Review

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# Recent advances in Chinese patent medicines entering the international market

**Bo Zhang[1], Wenjian Pei[2], Pingping Cai[2], Zhixue Wang[2], Fanghua Qi[2,*]**

[1] Department of Traditional Chinese Medicine Orthopedics, Neck-Shoulder and Lumbocrural Pain Hospital affiliated to Shandong First Medical University, Ji'nan, China;
[2] Traditional Chinese Medicine, Shandong Provincial Hospital affiliated to Shandong First Medical University, Ji'nan, China.

**SUMMARY** As an indispensable part of Traditional Chinese medicine (TCM), Chinese patent medicines have played an important role in preventing and treating diseases in China. Since they are easy to use, easy to store, and cost-effective, Chinese patent medicines have been generally accepted and widely used in Chinese clinical practice as a vital medical resource. In recent years, as TCM has developed and it has been accepted around the world, many Chinese patent medicine companies have gained international market access and successfully registered several Chinese patent medicines as over-the-counter (OTC) or prescription drugs in regions and countries that primarily use Western medicine such as the EU, Russia, Canada, Singapore, and Vietnam. Moreover, several Chinese patent medicines have been obtained the US Food and Drug Administration (FDA) approval conducting phase II or III clinical trials in the US. The current work has focused on several Chinese patent medicines that have been successfully registered or that have been submitted for registration abroad. Summarized here are recent advances in the efficacy and molecular mechanisms of these Chinese patent medicines to treat respiratory infectious diseases (Lianhua Qingwen capsules, Jinhua Qinggan granules, and Shufeng Jiedu Capsules), cardiovascular and cerebrovascular diseases (Compound Danshen Dripping Pills, Huatuo Zaizao pills, and Tongxinluo Capsules), cancers (a Kanglaite injection and a Shenqi Fuzheng Injection), and gynecological diseases (Guizhi Fuling Capsules). The hope is that this review will contribute to a better understanding of Chinese patent medicines by people around the world.

***Keywords*** Chinese patent medicines, global acceptance, respiratory infectious diseases, cardiovascular and cerebrovascular diseases, cancers, gynecological diseases

## 1. Introduction

Traditional Chinese medicine (TCM) is an ancient form of healthcare that has evolved over thousands of years in Asian countries, and especially China. During a long process of accumulating knowledge and practices, TCM has created a unique system of theories, diagnostics, and therapies regarding the prevention and treatment of diseases (*1*). In China, TCM is used daily to treat and prevent various diseases as part of the prevailing medical system. The typical TCM therapies mainly include Chinese herbal medicines, acupuncture, moxibustion, and massage. Chinese herbal medicines mainly include single herbs, prescriptions, and Chinese patent medicines. These TCM therapies have played an important role in the treatment of numerous ailments, providing effective treatments for various complex diseases such as cancer, ischemic stroke, and irritable bowel syndrome (*2,3*). A point particularly worth noting is that TCM has made great contributions to the prevention and treatment of coronavirus disease 2019 (COVID-19), and it has been used in over 90% of treatments across China (*4*). Several Chinese patent medicines in particular have displayed efficacy in combating COVID-19, such as Lianhua Qingwen capsules, Jinhua Qinggan granules, and Shufeng Jiedu capsules (*5*).

Despite the widespread use of TCM in clinical settings, proving its efficacy scientifically and assembling quality clinical evidence is still a challenge. Therefore, the quality of TCM-related clinical trials needs to be rationally and strictly controlled. To achieve the goals of better quality, safety, and efficacy, the national government and regulatory agencies of China are making every effort to encourage and promote the development of the TCM. A number of policies on TCM have been introduced, and a system to manage drug registration has essentially been established for Chinese herbal medicines (*6*).

The international recognition of TCM is increasing, especially since the 2015 Nobel Prize in Physiology or Medicine was awarded to Youyou Tu. On May 25, 2019, the World Health Organization (WHO) included TCM into the eleventh revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), which is a landmark for both TCM and the ICD. This initiative not only recognizes TCM for its past contributions to world healthcare, but it also acknowledges, and attempts to meet, the current need for TCM (*7*). At present, TCM has spread to 196 countries and regions around the world, and 29 member countries of the WHO have enacted laws to regulate TCM. More than one-third of the world's total population has received TCM therapies (*8*). Chinese herbal medicine has gradually entered the international system of medicines, and several Chinese patent medicines have been registered overseas (*9*).

An indispensable part of TCM, Chinese patent medicine mainly refers to a special Chinese medicine preparation prepared from Chinese medicinal materials. There are many dosage forms of Chinese patent medicine, including pills, tablets, capsules, liquids, and injections. Compared to Chinese herbal decoctions, Chinese patent medicines have the advantages of convenient management and accurate dosage, which is why they have been generally accepted and widely used in Chinese clinical practice as a vital medical resource (*10*). According to the 2021 Blue Book on National Supervision of Traditional Chinese Medicine, there were 2,225 Chinese medicine companies and 8,670 varieties of Chinese patent medicine in China by the end of 2021, with an annual operating income of 486.2 billion yuan that year (*11*).

In recent years, many Chinese medicine companies have continuously explored and attempted to register medicines overseas and expand the international market. Thus far, several Chinese patent medicines have successfully been registered as drugs in several countries and regions including Russia, Canada, England, the Netherlands, and Vietnam (Table 1) (*12*). Moreover, as shown in Table 2, several Chinese patent medicine companies have submitted Investigational New Drug (IND) applications to the US Food and Drug Administration (FDA), some of which are carrying out phase II or III clinical trials in the US (*https://clinicaltrials.gov/*).

The current review will focus on these Chinese patent medicines that have been successfully registered or that have been submitted for registration abroad. The mechanisms and of these Chinese patent medicines and clinical trials indicating their efficacy in treating respiratory infectious diseases, cardiovascular and cerebrovascular diseases, cancers, and gynecological diseases will be highlighted and summarized. A search of the literature will be mainly conducted in the

**Table 1. Product characteristics of Several Chinese patent medicines registered in some overseas countries and regions**

| Product name | Components | Main indications | Registration country | Year of approval |
|---|---|---|---|---|
| Huatuo Zaizao pill | Ligusticum chuanxiong, Tetradium ruticarpum, Borneolum and so on. | Cerebrovascular diseases | Russia | 2010 |
| Di'ao Xinxuekang capsule | Discorea nipponica Makino. | Cardiovascular disease | Netherlands | 2012 |
| Tongxinluo capsule | Panax ginseng, Hirudo nipponica Whitman, Scolopendra subspinipes mutilans, Eupolyphaga sinensis Walker, Buthus martensii Karsch, Cryptotympana pustulata Fabricius, Paeonia lactiflora, Borneolum, Santalum album, Burseraceae, Dalbergia odorifera, and Ziziphus jujuba Mill | Cardiovascular and cerebrovascular diseases | Vietnam | 2013 |
| Kangbingdu Koufuye | Radix Isatidis, Gypsum Fibrosum, Phragmites australis, Rehmannia glutinosa, Curcuma wenyujin, Anemarrhena asphodeloides Bunge, Acorus tatarinowii, Herba Pogostemonis and Fructus Forsythiae. | Influenza and wind heat cold | Canada | 2015 |
| Danshen Capsule | Salvia milthiorrhiza. | Mild menstrual pains | Netherlands | 2016 |
| Danning Pian (Biliflow) | Herba Taraxaci, Lysimachia christiniae Hance, Corydalis yanhusuo, Rheum palmatum, Mentha canadensis Linnaeus, Calculus Bovis Artifactus, Silymarin and Berberine. | Chronic cholecystitis and cholelithiasis | Canada | 2016 |
| Banlangen Keli | Radix Isatidis. | Common cold | United Kingdom | 2017 |
| Lemai Keli | Salviae miltiorrhizae, Tetradium ruticarpum, Paeonia lactiflora, Carthamus tinctorius, Cyperus Rotundus, Costustoot and Crataegus pinnatifida. | Cardiovascular and cerebrovascular diseases | Canada | 2017 |
| Xiaoyao Pian | Bupleurum chinense, Paeoniae Radix, Angelica sinensis, Atractylodes macrocephala, Poria Cocos, Glycyrrhiza uralensis and Mentha canadensis Linnaeus. | Irregular menstruation | Netherlands | 2020 |

**Table 2. Product characteristics of Several Chinese patent medicines which have been approves by the US Food and Drug Administration (FDA) carrying out Phase II or III clinical trails in the United States**

| Product name/Clinical registration No. | Conditions | Stage | Study Status | Start time |
|---|---|---|---|---|
| Lianhua Qingwen capsule | | | | |
| NCT02867358 | Acute uncomplicated influenza | Phase II | Ongoing | 2016 |
| Jinhua Qinggan granule | | | | |
| NCT04723524 | Mild-category patients of COVID-19 | Phase II | Finished | 2020 |
| Compound Danshen Dripping Pill | | | | |
| NCT03270787 | Acute mountain sickness | Phase II | Finished | 2016 |
| NCT01659580 | Angina pectoris | Phase III | Finished | 2012 |
| NCT02388984 | Non-proliferative diabetic retinopathy | Phase III | Unknown | 2013 |
| NCT01825759 | Coronary heart disease with essential hypertension | Phase III | Unknown | 2013 |
| NCT05295329 | Diabetic patients with coronary microcirculation disturbance | Unknown | Not yet recruiting | 2022 |
| Huatuo Zaizao pill | | | | |
| NCT01758536 | Acute ischemic stroke | Phase IV | Unknown | 2012 |
| NCT04910256 | Ischemic Stroke | Phase III | Unknown | 2021 |
| Tongxinluo Capsule | | | | |
| NCT01919671 | Acute ischemic stroke | Phase IV | Finished | 2014 |
| NCT04220372 | Microvascular angina pectoris | Phase IV | Ongoing | 2020 |
| NCT01721590 | Coronary artery disease | Phase IV | Finished | 2012 |
| NCT03792035 | Acute myocardial infarction | Phase IV | Unknown | 2019 |
| NCT05309343 | Cardiovascular diseases | Unknown | Recruiting | 2021 |
| NCT04026724 | Angina pectoris | Unknown | Unknown | 2019 |
| NCT04022031 | Atherosclerotic heart disease with angina pectoris | Unknown | Unknown | 2019 |
| Kanglaite injection | | | | |
| NCT03101514 | Head and neck cancer with radiotherapy | Phase II | Finished | 2017 |
| NCT02553187 | Cancer cachexia | Phase IV | Unknown | 2015 |
| NCT03631459 | Cancer cachexia | Unknown | Unknown | 2018 |
| NCT03986528 | Advanced non-small cell lung cancer | Phase IV | Recruiting | 2019 |
| NCT00733850 | Pancreatic cancer | Phase II | Finished | 2008 |
| Shenqi Fuzheng Injection | | | | |
| NCT03456609 | Carcinogenic fatigue | Unknown | Unknown | 2018 |
| NCT03455205 | Cancer-related fatigue | Unknown | Unknown | 2017 |
| Guizhi Fuling Capsule | | | | |
| NCT01588236 | Primary dysmenorrhea | Phase II | Unknown | 2012 |

databases of PubMed, Web of Science, Scopus, Springer, ScienceDirect, and the China Hospital Knowledge Database (CHKD). Overall, the hope is that this review will contribute to a better understanding of Chinese patent medicines by people around the world as TCM gains greater global acceptance.

