

# Chemical Constituents and Pharmacological Effects of Angelica Sinensis

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**ABSTRACT.** *Angelica Sinensis (AS) as a Traditional Herbal Medicine has been widely used in clinical for thousands of years and is proved to be the most effective Chinese medicine. As a natural herb, AS has various pharmacological effects in relation to its chemical constituents. To provide a basis for further study of AS, this article summarize the research on Angelica sinensis in recent two years, including its chemical constituents, pharmacological effects and mechanisms of action. In addition, its comprehensive and specific therapeutic aspects, toxicity, and adverse effects warrant further investigation in the future.*

**KEYWORDS:** *Angelica Sinensis; Pharmacological Effects*

## 1. Introduction

Angelica Sinensis (Chinese Angelica root; danggui) has been widely used in China, Korea and Japan as a spice, tonic and medicine for thousands of years and is still one of the most useful Traditional Herbal Medicine in China, as well as Europe.(1, 2)

With the development of science and technology, the pollution of the environment, and the intensification of competition, there is increasing pressure and worry. This leads to an increasing level of sickness, particularly manifesting as immune decline, premature aging, cancer onset, and other sub-health phenomena. So people have regarded health and longevity as a goal, to maintain health and slow down the function of aging. As a result of its various pharmacological effects AS is welcomed by the general consumer(3), such as anti-cancer(4-6), antidepressant(7), anti-oxidant (8), anti-obesity (9) and anti-inflammatory activities(10-12), in addition to effects on the immune system (13, 14). especially aimed at the treatment of women's reproductive problems, as an aid to recovery from blood loss after giving birth to child or surgery.(15, 16)

## 2. Polysaccharides

According to a study, *Angelica sinensis* polysaccharide (ASP) prepared by hot water extraction is a heteropolysaccharide, has a molecular mass of 82,000 Da and consists of arabinose, galactose and glucose (molar ratio of 6:1:1). (17)

A study showed that APS-1II, a new water-soluble polysaccharide, isolated from the roots of *Angelica sinensis*, has a molecular weight of 42.1 kDa, APS-1II consists of arabinose (Ara), glucose (Glc) and fucose (Fuc) with a molar ratio of 2.48:1.05:1.00. The backbone of APS-1II is composed of 1,3- $\alpha$ -1-Araf and 1,6- $\alpha$ -d-Glcp with the branches containing 1,5- $\alpha$ -1-Araf, 1,4- $\beta$ -d-Glcp, T- $\beta$ -d-Glcp, 1,3- $\alpha$ -1-Fucp and T- $\alpha$ -1-Fucp. (18)

five CAPSs displayed different activities which were associated with their different structural characteristics and CAPS70, with the molecular weights of 20.82kDa and consisting of mannose and glucose in the molar ratio of 1.20:1.01, possessed the strongest immuno-enhancement activity. (19)

### 2.1 The treatment of acute myocardial infarction (AMI)

About the mechanisms of *Angelica sinensis* for the treatment of acute myocardial infarction (AMI), a study used network pharmacology analysis and found that the cardioprotective effects of AS polysaccharide (ASP), a major component of AS, were validated both in H9c2 cells subjected to simulated ischemia by oxygen and glucose deprivation and in rats with AMI by ligation of the left anterior coronary artery. (20) Furthermore, ASP pretreatment could activate the PI3K/AKT and JAK1/STAT3 pathways via miR-22 in hypoxia-treated cells. (21)

### 2.2 The treatment of renal anemia

A present study found that ASP could enhance hypoxic induction of EPO in Hep3B cells, with a mechanism that involved the stabilization of HIF-2 $\alpha$  protein. In parallel, ASP rescued the inhibition of EPO, induced by proinflammatory factor TNF- $\alpha$  through blocking GATA2 and NF- $\kappa$ B activation. Furthermore, they found that ASP suppressed hepatic hepcidin expression, mobilized iron from spleen and liver and increased serum iron. These findings demonstrate that ASP elicits anti-anemic action by restoring EPO production and improving iron availability in the setting of CKD in rats. (13)

