Phytochemical and pharmacological studies on Radix Angelica sinensis

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[ABSTRACT] The roots of Angelica sinensis (RAS), are a Chinese herbal medicine traditionally used in prescriptions for replenishing blood, treating abnormal menstruation, and other women’s diseases. It has also been widely marketed as health food for women’s care in Asia, and as a dietary supplement in Europe and America. RAS is well-known for its hematopoietic, antioxidant, and immunoregulatory activities. RAS also possesses anti-cancer, memory, radioprotective, and neuroprotective effects. Phytochemical investigations on this plant led to organic acids, phthalides, polysaccharides, and other metabolites. Based on recent animal studies and clinical trials, RAS has been used in the treatment of gynecologic diseases, cardio-cerebrovascular disease, nervous system diseases, and nephrotic syndrome. In this review, the recent phytochemical and pharmacological studies, drug-drug interactions, clinical applications, and toxicity of RAS are summarized.

[KEY WORDS] Radix Angelica Sinensis; Chemical constituents; Pharmacological effect; Interactions; Clinical applications; Toxicity


1 Introduction

Radix Angelica Sinensis (RAS), known as Danggui in Chinese, is the root of Angelica sinensis (Oliv.) Diels (Apiaceae) (Fig. 1). RAS has been used for thousands of years in traditional Chinese medicines. It was first cited in the Shennong Bencao Jing (200–300 A.D., Han Dynasty) [1]. The described functions of RAS in the Shennong Bencao Jing were to replenish blood, invigorate blood, stop pain, and moisten the intestines. Called “female ginseng”, it is also predominantly renowned for its use in the treatment of a wide variety of gynecological conditions that are generally not easily treated with conventional therapies, such as menstrual disorders, amenorrhea, and dysmenorrhea. It has been used as a tonic, hematopoietic, and anti-inflammatory agent for thousands of years in traditional Chinese medicinal prescriptions. In the current Chinese Pharmacopoeia (Committee for the Pharmacopoeia of China, 2010), RAS is one of the most popular traditional Chinese medicines, and is contained in more than 80 composite formula. In clinical application, RAS is always prescribed in combination with Ligusticum chuanxiong. It has also been widely marketed as a health food for women’s care in Asia, as well as a dietary supplement in Europe and America [2-5].

The traditional uses were extended in large scale at present. Modern pharmacological studies showed that RAS and its active principles possessed wide pharmacological activities, such as anti-cancer, memory amelioration, radioprotective, neuroprotective, immunoregulatory, antioxidant, hematopoietic activities, and other effects. Currently, RAS has been used in the treatment of gynecologic diseases, cardio-cerebro-vascular disease, nervous system diseases, and nephrotic syndrome.

RAS has been chemically extensively studied. Phthalides, organic acids, polysaccharides, flavones, coumarin, and inorganic elements were isolated and identified as the main compositions. Among of them, phthalides, organic acids and polysaccharides, have been proved to have some good pharmacological effects, and were considered as the active compounds of RAS [6].

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In this review, advances in the phytochemical and pharmacological studies on RAS, as well as the drug-drug interactions, clinical applications and toxicity of RAS are summarized. The increasing data supports the utilization and development of natural and traditional drugs based on RAS.

2 Phytochemistry

Phytochemical investigation of RAS led to the isolation of organic acids, phthalides, and polysaccharides as the main components.

2.1 Organic acids

RAS contains a series of organic acids, such as ferulic acid, protocatechuic acid, caffeic acid, phthalic acid, 3-hydroxybenzoic acid, vanillic acid, folic acid, folinic acid, nicotinic acid, and succinic acid [5]. The ester of ferulic acid, coniferyl ferulate, is also found in RAS samples. Based on the stability study, two new terms, free ferulic acid and total ferulic acid, were suggested and defined. Free ferulic acid represents the natural content of ferulic acid in plants. Total ferulic acid refers to the sum of free ferulic acid plus the amount of related hydrolyzed components, which would be a better choice to assess the plant quality [7]. The chemical structures of the major organic acids of RAS are shown in Fig. 2.

