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In-depth exploration of bioactive constituents, biosynthetic pathways, and pharmacological mechanisms of *Angelica sinensis*: implications for therapeutic development

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ABSTRACT

Angelica sinensis, a well-known traditional Chinese medicinal herb with the unique property of being both a medicine and an edible plant, has been widely used for promoting blood circulation, modulating immunity, and relieving pain. This review comprehensively investigates the extraction methods, structural characteristics, and biological activities of its primary bioactive components, such as polysaccharides, volatile oils, organic acids, and flavonoids. The biosynthesis pathways of these compounds, along with the key enzymes and transcription factors involved, are investigated to understand the factors influencing their synthesis and accumulation. Additionally, the biological activities of *A. sinensis*, including hepatoprotective, anti-inflammatory, immune-modulatory, anti-tumor, circulatory benefits, and neuroprotection, along with their underlying mechanisms are introduced. These findings provide a solid foundation for the development of *A. sinensis* as a valuable resource in functional foods and pharmaceutical products.

1. Introduction

Angelica sinensis (Oliv.) Diels is a highly regarded traditional medicinal herb in Chinese clinical practice and also holds a significant position as an edible plant, embodying the concept of medicine-food homology[1]. Its origin can be traced back to the *Shennong Ben Cao Jing*, where it is classified as a moderate-grade herb and is a perennial plant highly regarded as the "sacred medicine for hematological diseases." This perennial plant is widely distributed across several provinces in China, with Min County in Gansu being the primary production region due to its high-quality and abundant yield[2]. *A. sinensis* has a warm nature and a sweet, pungent flavor, targeting the heart, spleen, and liver meridians[3]. It is well-known for its diverse biological properties, such as promoting blood circulation, regulating menstruation, relieving pain, and lubricating the intestines. Extracts of *A. sinensis* have demonstrated a wide range of biological activities, including immune enhancement, hematopoietic regulation, analgesic, anti-inflammatory, anti-tumor, hepatoprotective, and renoprotective effects[4].

The rich bioactive compounds in *A. sinensis*, including polysaccharides, phthalides, phenolic acids, flavonoids, and coumarins, are considered its main active components[5]. With the continuous advancement of extraction and separation technologies, optimized methods like ultrasound-assisted extraction and supercritical fluid extraction have emerged, these techniques not only enhance the extraction efficiency but also improve the purity and stability of the components. The choice of extraction method can significantly impact the structural and biological activities of the constituents. Hence, investigating the chemical composition,

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extraction techniques, and bioactivity of *A. sinensis* holds great research value.

In recent years, the biosynthetic pathways of the active components in *A. sinensis*, particularly those of phenolic acids, flavonoids, coumarins, and polysaccharides, have attracted significant attention. The phenylpropanoid pathway plays a crucial role in the synthesis of ferulic acid (FA) and chlorogenic acid, involving key enzymes such as phenylalanine ammonia lyase (PAL), cinnamic acid 4-hydroxylase (C4H), and 4-coumarate-CoA ligase (4CL). With the progress of molecular biology and omics technologies, the complex regulatory networks underlying the synthesis of these bioactive compounds are gradually being elucidated, involving transcription factors, enzyme gene expression regulation, and environmental factors (e.g., light, temperature, altitude). These studies provide guidance for the precision cultivation of *A. sinensis* and lay a theoretical foundation for its variety improvement and quality enhancement.

Research on the biological activities and molecular mechanisms of *A. sinensis* has confirmed its beneficial effects across multiple disease areas. The active components exert significant effects in immunomodulation, antioxidation, anti-tumor activities, and cardiovascular protection. For instance, *A. sinensis* polysaccharide (ASP) exhibits notable immunomodulatory and antioxidant properties, while FA demonstrates potential in antiplatelet aggregation and antithrombosis, and volatile oil components like ligustilide (LIG) display neuroprotective and anti-inflammatory activities.

This review aims to systematically examine the active components, biosynthetic pathways, biological activities, and molecular mechanisms of *A. sinensis*, with a focus on extraction technologies, structural characteristics, biosynthesis, and therapeutic mechanisms. The ultimate goal is to provide a scientific basis for the development of *A. sinensis* in the fields of functional foods and nutraceutical products.

2. Active composition and extraction methods of *A. sinensis*

Modern research has demonstrated that polysaccharides, volatile oils, and organic acids are the primary chemical constituents that exert a significant influence on the bioactivity and pharmacological effects of *A. sinensis*[6]. Among these compounds, the most representative active constituents identified are ASP, LIG, and FA, which are commonly found in abundant amounts, are adopted as quality markers for the evaluation of *A. sinensis*[7]. As extraction techniques and storage conditions improve continuously, research on *A. sinensis* monomers has become more comprehensive. This subsection summarizes and organizes its main active components to lay a solid foundation for further studies on bioactivity, pharmacological effects, and quality assessment.

2.1 Polysaccharides

2.1.1 The characteristics of ASP

ASP are water-soluble active ingredients in *A. sinensis*, playing important roles in blood supplementation, immune modulation, and metabolic regulation. Most of the polysaccharides isolated from *A. sinensis* are heteropolysaccharides, primarily composed of monosaccharides such as glucose, galactose, arabinose, rhamnose, fucose, xylose, and galacturonic acid[8]. The detailed structural information of the reported *Angelica* polysaccharides is presented in Table 1.

2.1.2 Extraction methods of ASP

Common extraction methods for ASP include hot water extraction, ultrasonic extraction, enzyme extraction, and microwave-assisted extraction[8,21-23]. Ultrasonic extraction generally yields a higher amount of polysaccharides compared to hot water

Table 1
Detailed structural information of the reported *Angelica* polysaccharides.