According to a study, ASP inhibited inflammatory hepcidin in both HepG2 cells and ACD rats by blocking the IL-6/STAT3 and BMP/SMAD pathways. In ACD rats, the administration of ASP increased ferroportin expression, mobilized iron from the liver and spleen, increased serum iron levels, caused an elevation of serum EPO, and effectively relieved the anemia. Furthermore, ASP inhibited NF- $\kappa$ B p65 activation via the I $\kappa$ B kinases- (IKKs-) I $\kappa$ B $\alpha$  pathway, thereby reducing the secretion of

interleukin-6 (IL-6) and TNF- $\alpha$ , which is known to inhibit erythropoiesis. These findings indicate that ASP is a potential treatment option for patients suffering from ACD(22)

### **2.3 Antioxidant**

A study suggest that oxidative stress is an important pathogenesis of OA, and ASP inhibits H<sub>2</sub>O<sub>2</sub>-mediated injury in human chondrocytes. Their data also suggest that PPAR $\gamma$  participates in oxidation and anti-oxidation of OA.(23)

According to a study, the ingredient-pathway-disease network showed that *A. sinensis* exerted protective effects against oxidative injury through its various active ingredients on regulation of multiple pathways. Their findings indicate that ASP, a major water-soluble component of AS, exerts protective effects against H<sub>2</sub>O<sub>2</sub>-induced injury in H9c2 cells by activating the ATF6 pathway, thus ameliorating ER and oxidative stress.(24)

In a study, polysaccharides from *Angelica sinensis* were extracted using the ultrasound-assisted extraction method. And the study showed that polysaccharides had certain antioxidant activities and that hydroxyl radicals have a remarkable scavenging capability.(8)

A study showed that it is noteworthy that ASP ameliorated SIPS of hematopoietic cells by the mechanism of protecting bone marrow stromal cells from chemotherapeutic injury via mitigating oxidative damage of stromal cells and improving their hematopoietic function.(25)

### **2.4 Immunological enhancement**

A study showed that ASP-PLGA could significantly promote the lymphocytes proliferation and increase the ratio of CD4<sup>+</sup> to CD8<sup>+</sup> T cells compared with ASP and blank PLGA. It provided strong evidence that the immunological enhancement of ASP was significantly improved through establishing a drug delivery system with PLGA.(13)

In addition, the effects of ASP on the nonspecific immunity of white shrimps (*Litopenaeus vannamei*) were investigated by feeding them with ASP-containing diets (0.5, 1 and 1.5 g/kg) during a 12-week breeding experiment. ASP exhibits immunostimulatory effects on Pacific white shrimps (*L. vannamei*) and may thus be used as a diet supplement for them. (17)

According to a study, APS-III, a new kind of AP, also increased the numbers of leukocytes and lymphocytes in peripheral blood, and significantly decreased plasma tumor necrosis factor, interleukin-2 and interferon- $\gamma$  levels in L1210-bearing mice. Moreover, APS-III administration concentration-dependently promoted the proliferation of the splenocytes, enhanced phagocytic activity of peritoneal macrophages and cytotoxicity of natural killer cells. These results suggest that

APS-III could effectively inhibit leukemia and induce a protective immune response, and it may be used as a suitable candidate reagent for leukemia therapy.(18)

### **2.5 Antiaging effects**

ASP treatment prevents HSC/HPCs senescence with decreased AGEs levels in the serum, reduced SA- $\beta$ -Gal positive cells, and promoted CFU-Mix formation in the D-gal administrated mouse. A study further found that multiple mechanisms were involved: (1) ASP treatment prevented oxidative damage as total antioxidant capacity was increased and levels of reactive oxygen species (ROS), 8-OHdG, and 4-HNE were declined, (2) ASP reduced the expression of  $\gamma$ -H2A.X which is a DNA double strand breaks (DSBs) marker and decreased the subsequent ectopic expressions of effectors in p16<sup>Ink4a</sup>-RB and p19<sup>Arf</sup>-p21<sup>Cip1/Waf</sup> senescent pathways, and (3) ASP inhibited the excessive activation of Wnt/ $\beta$ -catenin signaling in aged HSC/HPCs, as the expressions of  $\beta$ -catenin, phospho-GSK-3 $\beta$ , and TCF-4 were decreased, and the cyto-nuclear translocation of  $\beta$ -catenin was inhibited. Moreover, compared with the positive control of Vitamin E, ASP exhibited a better antiaging effect and a weaker antioxidation ability, suggesting a novel protective role of ASP in the hematopoietic system.(26) A study demonstrate that A. sinensis peptides (AsiPeps) are able to delay aging process in C. elegans through antioxidant activities independent of dietary restriction.(27, 28)

