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Investigation of traditional Chinese medicine for cancer treatment: Signaling pathways and anti-tumor microenvironment

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Abstract. Traditional Chinese Medicines (TCMs) have performed great efficacy in carcinoma treatment. Due to bidireactional and multitargeting capability and the small side effects of TCM, it has been used in cancer treatment in China and has been studied a lot in other countries. In the early research, two possible anti-tumor mechanisms of TCM have been proposed, first is directly affecting cancer cells by regulating the signaling pathway, the second is indirectly affecting cancer cells by regulating the immune system and tumor microenvironment. Herein we want to discuss systematically how these anti-tumor mechanisms of TCM work together to influence carcinoma treatment. This review will include several kinds of active extracts of TCM, such as ginsenoside, baicalein, baicalin, astraglan, berberine and ferulic, and several pathways influenced by TCM in the pathogenesis of cancer, such as Fas/FasL pathway, PI3K/Akt pathway, TGF-β/Smad pathway and the regulation of tumor microenvironment, such as repolarization of tumor-associated macrophages (TAMs) and PD1/PD-L1 interactions.

Keywords: traditional Chinese medicine, cancer, active extract, signaling pathway.

1. Introduction

The application of TCMs have a long history, whether TCMs have clear effects on disease treatments has attracted wide attention, many diseases have been confirmed to have an obvious therapeutic effect by using TCMs, such as coronary heart disease, liver disease, periarthritis of shoulder, depression, epilepsy, gynecological diseases. Since 2018, COVID-19 has posed a great threat to human health, and TCM has also played an important role in the prevention and control of COVID-19 [1-6]. The number of cancer cases remains high, a variety of malignant tumors shows low five-years survival rate, poor prognosis, high rates of recurrence and metastasis and multidrug resistance phenomenon in treatment [7-10]. The effect of TCM on the prevention and treatment of cancer has always attracted much attention. Many reports have reported the independent therapeutic effect of TCM on gastric cancer, lung cancer, breast cancer, colorectal cancer, esophageal cancer and other cancers, as well as the synergistic effect of combined treatment with other therapies [10-15]. In addition, TCM can assist chemotherapy,

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radiotherapy to improve the side reaction of human body and reverse multi-drug resistance phenomenon. What's more, TCM therapy can also prolong the survival time of cancer patients, improve the quality of life of cancer patients and prevent cancer [8,10]. However, the ingredients that play anti-cancer function in many TCM formulas and nature herbs are not clear, so it is not easy to determine the dose of active ingredients which play anti-cancer function. In the context of fine medicine, it is particularly important to explore the active cost of TCM. If the active ingredient and dosage can be clearly defined, it will be conducive to subsequent drug research and development, and introduce TCM which is originally apply in limited areas to the world, benefiting cancer patients all over the world. This paper focuses on six active extracts of TCMs, ginsenoside, baicalein, baicalin, astraglan, berberine and ferulic, and their anti-cancer mechanism. These TCM extracts demonstrate the ability to improve immune activity, induce apoptosis of cancer cells and regulate the tumor immune microenvironment. This review aims to summarize the function of the active components of some anticancer TCMs and provide reference for further research on the active components of TCMs.

2. Active Extract of TCM

In China, TCM has been applied for a long history. Because of its property of multitarget and low drug resistance and small side effect, TCM has been used for supplementary cancer treatment in China and has been studied to elucidate the mechanisms in other countries. However, the traditional way of taking TCM is to drink a bowl of unpalatable medicine soup three times a day after boiling the herb formula, it increases the difficulty of cancer patients to take the drug and reduces compliance. To maintain the efficacy of anti-tumor of TCM, while making it easier for patients to take, the active extract has been studied to replace the herb formula. Active extracts are the pure substances that have been extracted from nature herbs, which have the same function. The active extract could decrease the amount of drug that patients need to take daily, replacing a bowl of medicine soup with a few pills, meanwhile not affecting the therapeutic effect. What's more, by taking active extracts, patients could avoid absorbing some other substances that have no therapeutic effect or have some side effects. For instance, after taking ginseng, some patients get nosebleed.

