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Antitumour Effects of Salvia Miltiorrhiza based on the Theory of Homology of Food and Medicine

Jingxue Bai[1], Genping Lei[2,*], Ting Wang[2], Sheng Dong[2], Yingying Sun[3], Huijie Fu[1], Xian Lu[1], Dong Yang[1], Duo Deng[1]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang 712000, Shaanxi, China
[3]Liaoning University of Traditional Chinese Medicine, Shenyang 110032, Liaoning, China
**Correspondence Author*

Abstract: ***Salvia miltiorrhiza Bunge is a plant of the family Labiatae, which is of great value in traditional Chinese medicine. Salvia miltiorrhiza Bunge has a slight odour, slightly bitter and astringent taste. It is slightly cold. Salvia miltiorrhiza belongs to the heart and liver meridians. It has the functions of activating blood circulation, removing blood stasis, promoting menstruation, relieving pain, Clear and reduce stagnant heat, cooling blood and eliminating carbuncles. It is used in the treatment of chest paralysis and heart pain, epigastric and abdominal pain, accumulation of obstruction in the abdomen, insomnia, irregular menstruation, sores, swelling and pain, cancer, etc. It has high medicinal health value and has been listed as one of the most important medicinal drugs in the world. It is of high medicinal and health care value, and has been listed in the catalogue of medicinal dietary sources in China, which has a broad space for development and application. The purpose of this paper is to review the research progress of Salvia miltiorrhiza in processing methods and antitumour activity, and to elaborate the performance of Salvia miltiorrhiza in ancient and modern clinical applications by giving examples, with a view to providing reference and contribution to the in-depth research, clinical application and development of Salvia miltiorrhiza. The sources, functions and dosage forms of Salvia miltiorrhiza were comprehensively analysed through the analysis of traditional Chinese patent medicines, simple preparations and related health food products of Salvia miltiorrhiza queried by Yaozhi.com, with a view to providing references for the development of Salvia miltiorrhiza medicines and food products.***

Keywords: Salvia miltiorrhiza; Cancer; Tumour; Medicinal herbs**.**

1. Introduction

Cancer has emerged as one of the most significant global health concerns. By 2040, it is projected that there will be up to 28.4 million cancer cases worldwide, representing a 47% increase from 2020(Sung et al. 2021). Consequently, it is imperative to pursue research in cancer treatment strategies. Nevertheless, with the advancement of science and technology, there has been a gradual shift in people's demand for traditional treatment-focused health care towards disease prevention, healthcare and other diversified health management needs. Among these, medicinal food products are particularly favoured. There is a long history of research on the homology of food and medicine, and the Compendium of Materia Medica can be regarded as a classic work of herbology and therapeutic food and healthcare. Salvia miltiorrhiza is used both as food and medicine, it is a good medicine for activating blood circulation, regulating menstruation and relieving pain, and an alternative to health food (Deng et al. 2024).

Currently, Salvia miltiorrhiza has been shown to inhibit cancer cell proliferation (Bae et al. 2020), trigger apoptosis of tumour cells (Wu, Yang, et al. 2023), induce iron death of tumour cells (Xia et al. 2023), inhibit invasion and metastasis of tumour cells (Cui et al. 2022), and increase drug resistance of tumour cells (Lee et al. 2021). In this paper, we will review its preparation, antitumor effects and food value (Figure 1).

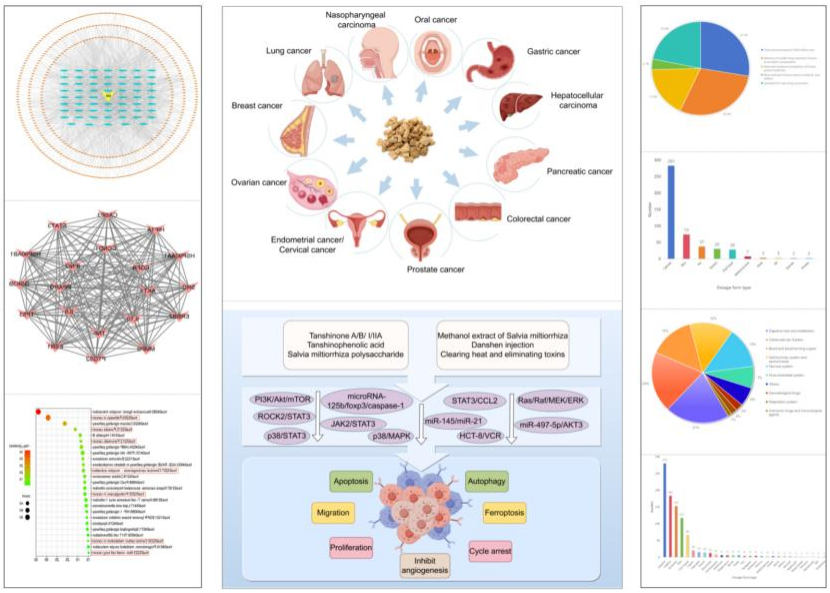

Figure 1: Flow chart.

2. Brief Introduction

Salvia miltiorrhiza, also called Qie Cicada, Red Ginseng, etc., is the dried root and rhizome of Salvia miltiorrhiza Bge. in the family Labiatae. It is usually dug in autumn, removed the baleen and dried. It is mainly distributed in Anhui, Shanxi, Hebei and other places in China. Salvia miltiorrhiza has a bitter taste and is mildly cold. It belongs to the heart and liver meridians. As a medicine, it has the effects of activating blood circulation, eliminating blood stasis, relieving menstruation and pain, clearing the heart and removing vexation, cooling the blood and eliminating carbuncles, etc. It is an important medicine in gynaecology, and is used in the clinical treatment of chest paralysis and heart pain, epigastric and abdominal dystocia, accumulation of obstruction in the abdomen, menstrual cramps and amenorrhea, disturbed and insomnia, and cancers. As food, its developed products have the effect of increasing bone density, improving sleep, immune regulation, weight loss, regulating blood fat, blood sugar and blood pressure, anti-fatigue, anti-oxidation, hypoxia resistance, and protecting against liver damage (Jung et al. 2020).