### **2.6 Protect liver**

Iron plays a fundamental role in cell biology and its concentration must be precisely regulated. It is well documented that excess iron burden contributes to the occurrence and progression of cancer. Hepcidin secreted by liver plays an essential role in orchestrating iron metabolism. In the present study, they aimed to investigate the ability of angelica sinensis polysaccharide (ASP) to decrease iron burden in tumor-bearing mice and the mechanism of ASP regulation hepcidin expression(29)

According to a finding reveal that ASP has potential to be used as a hepatoprotective agent for the management of APAP-induced liver injury.(30)

A study also showed a high aggregation of <sup>99m</sup>Tc-DTPA-ASP in liver. These results suggest that the distribution of ASP to the liver occurs via asialoglycoprotein receptor (ASGPR) mediated endocytosis and ASP could potentially be applied as a new carrier for delivering drugs to the liver.(31)ASP pretreatment could attenuate concanavalin A-induced liver injury through its anti-inflammatory and anti-oxidant actions in mice.(32)

### **2.7 Repress tumorigenesis**

This traditional Chinese medicine has been used for thousands of years for

treating gynecological diseases and used in functional foods for the prevention and treatment of various diseases, such as inflammation and cancer.(33) The antitumor activity of ASP is related to its biological activities, because it suppresses a variety of pro-proliferative or anti-apoptotic factors that are dramatically expressed in cancer cells of given types. In the study, they show that angelica sinensis polysaccharide induced apoptosis in breast cancer cells of T47D over-expressing the Cyclic AMP response element binding protein (CREB), inducing apoptosis-related signaling pathway activity. The result also found that ASP caused cell death was linked to caspase activity, accompanied by the loss of mitochondrial membrane potential, cytochrome c release, and Bax translocation from the cytosol to the mitochondria. We found that ASP significantly affected the poly-ADP-ribose polymerase (PARP), Bcl-2 Associated X Protein (Bax), Bcl-2, Bcl-xL and apoptotic protease activating factor-1 (Apaf1) protein expression in a dose- and time-dependent manner. Thus, these results suggest that ASP would be a promising therapeutic agent for breast cancer.(34)

Aimed at exploring the effects of AP on neuroblastoma SH-SY5Y cells as well as the underlying mechanisms, a study showed that AP was first identified to inhibit proliferation, migration, and invasion but induce apoptosis. Furthermore, AP might repress tumorigenesis of SH-SY5Y cells through miR-675-mediated inactivation of the PI3K/AKT and JAK/STAT pathways. Besides, KIF1B $\beta$  might be a target of miR-675.(35)

Myelosuppression is the most common complication of chemotherapy.(36)Decline of self-renewal capacity and stress-induced premature senescence (SIPS) of hematopoietic stem cells (HSCs) induced by chemotherapeutic agents may be the cause of long-term myelosuppression after chemotherapy.(37) Whether the mechanism of SIPS of hematopoietic cells relates to chemotherapeutic injury occurred in hematopoietic microenvironment (HM) is still not well elucidated.(37)This study explored the protective effect of Angelica sinensis polysaccharide (ASP), an acetone extract polysaccharide found as the major effective ingredients of a traditional Chinese medicinal herb named Chinese Angelica (Dong Quai),ASP ameliorated SIPS of hematopoietic cells by the mechanism of protecting bone marrow stromal cells from chemotherapeutic injury via mitigating oxidative damage of stromal cells and improving their hematopoietic function. This study provides a new strategy to alleviate the complication of conventional cancer therapy using chemotherapeutic agents.(25)

### **2.8 Others**

A study suggests that the distribution of ASP to the liver occurs via asialoglycoprotein receptor (ASGPR) mediated endocytosis and ASP could potentially be applied as a new carrier for delivering drugs to the liver.(31)

To investigate the absorption and delivery of ASP in gastrointestinal (GI) tract,