2.1. Ginsenoside Family

Ginseng has been verified in modern medicine that it has anti-tumor effects, and it has been turned out that ginsenoside shows great effect. Ginsenoside aliases triterpene saponin. Ginsenoside is not a single substance, actually many types of ginsenosides form ginsenoside family. Ginsenosides are a kind of sterol compound. Ginsenoside family represents several kinds of active extracts that have been separated from ginseng. Ginsenoside family includes ginsenoside Rg3, ginsenoside Rg5, ginsenoside Rh2, ginsenoside aPPD, ginsenoside Rk2, ginsenoside Rh3 and so on [9-11]. In these substances, only ginsenoside Rg3 had passed phase IV clinical trial of anti-tumor so far, and it showed great efficiency and safety in cancer treatment, and ginsenoside Rg3 only accounts for three parts per 100,000 in ginseng. In additional, ginsenoside Rh2 have passed phase III clinical trial of anti-tumor already, and ginsenoside Rh2 only accounts for one part per 100,000 in ginseng [16-20].

2.2. Baicalein and Baicalin

Scutellaria baicalensis is an ingredient in many anti-tumor formulas of TCM. Baicalein ($C_{15}H_{10}O_5$) and baicalin ($C_{21}H_{18}O_{11}$) are the main active components of scutellaria baicalensis. Under ordinary circumstances, baicalin could represent $C_{15}H_{10}O_5$ and $C_{21}H_{18}O_{11}$, herein to differentiate these two compounds, baicalin only represents for $C_{21}H_{18}O_{11}$, and baicalein was used for $C_{15}H_{10}O_5$ [21]. Baicalein also called noroxylin, it is one of the highest concentration of flavonoids of scutellaria baicalensis. After baicalein enters the animal body, it rapidly converted into baicalin in the blood. Baicalin is a flavonoid compound formed by baicalein and a molecule of glucuronic acid. Baicalin is not easily absorbed by mouth, but can be absorbed into the blood after enzymatic hydrolysis to baicalein in the intestine, and is quickly transformed into baicalin in the body [22]. In recent researches, baicalin and baicalein has shown anti-cancer properties [23].

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2.3. Astraglan

Astragalus polysaccharide (APS), a kind of effective component in Astragalus, is a hydrosoluble heteropolysaccharides extracted from Astragalus mongolicus or Astrafalus membranaceus. APS is made up of fructose, rhamnose, glucose, hexuronic acid, arabinose, glucuronic and galacturonic acid. APS has the function of immune enhancer or modulator, and antiviral, antitumor, antiaging, antiradiation, antistress, antioxidation [24-27].

2.4. Berberine (BBR)

BBR is a quaternary ammonium alkaloid isolated from Coptis chinensis. BBR has proven efficacy in the treatment of gastroenteritis and has been used as BBR hydrochloride tablets and BBR hydrochloride capsules [28,29]. In recent researches, BBR has been proven it also has anti-cancer properties and it showed multiple anticancer mechanisms.

2.5. Ferulic

Ferulic acid (FA) has a high content in asafoetida, Angelica, Chuanjian, cohosh, jujube kernel and other TCMs, and it is one of the active compounds of these TCMs. FA has anti-radiation, anti-oxidation, antibacterial and antiviral effects. In recent years, FA showed anticancer function.