No.	Compound name	Extraction method	Molecular weight (Da)	Monosaccharide composition	Linkage mode	Biological activity	Reference
1	ASP	Extracted with hot water extracting and ethanol precipitating method, then purified by Sevag method, and dried by frozen drier	1×10^4−1.1×10^5	Rha:Xyl:Ara:Glc:Gal = 1:2.2:5.8:178:12	ND	ND	[9]
2	WASP (water-soluble-ASP) 11	Extracted with hot water at 80 °C, then fractionated by aion-exchange chromatography and gel filtration chromatography respectively	3.8×10^5	Glc	ND	ND	[10]
3	WASP12		1.9×10^4	Ara, Gal			
4	W-ASP3		6.2×10^4	Gal, Ara, Rha, Glc, Man, GlcA			
5	AP	Extracted with boiling water, precipitation with three volumes of ethanol. Then, fractionated by chromatography	5×10^4	Rha:Ara:Man:Glc:Gal = 1.00:4.54:2.98:11.09:7.45	ND	Immunomodulation	[11]
6	APS-1cI	Purified by anion-exchange and gel-filtration chromatography	1.7×10^5	Glc	[→6)-*α*-*D*-Glc-(1→]$_n$	ND	[12]
7	APS-1cII		3.9×10^4	Glc	→4)-*α*-*D*-Glc-(1→6)-*α*-*D*-Glc-(1→[→4)-*α*-*D*-Glc-(1→4)-*α*-*D*-Glc-(1→6)-*α*-*D*-Glc-(1→4)-*α*-*D*-Glc-(1→4)-*α*-*D*-Glc-(1→]$_n$		
8	APS-2a	Water extraction deprotein ethanol precipitation and DEAE-sephades A-25 column chromatography respectively and was further purifed by Sephacryl S-400 and Sephadex G-100 column chromatography	7.4×10^5	Ara:Gal:Rha:Glc:GalA = 38.2:7.5:2.6:1.0:4.9	ND	Antitumor	[13]
9	APS-bII	Purified by anion exchange cellulose column and Sephadex G-100 gel column chromatography	1.3×10^4	Glc:Gal:Xyl:Ara = 8.4:2.7:1.8:1.0	ND	Antitumor	[14]

Table 1 (*Continued*)

No.	Compound name	Extraction method	Molecular weight (Da)	Monosaccharide composition	Linkage mode	Biological activity	Reference
10	ASP	Extracted with boiling water under reflux for 30 min, frozen at −70 °C and then lyophilised	ND	Saccharose (the major sugar, 18.55%), Glc and Fuc (the minor components)	ND	Antioxidant	[15]
11	ASP3a	Water extraction and ethanol precipitation, followed by purification steps including DEAE-cellulose and gel filtration chromatography	5.9×10^5	Glc:Gal:Ara:Rha:Man = 3.2:1.7:2.5:1.3:1.0	ND	Antitumor	[16]
12	ASP3b		2.3×10^5	Glc:Gal:Ara:Rha:Man = 2.3:5.4:6.8:1.0:1.2			
13	APS3c		1.4×10^4	Glc:Gal:Ara:Rha:Man:Xyl = 6.3:4.7:6.7:6.5:1.6:1.0			
14	APS-1d	Extracted with hot water extracting and ethanol precipitating method, then dialyzed and lyophilized to yield APS-0. APS-0 was purified through DEAE-sephadex A-25 and Sephadex G-100 columns with NaCl gradients to obtain APS-1d	5.1×10^3	Glc:Ara = 13.8:1.0	Main chain: 1,4-*α*-*D*-Glc; Branches: 1,6-*α*-*D*-Glc; Terminal: *β*-*L*-Ara	Antitumor	[17]
15	ASP	Extracted with hot water extracting and ethanol precipitating method, then purified with Sephadex G-50 column	7.29×10^3	Ara:Glc:Gal = 1:2.5:7.5	ND	Hepatoprotective	[18]
16	APS-2I	Extracted with hot water extracting and ethanol precipitating method, then fractionated by Sephadex A-25 column (APS-1 to APS-4) and Sephadex G-100 column (APS-1I to APS-4II), respectively	7.2×10^5	Man:Rha:GalA:Glc:Gal:Ara = 4:5:1:10:23:39	Main chain: →4)-*α*-*D*-GalA-(1→3)-*α*-*L*-Rha-(1→2)-*α*-*D*-Man-(1,6→6-OMe, 4)-*α*-*D*-Gal-(1→3)-*α*-*L*-Rha-(1→2)-*α*-*D*-Man-(1,6→*α*-*D*-T-Gal; Side chain 1: →2)-*α*-*D*-Man-(6→1)-*β*-*D*-Gal-(6→1)-*β*-*D*-Gal(→6; Side chain 2: 5→)-*α*-*L*-Ara-(1→3)-*α*-*L*-Ara-(1→3)-*α*-*L*-Ara-(1→3)-*α*-*L*-Ara-(1→4)-*β*-*D*-Gal-(1→6)-*α*-*D*-Man	Antitumor	[19]
17	ASP-4I	Extracted with hot water extracting and ethanol precipitating method, then fractionated by DEAE-sephadex A-25 and Sephadex G-100 column chromatography (APS-1 to APS-4), and further into APS-4I and APS-4II	1.61×10^4	Glc	[→6)-*α*-Glc-(1→]$_n$	Antitumor	[20]
18	APS-4II		1.11×10^4	Glc:Gal:Ara = 3.7:1.0:2.1	→6)-*α*-Glc-(1→6)-*α*-Glc-(1→5)-*α*-Ara-(1→5)-*α*-Ara-(1→3, 5)-*α*-Ara-(1→3)-*β*-Gal-(1→3)-*β*-Gal1→4)-*α*-Gal-(1→3)-*α*-Ara-(1→3,5)-*α*-Ara-(1→		

Note: Glc, Glucose; Gal, Galactose; Ara, Arabinose; Rha, Rhamnose; Man, Mannose; Xyl, Xylose; Fuc, Fucose; GalA, Galacturonic acid; ND, no data.

extraction, which is attributed to its ability to disrupt the cell walls and membranes, thereby enhancing the permeability of cellular contents[23-24]. Lü et al.[25] compared four extraction methods using the yield of polysaccharides as an indicator and found that enzyme extraction was the most efficient for extracting ASP. Li et al.[26] demonstrated that microwave extraction offers advantages such as time efficiency, higher efficacy, and energy conservation over ultrasonic extraction and direct heating methods. After purification, the polysaccharides need to be dried using methods like freeze drying or spray drying. The physicochemical properties of ASP can vary depending on the drying method. For example, vacuum drying results in excellent emulsifying and antioxidant properties, making it suitable for cosmetic additives; freeze drying reduces the product viscosity, improves the appearance, and produces smaller particle sizes, which is ideal for instant products; and hot air drying yields high viscosity, strong thrombin-inhibiting activity, and superior antioxidant capacity, making it highly bioactive and promising for use in food and pharmaceutical research[27]. Therefore, the extraction method of ASP should be optimized based on its intended application and properties to maximize its product value. The extraction methods of polysaccharides from *A. sinensis* are shown in Table 2.