3. Processing

There are a variety of preparation methods of Salvia miltiorrhiza in traditional medical texts, for example, "removing seedling and soil" in Song Dynasty, "pounding, treading, cutting and baking" in Tang Dynasty, and "wine-soaked Salvia miltiorrhiza, stir-fried with pig's heart and blood" with auxiliary materials in later times. "In Modern times, raw and wine-boiled products of Salvia divinorum are the main products. The process of preparing Salvia miltiorrhiza is diversified due to regional differences (Tu et al. 2021). (Table 1)

Table 1: Processing methods of Salvia miltiorrhiza in successive dynasties

Time	Artillery products	Artisanal process	Concoction Effects	Sources
Northern and Southern Dynasties	WSM	Soaked in wine	Soaked in wine and drunk to treat wind paralysis	*Annotations to the Compendium of Materia Medica*
Tang dynasty	SM	Boil until purple in colour, then pound and sieve to make a coarse powder.	Boiled to make purple, to break blood and lower the symptoms	*Prepare for Urgent Qian Jin Yao Fang*
Song Dynasty	SM	lightly trembled and stir-fried until black and yellow, remove the seeds, and remove the soil.	Slightly roasted, for treating kidney wind, lumbar and foot disorders; fried to make black and yellow, for treating epilepsy with gale.	*Saint Ji Zonglu*
Jin Dynasty	WSM	Stir-fried in wine	Stir-fried in wine, for treating heat entering the blood chamber.	*Orchid Room Secret Collection*
Ming Dynasty	WSM	Wash with wine and dry in the sun.	For limb paralysis, wind and foot weakness and pain, use wine alone.	*Introduction to Medicine*
Qing Dynasty	WSM	Stir-fry in wine or pig's heart blood.	The guidance of the heart tonic medicine, cover the heart to the heart, blood to guide the meaning of blood.	*The Harmful Benefits of Materia Medica*
Modern times	SM/WSM	Remove impurities and stems, wash, moisten and cut into thick slices.	Removing impurities and roasting in wine enhances the efficacy of activating blood circulation and removing blood stasis.	*Chinese Pharmacopoeia (1963 edition)*
		Remove impurities and stumps, wash, moisten, slice and dry.		*Chinese Pharmacopoeia (1977 edition)*
		Remove impurities and stumps, wash, moisten, and cut into thick slices.		*National Standard for Traditional Chinese Medicine Processing (1988 Edition)*
		Remove impurities and stumps, wash, moisten, cut into thick slices, dry and sieve off debris.		*Chinese Pharmacopoeia (1985-2020 edition)*
		Take Salvia divinorum slices, according to the method of wine roasted and fried dry.		

SM: Salvia miltiorrhiza WSM: Salvia miltiorrhiza in wine

4. Anti-Tumor Effect of Salvia Miltiorrhiza

4.1 Screening of Active Ingredients and Targets in Salvia Miltiorrhiza

We used Salvia miltiorrhiza as a keyword to search on the TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, https://old.tcmsp-e.com/index.php) (Ru et al. 2014). The active ingredients and their related action targets were picked according to the criteria of oral bioavailability (Xu et al. 2012) ≥ 30% and drug-likeness ≥ 0.18. Then, we translated the name into Gene Symbol format to obtain target genes for the main active ingredients of Salvia miltiorrhiza via Uniprot database (https://www.uniprot.org/). We imported the active ingredients and their targets of Salvia miltiorrhiza into Cytoscape 3.9.1 software to draw an "active ingredient-target" network. Next, we imported drug targets into the STRING database (http://string-db.org), species limited to “Homo sapiens”, to retrieve protein-protein interaction relationships, and imported them into Cytoscape 3.9.1 software to create a network diagram. Through the Metascape database (https://metascape.org/), we conducted the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis on the target. The results of KEGG signal pathways are introduced into the Bioinformatics database (http://www.bioinformatics.com.cn/) and presented in the form of a bar chart and selected pathways related to cancer (Figure 2).

The KEGG results showed that the targets of Salvia miltiorrhiza are associated with a variety of cancer pathways, especially prostate cancer, pancreatic cancer, and non-small cell lung cancer. So, the next main analysis is the anti-tumor effect of Salvia miltiorrhiza.

