Review Article

Application and Pharmacological Properties of Chinese Herb Danggui: A System Review

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Abstract

History of the usage of Angelica sinensis (Danggui in Chinese) is glorious, it often acts as monarch drug compatible in various classical formulations. Angelica sinensis can be widely used in treatment of gynecologic diseases and all kinds of blood-deficiency fever by tonifying blood and repairing vitality. It contains abundant volatile oil, organic acid and Angelica sinensis polysaccharide, coumarin, trace elements and amino acids, which possess extensive pharmacological activities include resistant to cancer and tumour, regulation of blood system, hepatoprotective effects, anti-inflammatory action, antioxidant activity, protection of nervous system, as well as cardiotropic effects. Based on numerous reports and the published scientific literature recent years, an extensive review of research on chemical components, pharmacological activities and the compatibility application of Angelica sinensis were conducted. The relationship between active ingredients and the corresponding pharmacological effects, as well as commonly used couplet medicines and the utility in clinic were simultaneously summarized.

Introduction

Angelica sinensis (Oliv.) Diels (AS) is one of the perennial herbs of Chinese medicine, which derived from the root of Angelica sinensis belonging to Umbelliferae. It was first recorded in Sheng Nong's herbal classic (200-300 AD) [1]. Living cool and humid environment, it is a special variety of high-altitude seedling raising and low-altitude transplanting. Angelica sinensis slices shows cylindrical shape slightly, flexible, epidermis with yellowish brown and oily embellish, yellow-white cross-section and strong odor are preferred, as showed in (Figure 1) [2, 3]. Angelica sinensis has been commonly used by the ancient physicians for more than two thousand years. It has the effect of tonifying and invigorating blood system, regulating menstruation and alleviating pain, relaxing bowels and relieving constipation, with remarkable curative effect. As a kind of the most frequently used drugs in prescriptions, Angelica sinensis has been widely used to treat many diseases, including all kinds of symptoms associated with blood deficiency, blood stasis, dizziness, palpitation, irregular menstruation, asthenia cold abdominalgia, bruises, carbuncle sore, rheumatic arthralgia, intestinal dryness with constipation, etc. For thousands of years in China and other Asian countries, Angelica sinensis has been used as a representative herbal medicine for traditional treatment of anemia, gynecological disorder and cardiovascular diseases. Many domestic and overseas scholars have carried out the research on the chemical components and pharmacology of Angelica sinensis, by means of literature research, and the techniques of phytochemistry, molecular biology, biochemistry, pharmacology, which made considerable progress and provide a basis for the application of Angelica sinensis. From the perspective of traditional Chinese medicine theory, Angelica sinensis can soothe the five viscera of body, strengthen the
physique, regulate emotions, and effective for both asthenic disease and Stasis diseases. In terms of chemistry and modern pharmacological research to understand, *Angelica sinensis* contains volatile oil, polysaccharides, organic acids, coumarin, trace elements, amino acids, flavonoids, vitamins etc. It has many pharmacological effects, such as anti-tumor, anti-oxidation, regulating immunity, anti-inflammation and so on. In this paper, the chemical constituents and pharmacological effects of *Angelica sinensis* in recent years were concluded, which is of great significance to reveal its mechanism in a more comprehensive way.