Most of the organic acids literatures focuses on the analysis of ferulic acid, which varies within the range of 0.211–1.75 mg·g<sup>−1</sup> [8]. Several methods, including TLC, HPLC, CE, and HPLC-MS, have been reported for the analysis of ferulic acid [9-11]. HPLC is the main analytical method for quantification of ferulic acid. Furthermore, HPLC and HPLC-MS were used to confirm the isomer transition of ferulic acid [12]. The trans-ferulic acid was transformed into cis-ferulic acid partly when its solution was deposited under some routine conditions, and the trans- and cis-ferulic acids could coexist in RAS. The contents of other organic acids, including nicotinic acid, 4-hydroxybenzoic acid, folic acid, vanillic acid, caffeic acid, protocatechuic acid, phthalic acid, and folic acid in the crude extracts of RAS could easily be determined in 60 min by HPLC and in 20 min by CE [13].

2.2 Phthalides

Phthalides are one kind of active compound in RAS, the key components of which are ligustilide (E and Z), butyldenedephthalide (E and Z), butylphthalide, senkyunolide A, senkyunolide I, senkyunolide H, senkyunolide P, levistolide A, riligustilide, tokinolide B, and neocnidilide [14]. To date, there are 28 phthalides isolated from this plant comprising monomeric phthalides and phthalide dimers. The chemical structures of the major phthalides of RAS are shown in Fig. 3.

Because the majority of the phthalides discussed are relatively non-polar, the extraction methods involve non-polar solvents or steam distillation. Although the results of solvent extraction are relatively harsh, it is still the most commonly used method. Modern extraction methods, including supercritical fluid extraction and pressurized liquid extraction, emerged in the early to mid-2000s.

For quantitative analysis, Z-ligustilide is often used as an important marker for assessing the quality of RAS. The concentration of Z-ligustilide in RAS varies within the range of 1.26–37.7 mg·g<sup>−1</sup>. HPLC and GC are the main analytical methods for the quantification of Z-ligustilide. The content of Z-ligustilide from HPLC is much higher than from GC [5]. Ligustilides (E and Z) are the volatile compounds that have been commonly analyzed by GC-FID or GC–MS in plant materials and/or products of RAS volatile oils [15-16]. However, ligustilides and some phthalides are thermally labile, and may easily be isomerized at high temperature. So it seems that GC is not very suitable for the quantitative analysis of ligustilide because of the use of high temperature. There are also several publications about ligustilides identified in fingerprints, quantified in plants or their essential oils using HPLC–DAD or HPLC–MS [17-18]. However, the determination of Z-ligustilide is interfered with other phthalides, such as butyldenedephthalide, senkyunolide, and so on.
2.3 Polysaccharides

Nowadays, the polysaccharides isolated from RAS have drawn the attention of researchers due to their outstanding biological activities. The physiochemical and structural features of a polysaccharide are defined by molecular weight, monosaccharide composition, sequence of monosaccharide, configuration, and so on. The typical analytical methods list the following [19-20]: the amount of total carbohydrates, uronic acids, and proteins were determined with improved phenol-sulfuric acid, \( m \)-hydroxyldiphenyl methods, and Serva Blue G dye binding, respectively. The monosaccharides contained in each of the polysaccharides were analyzed using paper chromatography and thin-layer chromatography. High performance gel filtration chromatography and high performance anion-exchange chromatography were employed to determine the relative molecular masses and charge characters of each polysaccharide. Infrared spectrometry was used to analyze the structures of the glucoside bonds of each sample. To sum up, general procedures for the analysis of polysaccharides include pretreatment, extraction, purification, purity evaluation, molecular weight measurement, constituent monosaccharides identification, and structural analysis. All of the above procedures could be finished only by the application of different, hyphenated analytical techniques.

To date, 36 polysaccharides were identified from the root of RAS. Most of the polysaccharides isolated from RAS reported in the literature are heteropolysaccharides. The constituent units of the polysaccharides from RAS contain fucose, galactose, glucose, arabinose, rhamnose, arabinose, mannose, and xylose [4]. A neutral polysaccharide (ASP1) and two acidic polysaccharides (ASP2 and ASP3) were also separated from RAS by hot water extraction.