## 2. Chinese patent medicines for respiratory infectious diseases

Respiratory infectious diseases are mainly caused by viruses or bacteria and are often contagious, posing a major public health problem worldwide. Over the past 3,000 years of Chinese history, TCM has worked well in treating respiratory infectious diseases. TCM has been used as the routine treatment of pandemic and endemic diseases including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), COVID-19, and seasonal epidemics caused by the influenza and dengue viruses (*13*). A point particularly worth noting is that several Chinese patent medicines such as Lianhua Qingwen capsules, Jinhua Qinggan granules, and Shufeng Jiedu Capsules have significant advantages in treating respiratory infectious diseases. Summarized here are recent advances in the efficacy (Table 3, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) and molecular mechanisms (Table 4, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) of these key common Chinese patent medicines that have been successfully registered or that have been submitted for registration abroad.

### 2.1. Lianhua Qingwen capsules

Lianhua Qingwen capsules, a Chinese patent medicine, were originally developed to treat SARS in 2003 and were approved by the China Food and Drug Administration (CFDA) in 2004. Lianhua Qingwen capsules come from two classic and effective prescriptions, Maxing-Shigan-Tang and Yinqiao-San. The capsules have 13 herb components including Fructus Forsythiae (Lianqiao) and Flos Lonicerae Japonicae (Jinyinhua) (Figure 1). The main active ingredients of Lianhua Qingwen capsules have been identified and include quercetin, kaempferol, luteolin, β-sitosterol, indigo, wogonin, and tryptanthrin (*14*).

Over the last few decades, Lianhua Qingwen capsules have been widely used to treat viral influenza, pneumonia caused by coronaviruses, the common cold, and other diseases. The capsules are effective as a broad-spectrum antiviral, anti-bacterial, antipyretic and anti-inflammatory, they reduce coughing and expectoration, and they regulate immunity in the respiratory system (*15*). A series of clinical trials and basic studies on Lianhua Qingwen capsules in the treatment of SARS, influenza,

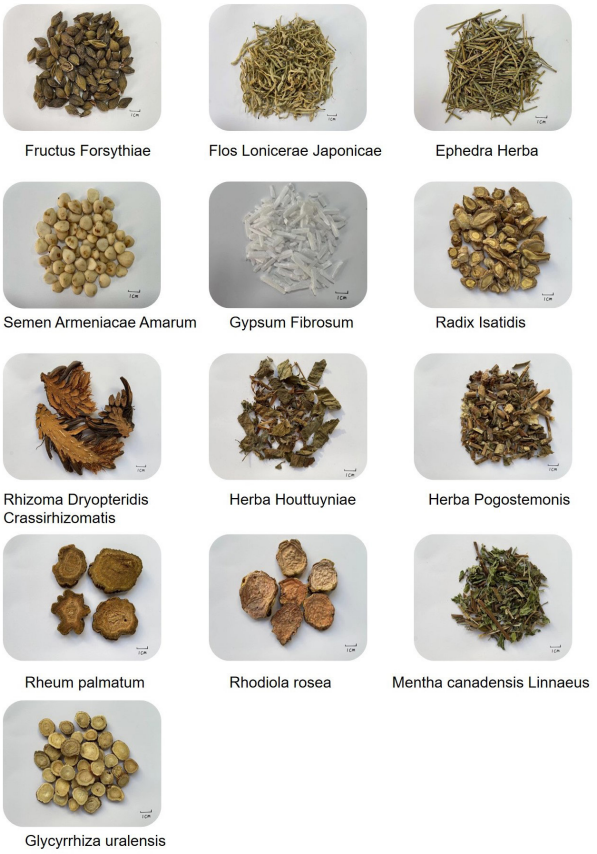


**Figure 1. Composition of Lianhua Qingwen capsules that can be used to treat respiratory infectious diseases.**

and COVID-19 have been conducted in China and other countries. Moreover, they have successfully entered a phase II clinical trial (NCT02867358) on treating acute uncomplicated influenza in the US (*https://clinicaltrials.gov/*). Lianhua Qingwen capsules are beginning to gain global acceptance. Thus far, Lianhua Qingwen capsules have gradually entered the international market and are successfully registered in 29 countries and regions.

SARS was responsible for the first pandemic of the 21st century, which was caused by SARS-COV in November 2002 in Guangdong Province, China (*16*). The disease was highly contagious and fatal, and the pandemic lasted until July 2003, affecting more than 8,000 people and causing 774 deaths in 26 countries on five continents. After the outbreak of SARS, Lianhua Qingwen capsules were quickly developed and used clinically, playing a significant role in China. Since SARS only lasted for 8 months, there was a lack of high-quality clinical trials on Lianhua Qingwen capsules.

Influenza is an acute respiratory infection caused by a negative-strand RNA virus of the Orthomyxoviridae family. There are three types of influenza viruses that infect humans: influenza A, B, and C. H1N1 and H7N9 are infamous subtypes of type A influenza. In 2009, a new H1N1 strain first identified in Mexico spread widely and caused millions of cases worldwide, with an estimated 18,500 laboratory-confirmed deaths (*17*). Lianhua Qingwen displayed anti-influenza activity clinically during the 2009 H1N1 pandemic in China. Wu *et al*. indicated that Lianhua Qingwen granules combined with a peramivir sodium chloride injection displayed marked potency in patients with influenza (*18*). It reduced the treatment time and increased levels of the inflammatory factors IL-6, CRP, and PCT. The overall efficacy in the experimental group was significantly higher than that in the control group (96.0% *vs.* 80%, $P = 0.014$). Yang *et al*. found that Lianhua Qingwen capsules inhibit early-stage replication of the influenza virus and prevent a severe inflammatory response (*19*). Levels of RANTES, IL-6, IL-8, IP-10, TNF-α, MCP-1, MIP-1β, and IFN-λ expression decreased *in vitro*, while *in vivo* results indicated that Lianhua Qingwen capsules did not reduce the lung viral load or mortality due to the influenza virus in mice, but the pathological changes in the lungs were alleviated with fewer inflammatory cells in the lungs. Moreover, Lianhua Qingwen capsules can be used as an adjunct to enhance the efficacy of oseltamivir in treating influenza. In addition, Gao *et al*. indicated that Lianhua Qingwen had a distinct metabolic influence on the treatment of influenza pneumonia, mainly targeting COX-2 in the arachidonic acid metabolism pathway (*20*).

COVID-19 broke out in 2019 and spread rapidly around the world, causing a global pandemic. As of August 15, 2022, nearly 600 million confirmed cases of COVID-19 have been documented globally. Unfortunately, there is still no specific drug that can cure COVID-19. Lianhua Qingwen capsules may be successful in preventing and treating infectious diseases. A meta-analysis of three trials (one randomized controlled trial (RCT) and two retrospective case-control studies) involving 245 COVID-19 patients indicated that Lianhua Qingwen capsules had significant efficacy in alleviating clinical symptoms such as a fever, cough, and fatigue and in curbing progression to severe or critical disease (*21*). Another meta-analysis of five RCTs involving 830 patients with mild or moderate COVID-19 indicated that the combination of Lianhua Qingwen capsules and conventional therapy was significantly associated with better clinical efficacy, a higher rate of improvement on chest computed tomography (CT), and a lower rate of conversion to severe cases (*22*).

However, the potential mechanism of Lianhua Qingwen capsules in treating COVID-19 remains unclear. In a pharmacology network-based study, Xia *et al*. investigated the potential therapeutic mechanisms of Lianhua Qingwen capsules in COVID-19 (*23*). They indicated that Lianhua Qingwen capsules made an indispensable contribution to preventing and curing COVID-19 by improving the inflammatory response and regulating cell apoptosis and the immune defence. They speculated that Akt1 might be a promising drug target for COVID-19. Another network pharmacology analysis indicated that Lianhua Qingwen capsules

modulated the inflammatory process, had antiviral action, and repaired lung injury caused by COVID-19 (*24*). Moreover, the capsules were also able to alleviate the cytokine storm and symptoms caused by abnormal angiotensin converting enzyme 2 (ACE2) (a SARS-CoV receptor, possibly the viral entry point in alveolar lung cells) expression. In addition, Li *et al*. found that Lianhua Qingwen inhibited SARS-CoV-2 replication in Vero E6 cells and reduced the production of pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) at the mRNA level, further resulting in the abnormal particle morphology of the virion in cells (*25*). These studies might provide theoretical substantiation of the use of Lianhua Qingwen capsules in the treatment of COVID-19. The exact mechanism and efficacy of Lianhua Qingwen capsules still need to be elucidated further using molecular biological techniques.