A study found that ASP could be absorbed after oral administration through endocytosis process mainly mediated by macropinocytosis pathway and clathrin- and caveolae (or lipid raft)-related routes, then be absorbed and circulated into blood. This study presents a comprehensive understanding of oral delivery of cASP, which will provide theoretical basis for the clinical application of ASP.(38) ASP had beneficial effects in preventing hyperglycemia, stimulating insulin secretion, promoting hepatic glycogen synthesis, regulating adipokine release, reducing liver fat accumulation, and attenuating liver injury. Moreover, mechanistic studies illustrated that ASP could upregulate the expression of PPAR $\gamma$  and liver insulin signaling proteins, including IRS-2, PI3K, Akt, p-Akt and GLUT2, increase anti-apoptotic protein Bcl-2, decrease pro-apoptotic protein Bax expressions, and protect the mice against hepatic damage. These findings revealed the potential mechanisms of ASP-mediated therapeutic effects in diabetic mice. It suggested that ASP might be used in prescriptions or functional foods for the prevention or treatment of diabetes and liver diseases.(39)

A result revealed that ASP efficiently exerted hypoglycemic and hypolipidemic benefits, and its potential effect was associated with the amelioration of IR. ASP can be applied in the prevention and treatment of diabetes.(40)



## 2. Volatile oil

According to a study, disorders of glycine, AA, L-glutamate, pyruvate, succinate metabolism might play an important part in the predisposition and development of LPS-induced inflammation. By applying gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography-time-of-flight mass spectrometry (LC-Q/TOF-MS) based on a metabolomics platform coupled with a network approach, the mechanisms of diseases are clearly elucidated.(41) In addition, the certain protective effects of *Angelica sinensis* volatile oil are determined on atherosclerosis in hyperlipidemia mice. With its essential oil and ethanolic extract having median complete protection times of 7.0 h (6.0-7.5) and 2.5 h (2.0-2.5),

respectively. Due to its low yield (0.02 %), pungent smell, and little cause of irritation, *A. sinensis* essential oil did not qualify as a candidate for further repellent assessment. The success of *A. sinensis* products, particularly that of hexane extract, has proved their potential as bioactive candidates in the next step for developing and producing alternative natural repellents with commercial aspirations.(42)

### 3. Phthalide

A study tested all isolated compounds for activities on the inhibition of COX-2 enzyme in vitro. And found that Compounds 1-6 exhibited inhibitory activity against COX-2(43)

The hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) plays a critical role in tumor angiogenesis. It has been reported that the acetone extract of *Angelica sinensis* (AE-AS) rich in phthalides is able to inhibit cancer cell proliferation. However, whether AE-AS reduces cancer angiogenesis remains unknown. According to a study, they demonstrated that AE-AS significantly inhibited the angiogenesis in vitro and in vivo evidenced by attenuation of the tube formation in hypoxic human umbilical vascular endothelial cells (HUVECs), and the vasculature generation in Matrigel plug, the chicken chorioallantoic membrane, and tumors. Notably, AE-AS-induced HIF-1 $\alpha$  protein degradation may, at least partly, attribute to inhibition of WSB-1-dependent pVHL degradation. Moreover, VEGFR2-activated PI3K/AKT/mTOR signaling pathway in hypoxic T24 cells was greatly inhibited by AE-AS. Collectively, AE-AS may be a potential anticancer agent by attenuating cancer angiogenesis via suppression of WSB-1/pVHL/HIF-1 $\alpha$ /VEGF/VEGFR2 cascade.(44)

### 4. Phenolic acid

A study investigate the influences of AS and four representative phthalide derivatives from AS on the structure and function of hemoglobin (Hb). From the spectroscopy and oxygen equilibrium experiments, they show that AS and the chosen phthalides inhibited the oxygenated Hb from transforming into the high-affinity “relaxed” (R) state, decreasing Hb's oxygen affinity. It reveals that phthalides cooperate with the endogenous Hb modulator, 2,3-bisphosphoglycerate (2,3-BPG) to synergetically regulate Hb allostery. From the docking modeling, phthalides appear to interact with Hb mainly through its  $\alpha_1/\alpha_2$  interface, likely strengthening four (out of six) Hb “tense” (T) state stabilizing salt-bridges. A new allosteric-modulating mechanism is proposed to rationalize the capacity of phthalides to facilitate Hb oxygen transport, which may be inherently correlated with the therapeutic activities of AS. The potential of phthalides to serve as 2,3-BPG substitutes/supplements and their implications in the systemic biology and preventive medicine are discussed.(45)