2.4 Quality control

The official drug of RAS is the roots of Angelica sinensis (Oliv.) Diels (Angelica polymorpha Maxim. var. sinensis Oliv.), Apiaceae. According to traditional experience, RAS cultivated in Minxian County, Gansu Province, China, is regarded as the authentic herb. However, several other substitute herbs, including Angelica acutiloba (Sieb. & Zucc.) Kitagawa (Japan), A. acutiloba Kitagawa var. sugiyamae (Japan), Angelica gigas Nakai (Taiwan), Angelica uchiyanana Yabe (Taiwan), and Levisticum officinale Koch (Europe), have also been used in clinical trials [9].

In the current Chinese Pharmacopoeia (Committee for the Pharmacopoeia of China, 2010), ferulic acid and Z-ligustilide have been officially used as the indicator compounds to characterize the quality of RAS. However, ferulic acid and Z-ligustilide exist in all of the above species. Therefore, chemical identification of RAS by simply using ferulic acid and Z-ligustilide as marker compounds seems to be insufficient. Nowadays, chromatographic fingerprints are being widely used in the quality control of RAS. Although there are some publications discussing the fingerprint of the volatile components by GC–MS, most publications on the quality control of RAS are related to the chromatographic fingerprint of the non-volatile components using HPLC–DAD or HPLC–MS.

Lu et al developed a HPLC–DAD–MS fingerprint of RAS based on the consistent chromatograms of forty RAS samples, containing the isolation and identification of the phthalides and the organic acids and their esters [21]. With respect to the correlation coefficient of the chromatograms and principal component analysis, the developed HPLC fingerprints could be used to differentiate Chinese Angelica from Japanese Angelica Root, Szechwan Lovage Rhizome, and Cnidium Rhizome. Chinese Angelica and Japanese Angelicae Root could be easily distinguished by either their chromatographic patterns, or the content of coniferyl ferulate. The amounts of senkyunoide A in Chinese Angelica, Szechwan Lovage Rhizome, and Cnidium Rhizome are relatively different, hence the chemical differentiation between these species becomes possible. By introducing discriminant analysis, Wang et al have established a criterion for distinguishing RAS from three areas of Dingxi District of Gansu Province, China [22]. Though the chromatograms of these samples were generally identical, the model established can
3 Pharmacological Effects

3.1 Anti-cancer effect

Diagnosis of a serious illness, such as cancer, is one of the most stressful experiences of modern life. A recent report indicated that cancer will become the leading cause of death worldwide. Recent years, more and more research groups have focused their effort on the study of traditional Chinese medicines that exhibits anticancer effects [23].

The study performed by Lai et al. found that Chinese traditional medicine products containing RAS are the most frequently prescribed for breast cancer [24]. The over expression of glutathione S-transferase (GST) with multidrug resistance is considered one of the major obstacles to successful cancer chemotherapy. Huang et al. performed high-throughput screening to search for inhibitors of GST from natural products [25]. Two compounds, 11-angeloylsenkyunolide F and tokinolide B, isolated from RAS had an inhibitory effect on GST and they acted as reversible, non-competitive inhibitors. So Huang suggested that RAS may be a potential source of GST inhibition for pharmaceutical use.

N-Butyldenephthalide (BP), isolated from the chloroform extract of RAS, has been examined for its antitumor effects on glioblastoma multiforme brain tumors [26] and hepatocellular carcinoma cells [27]. Tsai et al. examined the antitumor effects of BP on glioblastoma multiforme (GBM) brain tumors both in vitro and in vivo. BP triggered both p53-dependent and independent pathways for apoptosis in vitro. In vivo, BP can suppress growth of subcutaneous rat and human brain tumor, reduce the volume of GBM tumors in situ and significantly prolong survival rates (Fig. 4). In the following study, two hepatocellular carcinoma cell lines (HepG2 and J5) were treated with either BP or a vehicle. Administration of BP showed similar antitumor effects in both HepG2 and J5 xenograft tumors. Both in vitro and in vivo, BP induced apoptosis in hepatocellular carcinoma cells. So Chen et al suggested a potential clinical use of this compound for improving the prognosis of hepatocellular carcinoma cells.