### 2.2. Jinhua Qinggan granules

Jinhua Qinggan granules, a Chinese patent medicine, were originally developed to treat H1N1 in 2009 and were approved by the CFDA in 2016. Jinhua Qinggan granules were created from the two classical TCM formulae Maxing-Shigan-Tang and Yinqiao-San, and they contain 11 herbs including Flos Lonicerae Japonicae (Jinyinhua), Gypsum Fibrosum (Shigao), and Ephedra Herba (Ma huang) (Figure 2). The main chemical components of Jinhua Qinggan granules include chlorogenic acid, mangiferin, forsythoside A, baicalin, arctiin, wogonoside, and ammonium glycyrrhizinate (*26*). Since they were developed, Jinhua Qinggan granules have become the main force in fighting respiratory infectious diseases. In the past, Jinhua Qinggan granules have been utilized in the treatment of H1N1 influenza, and they have displayed marked efficacy in alleviating symptoms and promoting recovery in patients with influenza (*27*). Since the outbreak of COVID-19, Jinhua Qinggan granules have displayed marked efficacy in the fight against SARS-CoV-2, and they have been recommended as a medication in the Diagnosis and Treatment Protocol for COVID-19 in China. Moreover, they have successfully entered a phase II clinical trial (NCT04723524) on treating COVID-19 in the US (*https://clinicaltrials.gov/*), which means that Jinhua Qinggan granules are beginning to gain global acceptance.

Shah *et al*. conducted a phase 2/3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of treatment with Jinhua Qinggan granules in non-hospitalized patients with laboratory-confirmed mild COVID-19 (*28*). They found that Jinhua Qinggan granules displayed better clinical efficacy (82.67%) compared to a placebo (10.74%), and the recovery time from symptoms such as a cough, phlegm, a sore throat, and headaches in patients receiving Jinhua Qinggan granules was shorter than that in patients

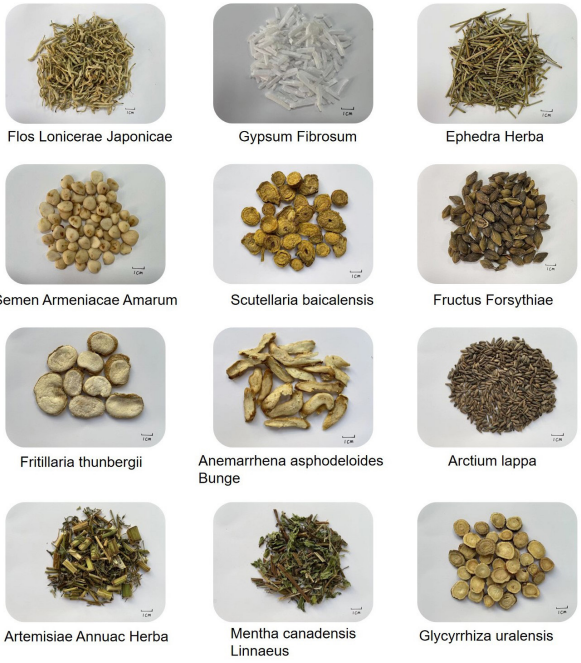


**Figure 2. Composition of Jinhua Qinggan granules that can be used to treat respiratory infectious diseases.**

receiving a placebo (6 days *vs.* more than 11 days). However, there was no significant difference in SARS-CoV-2 negativity in both groups. In a retrospective study conducted at an old age home in Hong Kong, Lin *et al*. presented preliminary evidence that Jinhua Qinggan granules potentially reduce hospitalization and mortality in elderly patients with COVID-19 who were partially vaccinated and who were at risk of progression to severe disease (*29*). An *et al*. indicated that Jinhua Qinggan granules combined with Western medicine relieved the clinical symptoms of a fever and poor appetite in patients with COVID-19, reducing the use of antibiotics to a certain extent (*30*).

However, the potential mechanism of Jinhua Qinggan granules in treating COVID-19 remains unclear. Kageyama *et al*. found that the clinical benefits of the use of Jinhua Qinggan granules to treat COVID-19 might be associated with their rapid immunomodulatory effects on IL-6, IFN-γ, and the neutrophil/lymphocyte ratio (NLR) (*31*). Their findings indicated that Jinhua Qinggan granules might be suitable not only for suppressing disease onset in suspected and asymptomatic cases but also at preventing disease progression in patients with a mild to severe infection.

### 2.3. Shufeng Jiedu capsules

Shufeng Jiedu Capsules, a Chinese patent medicine, were originally developed to treat H1N1 in 2009 and were approved by the CFDA in the same year. They were created from a Chinese folk prescription and consist of 8 herbs including Rhizoma Polygoni cuspidati (Huzhang), Fructus Forsythiae (Lianqiao), and Radix

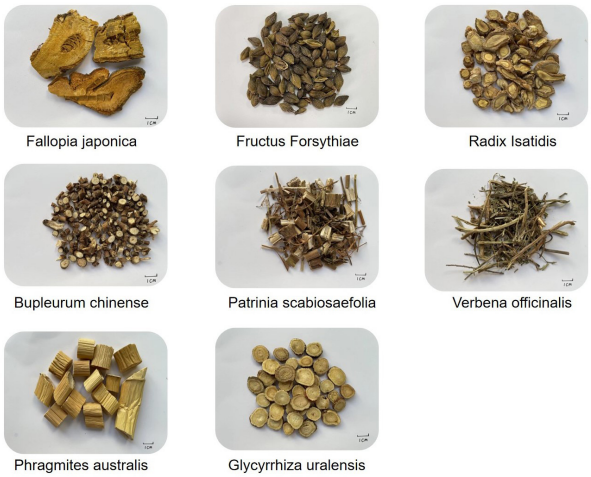


**Figure 3. Composition of Shufeng Jiedu Capsules that can be used to treat respiratory infectious diseases.**

Isatidis (Banlangen) (*32*) (Figure 3). Shufeng Jiedu Capsules are mainly used to treat upper respiratory tract infections such as the flu, swelling and pain in the throat, mumps, and strep throat with anti-inflammatory, immunomodulating, and antiviral properties.

Since 2009, Shufeng Jiedu Capsules have been used in China to treat H1N1 influenza based on governmental recommendations (NHC 2010), and they represent first-line TCM for the prevention and treatment of respiratory infectious diseases. Xia *et al*. conducted a meta-analysis of 13 RCTs involving 1,036 patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) (*33*). Results suggested the positive effects of Shufeng Jiedu Capsules in combination with antibiotics and symptomatic treatments in reducing treatment failure and the duration of hospitalization and alleviating symptoms. Moreover, a phase III clinical study on Shufeng Jiedu Capsules to help reduce antibiotic use in AECOPD is being conducted in England (ISRCTN26614726) (*https://www.isrctn.com/)*.

Since the outbreak of COVID-19, Shufeng Jiedu Capsules have displayed marked efficacy in the fight against SARS-CoV-2, and they have been recommended as a medication in the Diagnosis and Treatment Protocol for COVID-19 in China. Moreover, Shufeng Jiedu Capsules have been registered in Hong Kong (Registration No. PR025534) and Macao (Registration No. MAC-C00004), China, for the treatment of COVID-19. Chen *et al*. indicated that Shufeng Jiedu Capsules combined with Arbidol to treat common COVID-19 reduced the duration of symptoms and increased clinical efficacy without causing serious adverse reactions (*34*). Zhang *et al*. indicated that Shufeng Jiedu Capsules are capable of alleviating a sore throat, coughing, fatigue and a fever in patients infected with Omicron by inhibiting viral replication (*35*). The clinical cure rate was significantly higher in patients receiving Shufeng Jiedu Capsules than in the control group (76.9% *vs.* 64.1%, $p = 0.032$).

Despite the definite evidence of effective use of Shufeng Jiedu Capsules in the treatment of pneumonia caused by the influenza virus and SARS-CoV-2, the underlying mechanism of action remains unknown. A series of network pharmacology studies and cell/animal experiments have been conducted to explore the mechanisms of Shufeng Jiedu Capsules. Shufeng Jiedu Capsules combined with oseltamivir significantly attenuated influenza A virus-induced lung damage by reducing IL-1β and IL-18 levels in serum and bronchoalveolar lavage fluid (BALF), and they inhibited the expression of NLRP3-associated components and viral titers in lung tissues of rats (*36*). In another *in vivo* study, Shufeng Jiedu Capsules significantly reduced the viral load in the lungs of mice infected with HCoV-229E, they decreased the inflammatory factors IL-6, IL-10, TNF-α, and IFN-γ in the lungs, and they increased the amount of $CD^{4+}$ and $CD^{8+}$ cells in the blood compared to the model group (*37*). Several network pharmacology analyses revealed that the preventive and therapeutic effect of Shufeng Jiedu Capsules on COVID-19 might involve modulation of the immune system and anti-inflammatory and anti-viral action *via* quercetin, luteolin, kaempferol, baicalein, and other active ingredients on key targets such as IL-6, IL-10, TNF, NF-κB, and PI3K-Akt (*38,39*).

## 3. Chinese patent medicines for cardiovascular and cerebrovascular diseases

Cardiovascular and cerebrovascular diseases are common diseases related to blood vessels of the heart and cerebrum and mainly include heart failure, atherosclerosis, myocardial infarction, arrhythmia, hypertension, and stroke. Although prevention and treatment have improved in recent years, cardiovascular and cerebrovascular diseases remain a leading cause of disability and mortality worldwide. Recent studies have suggested that TCMs such as Compound Danshen Dripping Pills (Fufang Danshen Diwan), Huatuo Zaizao pills, and Tongxinluo Capsules might be a candidate for the preventive treatment of those diseases. TCM treatment was most likely to be used by patients with a long history of CHD or with a history of stroke. Summarized here are the recent advances in the efficacy (Table 5, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) and molecular mechanisms (Table 6, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) of these Chinese patent medicines that have been successfully registered or that have been submitted for registration abroad.

### 3.1. Compound Danshen Dripping Pills

Compound Danshen dripping pills are a Chinese

patent medicine that was approved by the CFDA in 1995, and they are commonly used to treat coronary heart disease (CHD), and especially angina pectoris, in China. They are also used to treat diabetic retinopathy and acute high-altitude exposure. Compound Danshen dripping pills were the first Chinese patent medicine to complete a phase II clinical trial (NCT00797953) on treating chronic stable angina in the US, and a phase III clinical trial (NCT03789552) on treating stable angina is underway (*https://clinicaltrials.gov/*). The pills are prepared from Salviae miltiorrhizae (Danshen), Panax notoginseng (Sanqi), and Borneolum (Bingpian) by modern techniques, and they activate blood circulation and eliminate blood stasis (Figure 4A). The main active ingredients of Compound Danshen dripping pills have been identified and include Danshensu, protocatechuic aldehyde, salvianolic acid, notoginsenoside, and ginsenoside (*40*).