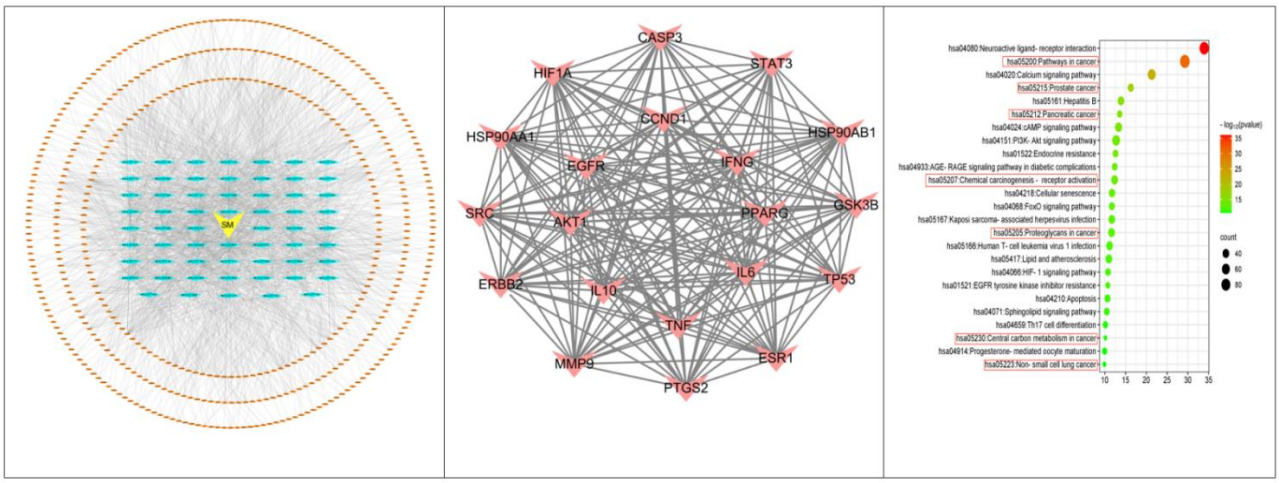

Figure 2: Relationship between active components of Salvia miltiorrhiza and cancer

4.2 Anti-cancer effect of Salvia Miltiorrhiza and Its Components

The chemical composition of Salvia divinorum is mainly divided into two main groups: fat-soluble terpenoids and water-soluble compounds. The fat-soluble terpenoids include diterpenoids, triterpenoids and polysaccharides. Among them, diterpenoids include tanshinone I, tanshinone IIA, tanshinone IIB, cryptotanshinone, dihydrotanshinone I, and iso-cryptotanshinone, which have excellent anticancer effect (Li et al. 2020). Studies have shown that danshen polysaccharides contain monosaccharides consisting of glucose, galactose, mannose and arabinose, which have biological activities such as antioxidant, antitumour and hepatoprotective (Li et al. 2023). Water-soluble compounds, on the other hand, are dominated by tansy phenolic acids, such as tansylic acid A, tansylic acid B, danshenin, caffeic acid, rosmarinic acid, and protocatechuic acid, which are clinically known for their anticoagulant, anti-inflammatory, and antioxidant effects (Shi et al. 2019). Of these two groups, the fat-soluble component tanshinone is more potent and safer, and plays a more active role in the areas of tumour (Zhang, Liu, et al. 2022), inflammation (Ye et al. 2020), oxidative stress (Wu, Guan, et al. 2023) and activation of immunity (Chen et al. 2019). Other constituents in Salvia divinorum are flavonoids, essential oils, amino acids and metallic elements.

In recent years, with the in-depth research on tansy, it has been found that the fat-soluble components in tansy, especially tanshinone, have excellent anticancer effects. Tanshinone exerts anticancer effects through various mechanisms, including inducing tumour cell death (apoptosis, autophagy, iron death and pyroptosis), inhibiting tumour cell proliferation, preventing tumour cell migration and invasion, decreasing tumour angiogenesis and permeability, increasing the sensitivity of radiotherapy and chemotherapy, as well as hindering tumour immune evasion. For example, tanshinone I induces apoptosis and autophagy by inactivating the PI3K/AKT/mTOR pathway to attenuate the malignant growth of ovarian cancer (Zhou et al. 2020), tanshinone IIA inhibits the reproduction of endometrial cancer through the MAPK/ERK/TRIB3 pathway (Zhang et al. 2023), and tanshinone IIA regulates autophagy and cell proliferation of endometrial cancer through microRNA-125b/foxp3/ caspase-1 signalling (Wang, Jin, and Wang 2021), tanshinone IIA induced iron death in gastric cancer cells through p53-mediated down-regulation of SLC7A11 (Guan et al. 2020), Tanshinone IIA sodium sulfate inhibits lung adenocarcinoma angiogenesis by mediating the miR-874/eEF-2K/TG2 axis, etc (Wang et al. 2023). Overall, tanshinone, a fat-soluble constituent of Salvia miltiorrhiza, has a promising application in cancer therapy.

As a water-soluble, weakly acidic drug, tansyphenolic acid has a wide range of applications in the fields of pharmaceuticals, nutraceuticals and cosmetics. In the field of medicine, salvianolic acid has demonstrated anticancer activity in a variety of cell lines, such as salvianolic acid A inhibited MMP-2 expression and suppressed cancer cell invasion through ERK signalling in human pharyngeal carcinoma (Chuang et al. 2020), salvianolic acid B slowed down the growth and progression of breast cancer cells by enhancing cell apoptosis and reducing oxidative stress, inflammation and angiogenesis (Katary et al. 2019), Salvianolic acid F inhibits the growth of KRAS-dependent lung cancer cells through the PI3K/AKT signalling pathway (Hou et al. 2023), making it an indispensable natural anticancer drug for clinical use. In the field of health care products, salvianolic acid is widely used in the production of health care products for its antioxidant, anti-inflammatory, anti-thrombotic and other biological activities, especially for the prevention and treatment of cardiovascular and cerebral vascular diseases and diabetic complications with significant efficacy. For example, Salvianolic acid A improves diabetic atherosclerosis by directly targeting PKM2 to regulate endothelial cell pyroptosis (Zhu et al. 2022). To date, studies have reported that Salvianolic acid B can be used to treat a variety of dermatological diseases in vitro and in vivo, such as dermatological fibrosis (Mei et al. 2020), and psoriasis (Nițescu et al. 2021), etc. It is also effective in helping to protect skin cells and reduce the damage caused by free radicals, which in turn improves skin texture and reduces wrinkles and discolouration, among other things. In conclusion, as a natural product, salvia phenolic acid has a variety of biological activities and application prospects, contributing to people's health and beauty.