Table 2
Extraction method of polysaccharides from *A. sinensis*.

Extraction methods	Process parameters	Yield (%)	Qualitative/quantitative methods	References
Hot water extraction	Solid-liquid ratio 1:5 (distilled water); extraction time 130 min; extract 5 times; anhydrous ethanol precipitation	5.6	ND	[23]
Ultrasonic extraction	Solid-liquid ratio 1:7, ultrasound power 180 W, extraction time 45 min, and extraction temperature 90 °C	6.96	ND	[24]
Enzyme extraction	1.0% cellulase, extraction temperature 60 °C, extraction time 60 min, pH 6.0, 1.0% pectinase, extraction temperature 50 °C, extraction time 60 min, pH 5.5	24.55 (cellulase); 24.81 (pectinase)	Qualitative: ND; Quantitative: ultraviolet spectrophotometer	[24-25]
Microwave-assisted extraction	Solid-liquid ratio 1:10, microwave high heat, extraction 3 times, each extraction for 4 min	14.1	Qualitative: ND; Quantitative: ultraviolet spectrophotometer	[25]

Note: ND, no data.

2.2 Volatile oils

Volatile oils are the main contributors to the characteristic aroma of *A. sinensis* and a major component of the plant. They primarily consist of phthalides, terpenes, phenols, and alkanes, with phthalides being the predominant active ingredients[28]. Over 100 volatile oil components have been isolated and identified so far[29], such as *Z*-hgustilide, angelicide, *n*-butylphthalide, senkyunolide 1, and levistolide A. The representative structures of these compounds are illustrated in Fig. 1A.

2.2.1 The characteristics of volatile oils

In terms of physical properties, the volatile oils of *A. sinensis* are typically colorless or pale-yellow liquids with a characteristic strong aroma. They have relatively low boiling points, which enable them to be easily volatilized during extraction processes[30]. The density of the volatile oils is generally lower than that of water, making them float on the water surface during separation. Their solubility in different solvents varies. For example, they are more soluble in organic solvents like ethanol, ether, and chloroform, while their solubility in water is relatively poor. This property influences the choice of extraction solvents and separation methods. Additionally, the refractive index of the volatile oils can be used as an important physical parameter for quality control and identification.

2.2.2 Extraction methods of volatile oils

Traditional extraction methods for volatile oils in *A. sinensis* include organic solvent extraction, steam distillation, and gas extraction[31]. LIG is the principal compound in *A. sinensis* volatile oil and was one of the first compounds isolated and identified from the herb. Its unsaturated phthalide structure is highly sensitive to moisture, heat, and light. Steam distillation can lead to partial denaturation of LIG, resulting in lower extraction efficiency[32]. To improve the yield of LIG during steam distillation, adding sodium chloride can reduce the solubility of the volatile oil in the aqueous phase[33]. By using sodium chloride at 1/5 of the weight of *A. sinensis*, the oil can reached 0.4%. Organic solvent extraction yields a higher LIG content than steam distillation, although residual solvents may remain in the final product. New extraction methods such as supercritical CO_2 extraction, microwave-assisted extraction, and ultrasonic-assisted extraction have improved extraction efficiency, preserved the chemical structure of active compounds, and minimized environmental impact. Supercritical CO_2 extraction can obtain

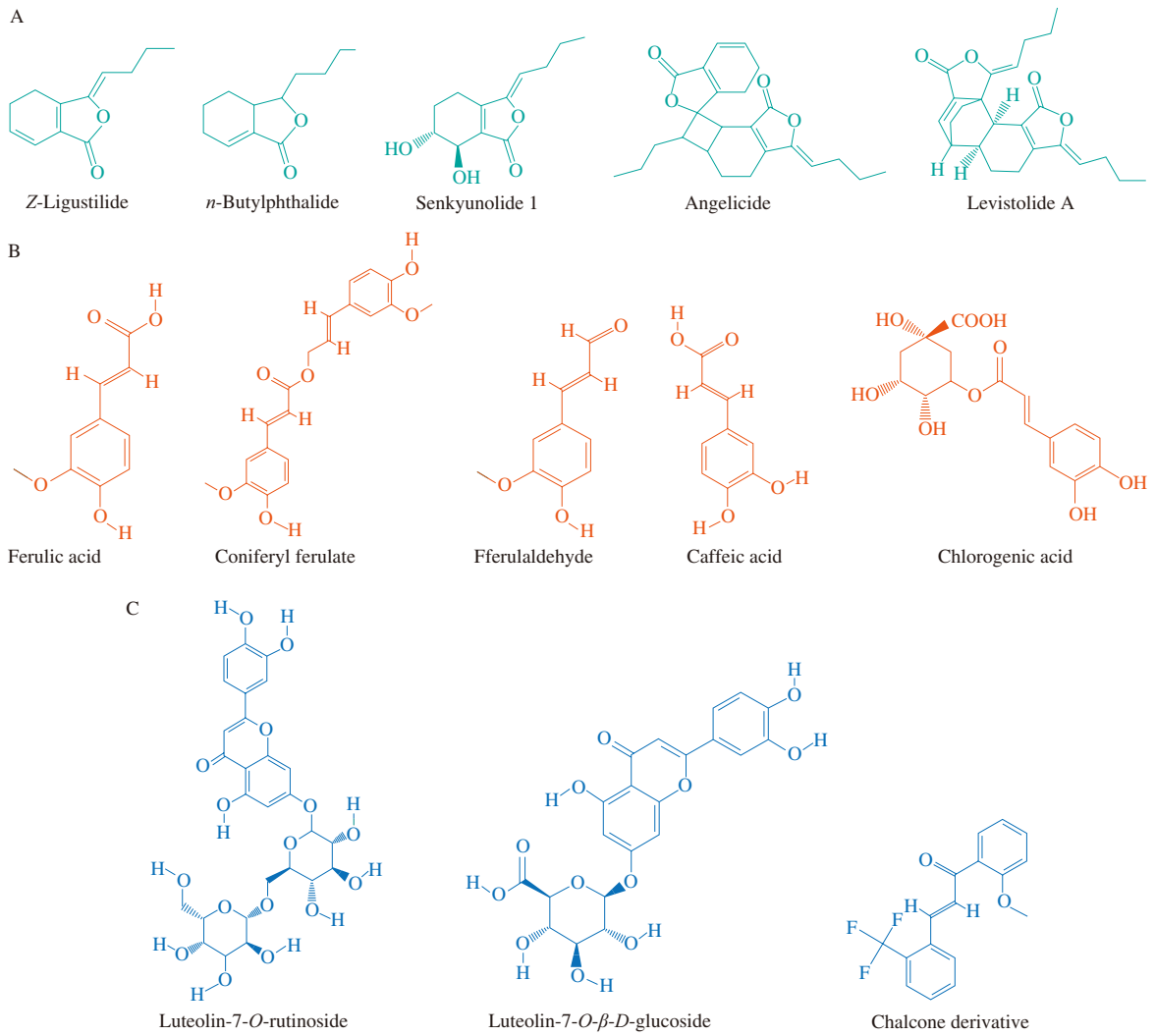

Fig. 1 Structures of volatile oils (A), organic acids and their derivatives (B) and flavonoids (C) in *A. sinensis*.