Recently, a series of systematic reviews have been conducted to assess the clinical efficacy of Compound Danshen dripping pills in patients with CHD. Li *et al*. conducted a meta-analysis of 12 RCTs involving 2,574 patients with CHD to systematically evaluate the efficacy of Compound Danshen dripping pills combined with percutaneous coronary intervention (PCI) in patients with CHD (*41*). They indicated that Compound Danshen dripping pills combined with PCI markedly reduced the incidence of major adverse cardiac events (MACE), improved cardiovascular function, and inhibited inflammation in patients with CHD. Luo *et al*. conducted a meta-analysis of 13 systematic reviews involving 34,071 patients with angina or acute myocardial infarction (AMI) to summarize the evidence from systematic reviews on the efficacy and safety of Compound Danshen dripping pills in patients with CHD (*42*). They concluded that the potential benefits of Compound Danshen dripping pills in patients with CHD included alleviating symptoms, improving ECG results, and causing few adverse reactions. In addition, Liang *et al*. conducted a meta-analysis of 21 RCTs involving 2,356 patients with unstable angina pectoris to evaluate the clinical efficacy and safety of Compound Danshen Dripping pills and isosorbide mononitrate (ISMN) in the treatment of unstable angina pectoris in the elderly (*43*). They indicated that Compound Danshen dripping pills were superior to ISMN in the treatment of elderly patients with unstable angina pectoris based on a comparison of clinical efficacy, ECG efficacy, blood viscosity, and other indicators.

Although Compound Danshen dripping pills have performed well in the treatment of CHD, their mechanism had not been clearly discussed. In rats with acute myocardial ischemia, Compound Danshen dripping pills provided an excellent cardioprotective effect by reversing echocardiographic abnormalities, attenuating histopathological lesions, and ameliorating circulating myocardial markers and inflammatory cytokines by simultaneously modulating the MAPK, PI3K/AKT, and PPAR pathways (*44*). In a mouse model of microvascular dysfunction, pre-treatment with Compound Danshen dripping pills prevented lipid infusion-induced systemic microvascular disorders including coronary and peripheral microvascular dysfunction, and their possible mechanisms involved down-regulated FOXO1 and decreased leukocyte adhesion (*45*).


**Figure 4. Compositions of Compound Danshen Dripping Pills (A) and Huatuo Zaizao pills (B) that can be used to treat cardiovascular and cerebrovascular diseases.**

### 3.2. Huatuo Zaizao pills

Huatuo Zaizao pills, a Chinese patent medicine, are listed as the preferred drug to treat stroke in the Chinese Pharmacopoeia (Pharmacopoeia Commission of the People's Republic of China, 2015). They are commonly used to treat cerebrovascular diseases and promote rehabilitation after stroke. A phase III clinical trial (NCT04910256) that evaluated the efficacy and safety of Huatuo Zaizao pills in patients after an ischemic stroke has been conducted in the US (*https://clinicaltrials.gov/*). Moreover, Huatuo Zaizao pills have been registered as a drug and sold in 29 countries or regions around the world, and they have ranked among the top exports of Chinese medicine for more than 10 years consecutively. They are a proprietary prescription prepared from ingredients such as Ligusticum chuanxiong (Chuanxiong), Tetradium ruticarpum (Wuzhuyu), and Borneolum (Bingpian), and they act by alleviating disrupted micro-circulation and by preventing cerebral thrombosis (Figure 4B) (*46*).

Over the past few years, a series of studies on the pharmacognosy, pharmaceutics, and pharmacology of Huatuo Zaizao pills have mostly been published in the Chinese medical literature and have only been partly published in English. Despite the fact that Huatuo Zaizao pills are administered to promote the rehabilitation of stroke patients, the mechanisms of their pharmacological action are still unclear. Combined administration of Huatuo Zaizao pills and aspirin prolonged the activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT) and it decreased

whole blood viscosity (WBV) and plasma viscosity (PV) in rabbits, potently affecting hemorrheology and blood coagulation (*47*). Huatuo Zaizao pills treatment increases the expression of brain-derived neurotrophic factor (BDNF) and the level of neurogenesis in animals with cerebral ischemia-reperfusion (I/R) injury, which may be associated with functional recovery after stroke (*46*). In addition, Zhang *et al*. investigated the effect of Huatuo Zaizao pills on hippocampal synaptic function and amyloid-β (Aβ) deposition in transgenic mice with Alzheimer's disease (AD) (*48*). They indicated that Huatuo Zaizao pills ameliorated hippocampus-dependent memory deficits and improved synaptic dysfunction by reversing long-term potentiation (LTP) impairment in APP/PS1 AD transgenic mice. Moreover, Huatuo Zaizao pills reduced amyloid plaque deposition by regulating α-secretase and γ-secretase levels.

### 3.3. Tongxinluo Capsules

Tongxinluo Capsules are a Chinese patent medicine that was approved by the CFDA in 1996. They are commonly used to treat ischemic cerebrovascular diseases and angina pectoris in China. They mainly consist of 12 traditional Chinese herbs including Panax ginseng (Renshen), Hirudo nipponica Whitman (Shuizhi), Scolopendra subspinipes mutilans (Wugong), Eupolyphaga sinensis Walker (Tubiechong), Buthus martensii Karsch (Quanxie), Cryptotympana pustulata Fabricius (Chantui), Paeonia lactiflora (Chishao), Borneolum (Bingpian), Santalum album (Tanxiang), Burseraceae (Ruxiang), Dalbergia odorifera (Jiangxiang), and Ziziphus jujuba Mill (Suanzaoren). The capsules promote blood circulation and eliminate blood stasis (*49*) (Figure 5). Modern pharmacological studies have indicated that Tongxinluo capsules can improve the function of vascular endothelial cells, reduce blood viscosity, regulate blood lipids, improve hemorheology, and stabilize atherosclerotic plaques (*50*).

Recently, a series of large-scale RCTs have been conducted to evaluate the clinical efficacy of Tongxinluo capsules for cardiovascular and cerebrovascular diseases. Zhang *et al*. conducted a multi-center, randomized, double-blind, parallel-group, placebo-controlled clinical trial (CAPITAL) involving 1,212 patients with sub-clinical carotid atherosclerosis to determine whether Tongxinluo capsules were efficacious at retarding the progression of carotid atherosclerotic lesions (*51*). They indicated that treatment with Tongxinluo capsules in addition to routine therapy retarded the progression of mean intima-media thickness, plaque area, and vascular remodeling of the carotid arteries in patients with sub-clinical carotid atherosclerosis with a good safety profile. Li *et al*. conducted a meta-analysis of 16 RCTs involving 1,877 patients with AMI to evaluate the potential efficacy and safety of Tongxinluo capsules for secondary prevention in patients with AMI (*50*).

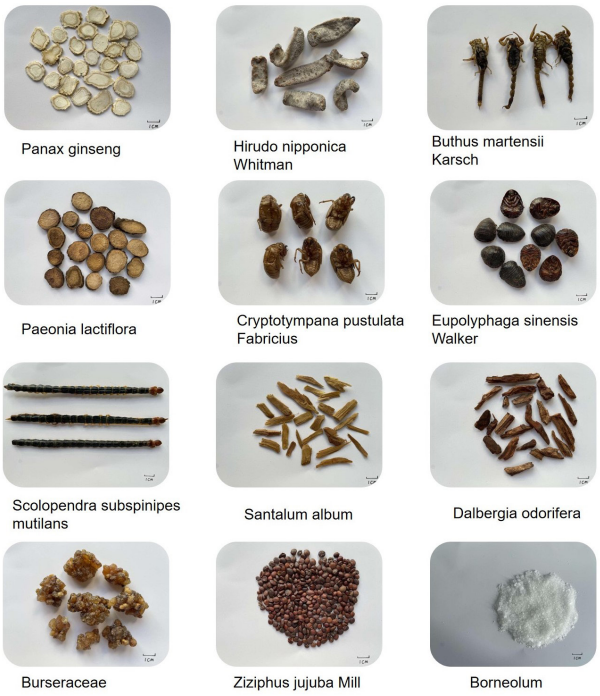


**Figure 5. Composition of Tongxinluo Capsules that can be used to treat cardiovascular and cerebrovascular diseases.**

They found that Tongxinluo capsules seemed to be beneficial for secondary prevention after AMI, allowing improvement of cardiac function (LVEF), regulation of lipid metabolism (TC, TG, and LDL), and inhibition of an inflammatory reaction (hs-CRP). The main adverse reaction was only gastrointestinal discomfort. Another meta-analysis suggested that Tongxinluo capsules as supplementation were associated with a significantly reduced risk of target vessel revascularization (TVR) or in-stent restenosis (ISR) after coronary revascularization and that the capsules might reduce the incidence of first or recurrent myocardial infarction (MI) and first or worsened heart failure (HF) within 12 months in patients with CHD without serious adverse reactions (*52*). Moreover, Tongxinluo capsules combined with atorvastatin effectively improved the clinical treatment of CHD, significantly reduced the frequency and duration of angina pectoris, decreased blood lipids, and improved inflammatory factors (*53*). In addition, the addition of Tongxinluo capsules to routine medication was beneficial to the treatment of a transient ischemic attack (TIA), significantly improving clinical efficacy and hemorheological characteristics, reducing blood viscosity, and promoting microcirculation (*54*).