Salvia miltiorrhiza polysaccharide (SMP), a natural polymer compound derived from the root of Salvia miltiorrhiza, has been shown to possess a variety of pharmacological effects

such as antioxidant, antitumour, hepatoprotective, anti-inflammatory, immunomodulatory and cardioprotective effects (Luo et al. 2023). Its application is becoming more and more widespread in the field of medicine and health care products. It can effectively regulate the activity of antioxidant enzymes in the body and has good antioxidant activity (Jing et al. 2023). SMP can also regulate the function of immune cells and inhibit the release of inflammatory mediators, thus reducing the inflammatory response, and have a positive effect on the treatment of inflammatory diseases, such as SMP and its related metabolite 5-methoxyindole-3-carbaldehyde, which improves experimental colitis by regulating the Nrf2/Keap1 signalling pathway (Fu et al. 2023). In addition, it exerts anti-tumour activity through mechanisms such as inhibiting tumour cell proliferation and inducing apoptosis, providing new possibilities for the prevention and treatment of malignant tumours. For example, SMP activate T lymphocytes in cancer patients by activating TLR-mediated MAPK and NF-kappaB signalling pathways (Chen et al. 2017), and inhibit the growth of rectal cancer cells by inducing apoptosis and inhibiting S-phase cell proliferation pathway and so on (Wang et al. 2018). It is believed that through further research on SMP, it will have greater potential in biomedical and food applications.

Salvia miltiorrhiza is a commonly used clinical drug with anti-tumor and other activities (Figure 3). After KEGG enrichment analysis, we mainly discussed the pharmacological effects of the anti-tumor effects of Salvia miltiorrhiza (Table 2). Studies have confirmed that Salvia miltiorrhiza and its extracts can reduce the proliferation, invasion and migration of cancers of the oral cavity, nasopharyngeal carcinoma, lung cancer, breast cancer, ovarian cancer, cervical cancer, endometrial carcinoma, prostate cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, colorectal cancer, and leukemia, and can promote their cell apoptosis (Figure 4).

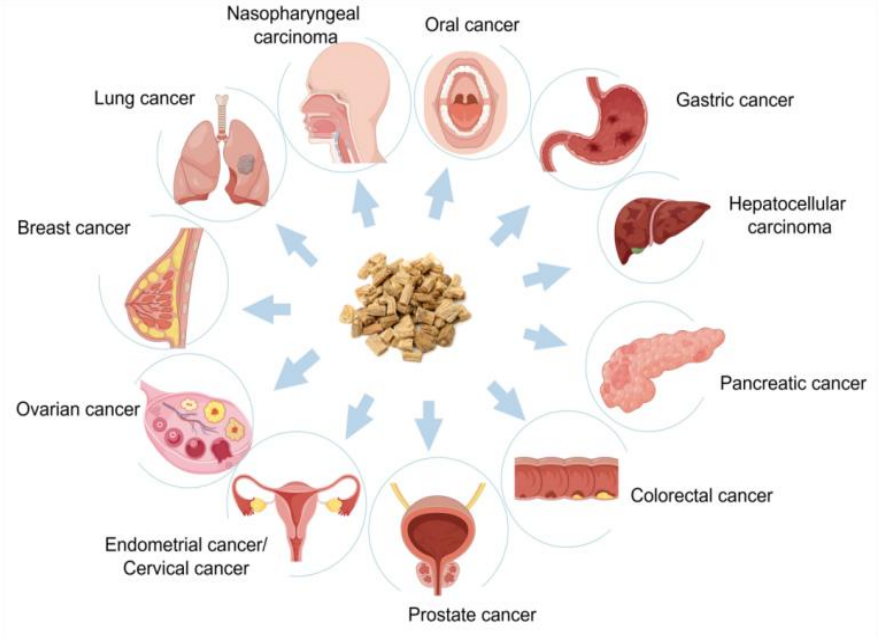

Figure 3: Relationship between Salvia miltiorrhiza and cancer

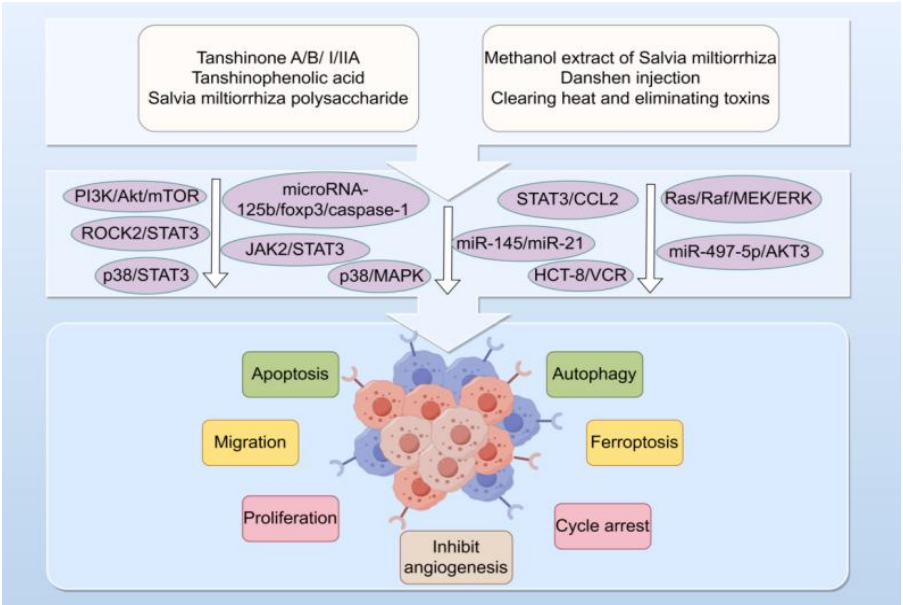

Figure 4: Mechanism of anti-tumor action of Salvia miltiorrhiza and its components

Table 2: Anti-cancer effect of Salvia miltiorrhiza and its components.