**Chemical Composition**

**I Volatile Oil**

*Angelica sinensis* contains a variety of volatile oil compounds (Figure 2), which is a kind of the most important active ingredients, with functions of relaxing smooth muscle, anti-platelet aggregation, improve cerebral ischemia, neuroprotection, improve immune function, analgesic anti-inflammatory and so on [4-10]. According to the property, the volatile oil of Angelica can be divided into neutral, phenolic and acidic. And the content of neutral oil is the highest, include principally E-ligustilide and Z-ligustilide, (3Z, 3'Z)-6, 8', 7, 3'-diligustilide, senkyunolide G, senkyunolide H, senk-unolide I, senkyunolide J, E-butylidene phthalalide (2), 3 and Z-butylidene phthalalide, bergapten, a-angelicalactone, conifery furulate, 3-N-butyl-pthalalide, triligustilides A, triligustilides B, levistolide A, angesinenolides A and B [6, 9]. Phenolic volatile oil contains 4-Methylbenzyl alcohol, guaiacol, Vanillin, 4-methyl-phenol, 2,4-Dihydroxyacetophenone, 4-(2-hydroxy-1-methoxyethyl)phenol, o-Hydroxyvalerphenone, Isoeugenol, 4-hydroxy-2-methylacetophenone eugenol, m-cresol. The components of acid oil are such as dimethyl phthalate, dimethyl azelate, dimethyl sebacate, glutaric acid hexaethylene pent-4-en-1-yl esterbutyldienedihydro-phthalalide, butyldiene phthalalide [9-15].

**II Organic Acids**

There are abundant and diverse organic acids in *Angelica sinensis*. As the most representative organic acid, ferulic acid is often used as one of key indicator to evaluate the quality of *Angelica sinensis* [16]. It has many functions such as antioxidant, anti-inflammatory, anti-coagulation, hepatic protection, dilatation of micro vessels, lowering cholesterol and improving immunity [17-20]. Chlorogenic acid, caffeic acid, vanilla acid, 3-O-feruloylquinic acid, phthalic acid, succinic acid, niacin, cetane carboxylic acid, anisic acid, azelaic acid, palmitic acid, linoleic acid, stearic acid, p-hydroxybenzoic acid, protocatechuic acid and other acidic components [21-24].
Angelica sinensis Polysaccharide

Angelica sinensis contains plentiful of polysaccharides, which are the main components of water-soluble extracts of Angelica sinensis. Angelica sinensis polysaccharides (ASP) have lots of physiological activities, not only have obvious effects on the body's blood system, but also have function of hematopoiesis, regulating immunity and material metabolism, anti-tumor, anti-oxidation, anti-radiation and other effects [25-30]. Therefore, more and more attention has been paid to the study of ASP. ASP is a β-D-pyranoid polysaccharide, which the average molecular weight is 72,900 Da, heteropolysaccharide is the main form of existence [31]. The configurations of sugars in ASP consists of α-glycosidic and β-glycosidic bonds, and the main monosaccharide components of ASP include glucose (Glc), arabinose (Ara), galactose (Gal), mannose (Man), rhamnose (Rha), xylose, fucose, galacturonic acid, glucuronic acid, etc. [32-35].

IV Coumarin

Angelica sinensis contains four kinds of coumarins, including simple coumarins, furanocoumarins, pyran coumarins and dicoumarins, which plays vital beneficial roles in anti-oxidation, anti-inflammatory, anti-platelet aggregation, osteoporosis, analgesic, reactive oxygen species, neuroprotection, ischemia, anti-arrhythmic, anti-tumor and cytotoxicity [36-39]. 14 coumarin components were identified by HPLC-Q-TOF-MS/MS, respectively, 8-Oxymethyl isoimperatorin, phellopterin, pabulenol, osthenol, alloisoimperatorin, xanthotoxol, xanthotoxin, isopimpinellin, marmesin, bergapten, oxypeucedanin, imperatorin, isodon, and psoralen [40].