Tongxinluo capsules have performed well in the treatment of cardiovascular and cerebrovascular diseases in clinical settings, and their mechanisms have also been actively studied. Tongxinluo capsules provided protection against blood-brain barrier (BBB) disruption after ischemic stroke (*55*). They inhibited the low-density lipoprotein receptor-related protein 1 (LRP-1) pathway, up-regulated the level of tight junction

(TJ) proteins such as occludin, claudin-5, and ZO-1, and subsequently protected against disruption of the BBB after cerebral ischemia in mice with permanent middle cerebral artery occlusion (pMCAO). In a rat model of cerebral ischemia/reperfusion (I/R) injury, Tongxinluo capsules effectively protected against I/R injury and reduced cell death *via* the Cx43/Calpain II/Bax/Caspase-3 pathway, helping to prevent and treat I/R injury (*56*). Moreover, in a rat model of intestinal I/R injury, pretreatment with Tongxinluo capsules significantly prevented the I/R-induced pathology of endothelial apoptosis, disruption of microvascular integrity, and the inflammatory reaction (57). Furthermore, Tongxinluo capsules might be as effective as simvastatin in stabilizing atherosclerotic plaques and they might provide an alternative therapy for atherosclerosis (*58*). They significantly reduce serum levels of lipids and inflammatory markers, attenuate the lipid content of plaque and the inflammatory reaction, and lower the incidence of plaque in a rabbit model of atherosclerosis.

## 4. Chinese patent medicines for cancers

Cancer has become a leading cause of death and an important obstacle to increasing life expectancy in every country of the world. Based on the Global Cancer Observatory (GLOBOCAN) registry, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 worldwide (*59*). Moreover, an estimated 28.4 million new cancer cases are projected to occur in 2040, a 47% increase from the corresponding 19.3 million cases in 2020. Thus, cancer prevention and treatment remain a major challenge for the world in the coming years. In recent decades, TCM has been increasingly used and has become well-known for its significant role in preventing and treating cancer. It is widely used by TCM physicians and other health care providers to alleviate the symptoms of patients with cancer and to control the adverse reactions to and the toxicities of cancer therapies, thus improving patient QOL, preventing recurrence, and prolonging survival (*1*). A point particularly worth noting is that several Chinese patent medicines such as a Kanglaite injection and a Shenqi Fuzheng Injection have significant advantages in treating cancers. Summarized here are the recent advances in the efficacy (Table 7, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) and molecular mechanisms (Table 8, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) of several Chinese patent medicines that have been successfully registered or that have been submitted for registration abroad. These Chinese patent medicines include a Kanglaite injection and a Shenqi Fuzheng Injection.

### 4.1. A Kanglaite injection


**Figure 6. Compositions of a Kanglaite injection (A) and a Shenqi Fuzheng Injection (B) that can be used to treat cancers.**

A Kanglaite injection, as an acetone extract of Semen Coicis Yokuinin (Figure 6A), is prepared as an herbal medicine using modern and advanced pharmaceutical technology. It is widely used to treat lung and liver cancer or complications of cancers, such as malignant pleural effusion, in China. In recent years, a Kanglaite injection has been approved by other countries such as Russia and the US. Since 2005, a Kanglaite injection has been approved as a prescription to treat cancer in clinical settings by the Ministry of Health of the Russian Federation. In addition, it has passed the review of the US FDA, and a phase III clinical trial is being conducted in the US.

A series of RCTs and systematic reviews have indicated that a Kanglaite injection is an effective adjunctive therapy for cancers. An overview was conducted by Lu *et al*. to map the evidence landscape based on 13 systematic reviews with meta-analyses published from 2004 to 2021 focusing on a Kanglaite injection to treat cancers and related conditions (*60*). They indicated that a Kanglaite injection was effective and safe as an adjunctive treatment for non-small cell lung cancer (NSCLC), malignant pleural effusion, and digestive system malignancies (such as hepatocellular carcinoma (HCC)). Adjunctive therapy with a Kanglaite injection improves clinical indices such as overall survival (OS), the disease response rate, and QOL, and it improves the values of immune indicators including the number of $CD^{4+}$ lymphocytes and the $CD^{4+}/CD^{8+}$ ratio. Moreover, a Kanglaite injection reduces the incidence of various adverse reactions caused by conventional chemotherapy drugs, such as gastrointestinal reactions, thrombocytopenia, and leukopenia. Another overview was conducted based on 20 systematic reviews with meta-analyses focusing on a Kanglaite injection to treat NSCLC (*61*). Results suggested that a Kanglaite injection whether combined with chemotherapy, radiotherapy, or targeted therapy, has an effect on the objective response rate (ORR) and QOL and decreases adverse reactions. Moreover, a Kanglaite injection combined with gefitinib

might increase the ORR, improve performance status, and increase the number of $CD^{4+}$ cells and NK cells and the ratio of $CD^{4+}/CD^{8+}$ but it did not reduce the toxicity of gefitinib or increase the number of $CD^{3+}$ cells and $CD^{8+}$ cells in patients with NSCLC (*62*).

A Kanglaite injection has performed well in the treatment of cancer in clinical settings, and its mechanism has also been actively studied. Shi *et al*. indicated that Kanglaite inhibited TNF-α-mediated epithelial mesenchymal transition (EMT) in colorectal cancer cell lines and a subcutaneous tumor model by inhibiting NF-κB signaling (*63*). Moreover, Kanglaite reversed the multidrug resistance (MDR) of human HCC by inducing apoptosis and cell cycle arrest *via* the PI3K/AKT signaling pathway (*64*). In addition, pre-treatment with Kanglaite increased the effects of cisplatin (DDP) on HepG2 cells, and it had a synergistic effect on the regulation of inflammation and chemo-resistance (*65*). The underlying mechanisms of pre-treatment with Kanglaite might involve the suppression of chemokine-like factor 1 (CKLF1) mediated NF-κB signaling and ATP-binding cassette drug efflux transporters in HepG2 cells.

### 4.2. A Shenqi Fuzheng Injection

A Shenqi Fuzheng injection is a Chinese patent medicine approved by the CFDA in 1999. It consists of two traditional Chinese herbs, Radix Astragali (Huangqi) and Codonopsis Pilosula (Dangshen) at a ratio of 1:1 (Figure 6B), and it is commonly used to improve immune function in chronic diseases including cancer and cerebrovascular diseases such as, angina, coronary heart disease, and heart failure (*2,66*). Recently, a number of trials have indicated that a Shenqi Fuzheng injection might play an important role in the treatment of various advanced cancers such as NSCLC and gastric cancer. Since 2017, it has passed the review of the US FDA, and a phase III clinical trial is being conducted in the US. This means that a Shenqi Fuzheng injection is beginning to gain global acceptance.

Over the past decade, a series of RCTs and systematic reviews have indicated that a Shenqi Fuzheng injection combined with chemotherapy, radiotherapy, or targeted therapy to treat various types of cancers is capable of improving clinical efficacy, immune function, and performance status and of reducing toxicity. A meta-analysis of 13 RCTs indicated that a Shenqi Fuzheng injection combined with chemotherapy yielded positive results in treating advanced gastric cancer in terms of the rate of complete remission (CR) and partial remission (PR), body weight, and decreased adverse reactions including grade 3-4 nausea and vomiting, grade 1-2 oral mucositis, grade 3-4 leucopenia, and grade 1-2 myelo-suppression (*67*). Another meta-analysis of 49 RCTs indicated that a Shenqi Fuzheng injection and conventional chemotherapy exhibited better efficacy, with a significantly better objective tumor response (*68*). Combined treatment with a Shenqi Fuzheng injection increased the number of NK, $CD^{3+}$, and $CD^{4+}$ cells and the $CD^{4+}/CD^{8+}$ ratio compared to conventional chemotherapy, suggesting that a Shenqi Fuzheng injection was efficacious in alleviating immune system damage caused by chemotherapy. Moreover, a Shenqi Fuzheng injection alleviated radiation-induced brain injury (*69*). It reduced impaired cognitive function, and especially memory impairment after brain radiation, by regulating the expression of inflammatory factors such as TGF-β1, TNF-α, and IL-10. A Shenqi Fuzheng injection also improved clinical efficacy and decreased radiation toxicity by regulating T-cell immune function in patients with NSCLC undergoing radiotherapy (*70*). In addition, a Shenqi Fuzheng injection combined with a first-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) markedly prolonged progression-free survival (PFS) and attenuated adverse reactions in patients with advanced NSCLC with EGRET-sensitive mutations (*71*). Compared to administration of an EGFR-TKI alone, combined treatment with a Shenqi Fuzheng injection resulted in a lower incidence of a rash and diarrhea in patients and was even better tolerated.

A Shenqi Fuzheng injection has performed well in the treatment of various advanced cancers in clinical settings, and its mechanisms have also been actively studied. A Shenqi Fuzheng injection might be useful in alleviating cancer-related fatigue (CRF) by inhibiting pro-inflammatory cytokines produced by peripheral immune cells, limiting the dysfunction of exhausted T cells, and improving anti-tumor immunity through the targets of PDL1, TIM3, and FOXP3 in tumor-bearing mice (*72*). Mitofusin-2 (Mfn2) is a mitochondrial GTPase that may be related to chemo-resistance. A Shenqi Fuzheng injection reversed DDP resistance through Mfn2-mediated cell cycle arrest and apoptosis in A549/DDP cells (*73*). Moreover, a Shenqi Fuzheng injection not only significantly improved physical status, survival, and spatial learning in mice treated with cranial radiation therapy (CRT), but it also attenuated all of the CRT-induced changes in brain tissues. It effectively attenuated irradiation-induced brain injury *via* inhibition of the NF-κB signaling pathway and microglial activation (*74*).

## 5. Chinese patent medicines for gynecological diseases

Gynecological disorders, including endometriosis, myoma uteri, infertility, primary dysmenorrhea, and premenstrual syndrome, are common phenomena among the female population. These disorders mostly generate a diversity of discomfort and inconvenience for women such as bothersome heavy menstruation, dysmenorrhea, and infertility; these disorders may not be genuine

threats to life, but they greatly affect women's QOL (*75*). TCM has been used to treat gynecological disorders for more than 2,000 years. The famous book Synopsis of the Golden Chamber written by Zhang Zhongjing during the Eastern Han Dynasty (25-220 A.D.) systematically recorded the prevention and treatment of women's pregnancy-related diseases, postpartum diseases, and other common diseases (*76*). A point particularly worth noting is that several Chinese patent medicines such as Guizhi Fuling Capsules have significant advantages in treating gynecological disorders. Summarized here are the recent advances in the efficacy (Table 9, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) and molecular mechanisms (Table 10, online data: *http://www.ddtjournal.com/action/getSupplementalData.php?ID=129*) of Guizhi Fuling Capsules. These capsules have passed the review of the US FDA. A phase II clinical trial (NCT01588236) of Guizhi Fuling Capsules for primary dysmenorrhea has been completed by the US FDA, which found them to be efficacious and safe (*77*).