Fig. 4 BP inhibition of tumor growth with improved survival rate in a syngenic rat GBM model [26]

Another study focused on polysaccharide from RAS and its anti-tumor activity. The polysaccharide APS-3c was isolated from RAS and the 3-(4, 5)-dimethylthiazol-2-(y)-1)-2,5-di-phenytetrazolium bromide (MTT) assay was used. The results of the MTT assay indicated that APS-3c inhibited the proliferation of human myeloblastic leukemia HL-60 cells in a concentration-dependent manner [28]. Cao et al. also reported that the model of mice transplanted sarcoma S-180 was used to study the anti-tumor effects of polysaccharide APS-2a from RAS in vivo [29]. The results indicated that the polysaccharide APS-2a could inhibit the proliferation of tumor cells in mice transplanted with S-180. The thymus indices and spleen indices in the groups treated with APS-2a were higher than the control group.

3.2 Memory amelioration

Cognitive impairment or dementia in the elderly is associated with many disorders. Characterized by extracellular deposits of fibrillar β-amyloid (Aβ) in the brain, a fulminant microglialmediated inflammatory reaction, and neuronal death, Alzheimer’s disease represents about 70% of the dementia patients.
of piracetam, but its action mechanism was somewhat different from that of piracetam and tacrine. Cheng et al investigated the effect of Z-ligustilide (LIG) on scopolamine-induced memory impairment in ICR mice [33]. LIG significantly improved spatial long-term memory and short-term memory impairment, inhibited central acetylcholinesterase activity, and increased choline acetyltransferase activity. Moreover, the efficacy of LIG in both neurobehavioral and cholinergic evaluation were comparable to tacrine. The data suggested that LIG may alleviate memory deficits probably via enhancing cholinergic function. Xu et al investigated whether there was effect on study and memory senility caused by D-galactose in rats which were injected with polysaccharide of Radix Angelica Sinensis (ASP) at a certain dose [34]. Comparing with the model group, ASP improved the study and memory ability of mice, decreased malondialdehyde (MDA) content, and increased the activities of superoxide dismutases (SOD) in blood serum and brain tissue, improved brain cell degeneration, and decreased the apoptotic index. The results suggested that ASP can improve the study and memory senility caused by D-galactose in rat, as well as inhibit the development of brain senility.

3.3 Radioprotective effect

During the last decade, radiation-induced apoptosis has been a focus of intense research. Recent studies have shown that exposure to radiation results in the induction of apoptosis in various mammalian cells. Some of the radioprotectors may reduce the frequency of DNA damage, which might activate apoptosis, as well as protect cells against radiation-induced apoptosis.

Yuan et al demonstrated the effect of SOD active of RAS on live tissue of the mice radiated [35]. The results indicated that RAS has a significant protecting effect for the liver of mice which has been radiated by Co-γ-rays. In the following years, Sun’s team has done a lot of research on the radioprotective effects of polysaccharides from RAS. In 2005, Sun et al. investigated the bioactivity of water-soluble polysaccharides from RAS [36]. The acidic polysaccharide (ASP3) was the major constituent of the crude extracts. The results showed that ASP3 has a potential radioprotective effect on acute radiation-injured mice because of its protective effects on leucocytes and lymphocytes against radiation induced damage. In 2007, Sun reported the radioprotective effect of ASP3 on sub-acute, radiation-injured mice [37-38]. ASP3 could speed the transformation rate of peripheral lymphocytes, as well as the content of SOD of liver, blood, brain, and bone-marrow, and enhance the radiation endurance of the body. Meanwhile, ASP3 pretreatment might prohibit the occurrence of apoptosis in radiation-damaged liver and bone-marrow [39].

3.4 Neuroprotective effect

Stroke remains one of the major causes of death and disability throughout the world. Neuroprotective agents with different modes of action and an extended application time window are urgently required in the clinic because of the socio-economic importance of stroke.

Some reviews have demonstrated the neuroprotective effect of RAS. Lin demonstrated the neuroprotective efficacy of a combination, including RAS, on mitigating brain infarction, global ischemia, and preventing neurodegeneration following ischemia [40]. In another review, Chao et al reported that LIG exerts neuroprotective effects [41].

Cui et al assessed the neuroprotective effects of RAS injection in the rat sciatic nerve crush injury (SCI) [42]. The findings suggested that RAS injection can improve the sciatic nerve crush injury through increasing brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) protein expression. Gu et al. investigated the inhibitory effects of RAS on the neurotoxicity and decreased expression of nicotinic acetylcholine receptors induced by β-amyloid protein in human neuroblastoma (SH-SY5Y) cells [43]. The results indicated that RAS at a safety dose inhibited the neurotoxicity and increased lipid peroxidation. Also, Ma et al demonstrated that RAS injection could increase the number of CA3 neurons and inhibit the proliferation of gliocytes caused by hypoxia because of up-regulating the expression of mRNA of vascular endothelial growth factor [44].