Pharmacological effect	Ingredient	Conclusion
Nasopharyngeal carcinoma	Tanshinone IIA	Regulation of microRNA-125b/foxp3/caspase-1 signaling inhibits nasopharyngeal carcinoma cell activity.
Lung cancer	Tanshinophenolic acid F	Promotes apoptosis by inhibiting activation of the downstream PI3K/AKT signaling pathway.
Lung cancer	Diterpenoid tanshinone	Inhibition of growth, proliferation and migration of lung cancer cells.
Lung cancer	Methanol extract of Salvia miltiorrhiza	Inhibition of apoptosis in non-small cell lung cancer cells through PTEN-mediated PI3K/Akt path way.
Breast cancer	Tanshinone A	Targeting PIM1 to block the ROCK2/STAT3 pathway inhibits breast cancer cell migration and pr omotes smooth muscle relaxation.
Breast cancer	Dihydrotanshinone I	Inhibition of neutrophil extracellular trap formation and lung metastasis of breast cancer.
Breast cancer	Danshen injection	Inhibition of breast cancer cell migration and invasion.
Breast cancer	Clearing heat and eliminati ng toxins	Reducing tumor markers, improving efficacy and mitigating adverse effects of chemotherapy.
Ovarian cancer	Cryptotanshinone	Activation of cysteine asparaginase cascade induces apoptosis in ovarian cancer A2780 cells and makes ovarian cancer cells more sensitive to chemotherapy
Ovarian cancer	compound danshen droplet	Targeting and inhibiting the JAK2/STAT3 pathway produces anti-rat ovarian cancer cell effects.
Cervical cancer	Tanshinone A	Tanshinone A in combination with oxybutynin synergistically inhibits H8 cells.
Cervical cancer	Tanshinone IIA	Reduces the stability and transcriptional activity of YAP mRNA.
Endometrial cancer	Dihydroisotanshinone I	Induction of iron death and apoptosis in endometrial cancer cells
Endometrial cancer	Tanshinone I	Increased ROS levels in endometrial cancer HEC-1-A cells and inhibited cell proliferation in a do se-dependent manner.
Prostate cancer	Tanshinone IIA	Induction of mitochondria-dependent apoptosis in prostate cancer cells, possibly through inhibitio n of the phosphocreatine 3-kinase/AKT pathway.
Prostate cancer	Tanshinone IIA	Leads to G0/G1 cell cycle arrest in LNCaP cells.
Prostate cancer	Dihydroisotanshinone I	Inhibition of STAT3/CCL2 signaling pathway targets crosstalk between macrophages and cancer cells.
Oral cancer	Tanshinone IIA	Increasing the sensitivity of human oral squamous cell carcinoma SCC090 to radiation therapy.
Gastric cancer	Tanshinone	Inhibition of gastric cancer angiogenesis through PI3K/Akt/mTOR signaling pathway.
Gastric cancer	Tanshinone I	Inhibition of epithelial mesenchymal transition in the p38/STAT3 pathway attenuates gastric prec ancerous lesions.
Gastric cancer	Tanshinone B	inhibited the proliferation of gastric cancer HGC-27 and AGS cell lines.
Hepatocellular carcinoma	Cryptotanshinone	Activation of AMPK/SIRT1 and Nrf2 signaling pathways attenuates ethanol-induced liver injury
Hepatocellular carcinoma	Salvia extracts	Inhibition of hepatocellular carcinoma progression by miR-145/miR-21-mediated Smad3 phospho rylation
Hepatocellular carcinoma	Salvia divinorum B	Induction of autophagy and apoptosis in hepatocellular carcinoma cells through the AKT/mTOR s ignaling pathway
Pancreatic cancer	Tanshinone IIA	Increased protein expression of PERK, ATF6, IRE1α, CHOP, caspase-3, and caspase-12 in pancre atic cancer BxPC-3 cell-derived xenograft tumors
Pancreatic cancer	Tanshinone IIA	Inhibits MiaPaCa-2 human pancreatic cancer cells through dual blockade of Ras/Raf/MEK/ERK a nd PI3K/AKT/mTOR pathways.
Colorectal cancer	aqueous extracts of tansy	Modulation of the Cox2/PGE2 cascade reduces colorectal tumor-associated macrophage infiltratio n and synergizes with anti-PD-L1.
Colorectal cancer	Tanshinone IIA	Induces apoptosis in colorectal cancer cells and prevents down-regulation of G0/G1 phase cells in volved in Transgelin-2 expression through the p38/MAPK signaling pathway.
Colorectal cancer	Salvianolic acid B	Reversal of multidrug resistance in HCT-8/VCR human colorectal cancer cells by increasing ROS levels.
Acute myeloid leukaemia	Tanshinone IIA	Regulation of proliferation, cell cycle and apoptosis in human acute myeloid leukemia cells throu gh miR-497-5p/AKT3 axis.
Acute myeloid leukaemia	Rosmarinic acid	Induces apoptosis and necrosis in a ROS-independent DNA damage and cysteine-independent ma nner.
Acute myeloid leukaemia	tanshinone I	Promoting malignant hematopoiesis through upregulation of MMP9 and ABCG2.