A study aimed to investigate the colorectal cancer preventive effect of the combined administration of phenolic acids and supercritical extracts from *Angelica sinensis*. The results showed that the combined administration of phenolic acids and supercritical extracts from *A. sinensis* suppressed the tumor growth and cell proliferation, and DNA damages and inflammatory responses were reduced in a dose-dependent manner. These results indicate that the combined administration of phenolic acids and supercritical extracts from *A. sinensis* have a certain effect in preventing carcinogenesis.(5)

## 5. Others

The aim of the study is to evaluate the detailed molecular mechanism for anti-inflammatory effects of *Angelica sinensis* root water extract (ASW). The study suggest that ASW exerts an anti-inflammatory effect on LPS-induced RAW 264.7 via NO-bursting/calcium-mediated JAK-STAT pathway.(46)

A study indicated that RAS could ameliorate obesity induced by HFD and that the molecular mechanism might be associated with the expression of the *FTO* gene.(47)

According to a study, they showed that ASR extract administration in the initial stage of the AOM/DSS model had cancer preventive effects with decreasing tumor incidence and a high-grade of intraepithelial neoplasia incidence. The study suggested that the cancer-preventive effect of ASR extract may be stage-dependent in the process of carcinogenesis.(48)

Hair loss is accompanied by keratinocyte apoptosis-regression during catagen and prolonged telogen. *Angelica sinensis* was reported to promote hair growth in vitro. Based on previous studies, mice treated with *A. sinensis* showed notably decreased apoptotic cells, along with a significant change in the expression of cleaved caspase-3 and the ratio of a pair of apoptosis-associated proteins: Bcl-2 and Bax. Also, *A. sinensis* inhibited the nuclear translocation of NF- $\kappa$ B, the phosphorylation of I $\kappa$ B- $\alpha$ , the phosphorylation of three mitogen-activated protein MAP kinases, and the activation of c-Jun with decreased TNF- $\alpha$ . These findings reveal a role of *A. sinensis* as an alternative treatment for hair loss that acts through hair cycle pathways associated with apoptosis regression during catagen.(49)

study suggest that topical application of AS might have efficacy for modulating pruritus and inflammation in AD. Further studies are required to further characterize the mechanism of actions of AS.(50) A study suggested that AS could provide a potential drug for the treatment of AD.It effectively rescued the symptoms of Alzheimer's disease (AD) in a rat model by inhibiting inflammation, apoptosis, and NF- $\kappa$ B signaling pathway.(51)

AS is widely used in Chinese traditional medicine for its beneficial effects against several diseases, including osteoarthritis. A study showed that sodium ferulate exhibited marked anti-inflammatory and anti-apoptotic properties by inhibiting the TNF/TNFR signal transduction pathway. On the other hand, the