high-purity LIG with high transfer rates under optimal conditions (e.g., extraction pressure around 10−30 MPa, temperature at 40−60 °C, and extraction time within 1−3 h)[34], with yields between steam distillation and organic solvent extraction and being more environmentally friendly, suggesting that supercritical extraction is superior for preparing LIG. Microwave-assisted extraction can rapidly heat the sample using microwave radiation, shortening the extraction time from several hours to tens of minutes[35]. Ultrasonic-assisted extraction creates cavitation effects to disrupt cell walls and improve extraction efficiency, often using an ultrasonic frequency of 20−50 kHz and an extraction time of 30−60 min[36]. When choosing extraction processes, factors such as yield, chemical stability, cost-effectiveness, and environmental sustainability must be considered, as eco-friendly methods are essential for maximizing extraction efficiency. The extraction methods of representative volatile oils from *A. sinensis* are shown in Table 3.

2.3 Organic acids

Several key organic acids have been identified in *A. sinensis* through extraction and identification of the active components, including FA, chlorogenic acid, caffeic acid, coniferyl ferulate, and ferulaldehyde (Fig. 1B)[8]. Among them, FA was one of the earliest active compounds identified and isolated from *A. sinensis*, and it remains a primary organic acid component in the herb. FA is also recognized as a quality control marker for *A. sinensis* in the *Chinese Pharmacopoeia*, as well as for other medicinal plants like *Ligusticum chuanxiong* and *Ligusticum sinense*.

2.3.1 The characteristics of organic acids

Organic acids in *A. sinensis* possess distinct structural characteristics that contribute to their diverse biological activities. FA, one of the prominent organic acids in it, has a phenylpropanoid structure with a methoxy group at the para-position of the benzene ring and a carboxylic acid group attached to the side chain, which endows it with antioxidant and anti-inflammatory properties as reported in previous studies. Another important organic acid, chlorogenic acid, features a cinnamic acid core structure esterified with quinic acid, enabling it to participate in multiple physiological processes such as anti-microbial and anti-cancer activities as documented by relevant researches. Additionally, caffeic acid present in *A. sinensis* contains a catechol group in its benzene ring along with a carboxylic acid moiety, which plays a significant role in its ability to scavenge free radicals and modulate cellular signaling pathways according to some investigations. These characteristic structural features of the organic acids in *A. sinensis* are closely associated with their pharmacological functions and have attracted extensive attention in the exploration of its medicinal value.

2.3.2 Extraction methods of organic acids

The preparation methods for FA include percolation, flash/ethanol reflux extraction, ultrasound, and supercritical CO_2 extraction. Percolation is a commonly used method for extracting FA from *A. sinensis*, but it requires large amounts of solvent, extended processing time, and involves complex operations. A comparison between flash extraction and ethanol reflux extraction showed that, through response surface methodology optimization, flash extraction required only 1 min, which was only 1/150 of the time needed for ethanol reflux extraction, while also being simpler and yielding higher FA content[37]. As a polar solvent compound, the extraction rate of FA in *A. sinensis* can be improved with supercritical CO_2 extraction by selecting suitable entrainers[38]. In recent years, ultrasound-assisted enzymatic hydrolysis has been experimentally validated for obtaining high yields of FA, although enzymatic methods are often unstable and influenced by external factors. Research comparing ultrasonic-microwave enzymatic hydrolysis and ultrasonic-microwave alkaline hydrolysis concluded that the latter was more optimized, with lower costs, higher yields, and shorter extraction times[39]. A novel, efficient

Table 3
Extraction method of volatile oils from *A. sinensis*.

Ingredients	Extraction methods	Process parameters	Yield (%)	Qualitative/quantitative methods	References
Volatile oils (LIG)	Organic solvent extraction	Solid-liquid ratio 1:12 (g/mL, 70% ethanol), extraction 1 h, extraction temperature 50 °C	1.58	Qualitative: Thin layer chromatography; Quantitative: HPLC	[32]
	Steam distillation	Solid-liquid ratio 1:6, extraction 8 h, and the mass ratio of NaCl to the liquid is 1:5	0.42	Qualitative: ND; Quantitative: HPLC	[33]
	CO_2 supercritical fluid extraction	Extraction pressure 10 MPa, extraction temperature 50 °C, extraction time 20 min	ND	Qualitative: ND; Quantitative: HPLC	[34]

Note: HPLC, high-performance liquid chromatography; ND, no data.

Table 4
Extraction method of active ingredients from *A. sinensis*.

Ingredients	Extraction methods	Process parameters	Yield (%)	Qualitative/quantitative methods	References
Organic acids (FA)	Flash/ethanol reflux extraction	Solid-liquid ratio 1:12 (70% ethanol), extraction 1 min for flash, and 150 min for eflux extraction	0.60 (flash); 0.69 (ethanol reflux)	Qualitative: UV spectrum; Quantitative: HPLC	[37]
	Ultrasound extraction	Solid-liquid ratio 1:8 (1% NaOH), extraction temperature 51.8 °C, and extraction time 4.49 min	0.81	Qualitative: ND; Quantitative: HPLC	[38]
	Supercritical CO_2 extraction	Particle size was between 0.30−0.85 mm, the extraction pressure was 35 MPa, and the program of extraction temperature was 60−50−45 °C, 80% C_2H_5OH as entrainer	0.004 2	Qualitative: UV spectrum; Quantitative: HPLC, and GC-MS	[39]
	Temperature-controlled hydrophobic ionic liquids-based ultrasound/heating-assisted extraction	Solid-liquid ratio 1:40, extraction temperature 60 °C, ultrasound time 9 min, centrifugal speed 11 000 r/min and the centrifugal time 5 min	0.86	Qualitative: ND; Quantitative: HPLC	[40]

Note: UV, ultraviolet; ND, no data.

method for FA extraction and determination in *A. sinensis* involves hydrophobic ionic liquid-assisted ultrasound/heating extraction combined with HPLC[40]. This approach offers a simple, innovative, and effective way to extract active natural compounds, ensuring reliable development of *A. sinensis* products. The extraction methods of representative active ingredients from *A. sinensis* are shown in Table 4.