Guizhi Fuling Capsules are a Chinese patent medicine approved by the CFDA in 1995, and they are widely used to treat gynecological conditions in China. The capsules were developed from Guizhi Fuling Pills, a classic and effective prescription that was first recorded in the famous book Synopsis of the Golden Chamber written by Zhang Zhongjing during the Eastern Han Dynasty (25-220 A.D.). According to the Chinese Pharmacopoeia (Pharmacopoeia Commission of the People's Republic of China, 2015), the capsules consist of five ingredients: Guizhi (Cinnamon Cortex), Shaoyao (Paeoniae Radix), Mudanpi (Moutan Cortex), Taoren (Persicae Semen), and Fuling (Poria Cocos) (Figure 7). The main active ingredients of Guizhi Fuling Capsules have been identified and include paeonol, coumarin, cinnamic alcohol, cinnamic acid, paeoniflorin, and amygdalin (*78*). In modern medicine, Guizhi Fuling Capsules are commonly used to treat endometriosis, myoma uteri, primary dysmenorrhea, menopausal syndrome, and other gynecological diseases caused by an estrogen and progesterone imbalance.

Over the past decade, a series of RCTs and systematic reviews have indicated that Guizhi Fuling Capsules are an effective adjunctive therapy for gynecological diseases. A systematic review of 30 RCTs involving 3,586 patients was conducted to evaluate the efficacy and safety of Guizhi Fuling Capsules/Pills in the treatment of chronic pelvic inflammatory disease. Results indicated that Guizhi Fuling Capsules/Pills combined with Western medicine were more effective than Western medicine alone in terms of clinical efficacy, the rate of recurrence, anti-inflammation, and plasma viscosity (*79*). Another systematic review of 38 RCTs involving 3,816 patients indicated that the Guizhi Fuling Formula plus mifepristone may be more effective than mifepristone alone in the treatment of

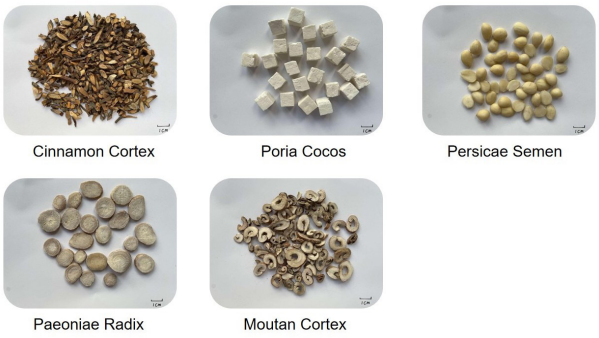


**Figure 7. Composition of Guizhi Fuling Capsules that can be used to treat gynecological diseases.**

uterine fibroids (*80*). In addition, a meta-analysis of 10 RCTs involving 1,052 patients indicated that the Guizhi Fuling Formula as an adjuvant therapy to mifepristone appeared to have additional benefits in preventing the recurrence of endometriosis and improving pregnancy among women with endometriosis (*81*).

Guizhi Fuling Capsules/Pills have performed well in the treatment of various advanced cancers in clinical settings, and their mechanisms have also been actively studied. Guizhi Fuling Capsules displayed promising efficacy in a mouse model of endometrial hyperplasia induced with estradiol (*82*). The capsules attenuated estrogen-induced endometrial hyperplasia in mice by triggering ferroptosis *via* the p62-Keap1-NRF2 pathway. Guizhi Fuling Pills also alleviated insulin resistance in polycystic ovary syndrome (PCOS) with an underlying mechanism of regulating intestinal flora to control inflammation (*83*). Moreover, Guizhi Fuling Pills inhibited the over-activation of autophagy and apoptosis of ovarian granulosa cells in rats with PCOS by activating the PI3K/AKT/mTOR pathway, thus improving ovarian function and restoring ovulation (*84*). In addition, a metabonomic study had been conducted by Lang *et al*. to investigate the efficacy and mechanism of action of Guizhi Fuling capsules in rats with dysmenorrhea induced with oxytocin (*85*). They found that Guizhi Fuling capsules were efficacious in rats with dysmenorrhea by regulating multiple metabolic pathways including sphingolipid metabolism, steroid hormone biosynthesis, glycerophospholipid metabolism, amino acid metabolism, lipid metabolism, and energy metabolism.

## 6. Conclusion

An indispensable part of TCM, Chinese patent medicines have played an important role in preventing and treating diseases in China. Most Chinese patent medicines are derived from ancient TCM prescriptions and are clinically efficacious. Since they are easy to use, easy to store, and cost-effective, Chinese patent medicines have been generally accepted and widely used in Chinese clinical practice as a vital medical

resource. In recent years, as TCM has developed and it has been accepted around the world, many Chinese patent medicine companies have gained market access and successfully registered several Chinese patent medicines as over-the-counter (OTC) or prescription drugs in regions and countries that primarily use Western medicine such as the EU, Russia, Canada, Singapore, and Vietnam. Moreover, several Chinese patent medicines have obtained FDA approval and are undergoing phase II or III clinical trials in the US.

Therefore, the current review has focused on several Chinese patent medicines that have been successfully registered or that have been submitted for registration abroad. Summarized here are recent advances in the efficacy and molecular mechanisms of these Chinese patent medicines for respiratory infectious diseases (Lianhua Qingwen capsules, Jinhua Qinggan granules, and Shufeng Jiedu Capsules), cardiovascular and cerebrovascular diseases (Compound Danshen Dripping Pills, Huatuo Zaizao pills, and Tongxinluo Capsules), cancers (a Kanglaite injection and a Shenqi Fuzheng Injection), and gynecological diseases (Guizhi Fuling Capsules). The hope is that this review will contribute to a better understanding of Chinese patent medicines by people around the world.

Since 1996, the Chinese Government has issued calls and proposals for the global acceptance of TCM. Chinese patent medicines are becoming increasingly popular in the international market, which represents a breakthrough for the global acceptance of TCM. Given their confirmed efficacy and safety, these Chinese patent medicines can play an increasingly important role in global healthcare, but there is still a long way to go for the global acceptance of TCM. Currently, challenges to the registration of Chinese patent medicines overseas mainly lie in control of the quality of raw materials, the manufacturing process, and evidence of safety and efficacy. To ensure the consistent and acceptable quality of final products, Chinese patent medicine companies should pay attention to all of the links in the production chain. Moreover, high-quality clinical data in accordance with international standards, as well as identification of definite mechanisms of action, are absolutely essential to the further development and acceptance of Chinese patent medicines around the world. In short, the hope is that more Chinese patent medicines will enter the international market and benefit people around the world in the future.

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**References**

1. Zhang X, Qiu H, Li C, Cai P, Qi F. The positive role of traditional Chinese medicine as an adjunctive therapy for cancer. Biosci Trends. 2021; 15:283-298.
2. Qi F, Zhao L, Zhou A, Zhang B, Li A, Wang Z, Han J. The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer. Biosci Trends. 2015; 9:16-34.
3. Zhang B, Shi H, Cao S, Xie L, Ren P, Wang J, Shi B. Revealing the magic of acupuncture based on biological mechanisms: A literature review. Biosci Trends. 2022; 16:73-90.
4. Wang J, Qi F. Traditional Chinese medicine to treat COVID-19: the importance of evidence-based research. Drug Discov Ther. 2020; 14:149-150.
5. State Administration for Market Regulation. Measures for the Administration of Drug Registration (issued on January 22, 2020 and implemented issued on July 1, 2020. *https://gkml.samr.gov.cn/nsjg/fgs/202003/t20200330_313670.html* (accessed June 16, 2022) (in Chinese)
6. Qi F, Tang W. Traditional Chinese medicine for treatment of novel infectious diseases: Current status and dilemma. Biosci Trends. 2021; 15:201-204.
7. Lam WC, Lyu A, Bian Z. ICD-11: Impact on traditional Chinese medicine and world healthcare systems. Pharmaceut Med. 2019; 33:373-377.
8. World Federation of Chinese Medicine Societies. The World Federation of Chinese Medicine Societies' Five-year Development Plan. *http://www.wfcms.org/show/21/3260.html* (accessed June 16, 2022)
9. The State Council Information Office of the People's Republic of China, December 2016, First Edition 2016. Traditional Chinese Medicine in China. *http://www.scio.gov.cn/zfbps/32832/Document/1534710/1534710.htm* (accessed June 16, 2022)
10. Liang SB, Fang M, Liang CH, Lan HD, Shen C, Yan LJ, Hu XY, Han M, Robinson N, Liu JP. Therapeutic effects and safety of oral Chinese patent medicine for COVID-19: A rapid systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2021; 60:102744.
11. The scale and level of the traditional Chinese medicine industry have significantly increased. *https://www.cs.com.cn/cj2020/202207/t20220720_6285595.html* (accessed July 20, 2022) (in Chinese)
12. Wang S, Meng F, Zhou Y. Study on the overseas registration and development of traditional Chinese medicine products under the background of belt and road initiative. World Chin Med. 2021; 16:1497-1500. (in Chinese)
13. Huang K, Zhang P, Zhang Z, Youn JY, Wang C, Zhang H, Cai H. Traditional Chinese Medicine (TCM) in the treatment of COVID-19 and other viral infections: Efficacies and mechanisms. Pharmacol Ther. 2021; 225:107843.
14. Jia W, Wang C, Wang Y, Pan G, Jiang M, Li Z, Zhu Y. Qualitative and quantitative analysis of the major constituents in Chinese medical preparation Lianhua-Qingwen capsule by UPLC-DAD-QTOF-MS. Scie World J. 2015; 2015:731765.
15. Shen X, Yin F. The mechanisms and clinical application of Traditional Chinese Medicine Lianhua-Qingwen capsule.