Among the studies relating to the neuroprotective effects of RAS, most are focused on LIG. Chen et al investigated the neuroprotective potential of LIG after experimental subarachnoid hemorrhage (SAH) in rats [45]. As shown in Fig. 5, the spontaneous activity scores in the SAH + LIG20 group were significantly better than those in the SAH + vehicle or SAH + LIG5 groups on days 3 and 4. The results showed that LIG treatment reduced neurobehavioral deficits, mortality, brain edema, blood-brain barrier permeability, and cerebral vasospasm. Another study focused on LIG was carried out by Feng and co-workers who investigated the protective effects of LIG on parietal cortex and hippocampus of rats in a chronic cerebral hypoperfusion model [46]. The results demonstrated that LIG shows obvious neuroprotective potential for treating chronic cerebral hypoperfusion injury. The mechanism may be attributed to its anti-apoptosis of neurons and anti-proliferation of astrocytes in both the cortex and hippocampus.

Fig. 5 The effects of LIG treatment on neurobehavioral function after SAH brain injury [45]
3.5 Immunoregulatory activity

It is well-known that macrophages play a key role in the host defense mechanism, and many plant extracts activate immune responses primarily by activation of macrophages, although direct activation of B cells, and other immune cells, are also implicated. Activated macrophages release many inflammatory cytokines to exert their biological effects, including nitric oxide (NO), tumor necrosis factor-α (TNF-α), and reactive oxygen species (ROS), which play critical roles in the non-specific immune defense against tumors and bacterial infection [47].

Queiroz et al. studied the effects of a dried extract of the roots of RAS on the growth and differentiation of granulocyte-macrophage progenitor cells (CFU-GM) in normal and Listeria monocytogenes-infected mice [48]. The RAS extract could probably disengage Listeria-induced suppression of these responses by inducing a higher reserve of myeloid progenitors in the bone marrow in consequence of biologically active cytokine release (tumor necrosis TNF-α). Yang et al. examined the immunomodulatory activities of an ASP, in vitro in relation to the specificity to immune cells [49]. Cell proliferation results showed that proliferation of total spleen cells, macrophages, and T cells (Th) were promoted by the action of ASP. The time-effect relation of cytokine response suggests that macrophages and natural killer cells involved in non-specific immunity were primarily activated, and helper T cells were secondarily affected by ASP. It was concluded that ASP has immunomodulatory activity by regulating the expression of Th1- and Th2-related cytokines. Sun et al. explored the features of immune responses activated by ASP [50]. The results demonstrated that ASP could activate the mice to produce the corresponding antibodies and the cross-reactive antibodies.

3.6 Antioxidant activity

Oxygen free radicals or ROS are well-recognized to play a dual role in biological systems, because they can be either harmful or beneficial to living systems. However, a high concentration of ROS can induce damage of cell structures, harmful or beneficial to living systems. However, a high concentration of ROS can induce damage of cell structures, which occupies 19% of ASP and contains 0.53% protein, was investigated with Epo on promoting hematopoiesis. Epo has significant impact on the expression of STAT5. They found that ASP was the major component responsible for the hematopoietic effect of RAS. The results demonstrated that the potential of ASP for the treatment of anemia. Li et al. studied the effects of ASP on hemopoietic rehabilitation of radiated mice [58]. They concluded that RAS can resist X-radiation and enhance bone marrow cell proliferation and the production of antibodies.

Lee et al. aimed to separate and identify the major hematopoietic fraction from ASP [59]. The ASP was separated into four fractions (F1, F2, F3, and F4). The F2 fraction, which occupys 19% of ASP and contains 0.53% protein, was found to have the highest hematopoietic activity. Hua et al. investigated the signal transduction and regulation in erythropoiesis by ASP to clarify the mechanism of promoting hematopoiesis [60]. The results indicated that ASP cooperated with Epo has significant impact on the expression of STAT5. They concluded that the JAK2 and STAT5 signal transduction molecule plays an important role in the effect of ASP cooperated with Epo on promoting hematopoiesis.