2.4 Flavonoids

2.4.1 The characteristics of flavonoids

Flavonoids are a class of important secondary metabolites in *A. sinensis*, which play significant roles in exerting various biological activities[41]. The flavonoids isolated from *A. sinensis* include luteolin-7-*O*-rutinoside, luteolin-7-*O*-*β*-*D*-glucoside, and chalcone derivatives (Fig. 1C). These compounds possess unique chemical structures that contribute to their potential pharmacological effects and have drawn considerable attention in the study of *A. sinensis*.

2.4.2 Extraction methods of flavonoids

There are various methods for extracting flavonoids from *A. sinensis*[42]. Decoction, reflux, and ultrasonic methods were employed for extracting total flavonoids from *A. sinensis*, finding that the ethanol reflux method yielded a higher total flavonoid content than the other two methods[43]. Total flavonoids were extracted from *A. sinensis* using ethanol extraction and determined that the optimal conditions for the highest flavonoid yield were a material-to-liquid ratio of 1:11 (g/mL), an ethanol concentration of 70%, and a temperature below 60 °C[44]. Excessive temperatures can reduce the stability of flavonoids and cause excessive extraction of impurities. Besides temperature, the concentration of ethanol also affects flavonoid extraction. Moreover, the concentration of ethanol also has a notable impact on flavonoid extraction. The ethanol extraction was used to obtain total flavonoids from *A. sinensis* leaves, finding that an ethanol concentration of 40%−60% was optimal for extracting flavonoid glycosides without interference from chlorophyll in the leaves[45]. The resulting extract had a high content of total flavonoids with a brown-yellow color. The extraction methods of representative flavonoids from *A. sinensis* are shown in Table 5.

2.5 Other components

Coumarins are one of the chemical components in *A. sinensis*, including compounds such as psoralen, isoimperatorin, imperatorin, osthol, xanthotoxin, and bergapten[46]. These compounds exhibit pro-apoptotic effects on growing cells, significantly inhibiting tumor cell proliferation, and also possess activities such as antidepressant, antiarrhythmic, and reduction of myocardial contractility[47].

Amino acids in *A. sinensis* are abundant and can be isolated by means of such as solubility separation and isoelectric precipitation. *A. sinensis* was extracted with hydrochloric acid and used an automatic amino acid analyzer to identify over 16 amino acids, with arginine, aspartic acid, and glutamic acid being the most abundant[48]. In 10 batches of *A. sinensis* samples, the total amino acid content ranged from 3.90% to 8.66%. The amino acid content was analyzed in different parts of *A. sinensis* and found that total extractable content varied by part, with amino acid levels in the order of head > body > whole > tail[49]. Given the physiological importance of amino acids along with the presence of nucleosides and bases in *A. sinensis*, it can be regarded a potential health food and is suitable for the development of nutraceutical products.

A. sinensis also contains 23 trace elements, including potassium, calcium, sodium, magnesium, aluminum, zinc, iron, silicon, phosphorus, manganese, nickel, copper, arsenic, selenium, strontium, tin, titanium, molybdenum, boron, rhenium, barium, vanadium, and chromium, of which 16 are essential for human health. Research on the vitamins in *A. sinensis* is limited, though it has been found to contain vitamin B_{12} and vitamin A. Additionally, *A. sinensis* includes other chemical components such as uracil, choline, adenine, phospholipids, and 5-hydroxymethylfurfural[6]. The extraction methods of representative active ingredients from *A. sinensis* are shown in Table 2.

3. Biosynthetic pathways of active components in *A. sinensis*

In recent years, the biosynthetic pathways of certain key components of *A. sinensis* have been studied by various methods such as molecular biology, synthetic biology, omics technologies, and artificial intelligence[50]. Through elucidation of these pathways and cloning and expression analysis of related key enzyme genes and transcription factors, the synthesis mechanisms of *A. sinensis* active components are gradually being revealed. Moreover, early bolting and cultivation conditions have been identified as critical factors regulating the synthesis and accumulation of these components by influencing gene expression. Therefore, this section will comprehensively analyze the biosynthetic pathways and regulatory factors of known active components in *A. sinensis*, providing a theoretical basis for quality improvement, variety enhancement, and precise cultivation.

Medicinal plants often encounter various ecological stresses during their growth and development, including pest infestations and abiotic stress, which can restrict the synthesis of active components, reduce their content, and alter the chemical structure, thus affecting the quality and efficacy of the medicinal materials[51].

Table 5
Extraction method of flavonoids from *A. sinensis*.

Extraction methods	Process parameters	Yield (%)	Qualitative/quantitative methods	References
Ethanol refluxing extraction	Solid-liquid ratio 1:40 (80% ethanol), extraction temperature 85 °C, extraction time 2 h	1.0	Qualitative: ND; Quantitative: ultraviolet spectrophotometer	[43]
Ethanol extraction	Solid-liquid ratio 1:11 (70% ethanol), extraction time of 2.5 h, and extraction temperature of 60 °C	0.002 3	Qualitative: ND; Quantitative: ultraviolet spectrophotometer	[44]
Ethanol refluxing extraction	Solid-liquid ratio 1:40 (40% ethanol), extraction temperature 85 °C, extraction time 1.5 h	9.2	Qualitative: ND; Quantitative: ultraviolet spectrophotometer	[45]

Note: ND, no data.