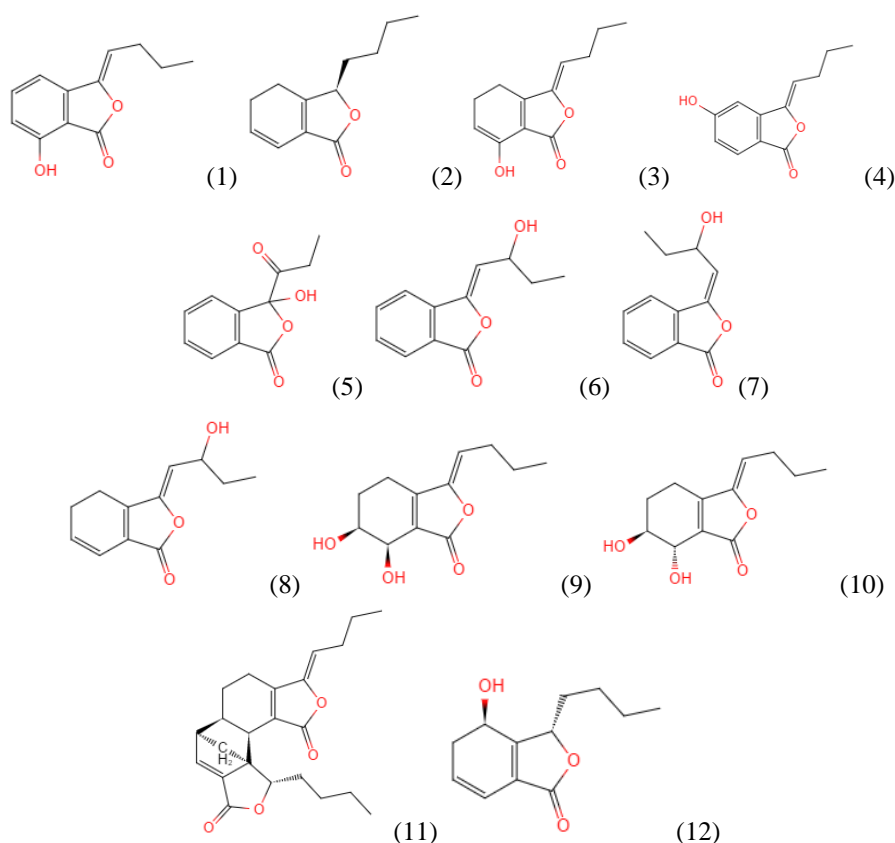


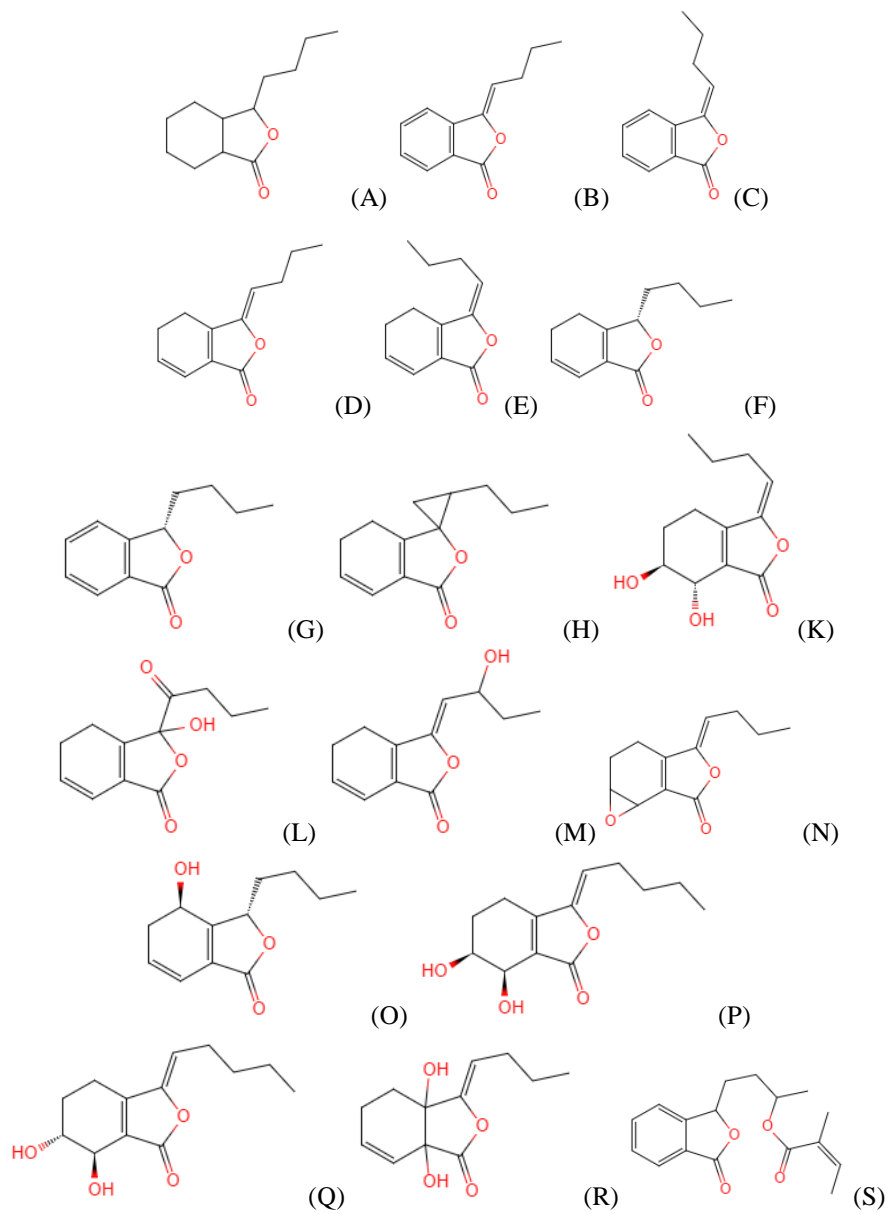
polysaccharidic fraction which contains a mixture of various carbohydrates was found to promote proteoglycan biosynthesis in cartilage matrix by stimulating the activity of the UDP-glycosyltransferases that synthesize the chondroitin sulfate chains of aggrecans. It is suggested that the combined action of sodium ferulate and polysaccharidic fraction would prevent cartilage destruction in osteoarthritis and favor cartilage repair.