V Trace Elements and Amino Acids

Trace elements in TCM act as a role of enhancing the efficacy of medicinal, they are involved in various biochemical reactions in the body with highly biological activity, which is crucial to maintain normal metabolism [1]. According to the result of determination by ICP-OES with Microwave Digestion, suggest that the contents were K, P, Ca, Mg, Fe, Al, Na, Zn, Cu, Mn, Sr, B, Ba, Cr, Ni, Pb, Cd, as in descending order [41]. Besides, Si, Mo, Sn, Re, Sc, Ti and V also be found in Angelica sinensis [42, 43]. Angelica sinensis is rich in various amino acids, especially the arginine, which possess multiple biological properties, as anti-inflammation, anti-fatigue, anti-cancer, platelet protection, myocardial protection, etc. [44-46]. Many components have been reported, such as tryptophan, aspartic acid, threonine, serine, glutamic acid, glycine, alanine, proline, methionine, isoleucine, dermatine, glutamic acid, phenylalanine, histidine, valine, lysine, β-amino butyric acid, leucine [32, 45, 47]. And uracil, adenine, Vitamin B12, Vitamin E, β-sitosterol, folinic acid also be found in Angelica sinensis [44, 48].

Figure 3: Chemical constituents of Angelica sinensis and the corresponding pharmacological effects.

Pharmacologic Effects

I Anti-Carcinogenic and Anti-Neoplastic Activity

The incidence and mortality of cancer are still increasing by years, which is the main cause of death nowadays. As a natural ethical medicine resources with potential anti-cancer activity, TCM has been widely studied and applied for its low side effects [49]. Among them, the anti-carcinogenic and anti-tumorigenic research of Angelica sinensis is also fairly extensive. Phthalides-enriched Angelica sinensis extract is able to inhibit metastasis and growth of bladder carcinoma, by antagonizing HIF-1α/ WSB-1/pVHL/VEGF signaling [50]. N-butylideneephallide
(BP), an active ingredient of phthalides in *Angelica sinensis*, has been exhibited cancer-resistant properties in various cancers. BP can suppress the growth of gastric cancer cells, via induction of the REDD1 expression to lead inhibition in mTOR signal pathway [51]. BP can inhibit the migration of cancer cells, and induce the cancer cells apoptosis, such as bladder cancer cells and breast cancer cells, by activating PARP, caspase-9 and caspase-3, respectively [52, 53]. In addition, it can regulate the ER stress and mitochondria-intrinsic pathway, causing prostate cancer cells apoptosis [54]. Moreover, research indicated that Z-ligustilide may function as a kind of adjuvant chemotherapy for resist chemoresistance, though interrupting the autophagosome-lysosome fusion [55]. *Angelica sinensis* polysaccharide (ASP) can reduce the expression of hepcidin, thus suppressing tumor growth in liver [56]. APS effectively stimulating the apoptosis of glioma cells and prohibiting their growth, by promoting E-cadherin in expression and suppressed the TGF (transforming growth factor-β) signaling pathway [57].

**II Effects on Hematological System**

*Angelica sinensis* is widely recognized for treatment against various of blood diseases, anemia is the most typical one. Alcohol extract of *Angelica sinensis* (contains Z-ligustilide, n-butylidenephthalide and ferulic acid) caused the level of red blood cells increase remarkably, as well as hemoglobin concentrations in anaemia model [58, 59]. Furthermore, ASP has an enforced effect on hematological parameters, such as increased the level of Hb and RBCs, and it’s also involved in elevating ferroprotein expression and serum EPO, meanwhile inhibiting NF-κB p65 activation and inflammatory hepcidin [60-62].

ASP can enhance the JAK2/STAT5 signaling pathway mediated by EPO and sensitized K562 cells to EPO dramatically, moreover, it can decrease the level of interferon-γ, interleukin-2 and plasma tumor necrosis factor [63, 64]. ASP showed obvious effects in hampering the growth of K562 cell and arrested the cells in G0/G1 phase, and up-regulated the P16-Rb signaling pathways, thereby accelerating leukemia cell senescence [63, 65, 66]. These results propose that *Angelica sinensis* might be a potential agent for anti-leukemia.