3.1 Polysaccharides

Plant polysaccharides, with their complex and diverse structures, have drawn research focus mainly on extraction techniques, structural analysis, and pharmacological functions, while studies on their biosynthetic pathways are relatively limited. However, understanding these pathways is crucial for grasping the formation and functions of polysaccharides in *A. sinensis*. The biosynthetic pathway of polysaccharides in plants generally involves three key steps[52]. First, sucrose converts into uridine diphosphate (UDP)-glucose, guanosine diphosphate (GDP)-mannose, and GDP-fucose. Second, UDP-glucose is further changed into other nucleoside diphosphate monosaccharides. Third, glycosyltransferases transfer monosaccharides from nucleotide sugar donors to build and export the polysaccharide polymer. Key enzymes involved include sucrose synthase, sucrose-phosphate synthase, invertase (INV), hexokinase, UDP-glucose pyrophosphorylase (UGPase), phosphomannomutase, and UDP-glucose-4-epimerase (UGE). Based on the composition of APS, INV, UGE, and UGPase are likely key enzymes in the biosynthetic pathway of ASP. Research on tissue expression of *A. sinensis* GAPDH revealed consistent and stable expression levels in the roots, petioles, and leaves, indicating that AsGAPDH may play a significant role in APS biosynthesis research[53].

Previous studies have offered more insights. For instance, some research on related plants revealed regulatory mechanisms where transcription factors were linked to key enzyme expression in polysaccharide biosynthesis, emphasizing a coordinated network[54]. Others focused on environmental factors influencing key enzyme activities, showing how temperature, light, etc., could affect reactions in synthesis[55]. Overall, though our knowledge is still growing, integrating past findings helps understand ASP biosynthesis better, highlighting the need for continued research.

3.2 Volatile oils

Volatile oils exhibit instability and are prone to undergo conversion under the influence of factors such as light and temperature. This results in the formation of diverse structures, thereby augmenting the complexity and difficulty in studying the biosynthesis of volatile oils in *A. sinensis*[53]. Phthalides, serving as significant components within the volatile oils of *A. sinensis*, have been the subject of extensive research. To date, a total of 53 phthalides, including *Z*-LIG, *E*-LIG, *n*-butylphthalide, LIG I, LIG H, LIG G, LIG A, LIG J, LIG, and others, have been identified from the extracts of *A. sinensis*[56]. Among them, the content of LIG is the highest. Previous studies have demonstrated that during different growth stages of *A. sinensis*, LIG can be converted into LIG A, LIG H, LIG I, angelicola A, and *n*-butylphthalide. However, it is worth noting that the content of LIG is substantially greater than that of its transformation products, which strongly suggests that LIG constitutes the core component among the phthalide compounds. The biosynthetic pathway of phthalides in *A. sinensis* remains largely unexplored, with numerous catalytic enzymes, metabolic substrates, and products yet to be identified. Studies suggest that enzymes such as 2-dehydro-3-deoxyphosphoheptanoate aldolase, shikimate dehydrogenase, primary amine oxidase, polyphenol oxidase, tyrosine decarboxylase, and shikimate-*O*-hydroxycinnamoyl transferase may be involved in the biosynthesis pathway of phthalide compounds[55].

3.3 Organic acids

FA is a quality control marker compound in *A. sinensis*, while chlorogenic acid serves as a key marker for its anti-inflammatory activity[57]. Therefore, this section focuses on summarizing the key enzymes and transcription factors for these two phenolic acid compounds. FA is a major product of the phenylpropanoid pathway, where the first three key enzyme-catalyzed reactions, PAL, C4H, and 4CL, are considered core to the entire metabolic process[58]. Other important enzymes include hydroxycinnamoyl transferase (HCT), cinnamoyl-CoA reductase (CCR), cinnamyl alcohol dehydrogenase (CAD), chalcone synthase (CHS), chalcone isomerase (CHI), coumarate-3-hydroxylase (C3H), flavanone 3-hydroxylase (F3H), flavonoid 3′-hydroxylase (F3′H), and F3′5′H, all of which play essential roles in the phenylpropanoid pathway. In *A. sinensis*, the synthesis and accumulation of FA proceed via the caffeic acid-*O*-methyltransferase (COMT) pathway and the caffeoyl CoA-*O*-methyltransferase (CCoAOMT) pathwayin[59]. The COMT pathway primarily synthesizes pharmacologically active compounds such as caffeic acid and FA, while the CCoAOMT pathway mainly produces compounds like coniferyl aldehyde and lignans, which have limited pharmacological activity[60]. In the CCoAOMT pathway, lignin synthesis occurs downstream of FA, and regulating key genes in this pathway can increase FA content while reducing lignin accumulation[59].

The key enzyme genes *AsPAL*[61], *As4CL*[62], *AsC3H*[63], and *AsCOMT*[64] have been successfully cloned and analyzed for expression in *A. sinensis*. Joint transcriptomic and metabolomic analyses comparing differentially expressed genes and metabolites between the head and tail of *A. sinensis* revealed that the tail had significantly higher FA content, and PAL, COMT, and peroxidase genes were more highly expressed[65]. These findings further support a close relationship between FA content and enzyme genes *AsPAL* and *AsCOMT*. The phenylpropanoid pathway is regulated not only by genes directly encoding biosynthetic enzymes but also by various regulatory genes, including transcription factors like v-myb avian myeloblastosis viral oncogene homolog (MYB), which influence the generation and accumulation of pathway products[66]. AsMYB4[67] and AsMYB44[68] may regulate the biosynthesis and accumulation of FA in *A. sinensis*. AsMYB44 potentially regulates the expression of genes like PAL, C4H, 4CL, and COMT within the phenylpropanoid pathway, thus positively controlling the synthesis and metabolism of phenolic acid compounds. While extensive research exists on key enzyme genes involved in FA biosynthesis, there is limited information on the regulatory function of transcription factors in this pathway, requiring further investigation.

Chlorogenic acid is also a product of the phenylpropanoid pathway in *A. sinensis*[59]. Currently, three proposed biosynthetic pathways for chlorogenic acid exist in plants, with key enzymes in these pathways including HQT, HCT, and C3H[69]. In the first pathway, HQT catalyzes the formation of chlorogenic acid from quinic acid and caffeoyl-CoA. In the second pathway, chlorogenic acid is synthesized from quinic acid and caffeoyl-*D*-glucose through catalysis by hydroxycinnamoyl glucose. In the third pathway,

chlorogenic acid is derived from *p*-coumaroyl quinic acid, catalyzed by HQT. The first pathway is currently considered the primary chlorogenic acid biosynthetic pathway[70]. Unfortunately, no relevant genes or transcription factors involved in the biosynthetic pathway of chlorogenic acid in *A. sinensis* have been reported to date.