3. Anti-tumor Signaling Pathways of Active Extract

3.1. Fas/FasL Pathway

Fas and its ligand FasL fall within tumor necrosis factor (TNF) receptor supergene family, they are membrane surface molecules involved in apoptosis. Fas is a death receptor that mediates programmed apoptosis. The interaction between Fas and its ligand FasL trimer complex forms Fas trimers on the surface of target cells [30-34]. After that, the death domains in the cytoplasm gather together into clusters, which bind to the Fas associated death domain protein (FADD), thereby recruiting and activating caspase8, which is then signaled by downstream caspase cascade to initiate apoptosis [30]. Fas/FasL Pathway is one of the main ways that cytotoxic T cells kill target cells and one of the main ways of immune escape in vivo. Normally, FasL is expressed in cytotoxic T cells, FasL will bind with Fas on the target cell and cause its death [30-33]. What worths mentioning is that Fas is been expressed in cytotoxic T cells, so cytotoxic T cells could be induced to apoptosis as well since FasL could be expressed in other kinds of cells too. However, in many kinds of cancer cells, the content of functional Fas is extremely low, so protecting themselves from attacking by immune cells, meanwhile their amount of FasL is been increase largely, so cancer cells could actively attack cytotoxic T cells to induce cytotoxic T cells to apoptosis.

In lung cancer, Ginsenoside and BBR resulted in up-regulated expression of Fas molecules, thus immune escape of tumor cells was been weakened [30]. In addition, in gastric cancer, herb formula Yang Wei Kang Liu Granule (YWKL), which includes ginseng and astragalus, could lead to up-regulated FasL expression and down-regulated Fas expression of T cells, meanwhile down-regulate FasL expression of gastric cancer cells. This indicates that ginsenoside and APS may have the ability to regulate Fas/FasL pathway in stomach cancer [19, 21, 30].

3.2. PI3K/Akt Pathway

PI3K/AKT pathway is an intracellular signal pathway that influences other signal pathway related to itself, such as cell apoptosis, growth etc., and some extracellular signals, such as angiogenesis [29, 35]. Among the KEGG databases, 71 pathway types were directly related to the PI3K/AKT pathway. Phosphatidylinositide 3-kinase (PI3K) is intracellular phosphatidylinositide 3-kinase [35]. This enzyme is a complex that included a regulatory subunit and a catalytic subunit. PI3K can be classified according to catalytic subunits. Three types of PI3K catalytic subunits are expressed in human cells, and the PI3K/Akt pathway only includes Class I catalytic subunits. Four types of Class I catalytic subunits are expressed in mammals. All of these catalytic subunits can phosphorylate PIP2 to PIP3, which is the

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second messenger of PI3K/Akt pathway. PIP3 phosphorylates Akt, activating it. AKT or PKB is a proto-oncogene [32]. AKT has three main domains: the PH domain (which has an affinity for PIP3), the catalytic domain, and the regulatory domain. Once activated, AKT can be transferred from membrane to cytoplasm and nucleus. AKT influences several types of downstream pathways through phosphorylation, such as it blocks related BAD activation, thereby inhibiting apoptosis [16, 20, 28, 32, 33]. PI3K/Akt pathway could regulate the expression of HIF-1α and VEGF. At present, many studies have found that PI3K/Akt is an essential signal transduction pathway because it inhibits apoptosis as good as promotes cell survival. PI3K/Akt pathway can inhibit apoptosis induced by hypoxia and up-regulate the content of HIF-1α and VEGF of tumor, which promotes angiogenesis [30, 32, 33].

In leukemia, Ginsenoside Rg3 inhibited angiogenesis and induced apoptosis through blocking PI3K/Akt pathway and cell cycle by inhibiting activation of NF-Kb through inhibiting PI3K/Akt pathway. In melanoma, FA demonstrated antiangiogenic ability by targeting the regulation of PI3K/Akt pathway. Herb formula Weipixiao (WPX) could decrease the content of PI3K and Akt and HIF-1α in gastric cancer [34-37]. Further study is needed to explore the active extracts of the formula.