**III Hepatoprotective Effects**

Hepatic Stellate Cells (HSCs), as the main cell group in the synthesis of extracellular matrix in the liver, the treatment of HSC is the core link to prevent the fibrosis process of liver diseases [67]. Studies have shown that Levisistilide A can inhibit HSCs proliferation and angiogenesis in CCl4-induced fibrotic rats. The mechanism of Levisistilide A against liver fibrosis is related to reducing the expression of VEGF-R2, VEGF and CD31 [68]. ASP also be used as a potential hepatoprotective agent for relieve liver the injury. ASP significantly alleviated liver damage by increasing the level of GSH and curbing hepatic apoptosis [69]. Furthermore, ASP attenuated the hepatic apoptosis though Caspase-8 and JNK-mediated pathway and suppressed the activation of NF-κB and IL-6/STAT3 signaling pathways in concanavalin A-induced liver damage [70]. Volatile oils of *Angelica sinensis* also exhibits liver protection effects by its anti-inflammatory properties [71].

**IV Anti-Inflammatory Effects**

Volatile oils of *Angelica sinensis* (VOAS) has good effects on inflammatory, by inhibiting the production of the pro-inflammatory cytokines (IL-6, IL-1b and TNF-a), the inflammatory mediators (5-HT, NO and PGE 2), the inflammation-related enzymes (COX-2) (Figure 3), at the meanwhile promoting the generation of the anti-inflammatory cytokines IL-10, in acute inflammation rat model [71, 72]. Ligustilide can relieve vascular inflammatory and activate the endothelial cell defense system, by suppression of ROS/NF-κB activation in HUVECs [73]. This shows that VOAS can markedly affect the NF-κB/IL-6/STAT3 inflammatory axis, which is highly correlated in a variety of inflammation-related disease [74].

*Angelica sinensis* aqueous extract can inhibit the secretion of NO and repress lipopolysaccharide-induced inflammation, via JAK-STAT pathway associated with NO- bursting/calcium [75]. ASP exerted a notably anti-Inflammation and anti-apoptotic effects, by activating PI3K/AKT pathway and down-regulating expression of COX-1 in PC12 Cells [76]. And ferulic acid also has the same activity. The mechanism involved NF-κB mediated inflammatory pathways, mitochondria apoptosis as well as autophagy induction [77].

**V Antioxidant and Antiaging Effects**

Studies indicated that ferulic acid and ASP have certain antioxidant activities, which increased with the increasing concentration of the ASP solution [78, 79, 80]. ASP acts as a protective role against H2O2-induced damage in H9c2 cells via activating the ATP6 (transcription factor 6) pathway, to ameliorating oxidative stress [81]. Furthermore, a kind of exopolysaccharide isolated from *Angelica sinensis*, exerted strong antioxidant activity [82]. ASP had an extraordinary antiaging effect, via prevented oxidative damage and reduced the levels of ROS, 8-OhDG, and 4-HNE, as well as lowered the expression of γ-H2A. X and inhibited the signaling pathway of P19 Arf-Mdm2-p53-p21 Cip1/Waf1 to preventing DNA damage [83].

**VI Other Effects**

The essential oil of *Angelica sinensis* has been proven to possess obvious neuroprotective effects, such as ligustilide, Z-butylidene phthalide and tokinolide A and so on [84]. Ligustilide exhibited notably neuroprotective effects on rats of chronic cerebral hypoperfusion, which may be ascribed to its anti-apoptosis of neuron and anti-proliferation of astrocyte [85]. Researches still demonstrated that combination treatment with sodium ferulate and n-butylidene phthalide, enhances expression of astrocyte-derived VEGF and BDNF though raising protein kinase B/mammalian target of rapamycin (AKT/mTOR) expression in an oxygen-and glucose-deprived (OGD) circumstances, and significantly ameliorated neurological damage after stroke [86].

The cardioprotective role of *Angelica sinensis* has been explored in previous research, ASP against the ischemic injury by activating ATf6 and AMPK-PGC1α pathway to ameliorate the detrimental ER stress [87]. The PI3K/AKT and JAK1/STAT3 pathways were activated by ASP pretreatment via miR-22 in hypoxia-treated cells, by reducing the expression ofmiR-22 [88]. Ferulic acid is a phenolic compound with strong antioxidant activity, it has protective effect on myocardial toxicity
induced by doxorubicin in rats by adjusting the expression of ANP and BNP [78].