In nasopharyngeal carcinoma, tanshinone IIA inhibits nasopharyngeal carcinoma cell activity by regulating microRNA-125b/foxp3/caspase-1 signalling (Wang, Jin, and Wang 2021). In lung cancer, tanshinophenolic acid F promoted apoptosis by inhibiting downstream PI3K/AKT signalling pathway activation, resulting in a significant reduction in tumour number and size in a series of KRAS G12D-mutant mouse models, suggesting that tanshinophenolic acid F may be a novel anti-KRAS G12D inhibitor (Hou et al. 2023). It was demonstrated that the diterpenoid tanshinone improved the inflammatory tumour microenvironment by modulating macrophage polarisation and inhibiting lipopolysaccharide-associated immune response, thereby inhibiting the growth, proliferation and migration of lung cancer cells (Xu et al. 2024). Methanolic extract of Salvia miltiorrhiza inhibits induction of apoptosis in non-small cell lung cancer cells via PTEN-mediated inhibition of the PI3K/Akt pathway (Ye et al. 2017). These findings provide a strong theoretical basis for tanshinone IIA and tanshinophenolic acid F as potential anticancer agents; however, more studies are needed to validate their safety and efficacy in humans in order to provide better therapeutic options for patients.

Breast cancer, ovarian cancer, cervical cancer and endometrial cancers are the most prevalent cancers and the leading cause of death in women. Studies have found that Salvia divinorum has potential benefits in the treatment of gynaecological tumours.In breast cancer, the active ingredient of Salvia divinorum, neo-psilvaquinone A, inhibits breast cancer cell migration and promotes smooth muscle relaxation by targeting PIM1 to block the ROCK2/STAT3 pathway (Zhao et al. 2023). Dihydrotanshinone I inhibits lung metastasis of breast cancer by inhibiting neutrophil extracellular trap formation (Zhao et al. 2022). In addition, dihydroisotanshinone I induces iron death and apoptosis in

breast cancer cells and improves the survival rate of breast cancer patients (Jiang et al. 2017). In ovarian cancer, cryptotanshinone effectively inhibited the invasion and migration of ovarian cancer cells by activating the cysteine asparaginase cascade reaction, induced apoptosis in ovarian cancer A2780 cells, and made ovarian cancer cells more sensitive to chemotherapy (Dalil, Iranzadeh, and Kohansal 2022). Dihydrotanshinone I activates oxidative stress and inhibits ovarian tumour growth through Keap1-mediated ubiquitination degradation of Nrf2 (Sun et al. 2022). In cervical cancer, effective treatment of cervical intraepithelial neoplasia can prevent cervical cancer. In vitro studies have shown that tanshinone A in combination with oxysulfradine synergistically inhibits H8 cells, providing potential treatment for cervical intraepithelial neoplasia (Leng et al. 2022). Tanshinone IIA also inhibited migration and invasion of cervical cancer stem cell-like cells in a dose- and time-dependent manner by reducing the stability and transcriptional activity of YAP mRNA (Qin et al. 2018). In endometrial cancer, dihydroisotanshinone I induced iron death and apoptosis in endometrial cancer cells, resulting in reduction of tumour size without adverse effects (Wu, Yang, et al. 2023). In addition, tanshinone I elevated ROS levels in endometrial cancer HEC-1-A cells, inhibiting cell proliferation in a dose-dependent manner (Li et al. 2018).

Prostate cancer (PCa) is the second most common malignant tumor of the male urinary system, with a global incidence that varies by geography and population. Surgical treatment of early prostate cancer is effective, but advanced PCa is often difficult to achieve due to multiple mechanisms of adaptation and tolerance to androgen denervation-related drugs. Several studies have shown that tanshinone can target a variety of molecular pathways in PCa, including the signal transducer and activator of transcription 3 (STAT3) pathway (Wu et al. 2017), the androgen receptor (AR) pathway (Chiu et al. 2013), and the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway (Won et al. 2010).

In the treatment of oral cancer, the results of the study showed that tanshinone IIA increased the sensitivity of human oral squamous cell carcinoma SCC090 to radiation compared to single drug or single radiation therapy, while promoting the generation of ROS in the cancer cells as well as autophagy in the cancer cells (Ding et al. 2016). In addition, the alcoholic extract of Salvia miltiorrhiza also showed significant anticancer effects on oral squamous cell carcinoma cells (Wang et al. 2017).

In gastric cancer, gastric cancer is a malignant cancer worldwide. It has been widely recognised that tansy exerts anti-gastric cancer effects. For example, the diterpenoid tanshinone can cause significant changes in the content of angiogenesis-related factors and proteins in cells and animals, and in vitro and in vivo experiments have confirmed that tanshinone can inhibit angiogenesis in gastric cancer through the PI3K/Akt/mTOR signalling pathway (Yu et al. 2024). Gastric precancerous lesion (GPL) is the precursor of gastric cancer (GC), which progresses with a series of pathological changes in the gastric mucosa. Tanshinone I was shown to attenuate gastric precancerous lesions by inhibiting epithelial mesenchymal transition in the p38/STAT3 pathway (Liang et al. 2023). Tanshinone B also showed significant inhibitory effects on gastric cancer HGC-27 and AGS cell lines (Chen et al. 2020).

In hepatocellular carcinoma, cryptotanshinone from Salvia miltiorrhiza attenuated ethanol-induced liver injury by activating the AMPK/SIRT1 and Nrf2 signalling pathways (Nagappan et al. 2019). The compounds Astragalus and Salvia extracts also inhibited hepatocellular carcinoma progression through miR-145/miR-21-mediated Smad3 phosphorylation (Wu et al. 2019). Salvia divinorum B may induce autophagy and apoptosis in hepatocellular carcinoma cells through the AKT/mTOR signalling pathway (Gong et al. 2016).