3.3. TGF-β/Smad Pathway

TGF-β superfamily is significant in the regulation of growth, development and differentiation of cells in many biological systems [28]. TGF-β superfamily contains TGF-β and some other protien [32, 33], activins and related proteins. TGF-β receptor has two types, TβRI and TβRII. TβRII could phosphorylate and activate TβRI kinase, it then phosphorylates and activates Smad transcription factors. Smad has eight types: Smad1~8. Smad2 and Smad3 were initiated by TGF-β, while Smad1, Smad5 and Smad8 could not. Under normal conditions, this pathway starts with Akt receptor's oligomerization induced by ligand and phosphorylation of Smad2 and Smad3 [31]. After phosphorylation of carboxyl terminal of Smads, it binds to Smad4, and it will transport to the nucleus. Activatory Smads could regulate a variety of different reaction that happened in vivo, resulting in specific regulation of transcription.

TGF-β has shown two different or opposite effects on cancer. In the early stage of tumor development, it acts as a cancer suppressor by inducing growth inhibition [31, 38]. Whereas, in the later stage of cancer development, TGF-β plays a role in pro-angiogenesis in tumor, tumor cell infiltration, invasion, metastasis and immunosuppression. Therefore, the inactivation of intercellular components in this pathway will lead TGF-β to induce inhibition of growth and apoptosis signal dysregulation.

Baicalein is a kind of TGF-β inhibitor. Baicalein could inhibit cell proliferation mediated by mTOR/p70S6K signal pathway and cell invasion mediated by epithelial-mesenchymal transition (EMT) in cervical cancer [33, 39, 40]. In stomach cancer, prostate cancer etc., baicalein blocked Akt/mTOR signaling pathway through multiple pathways, thereby inhibiting cancer. Herb formula WPX could down-regulate the expression of TGF-β/Smad signaling pathway related activating proteins in gastric cancer. Yangyin fuzheng decoction led to down-regulated expression of TGF-β in lung cancer. These formulas are worthy of further exploration.

4. Anti-tumor Microenvironment Effects of Active Extract

4.1. Repolarization of Tumor-associated Macrophages (TAMs)

As a vital part of the tumor microenvironment, TAMs affect growth, metastasis and angiogenesis of cancer, immune regulation, and chemotherapy resistance [32, 41, 42]. It gradually revealed that, in different kinds of tumors of different animals, a strong correlation between increased numbers or density of TAM and poor prognosis. Therefore, recruitment and activation of TAM are essential for tumor progression, and TAM are popular targets for therapeutic intervention. Macrophages are multifunctional immune cells involved in regulating tissue homeostasis, defending against pathogens and promoting wound healing. Macrophages that infiltrate tumor tissue or congregate in the solid tumor microenvironment are defined as TAM. Monocytes in the blood are recruited around tumor cells under the action of various chemokines and cytokines, and thus become TAM. Influenced by tumor microenvironmental cytokines, macrophages polarize into different types, mainly M1 and M2, which

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are called polarization. M1 macrophages are considered as tumor-killing macrophages, primarily anti-tumor and pro-immune [30-32]. M2 macrophages are immunosuppressive [43], promoting tissue repair and tumor development. Both M1-type and M2-type TAM were present in all stages of tumor. In the early stage, M1 type was dominant, and in the middle and late stages, M2 type was dominant. With the progression of tumor, some M1-type repolarized to M2-type, and the increase of M2 macrophages also indicates poor prognosis. M1-type TAM secretes pro-inflammatory cytokines, such as IL-12, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) [32], and produces high levels of iNOS, while M2-type TAM secretes anti-inflammatory cytokines, such as IL-10, IL-13, and IL-4. Repolarization of TAMs have affection on tumor-promoting function. M2 macrophages and M1 macrophages have opposite functions in tumor growth and metastasis. Therefore, when pro-tumor M2 TAM repolarizes into the anti-tumor M1 TAM, it will inhibits TAMs and thus delay tumor development.

Baicalin enabled TAM to reprogram to repolarize M2 macrophages to M1 macrophages, promoting the content of pro-inflammatory cytokines in liver cancer. For example, Baicalin increased the content of IFN-γ and IL-12 to activate the anti-cancer effect in immune response [32]. Ganoderma lucidum spore powder can inhibit the polarization of M2 macrophages [44]. Notoginseng root aqueous extract could induce the polarization of M1 macrophages and inhibit the polarization of M2 macrophages. Ginseng and astragalus aqueous extract could induce the polarization of M1 macrophages and inhibit the polarization of M2 macrophages in lung cancer [45].