Biomed Pharmacother. 2021; 142:111998.
16. Peiris JS, Yuen KY, Osterhaus AD, Stöhr K. The severe acute respiratory syndrome. N Engl J Med. 2003; 349:2431-2441.
17. Gaitonde DY, Moore FC, Morgan MK. Influenza: Diagnosis and treatment. Am Fam Physician. 2019; 100:751-758.
18. Wu J, Wang Q, Yang L, Li Z, Wang X. Potency of Lianhua Qingwen granule combined with paramivir sodium chloride injection in treating influenza and level changes of serum inflammatory factors. Am J Transl Res. 2021; 13:6790-6795.
19. Yang C, Wang Y, He J, Yan W, Jiang H, Chen Q, Li L, Yang Z. Lianhua-Qingwen displays antiviral and anti-inflammatory activity and synergistic effects with oseltamivir against influenza B virus infection in the mouse model. Evid Based Complement Alternat Med. 2020; 2020:3196375.
20. Gao D, Niu M, Wei SZ, Zhang CE, Zhou YF, Yang ZW, Li L, Wang JB, Zhang HZ, Zhang L, Xiao XH. Identification of a pharmacological biomarker for the bioassay-based quality control of a thirteen-component TCM formula (Lianhua Qingwen) used in treating influenza A virus (H1N1) infection. Front Pharmacol. 2020; 11:746.
21. Zhuang J, Dai X, Wu Q, Cai H, Fu X, Zhang W, Chen B. A meta-analysis for Lianhua Qingwen on the treatment of Coronavirus disease 2019 (COVID-19). Complement Ther Med. 2021; 60:102754.
22. Shi C, Wu M, Yang K, Wang X. Lianhua Qingwen capsules reduced the rate of severity in patients with COVID-19: A system review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2022; 2022:9617429.
23. Xia QD, Xun Y, Lu JL, Lu YC, Yang YY, Zhou P, Hu J, Li C, Wang SG. Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. Cell Prolif. 2020; 53:e12949.
24. Zheng S, Baak JP, Li S, Xiao W, Ren H, Yang H, Gan Y, Wen C. Network pharmacology analysis of the therapeutic mechanisms of the traditional Chinese herbal formula Lian Hua Qing Wen in Corona virus disease 2019 (COVID-19), gives fundamental support to the clinical use of LHQW. Phytomedicine. 2020; 79:153336.
25. Runfeng L, Yunlong H, Jicheng H, *et al*. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacol Res. 2020; 156:104761.
26. Liu Q, Bai J, Zhang Y, He C, Wang W. Study on quality evaluation of Jinhua Qinggan Granules based on fingerprint, pattern recognition and multi-components determination. Chin J Modern Applied Pharmacy. 2021; 38:2701-2707. (in Chinese w/ English abstract)
27. Tao Z, Yang Y, Shi W, Xue M, Yang W, Song Z, Yao C, Yin J, Shi D, Zhang Y, Cai Y, Tong C, Yuan Y. Complementary and alternative medicine is expected to make greater contribution in controlling the prevalence of influenza. Biosci Trends. 2013; 7:253-256.
28. Shah MR, Fatima S, Khan SN, Ullah S, Himani G, Wan K, Lin T, Lau JYN, Liu Q, Lam DSC. Jinhua Qinggan granules for non-hospitalized COVID-19 patients: A double-blind, placebo-controlled, and randomized controlled trial. Front Med (Lausanne). 2022; 9:928468.
29. Lin TPH, Lau EMC, Wan KH, Zhong L, Leung E, Ko CN, Lu A, Shah MR, Bian Z, Lam DSC. Initial observations of Jinhua Qinggan Granules, a Chinese medicine, in the mitigation of hospitalization and mortality in high-risk elderly with COVID-19 infection: A retrospective study in an old age home in Hong Kong. Front Med (Lausanne). 2022; 9:948149.
30. An X, Xu X, Xiao M, *et al*. Efficacy of Jinhua Qinggan Granules combined with Western medicine in the treatment of confirmed and suspected COVID-19: A randomized controlled trial. Front Med (Lausanne). 2021; 8:728055.
31. Kageyama Y, Aida K, Kawauchi K, Morimoto M, Nakamura T. Jinhua Qinggan granule, a Chinese herbal medicine against COVID-19, induces rapid changes in the neutrophil/lymphocyte ratio and plasma levels of IL-6 and IFN-γ: An open-label, single-arm pilot study. World Acad Sci J. 2022; 4:1-8.
32. Xu Y, Yang L, Wang L, Chen F. Potential therapeutic effect of Shufeng Jiedu capsule and its major herbs on coronavirus disease 2019 (COVID-19): A review. Drug Discov Ther. 2022; 15:289-299.
33. Xia RY, Hu XY, Fei YT, Willcox M, Wen LZ, Yu MK, Zhang LS, Dai MY, Fei GH, Thomas M, Francis N, Wilkinson T, Moore M, Liu JP. Shufeng Jiedu capsules for treating acute exacerbations of chronic obstructive pulmonary disease: A systematic review and meta-analysis. BMC Complement Med Ther. 2020; 20:151.
34. Chen J, Lin S, Niu C, Xiao Q. Clinical evaluation of Shufeng Jiedu Capsules combined with umifenovir (Arbidol) in the treatment of common-type COVID-19: A retrospective study. Expert Rev Respir Med. 2021; 15:257-265.
35. Zhang J, Liu L, Zhang G, Li M, Ma B, Yang W. Treating patients infected with the SARS-CoV-2 Omicron variant with a traditional Chinese medicine, Shufeng Jiedu capsule. Biosci Trends. 2022; 16:238-241.
36. Ji S, Bai Q, Wu X, Zhang DW, Wang S, Shen JL, Fei GH. Unique synergistic antiviral effects of Shufeng Jiedu Capsule and oseltamivir in influenza A viral-induced acute exacerbation of chronic obstructive pulmonary disease. Biomed Pharmacother. 2020; 121:109652.
37. Xia L, Shi Y, Su J, Friedemann T, Tao Z, Lu Y, Ling Y, Lv Y, Zhao R, Geng Z, Cui X, Lu H, Schröder S. Shufeng Jiedu, a promising herbal therapy for moderate COVID-19: Antiviral and anti-inflammatory properties, pathways of bioactive compounds, and a clinical real-world pragmatic study. Phytomedicine. 2021; 85:153390.
38. Tao Z, Zhang L, Friedemann T, Yang G, Li J, Wen Y, Wang J, Shen A. Systematic analyses on the potential immune and anti-inflammatory mechanisms of Shufeng Jiedu Capsule against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused pneumonia. J Funct Foods. 2020; 75:104243.
39. Zhuang Z, Zhong X, Zhang H, Chen H, Huang B, Lin D, Wen J. Exploring the potential mechanism of Shufeng Jiedu Capsule for treating COVID-19 by comprehensive network pharmacological approaches and molecular docking validation. Comb Chem High Throughput Screen. 2021; 24:1377-1394.
40. Yan KJ, Chu Y, Huang JH, Jiang MM, Li W, Wang YF, Huang HY, Qin YH, Ma XH, Zhou SP, Sun H, Wang W. Qualitative and quantitative analyses of Compound Danshen extract based on 1H NMR method and its application for quality control. J Pharm Biomed Anal. 2016; 131:183-187.
41. Li C, Li Q, Xu J, Wu W, Wu Y, Xie J, Yang X. The

