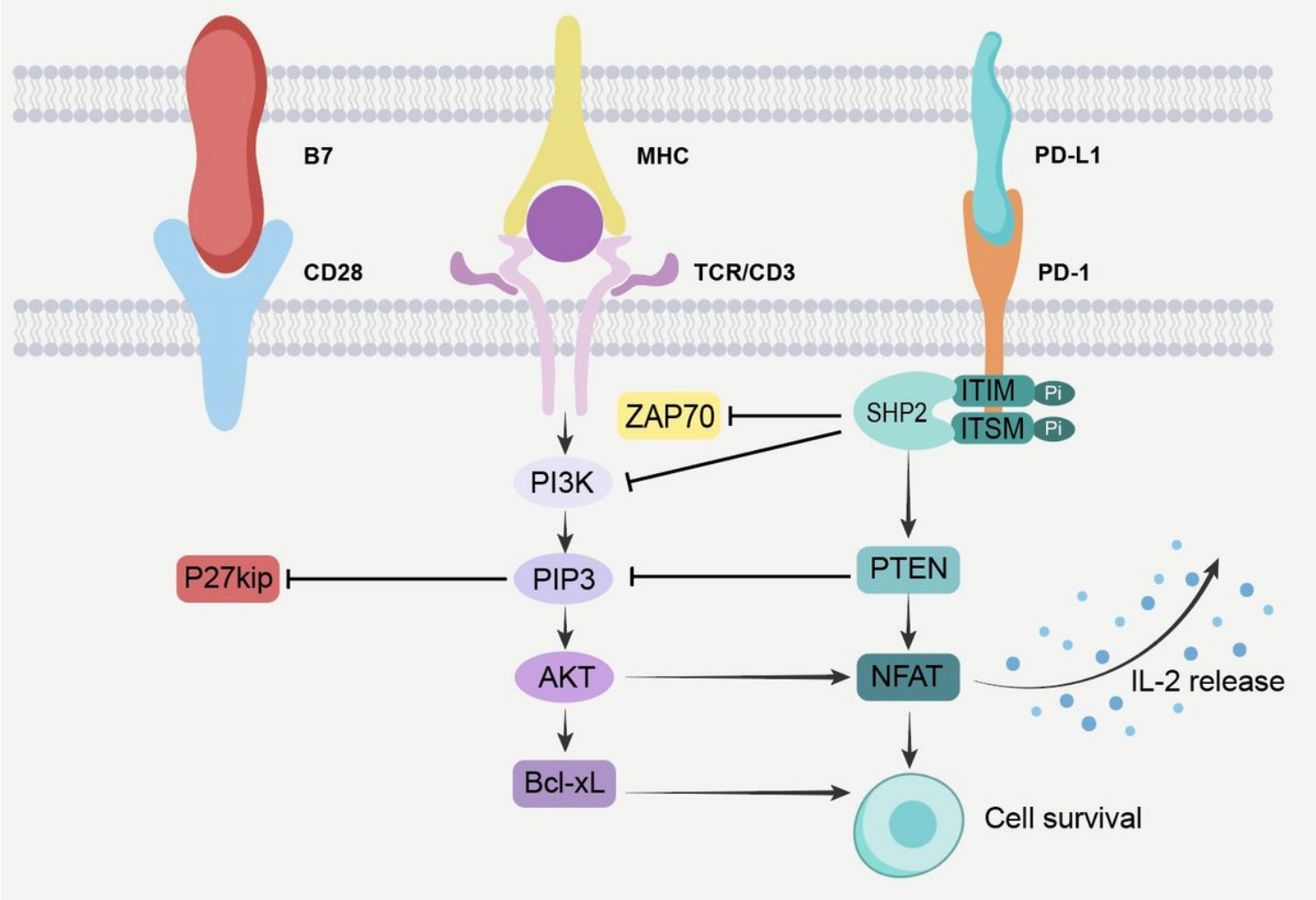

Figure 1

PD-1/PD-L1 pathway

Supplementary Files

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