Analytical Methods

Single herb of TCM contains abundant chemical constituents and various active ingredients, which are also the basis condition to let it reduce the pharmaceutical action. However, TCM has the characteristics of integrity, multi-target and synergy. It is impossible to scientifically interpret the complex system of TCM by evaluating the quality/efficacy of medicinal materials only from the level of single chemical composition. So how to integrate effective ingredients with pharmacological action and the target is a key issue.

New progress has been achieved in evaluation of overall pharmacodynamic material basis of TCM, with the development of network pharmacology and metabolomics (include chinmedomics) [89]. And the related technology platform mainly includes by nuclear magnetic resonance (NMR), gas-mass spectrometry (GC-MS) and liquid-mass spectrometry (LC-MS). At the same time combined with multivariate statistical methods, they are more in line with the integral characteristics of TCM [90]. Chan et al. had measured glucose, fructose, threonine and ferulic acid by 1H-NMR metabolic profiling and got qualitative information of Angelica sinensis [91]. Volatile oil is important index assessing the quality of Angelica sinensis, Zhong et al. associated the anti-inflammatory mechanism with essential oils via GC-MS-based metabolomics [92]. Wu et al. applied LC-ESI-MS to analyze the differential composition and quality of different medicinal parts of Angelica sinensis, to explain the therapeutic effects of different parts of it [93].

Network pharmacology is based on the theory of system biology, which emphasizes the multi-channel regulation of signal pathway and selects specific signal nodes for multi-target drug molecular design [94]. Sun Hui et al. utilized method network pharmacology combined with chinmedomics demonstrated the mechanism of mirablibe in inhibiting colorectal cancer, which mainly involved in regulating bile acid metabolism [95]. Niu et al. constructed the constituent-disease network and screen the major targets of Angelica sinensis for the treatment of acute myocardial by methodology of network pharmacology [87].

Chinmedomics integrates the theory and technology of system biology and serum pharmacochmistry of TCM, forms the biomarkers for identifying syndromes, establishes the evaluation system of prescription effectiveness, and discovers the applied science of pharmacodynamic substance basis [96]. Han et al used the approach of chinmedomics to investigate 13 potential biomarkers associated with multiple metabolic pathways and illuminated effectiveness of Acanthopanax senticosus Harms against acute promyelocytic leukemia [97].

Clinical Application

As a relatively fixed minimum prescription unit in TCM compound prescription, the couplet medicines are the basic form of TCM compatibility application. It can not only improve curative effect, but also reduce toxicity and side effects, which is of special significance in clinical practice. Yang et al. investigated the prescription regularity of formulas contained Angelica sinensis, and analyzed the main indications, syndrome distribution and common pharmaceutical compositions of Angelica-containing prescriptions, based on the Traditional Chinese Medicine Inheritance Assistant Platform [98]. The results showed that the main symptoms of Angelica sinensis were stagnation of Qi and blood and deficiency of Qi and blood. Angelica sinensis is often used in combination with drugs of invigorating qi and replenish blood, especially the compatible with Radix Paeoniae Alba, Astragalus membranaceus, Rhizoma Chuanxiong are used in high frequency, it can achieve different therapeutic purposes in combination with different drugs, so it is widely used in clinical practice [99].

I Compatibility of Angelica and Paeonia

Angelica Paeoniae Powder (APP) is kind of blood regulating agent, originated from Synopsis of the Golden Chamber, has the functions of nourishing blood and regulating liver. It is mainly used in gynecology and analgesia, such as pregnancy-associated diseases and woman abdominal pain [100, 101]. Shi take44 cases of dysmenorrhea and 44 cases of pelvic inflammation as the observation group, the symptom score after treatment and PGF2α/PGF2 were used as indicators. Results indicate that the clinical effect of APP in treating dysmenorrhea and pelvic inflammation is remarkable [102]. Wang et al. investigated the molecular mechanisms of APP based on Biological Network, pointed out that APP mainly affects the release of corticotropin-releasing hormone in the central nervous system and influence peripheral IL and PGF2α to improve dysmenorrhea symptoms [103].