3.4 Flavonoids

Flavonoid components play a significant role in the growth, development, and ecological defense of plants. When subjected to stress, flavonoids accumulate in large quantities, enhancing the plant's tolerance and resistance to adverse conditions[71]. In the biosynthetic pathway of flavonoids, phenylalanine is converted into *p*-coumaroyl CoA by three key enzymes: PAL, C4H, and 4CL. CHS is the key enzyme and rate-limiting step that directs the phenylpropanoid pathway towards the synthesis of flavonoid components. After CHS catalyzes the reaction of *p*-coumaroyl CoA to form naringenin chalcone, CHI can further catalyze the conversion of naringenin chalcone into naringenin[72].

Researchers have reported on the biosynthesis of flavonoid components in *A. sinensis* noting that the content of flavonoids in purple-stem *A. sinensis* is significantly higher than that in green-stem *A. sinensis*[73]. In the study of the differential mechanism of flavonoid biosynthesis between two varieties of *A. sinensis*, differentially expressed genes involved in the biosynthesis of flavonoid components were identified, including CHS1, CHI3, FHT, dihydroflavonol-4-reductase (DFR), flavonoid 3-*O*-glucosyltransferase 1 (F3GT1), UDP-glycosyltransferase 73C6 (UGT73C6), anthocyanidin synthase (ANS), and 3-malonyl-anthocyanin transferase 8 (3MAT8)[74]. This study further confirmed the important role of CHS and CHI in the biosynthesis of flavonoid components in *A. sinensis*. At the transcriptional level, the biosynthetic pathway of flavonoid components is mainly regulated by transcription factors such as MYB, basic helix-loop-helix (bHLH), and WD repeat-containing protein 40 (WD40)[75]. The MYB-bHLH-WD40 complex formed by these transcription factors can participate in the jasmonic acid signaling pathway in plants, affecting the synthesis of plant secondary metabolites by regulating the expression of downstream genes. The expression of the *CHS* gene is also regulated by transcription factors such as MYB, bHLH, WD40, and basic leucine zipper (bZIP)[76].

3.5 Coumarins

The biosynthetic pathways of some coumarin compounds have been reported, such as umbelliferone, scopoletin, and LIG. The biosynthesis process begins with the reaction of glucose to produce shikimic acid, which is then converted into aromatic amino acids like phenylalanine and tyrosine through the shikimate pathway. Phenylalanine can be converted into cinnamic acid, the starting material for coumarin synthesis, under the action of PAL[77]. Through the joint analysis of the genome, transcriptome, and metabolome of *A. sinensis*, researchers have identified key genes involved in the synthesis and regulation of simple coumarins in *A. sinensis*, and have mapped out the biosynthetic pathway for simple coumarins[78]. The study identified 81 enzyme genes that may be involved in the biosynthesis of simple coumarins, including *C4H*, *C3H*, *4CL*, *HCT*, *COMT*, *CCoAOMT*, coumarin synthase genes, and feruloyl-CoA-6′-hydroxylase (*F6′H*) genes. The study also calculated the correlation coefficients between the expression levels of these genes and the content of 4 metabolites: umbelliferone, scopoletin, LIG, and FA, laying the foundation for the functional validation of genes related to the biosynthesis of coumarin compounds in *A. sinensis*.

In summary, in this section, we have systematically sorted out the biosynthetic pathways of the identified active components in *A. sinensis* as well as the related functional genes. By summarizing the influencing factors on the synthesis and accumulation of active components in *A. sinensis*, we have provided a theoretical basis for improving the quality, breeding improved varieties, and implementing precision cultivation of *A. sinensis*. Moreover, we have also summarized some of the functional genes or regulatory genes involved in the biosynthesis of active components in *A. sinensis*. For detailed information, please refer to Table 6. In addition, the currently known biosynthetic pathways of the important active components in *A. sinensis* are illustrated in Fig. 2.

Table 6
Overview of cloned genes identified in *A. sinensis Radix*.

Gene name	Classification and function	Expression and effects in *A. sinensis*	References
AsCOMT	Involve in methylation, possibly participating in FA biosynthesis	Expression is high in roots and flowers; low expression in leaves	[64]
AsPAL	Involve in phenylpropanoid metabolic pathway, responsible for controlling the rate-limiting step of biosynthesis	Expression is high in roots, possibly involved in FA and coniferyl aldehyde biosynthesis	[61]
As4CL	Involved in the biosynthesis of various phenylpropanoid metabolites across species	Expression is high in roots, stems, and leaves; likely regulates FA biosynthesis	[62]
AsMYB4	MYB transcription factor family	Expression is low in roots, possibly involved in regulating phenylpropanoid metabolism	[67]
AsC3H	Involved in the P450 family, catalyzing the hydroxylation of *p*-coumaric acid at the C3 position in the lignin biosynthesis pathway	Expression is specific to certain tissues and may differ across tissues in response to environmental stimuli	[63]
AsDXR	Involved in the methylerythritol phosphate (MEP) pathway, crucial for the synthesis of terpenoids, including monoterpenoids, sesquiterpenoids, and diterpenoids	Expression is high in roots and low in other tissues, suggesting a role in the MEP pathway for key metabolites	[79]
AsEF-1β	Involve in protein synthesis and the response to abiotic stress	May be involved in the response to UV-B radiation	[80]
FT, *SOC1* (*SOC1-4*)	Important flowering-related genes	May be involved in the regulation of flowering time in *A. sinensis*	[81]
GA2ox6, *GA20ox1*	Repress *MADS-box* gene expression and regulate GA biosynthesis, delaying flowering; GA20ox1 converts GA12 to GA9	May be involved in the flowering regulation pathway in coordination with hormonal signals	[82]