4.2. PD-1 and PD-L1

PD-1 or CD279 is a molecule that shows great efficiency in immunosuppression [19, 33]. PD-1 regulates the immune system and promotes self-tolerance by down-regulating the immune system's response to human cells, as well as by suppressing T cell inflammatory activity. PD-1 as an immune checkpoint prevents autoimmunity by promoting apoptosis of T cells [46-48] and reduces apoptosis of regulatory T cells (anti-inflammatory, inhibitory T cells) [32, 34]. It prevents autoimmune diseases, but also prevents killing cancer cells [18, 49]. PD-1 has two ligands named PD-L1 and PD-L2. PD-L1 is also known as cluster of differentiation 274 (CD274), or B7 homolog 1 (B7-H1), is a protein in human that is encoded by the CD274 gene. PD-L1 is highly expressed in several cancers, so PD1 is very important in cancer immune escape. PD-L2, alias CD273or B7-DC and PD-L1 belong to the B7 family of proteins. It is the second important ligand found after PD-L1, and PD-L2 could inhibit the function of immune cells after binding to PD-1 [39, 40, 50]. PD-L1 is well known as overexpressed by a variety of tumor cells, and PD-L1 can bind to the PD-1 and lure T cell depletion, activation and proliferation. Several different antibodies that block PD-1 and its ligands are currently in clinical use, achieving lasting remission in a small percentage of patients in various types of cancer.

In melanoma, APS has been reported that decrease the amount of PD-L1. This may indicate it is related to the regulation of PD-1/PD-L1 pathway [40, 48, 50] to increase antitumor immune capacity of T cells [19, 32, 33]. Various ginsenosides could inhibit the interaction between PD-1 and PD-L1. BBR could cause the degradation of PD-L1 [21]. Resveratrol could interfere modification of PD-L1 in breast cancer. Triptolide could inhibit expression of PD-L1 in many kinds of cancers, such as breast cancer, glioma and oral cancer. In tongue squamous cell carcinoma, curcumin could inhibit expression of PD-L1 to reverse immunosuppression. Lycopene could inhibit the expression of PD-L1 in lung cancer cells. Apigenin could down-regulate the expression of PD-L1 in breast cancer cells and melanoma cells [51,52]. Epigallocatechin gallate (EGCG) could inhibit the expression of PD-L1 in non-small cell lung cancer (NSCLC) [43]. Herb formula yangyin fuzheng decoction could reduce the expression of PD-L1 and PD-1 in lung cancer cells, thereby reversing the depletion of T cells [32]. Looking forward to more researches on the formula.

5. Conclusion

Active extracts from TCM show great efficiency in cancer treatments. Some of them have already become medicines to help cancer patients relieve their pain. The mechanism of TCM in cancer treatment is to prevent tumor metastasis and growth by regulating the molecular signaling pathway in the

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pathogenesis of cancer and the tumor microenvironment. However, many active ingredients of TCM formula are still unknown.This paper is different from the previous TCM anti-cancer review, this paper focuses on the anti-cancer mechanism of TCM active ingredients, and hope to attract more attention in this field. Future research should focus on exploring the active ingredients of TCM formula which have been proven anticancer effect through modern medicine and of anticancer TCM formula from ancient medical books, so curative effect of active ingredients will be revealed clearly, then conforming them into drugs. After that putting these active ingredients and their drugs into the *Guidelines of Diagnosis and Therapy in Oncology with Traditional Chinese Medicine.* At the same time to promote global researchers to build a anti-tumor TCM database together, tracking patients treatment, recording five-years survival rate, and tumor metastasis and recurrence rate and so on long-term observation data to enhance understanding of anticancer TCM, promoting the modern application of TCM.

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Mengqi He and Yi Liao contributed equally to this work and should be considered co-first authors.

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