Table 1 summarizes the active ingredients and the functions of each active ingredient concerning the pharmacological effects.

4 Drug-drug Interactions

Interactions between plant drugs and drugs may increase or decrease the pharmacological or toxicological effects of either component. To now, there are some reports focus on oxidation resistance, inhibiting melanocyte proliferation, decreasing tyrosinase activity, and improving hemorheology. Jiang et al. designed a study to investigate the effect of ASP on free radical generation, as well as lipid peroxidation and its modulatory effects on immunity activity in middle-aged women [54]. They concluded that ASP intake decreased oxidant stress-injured injury and improved immunity activities in middle-aged women subjects. Zhang demonstrated antioxidant activity of the polysaccharides in ischemia-reperfusion rats [55]. The results showed that ASP treatment significantly reduced myocardial infarction size, enhanced antioxidant enzyme activity, and down-regulated caspase-12 mRNA expression in rats. Long et al. studied the free radical scavenging and antioxidant activities of RAS lactones [56]. The results showed that RAS lactones had strong scavenging effects on hydroxyl radicals and DPPH. RAS lactones also exhibited a concentration-dependent inhibition of rat erythrocytes hemolysis and lipid peroxidation in linoleic acid induced by H2O2. They suggested that RAS lactones showed significant free radical scavenging and antioxidant activities.

3.7 Hematopoietic activity

Anemia is a widespread public health problem, particularly among females. RAS is a Chinese herbal medicine traditionally used in prescriptions for replenishing blood.

Liu et al. assessed the hematopoietic effects of RAS and the possible mechanism related to its hematopoietic activity [57]. They found that ASP was the major component responsible for the hematopoietic effect of RAS. The results demonstrated the potential of ASP for the treatment of anemia. Li et al. studied the effects of ASP on hemopoietic rehabilitation of radiated mice [58]. They concluded that RAS can resist X-radiation and enhance bone marrow cell proliferation and the production of antibodies.
Table 1 Summary of RAS pharmacological effects

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Pharmacological effects</th>
</tr>
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<tbody>
<tr>
<td>RAS extracts</td>
<td>Prolong the latency induced by scopolamine and cycloheximide [31], protect the liver of mice radiated by Co-γ-rays [35], inhibit the neurotoxicity, increase lipid peroxidation [43], induce biologically active cytokine release [48], antioxidants [52-53], resist X-radiation, enhance bone marrow cell proliferation and the production of antibodies [56]</td>
</tr>
<tr>
<td>RAS injection</td>
<td>Improve the sciatic nerve crush injury [42], improve the intra-uterine hypoxic condition, increase the number of dentate gyrus neurons, improve the learning and memory deficits of the juvenile rats, inhibit proliferation of gliaocytes [44]</td>
</tr>
<tr>
<td>Ferulic acid</td>
<td>Memory amelioration [30], enhance the cholinergic activities and cerebral blood circle [52]</td>
</tr>
<tr>
<td>Coniferyl ferulate</td>
<td>Memory amelioration [30]</td>
</tr>
<tr>
<td>Z-ligustilide</td>
<td>Improve spatial memory impairment, inhibit central acetylcholinesterase activity, increase choline acetyltransferase activity [53], reduce neurobehavioral deficits, mortality, brain edema, blood-brain barrier permeability and cerebral vasospasm [48], anti-apoptosis of neuron and anti-proliferation of astrocytes both in cortex and in hippocampus [56]</td>
</tr>
<tr>
<td>11-angeloylsenkyunolide F</td>
<td>Glutathione S-transferase inhibitor [25]</td>
</tr>
<tr>
<td>Tokinolide B</td>
<td>Glutathione S-transferase inhibitor [25]</td>
</tr>
<tr>
<td>Butylidenephthalide</td>
<td>Trigger pathways for apoptosis, suppress growth of brain tumor [26-27]</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>Improve the study and memory ability of mice, decrease MDA content, increase the activities of SOD in blood serum and brain tissue, improve brain cell degeneration, decrease apoptotic index [14], promote proliferation of total spleen cells, macrophages and T cells [49], produce antibodies [50], antioxidants [54-55], promote hematopoiesis [57-58], stimulate the human peripheral blood mononuclear cells [59]</td>
</tr>
<tr>
<td>Polysaccharide APS-3c</td>
<td>Inhibited the proliferation of human myeloblastic leukemia [28]</td>
</tr>
<tr>
<td>Polysaccharide APS-2a</td>
<td>Inhibit the proliferation of tumor cells [29]</td>
</tr>
<tr>
<td>Polysaccharide (ASP3)</td>
<td>Protection effect on leucocytes and lymphocytes of mice against radiation induced damage [16], speed transformation rate of peripheral lymphocytes and content of SOD of liver cells, prohibit formation of micronucleus of polychromatic erythrocytes in bone-marrow, enhance the radiation endurance of the body [37-38], prohibit the occurrence of apoptosis in radiation-damaged liver and bone-marrow [39]</td>
</tr>
<tr>
<td>Lactones</td>
<td>Free radical scavenging and antioxidant activities [56]</td>
</tr>
</tbody>
</table>