II Compatibility of Angelica Sinensis and Astragalus Membranaceus

Angelica and Astragalus are common couplet medicines for supplementing both qi and blood in traditional Chinese medicine. Cell culture experiments proved that the active ingredients of Angelica sinensis could enhance the membrane permeability of formononetin and isoflavone in Astragalus membranaceus [104]. Danggui Buxue Decoction (DBD) is a typical representative prescription, which mainly used for relevant symptoms caused by blood deficiency and gynecological disease [105]. In the enrichment analysis of KEGG pathways for the selected targets based on Network Pharmacology, the pathways for the treatment of anemia by angelica buxue decoction were selected, Li et al screened out the main pathways of DBD in the treatment of anemia, including cell cycle, P53 signaling pathway, thyroid hormone signaling pathway, FoxO signaling pathway, HIF-1 signaling pathway, PI3K-Akt signaling pathway, JAK-STAT signaling pathway. DBD used for alleviating menopausal symptoms, the mechanism may be related to regulating the immune system, accelerating osteoblast proliferation and differentiation, and activating the NF-kB signaling [106, 107].

III Compatibility of Angelica Sinensis and Ligusticum Chuanxiong
Angelica sinensis and Ligusticum Chuanxiong are both good at nourishing and invigorating blood, the two drugs combined is often used to promote blood circulation and remove blood stasis. Study based on systematic pharmacology show that Ligusticum chuanxiong can treat cardiovascular diseases mainly by regulating four signal transduction pathways, namely calcium signaling pathway, PI3K-Akt signaling pathway, cGMP-PKG signaling pathway and vascular endothelial growth factor signaling pathway [108]. Li et al. set up a database to summarize 792 prescriptions regarding Danggui-Chuanxiong herb pair, found that brain diseases coincided with characteristic and action of the two drugs [109]. Encephalopathy is closely related to the abnormalities of hemodynamics and hemorheology, they can improve the hemorheology and coagulation function parameters of the organism in the state of blood stasis. Angelica sinensis still plays a major role in nourishing and activating blood in the prescription.

Conclusion

As a traditional medicinal plant with a long history, Angelica sinensis is rich in volatile oils, organic acids, polysaccharides, coumarin, various amino acids and trace elements. The chemical constituents of Angelica sinensis polysaccharide have been studied comprehensively, but the corresponding pharmacological effects of the chemical constituents have not been researched sufficiently. Studies of volatile oil and Angelica sinensis polysaccharide are extensively and adequately, anti-cancer and anti-inflammatory effects are mainly exerted by volatile oil, Angelica sinensis polysaccharide has the function of antioxidant, liver protection, regulation and improvement of blood system, etc. The other components of Angelica sinensis, by contrast, have been less studied, especially the coumarins in Angelica sinensis, and the target and mechanism of action are not clear enough. In addition, most studies on organic acids of Angelica sinensis are mainly concentrated on ferulic acid, while the pharmacological and pharmacodynamic effects of other organic acids remain to be further studied.

Because of the complexity and diversity of the components of TCM, as well as the multi-target, multi-channel and multi-effect of pharmacological action, it is difficult to directly relate the active ingredients to clinical efficacy, which is the key problem hindering the research of pharmacodynamic substances basic of TCM. The development of network pharmacology and metabolomics has provided a strong support to solve this problem, but it still faces challenges. The database resources are limited, and the existing technology is still difficult to fully analyze all metabolites and the pathways of action. Therefore, the related technologies need to be developed and matured constantly, and how to accurately correlate the complex active ingredients in TCM with the target is still worthy of further study.

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Conflicts of Interest

None.

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