Pancreatic cancer is a kind of digestive system tumor with high degree of malignancy, and early diagnosis and treatment are of great significance to improve the survival rate of patients. In recent years, more and more studies have shown that danshen and its active ingredients have potential applications in the treatment of pancreatic cancer. For example, tanshinone IIA increased the protein expression levels of PERK, ATF6, IRE1α, CHOP, caspase-3 and caspase-12 in pancreatic cancer BxPC-3 cell-derived xenograft tumors (Chiu and Su 2017). Tanshinone IIA inhibits MiaPaCa-2 human pancreatic cancer cells through dual blockade of Ras/Raf/MEK/ERK and PI3K/AKT/mTOR pathways (Su 2018).

In colorectal cancer treatment, aqueous extracts of tansy were shown to be effective in reducing colorectal tumour-associated macrophage infiltration by modulating the Cox2/PGE2 cascade reaction, which works synergistically with anti-PD-L1 (Song et al. 2023). Tanshinone IIA induced apoptosis in colorectal cancer and blocked the down-regulation of G0/G1 phase cells involved in Transgelin-2 expression through the p38/MAPK signalling pathway (Zhang, Zhao, et al. 2022). In addition, Salvianolic acid B also reversed multidrug resistance in HCT-8/VCR human colorectal cancer cells by increasing ROS levels (Guo et al. 2017).

Tanshin is also used in the treatment of malignancies including acute myeloid leukaemia. It has been shown that tanshinone IIA regulates proliferation, cell cycle and apoptosis in human AML cells through the miR-497-5p/AKT3 axis (Nie et al. 2020). Rosmarinic acid, a water-soluble extract of Salvia miltiorrhiza, was able to induce apoptosis and necrosis in a ROS-independent DNA damage and cysteine-independent manner (Wu et al. 2015). In addition, a research team from Zhejiang University revealed that tanshinone I possesses novel EZH2 inhibitory properties and can inhibit malignant hematopoiesis by upregulating MMP9 and ABCG2. However, tanshinone I was also found to have negative effects on normal haematopoiesis. Therefore, it should be carefully controlled and monitored in clinical use (Huang et al. 2021).

5. Application of Salvia Miltiorrhiza

5.1 The Medicinal Value of Salvia Miltiorrhiza

Salvia miltiorrhiza has been widely used since ancient times,

and its preparations are also highly regarded in the medical field. Studies have shown that compound danshen droplet has the effect of targeting and inhibiting the JAK2/STAT3 pathway, thus producing anti-rat ovarian cancer cells (LI Hang and al. 2019). In vitro experiments showed that the inhibition of breast cancer cell migration and invasion by Danshen injection may be related to its inhibition of platelet-induced epithelial mesenchymal transition (TIAN H and al. 2023). Clearing heat and eliminating toxins and eliminating symptoms soup combined with relief therapy can effectively improve the clinical symptoms of breast cancer patients, reduce the tumour markers, improve the therapeutic efficacy, alleviate the adverse effects of chemotherapy, and enhance the quality of survival (QIAO Lili et al. 2023).

Search for proprietary Chinese medicines and simple preparations containing Salvia miltiorrhiza by using "Salvia miltiorrhiza" as a keyword on the website of Pharmaceutical Intelligence (http://db.yaozh.com/). Ministry of Health Drug Standard for Chinese Medicine Prescription Preparations, Chinese Pharmacopoeia 2020 First Edition, Conversion Standard for New Drugs, National Standard Competition for Chinese Medicine, and National New Drugs for Chinese Medicine 2nd Edition. There are 921 types of proprietary Chinese medicines and simple preparations containing Danshen (Figure 5). In terms of dosage forms, there are 17 types of proprietary Chinese medicines and simple preparations containing Salvia miltiorrhiza, of which tablets are the main ones, followed by granules and capsules (Figure 6).

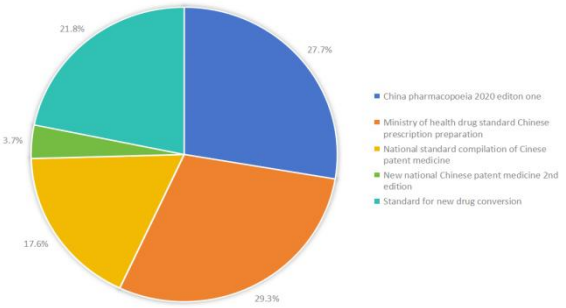

Figure 5: Source and quantity of Chinese patient medicine containing Salvia miltiorrhiza

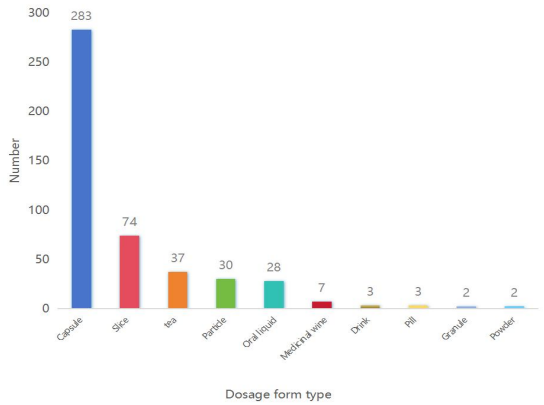

Figure 6: Chinese medicine dosage form containing Salvia miltiorrhiza

We have summarised the efficacy of the 921 varieties of proprietary Chinese medicines and simple preparations containing Salvia miltiorrhiza, which can be broadly classified into 11 categories (Figure 7). Based on the efficacy analysis, proprietary Chinese medicines and simple preparations containing Salvia miltiorrhiza are mainly concentrated in the digestive tract and metabolism, musculoskeletal system, as well as the genitourinary system and sex hormones.