Notes: MDA: malondialdehyde, SOD: superoxide dismutases

Lo et al studied the effects of RAS on the pharmacokinetics and pharmacodynamics of warfarin in rabbits [45]. RAS treatment did not affect prothrombin time (PT) by itself, but significantly lowered PT values three days after co-treatment with single dose warfarin. The results indicate that precautionary advice should be given to patients who self-medicate with RAS while on chronic treatment with warfarin. Heck et al reported that a woman who had been taking warfarin 5 mg·d−1 for nearly two years and had an international normalized ratio (INR) stabilized at 2-3, experienced a sudden increase in her INR to 4.9. The patient said there were no changes in her medication regimen, diet, alcohol consumption, or other lifestyle factors except for the recent addition of RAS once or twice daily during the preceding four weeks for the management of menopausal symptoms. The patient was instructed to discontinue RAS, and her INR declined to the therapeutic range within four weeks. In view of this, patients receiving warfarin should be advised to avoid RAS [62].

Plant drug-drug interactions, especially cytochrome P450 (CYP)-mediated interactions, cause an enhancement or attenuation in the efficacy of co-administered drugs. In 2006, Tang et al assessed the effect of water and ethanol extracts of RAS on cytochrome P450 [63]. The water extract of RAS strongly increased the activities of CYP2D6 and 3A, and so did the ethanol extract of RAS. Since extract treatments had significant effects on CYP isoforms activities, caution should be paid to the possible drug interactions of RAS and CYP substrates.

5 Clinical Applications

5.1 Gynecologic diseases

When the Women’s Health Initiative (WHI) was discontinued owing to unanticipated increases in the risk for stroke, heart attack, breast cancer, and blood clots among women taking estrogen plus progestin, the search for alternative treatments that were perceived to offer beneficial effects with less risk intensified. Some women turned to botanical dietary...
supplements which are relatively safe and effective [65]. RAS is one of the most commonly used.

A study explored the curative effects of climacteric metrorrhagia and metrorrhagia treated by the integration of Chinese medicine and Western medicine [65]. The results indicated that the integration of a decoction containing RAS and Western medicine has great effects on the treatment of climacteric metrorrhagia and metrorrhagia. Meanwhile, the clinical effects of treating bleeding after miscarriage by the integration of traditional Chinese medicine and Western medicine were also investigated [66]. More positive effects were observed than the single use of an intramuscular injection of oxytocin. Another study observed that RAS and Paeonia lactiflora Pall. analgesic soup in the treatment of primary dysmenorrhea provided clinical efficacy [67]. Cui explored the regularity of Chinese medicines in the treatment of endometriosis [68]. Eighty-six reports were chosen, and the Chinese traditional medicines were classified by SPSS. One of the most frequently used Chinese herbs was RAS with functions of activating blood circulation to dissipate blood stasis, invigorating for deficiency and clearing heat-toxin.