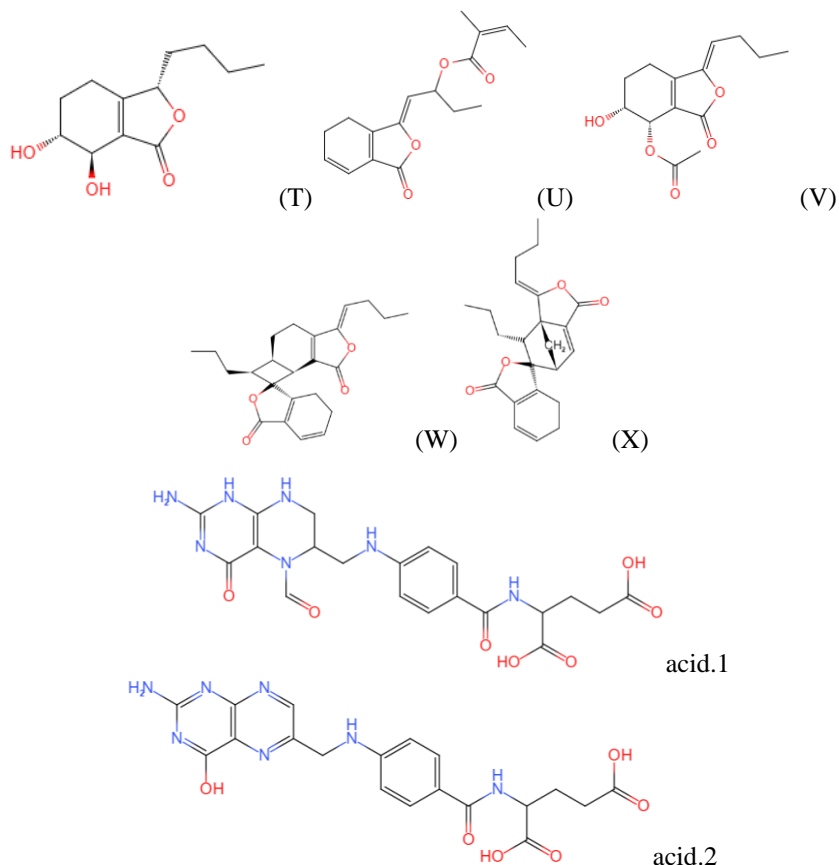
Western blotting analysis further identified that ASP markedly sensitized K562 cells to exogenous erythropoietin (EPO) by activating EPO-induced JAK2/ STAT5 tyrosine phosphorylation, thus augmenting the EPO-mediated JAK2/STAT5 signaling pathway. On the basis of these findings, we propose that ASP might be developed as a potential candidate for chronic myelogenous leukemia inducing differentiation treatment.(52)

The reversing blood-deficiency mechanism of AS might involve regulating synthesis and degradation of ketone bodies, Pyruvate metabolism, TCA cycle, and Glycolysis/Gluconeogenesis.(53)

#### Some chemical structures of the Angelica Sinensis







## 6. Future Prospects

As a Traditional Herbal Medicine, AS has very long medical history in China. Study of AS is mainly focused on between its chemical constituents and pharmacological effects. Being the most significant chemical constituents of AS, ASP has become particularly significant because of its many pharmacological effects. It can be used to treat many clinical diseases related to its structure. When it comes to the treatment of kinds of diseases, The study of PSP pharmacodynamics, chemical composition, and molecular structure are still incomplete. Therefore, we should pay much attention to the further study, especially aim at mechanisms of action. It has also provided a new prospect for further research on the AS mechanism of action, and improvement of therapeutic agents employing AS and will facilitate the development of its bioactive compounds into effective drugs.

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