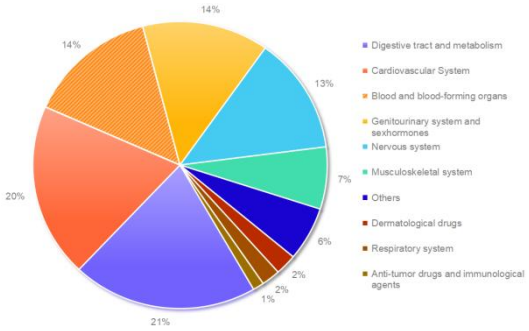

Figure 7: Anatomic Therapeutic Chemical classification of Chinese patient medicine

5.2 Edible Value of Coix Seed

In recent years, there has also been a proliferation of health food products using danshen as the main ingredient. Searching for the keyword "Salvia divinorum" on the Pharmaceutical Intelligence website (http://db.yaozh.com/), a total of 496 Salvia divinorum-related health food products were approved by the State Food and Drug Administration, such as Pueraria Mirifica and Salvia divinorum granules, Salvia divinorum angelica capsule, Salvia divinorum chrysanthemum tea, and Panax ginseng and salvia divinorum powder, etc., which are characterized by the efficacy of immune modulation, increase in bone mineral density, antioxidant, and regulation of blood lipids, blood glucose, and blood pressure. In terms of healthcare efficacy, the statistics of healthcare functions involved in Salvia divinorum-related healthcare products are shown in Figure 8 (Figure 8). So far, there are mainly 29 kinds of Salvia divinorum health food formulations used (Figure 9). The development of health food functions of Salvia miltiorrhiza is very diverse in form, and the products and dosage forms are also varied, which can meet the specific needs of different groups of people.

5.3 Usage of Salvia Miltiorrhiza

Salvia miltiorrhiza has been shown in modern studies to have a wide range of efficacy including, but not limited to, therapeutic effects on cardiovascular diseases, inflammatory diseases, and tumours. Its value in food applications is mainly in the form of anti-inflammatory, antioxidant, anticoagulant, lipid regulator and microcirculation promoter. People who are suitable to consume Salvia miltiorrhiza mainly include patients with cardiovascular diseases, inflammatory diseases and some tumour patients. However, Salvia divinorum is not suitable for pregnant women, lactating women, children and patients with bleeding disorders. Salvia should also be avoided before and after surgery. For patients with long-term illnesses or other special conditions, it is recommended to use Salvia divinorum under the supervision of a doctor. Before

consuming Salvia divinorum, it is advisable to consult a doctor or herbalist to ensure safe and effective use.

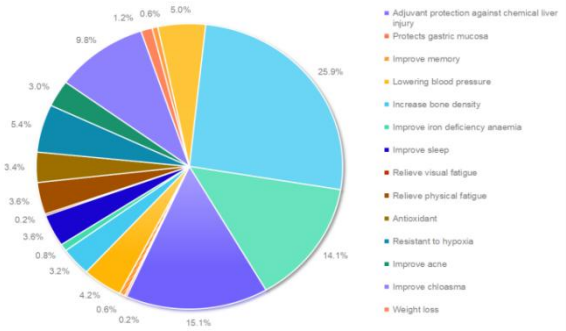

Figure 8: Function statistics of health care products containing Salvia miltiorrhiza.

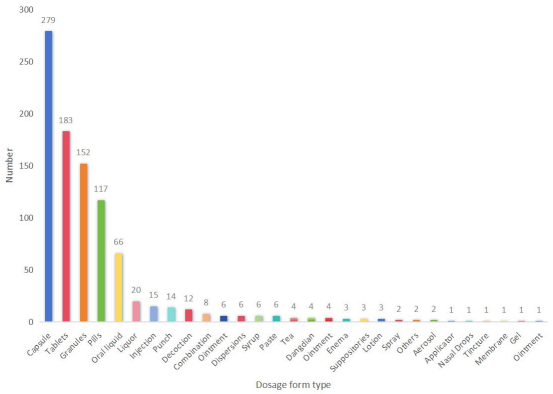

Figure 9: Dosage form containing Salvia miltiorrhiza health care products.

6. Discussion

In this paper, effective components of Salvia miltiorrhiza such as tanshinone, salvia phenolic acid, and salvia polysaccharide were analyzed from the perspective of medicinal food, and the first two were more commonly used. In addition, KEGG analysis of the active ingredient targets of Salvia miltiorrhiza was carried out using bioinformatics methods, which proved that Salvia miltiorrhiza did have antitumor effects. In order to collect information about the general use, phytochemical composition, pharmacological properties and anticancer effects of Salvia miltiorrhiza, we conducted literature searches in five databases, including PubMed, Web of Science, China Knowledge Initiative (CNKI), and Springer, in both Chinese and English, and conducted a systematic A systematic review of the antitumor effects of Salvia miltiorrhiza was conducted. In addition, the applications of Salvia divinorum in proprietary Chinese medicines, simple preparations and foods were summarized and sorted out, and the relevant data were shown through graphs and charts, and the current market applications of medicines and healthcare products with Salvia divinorum as the main ingredient have a very promising prospect.

7. Conclusion

In recent years, studies have shown that Salvia miltiorrhiza has the effect of inhibiting the growth and metastasis of cancer cells, and can reduce the mortality rate of cancer, thus attracting much attention. With the emphasis on healthy diet and the popularization of the concept of "preventing illness before it occurs", Salvia divinorum has received more attention in the food and pharmaceutical fields. In the future, Salvia divinorum is expected to be developed into a new type of health care product to fulfill people's demand for health and beauty, and used for researching new medicinal ingredients and treatments. The shortcoming of this paper is that it does not further sort out the related pathways between Salvia divinorum and diseases as well as clinical validation, which is to be improved in the future. In addition, the development of medicinal health food in China faces some challenges, such as insufficient attention, too few varieties, low level of scientific research, and imperfect regulations. In addition, the oral bioavailability of tanshinone is poor, and the structure needs to be optimized to improve its utility.

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