5.2 Cardio-cerebrovascular disease

Sodium ferulate (SF) or 3-methoxy-4-hydroxy cinnamate, an active principle from RAS, alone, or in combination with Western drugs, appeared to have a therapeutically beneficial effect in patients with angina pectoris and acute myocardial infarction [69]. The integrated treatment with SF and Western drugs, such as nitrates, β-adrenoceptor antagonists, calcium channel antagonists, and angiotensin-converting enzyme inhibitors, produced better results than Western drugs alone. The combined therapy improved clinical symptoms, specific ischemic ECG changes, heart function tests, and peak levels of myocardial enzymes, and reduced the incidence of heart failure and arrhythmias during hospitalization. For patients who could not tolerate β-adrenoceptor or nitrate antagonists, SF injections alone could markedly improve the clinical symptoms and ECG changes. Li investigated the efficacy of a decoction containing RAS and Western medicine used to treat peripheral angiopathy from diabetes mellitus [70]. A decoction containing RAS had significant efficacy for diabetes mellitus peripheral angiopathy. The RAS has many kinds of bioactive ingredients and extensive pharmacological effects. It has been used in the clinic to treat anemic cerebrovascular disease, and a good curative effect was observed. As reported, RAS injection could play a protective role for neurons in the cerebrum of embryonic rats in anoxia [71].

5.3 Nervous system diseases

The causes of Alzheimer’s disease are complex and there is few special clinical drug to cure this disease. Many active compositions of RAS show pharmacological effects to treat Alzheimer’s disease. This provides new ideas for the clinical treatment of Alzheimer’s disease [72]. Wang et al discussed the clinical effects of a decoction containing RAS on the treatment of diabetic peripheral nerve lesions [73], where a decoction containing diabetic peripheral nerve lesions showed great therapeutic effects.

5.4 Nephrotic syndrome

A mixture of two Chinese herbs, Astragalus and RAS (A & R), has been used for the treatment of nephrotic syndrome (NS) in China for years. The effect of A & R in the treatment of NS was evaluated in the early 1950s, and a positive conclusion was observed. Wang et al systematically studied the curative effect, mechanism and indication of A & R on renal protection, protein metabolism, and hyperlipidemia of nephrotic syndrome. A & R improved the histologic changes and ameliorated the deterioration of renal function. The renal local effect of A & R is in diminishing the progression of chronic renal damage which is associated with the reduction of renal transforming growth factor and osteopontin, following a reduced infiltration of macrophages and a limitation of renal intrinsic cell activation. Meanwhile, A & R can also overcome the disturbances of protein and lipid metabolism by correcting hypoalbuminemia and hyperlipidemia in NS patients and in animal models [74].

6 Toxicity

Yang et al explored the toxicity of RAS injection in the chick embryo chorioallantoic membrane (CAM) model [75]. The results indicated that the survival of chick embryos was not inhibited by RAS injection. There were no differences between the treatment groups and the negative control (P > 0.05), indicating that the toxicity is very limited. Wang et al observed the acute toxicology of RAS polysaccharide-iron complex (APIC) by oral administration in mice [76]. Because no obvious acute toxicology appeared in all of the groups, the maximum tolerated dose (MTD) was used to be the index of toxicology instead of the LD₅₀. The MTD of APIC in mice was 4 800 mg·kg⁻¹, and it was 1 920 times the adult daily dose. Thus it was concluded that APIC for oral use is safe.

7 Conclusion

Overall, RAS, as a Traditional plant medicine possessing multiple pharmacological actions, has considerable potential value clinically. Since ASP have outstanding biological activities, more attention should be paid to the chemical and toxicity studies of ASP. Meanwhile, the quality control methods concerning ASP in different species still need further studies besides the fingerprint. On the other hand, geriatric diseases, such as Alzheimer’s disease, are currently attracting increased attention. The memory amelioration activities of RAS shed light on future research as a new drug either in single or compound prescriptions.

References


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当归植物化学和药理学研究进展

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【摘要】 当归是传统中药处方中一味常用的草药，可以补血、治疗痛经和其他妇科疾病。作为保健食品和食品添加剂，当归也在亚洲和欧美地区销售。它的补血、抗氧化和免疫调节作用已经广为人知。近期研究表明，当归在抗肿瘤、改善记忆力、抗辐射和神经保护方面也有一定作用。植物化学研究从当归中分离得到了有机酸、苯酞和多糖等多类物质。根据最近的动物研究和临床实验，当归可以用于治疗妇科疾病、心脑血管疾病、神经系统疾病和肾病综合症。综述了近年来有关当归植物化学、药理学、药物相互作用、临床应用和毒性方面的研究进展，以使其药用价值得到进一步的认识，并使其应用前景更广阔。

【关键词】 当归；植物化学；药理学；药物相互作用；临床应用；毒性

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