efficacy and safety of Compound Danshen Dripping Pill combined with percutaneous coronary intervention for coronary heart disease. Evid Based Complement Alternat Med. 2020; 2020:5067137.
42. Luo J, Song W, Yang G, Xu H, Chen K. Compound Danshen (Salvia miltiorrhiza) dripping pill for coronary heart disease: An overview of systematic reviews. Am J Chin Med. 2015; 43:25-43.
43. Liang Y, Zou J, Zhang X, Wang Y, Tai J, Guo D, Cui C, Wang J, Cheng J, Shi Y. The relationship between Compound Danshen Dripping Pills with isosorbide mononitrate in the treatment of elderly patients with unstable angina pectoris. Evid Based Complement Alternat Med. 2018; 2018:3429151.
44. Lei W, Li X, Li L, Huang M, Cao Y, Sun X, Jiang M, Zhang B, Zhang H. Compound Danshen Dripping Pill ameliorates post ischemic myocardial inflammation through synergistically regulating MAPK, PI3K/AKT and PPAR signaling pathways. J Ethnopharmacol. 2021; 281:114438.
45. Zhang Y, Zhao J, Ding R, Niu W, He Z, Liang C. Pre-treatment with compound Danshen dripping pills prevents lipid infusion-induced microvascular dysfunction in mice. Pharm Biol. 2020; 58:701-706.
46. Duan S, Wang T, Zhang J, Li M, Lu C, Wang L, Zou Y, Fu F. Huatuo Zaizao pill promotes functional recovery and neurogenesis after cerebral ischemia-reperfusion in rats. BMC Complement Altern Med. 2017; 17:19.
47. Qu S, Wang T, Zhang J, Sun X, Yu P, Kong L, Chong Y, Qiu X, Fu F. Effects of the coadministration of Huatuo Zaizao pills and aspirin on hemorrheology and blood coagulation in rabbits. Biomed Rep. 2013; 1:459-463.
48. Zhang JH, Yu LJ, Yang H, Hui Z, Jiang S, Chen L, Zhao Y, Wang SL, Liu Y, Xu Y. Huatuo Zaizao pill ameliorates cognitive impairment of APP/PS1 transgenic mice by improving synaptic plasticity and reducing Aβ deposition. BMC Complement Altern Med. 2018; 18:167.
49. Pharmacopoeia. The Pharmacopoeia of the People's Republic of China. Beijing: China Medical Science Press. 2020.
50. Li M, Li C, Chen S, Sun Y, Hu J, Zhao C, Qiu R, Zhang X, Zhang Q, Tian G, Shang H. Potential effectiveness of Chinese patent medicine Tongxinluo Capsule for secondary prevention after acute myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2018; 9:830.
51. Zhang M, Liu Y, Xu M, Zhang L, Liu Y, Liu X, Zhao Y, Zhu F, Xu R, Ou Z, Wang Y, Liu Q, Ma S, Wang T, He M, Lu Q, Li H, Huang J, Zhang Y. Carotid artery plaque intervention with Tongxinluo capsule (CAPITAL): A multicenter randomized double-blind parallel-group placebo-controlled study. Sci Rep. 2019; 9:4545.
52. Lv J, Liu S, Guo S, Gao J, Song Q, Cui X. Tongxinluo capsule as supplementation and cardiovascular endpoint events in patients with coronary heart disease: A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials. J Ethnopharmacol. 2022; 289:115033.
53. Liu Q, Dong T, Xi M, Gou L, Bai Y, Hou L, Li M, Ou L, Miao F, Wei P. Tongxinluo Capsule combined with atorvastatin for coronary heart disease: A systematic review and meta-analysis. Evid Based Complement Alternat Med. 2021; 2021:9413704.
54. Yang P, Liu P, Yang R. Systematic review of Tongxinluo Capsule on the therapeutic effect and hemorheology of patients with transient ischemic attack. Evid Based Complement Alternat Med. 2021; 2021:5541768.
55. Chang L, Hu L, Wei C, Zhang H, Liu S. Chinese medicine Tongxinluo capsule protects against blood-brain barrier disruption after ischemic stroke by inhibiting the low-density lipoprotein receptor-related protein 1 pathway in mice. J Stroke Cerebrovasc Dis. 2020; 29:105071.
56. Cheng X, Hou Z, Sun J, Huang Y, Wang L, Zhou Z, Zhou LH, Cai Y. Protective effects of Tongxinluo on cerebral ischemia/reperfusion injury related to Connexin 43/Calpain II/Bax/Caspase-3 pathway in rat. J Ethnopharmacol. 2017; 198:148-157.
57. Zhang JX, Li SD, Liu Y, Yang MH. Preventive effect of Tongxinluo on endothelial survival and vascular integrity, together with inhibition of inflammatory reaction in rats model of intestine ischemia/reperfusion injury. Pak J Pharm Sci. 2018; 31(6):2403-2410.
58. Chen WQ, Zhong L, Zhang L, Ji XP, Zhao YX, Zhang C, Jiang H, Wu YL, Zhang Y. Chinese medicine Tongxinluo significantly lowers serum lipid levels and stabilizes vulnerable plaques in a rabbit model. J Ethnopharmacol. 2009; 124:103-110.
59. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71:209-249.
60. Lu C, Wu S, Ke L, Liu F, Shang W, Deng X, Huang Y, Zhang Q, Cui X, Mentis AA, Xie Y, Wang Z. Kanglaite (coix seed extract) as adjunctive therapy in cancer: Evidence mapping overview based on systematic reviews with meta-analyses. Front Pharmacol. 2022; 13:901875.
61. Lu T, Yu J, Gao R, Wang J, Wang H, Wang X, Xu B, Cao L, Wu J, Ni B, Li S, Li J. Chinese patent medicine Kanglaite injection for non-small-cell lung cancer: An overview of systematic reviews. J Ethnopharmacol. 2022; 115814.
62. Hailang H, Jiping Z, Ailing C, Xianmei Z. The effect of kanglaite injection in combination with gefitinib versus gefitinib alone in patients with nonsmall cell lung cancer: A meta-analysis. J Cancer Res Ther. 2020; 16:745-751.
63. Shi G, Zheng X, Zhang S, Wu X, Yu F, Wang Y, Xing F. Kanglaite inhibits EMT caused by TNF-α *via* NF-κB inhibition in colorectal cancer cells. Oncotarget. 2017; 9:6771-6779.
64. Yang C, Hou A, Yu C, Dai L, Wang W, Zhang K, Shao H, Ma J, Xu W. Kanglaite reverses multidrug resistance of HCC by inducing apoptosis and cell cycle arrest *via* PI3K/AKT pathway. Onco Targets Ther. 2018; 11:983-996.
65. Chen C, Ai QD, Wei YH. Kanglaite enhances the efficacy of cisplatin in suppression of hepatocellular carcinoma *via* inhibiting CKLF1 mediated NF-κB pathway and regulating transporter mediated drug efflux. J Ethnopharmacol. 2021; 264:113388.
66. Wang W, Zhang Z, Deng Y, Yang Z, Hou J, Long H, Lei M, Wu W. Anti-neuroinflammatory activity of Shenqi Fuzheng Injection and its main active constituents. Biosci Trends. 2021; 15:231-239.
67. Li J, Wang JC, Ma B, Gao W, Chen P, Sun R, Yang KH. Shenqi Fuzheng Injection for advanced gastric cancer: A systematic review of randomized controlled trials. Chin J Integr Med. 2015; 21:71-79.
68. Yang Y, Ting W, Xiao L, Shufei F, Wangxiao T, Xiaoying W, Xiumei G, Boli Z. Immunoregulation of Shenqi Fuzheng Injection combined with chemotherapy in cancer

patients: A systematic review and meta-analysis. Evid Based Complement Alternat Med. 2017; 2017:5121538.
69. Chen LJ, Zhang RG, Yu DD, Wu G, Dong XR. Shenqi Fuzheng Injection ameliorates radiation-induced brain injury. Curr Med Sci. 2019; 39:965-971.
70. Wu C, Liang Y, Fu F. Effect of Shenqi Fuzheng Injection on leukopenia and T-cell subsets in patients with non-small cell lung cancer undergoing radiotherapy. Evid Based Complement Alternat Med. 2022; 2022:2832739.
71. Wang JL, Chen CS, Jia ZR, Miao LY, Xie J, Pan ZZ, Duan YL, Liu S, Hou MJ, Ding XS. Efficacy and safety of EGFR-TKIs plus Shenqi Fuzheng injection for non-small cell lung cancer patients with EGFR-sensitive mutations. J Cancer Res Clin Oncol. 2022 Aug 26. doi: 10.1007/s00432-022-04297-3. Epub ahead of print.
72. Zhu G, Zhang B, Jiang F, Zhao L, Liu F. ShenQi FuZheng Injection ameliorates fatigue-like behavior in mouse models of cancer-related fatigue. Biomed Pharmacother. 2019; 111:1376-1382.
73. Xiong Y, Zhao Q, Gu L, Liu C, Wang C. Shenqi Fuzheng Injection reverses cisplatin resistance through mitofusin-2-mediated cell cycle arrest and apoptosis in A549/DDP cells. Evid Based Complement Alternat Med. 2018; 2018:8258246.
74. Zhang J, Tong F, Cai Q, Chen LJ, Dong JH, Wu G, Dong XR. Shenqi Fuzheng injection attenuates irradiation-induced brain injury in mice *via* inhibition of the NF-κB signaling pathway and microglial activation. Acta Pharmacol Sin. 2015; 36:1288-1299.
75. Afrin S, AlAshqar A, El Sabeh M, Miyashita-Ishiwata M, Reschke L, Brennan JT, Fader A, Borahay MA. Diet and nutrition in gynecological disorders: A focus on clinical studies. Nutrients. 2021; 13:1747.
76. Zhou J, Qu F. Treating gynaecological disorders with traditional Chinese medicine: A review. Afr J Tradit Complement Altern Med. 2009; 6(4):494-517.
77. Li BQ, Li XK, Lin Y, Li ZY, Zhang XZ, Feng N, Ma AJ, Chen CY, Tan LF. Development and validation of ultra-high performance supercritical fluid chromatography method for quantitative determination of six compounds in Guizhi Fuling capsule and tablet samples. J Sep Sci. 2021; 44:3199-3207.
78. Zhang LS, Yang FW, Zhang JH, Zheng WK, Zhang MY, Li Y, Zhao HJ. Guizhi Fuling capsule/pill treatment for chronic pelvic inflammatory disease: A systematic review of randomized clinical trials. Zhongguo Zhong Yao Za Zhi. 2017; 42:1500-1509. (in Chinese w/ English abstract)
79. Chen NN, Han M, Yang H, Yang GY, Wang YY, Wu XK, Liu JP. Chinese herbal medicine Guizhi Fuling Formula for treatment of uterine fibroids: A systematic review of randomised clinical trials. BMC Complement Altern Med. 2014; 14:2.
80. Meng W, Ta N, Wang F. Add-on effect of Guizhi Fuling formula to mifepristone for endometriosis: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019; 98:e16878.
81. Zhang M, Zhang T, Song C, Qu J, Gu Y, Liu S, Li H, Xiao W, Kong L, Sun Y, Lv W. Guizhi Fuling Capsule ameliorates endometrial hyperplasia through promoting p62-Keap1-NRF2-mediated ferroptosis. J Ethnopharmacol. 2021; 274:114064.
82. Zhu Y, Li Y, Liu M, Hu X, Zhu H. Guizhi Fuling Wan, Chinese herbal medicine, ameliorates insulin sensitivity in PCOS model rats with insulin resistance *via* remodeling intestinal homeostasis. Front Endocrinol (Lausanne). 2020; 11:575.
83. Liu M, Zhu H, Zhu Y, Hu X. Guizhi Fuling Wan reduces autophagy of granulosa cell in rats with polycystic ovary syndrome *via* restoring the PI3K/AKT/mTOR signaling pathway. J Ethnopharmacol. 2021; 270:113821.
84. Lang L, Meng Z, Sun L, Xiao W, Zhao L, Xiong Z. Intergrated metabonomic study of the effects of Guizhi Fuling capsule intervention on primary dysmenorrheal using RP-UPLC-MS complementary with HILIC-UPLC-MS technique. Biomed Chromatogr. 2018; 32(2).
85. Xiong Y, Li M, Sun P, Liang W, Hornbeck RG, Che X, Rao C, Zhao Y, Guo L, Huang Y, Yang H, Li P, Kroes BH, Cui X, Franz G, Wang M. Market access for Chinese herbal medicinal products in Europe-A ten-year review of relevant products, policies, and challenges. Phytomedicine. 2022; 103:154237.

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**Address correspondence to:*
Fanghua Qi, Traditional Chinese Medicine, Shandong Provincial Hospital affiliated to Shandong First Medical University, No.324 Jingwuweiqi Road, Ji'nan, Shandong, China.
E-mail: qifanghua2006@126.com

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