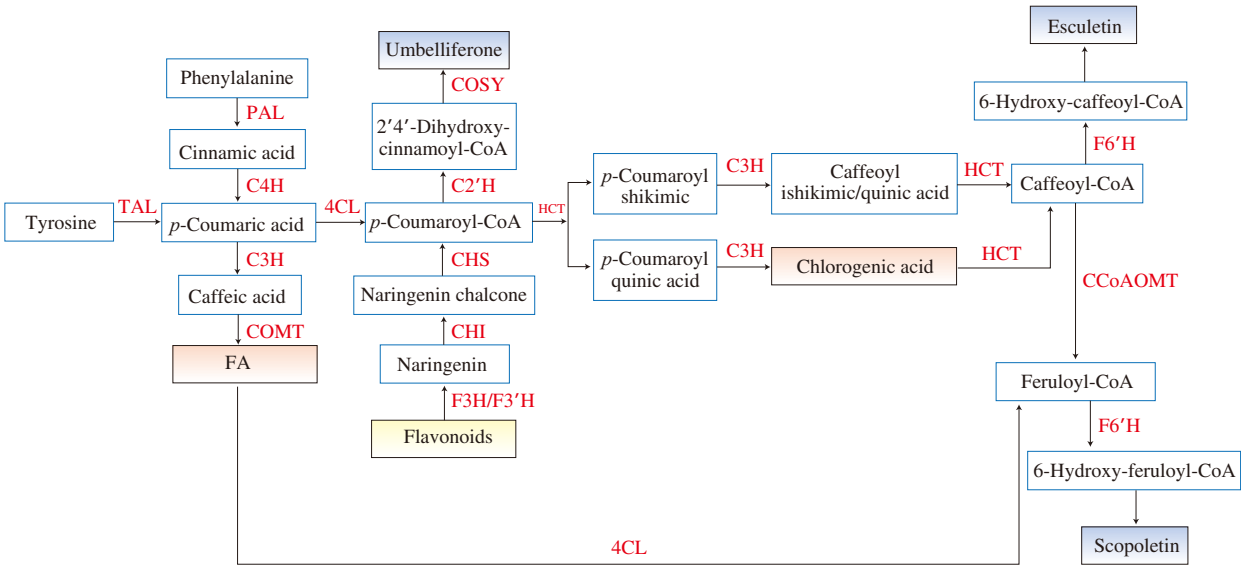

Fig. 2 Biosynthetic pathways of important active ingredients of *A. sinensis Radix*[41].

4. The bioactivity of *A. sinensis*

The bioactivity of *A. sinensis* has been extensively explored through numerous studies, and many *in vitro* and *in vivo* experiments have confirmed its broad health-promoting effects, including hepatoprotective, anti-inflammatory, immunomodulatory, anti-tumor, vasodilation, antihypertensive, neuroprotective effects (Table 7). The active components such as ASP, volatile oil, and organic acids[83-84], which can mediate various receptor molecules and multiple signaling pathways to improve hemodynamics, anti-platelet aggregation, inhibit inflammatory responses, combat oxidative stress reactions, and regulate blood lipids, having significant health benefits on the human circulatory, immune, nervous, and other systems.

4.1 Hepatoprotective

A. sinensis exerts multifaceted hepatoprotective effects through various bioactive components, acting via antioxidant, anti-inflammatory, immune regulation, anti-apoptotic, and bile secretion regulation mechanisms to protect against liver injuries caused by diverse factors. The primary component responsible for the hepatoprotective effects of *A. sinensis* is ASP, which primarily act by inhibiting lipid synthesis and enhancing lipid uptake. Ma et al.[85] conducted a detailed study on the hypolipidemic effect of ASP on non-alcoholic fatty liver disease. Their findings revealed that ASP could effectively reduce lipid content within the liver, inhibit fat regeneration, and significantly improve hepatic steatosis. This indicates its promising potential as a treatment for non-alcoholic fatty liver disease. The hepatoprotective effects of ASP are also prominently manifested in its ability to combat liver fibrosis and promote the regeneration and repair of damaged liver cells. Wang et al.[86] found it inhibits hepatic stellate cell activation through the interleukin (IL)-22/signal transducer and activator of transcription 3 (STAT3) pathway to alleviate carbon tetrachloride-induced chronic liver fibrosis. Moreover, ASP scavenges free radicals, combats oxidative stress-induced liver injury. Cao et al.[87] studied the acute liver injury induced by paracetamol and found that ASP significantly reduced the levels of serum alanine aminotransferase/aspartate aminotransferase in liver injury model mice, inhibited apoptosis and oxidative stress in liver tissue, upregulated the content of glutathione, indicating that ASP can be used as a hepatoprotective agent for the treatment of liver injury. ASP has high liver specificity. ASP has high liver specificity. Zhang et al.[88] found that fluorescein-labeled ASP was rapidly eliminated from the blood and distributed to the liver after intravenous injection. This is because ASP has a high density of galactose and branched-chain structures, which have a strong affinity for asialoglycoprotein receptors. These receptors mediate endocytosis and distribute the drug to the liver, making ASP a promising candidate as a new intrahepatic drug delivery vehicle. Leveraging the liver-targeting properties and inherent pharmacological activities of ASP can provide information for the development of preparations with preventive or therapeutic effects and can be developed as a new type of potential antioxidant.

Despite extensive animal experimental studies on the hepatoprotective effects of *A. sinensis*, clinical evidence is scarce, and more scientific and clinical experiments are needed to verify its hepatoprotective effects.

4.2 Anti-inflammatory and immunomodulatory activities

Excessive inflammatory responses can lead to a variety of diseases, thus inhibiting the occurrence of inflammatory reactions can reduce the incidence of diseases[122]. Zhou et al.[89] found that ASP can promote the proliferation of lipopolysaccharide (LPS)-induced mouse hippocampal neuronal HT22 cells, inhibit cell apoptosis, and suppress the production of IL-1β, tumor necrosis factor (TNF)-α, and IL-6 in inflammatory cells. The anti-inflammatory activity of ASP may be due to the upregulation of miR-10a expression in LPS-induced HT22 cells, blocking the activation of nuclear factor-kappa B (NF-κB) and Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathways. Xu et al.[90] discovered that ASP have a protective effect on sodium nitroprusside (SNP)-induced

Table 7
Biological activity and potential mechanism of active ingredients in *A. sinensis*.

Ingredients	Biological activity	Mechanism	References
ASP	Hepatoprotective	Reduce lipid accumulation and fatty regeneration	[85]
ASP	Hepatoprotective	Alleviates chronic liver fibrosis by inhibiting hepatic stellate cell activation through the IL-22/STAT3 pathway	[86]
ASP	Hepatoprotective	Suppress lipid peroxidation and oxidative stress, along with the inhibition of apoptosis to improve acetaminophen-induced acute liver injury	[86-87]
ASP	Hepatoprotective	High liver specificity due to affinity for asialoglycoprotein receptors, aiding in drug delivery to the liver	[88]
Angelica polysaccharide	Anti-inflammatory and immunomodulatory	Repress NF-κB and JAK2/STAT3 pathways by regulating miR-10a to mitigate LPS-evoked inflammatory injury	[89]
ASP	Anti-inflammatory and immunomodulatory	Activate ERK1/2-dependent autophagy in chondrocytes to rescue SNP-induced apoptosis	[90]
ASP	Anti-inflammatory and immunomodulatory	Inhibit myeloperoxidase activity, pro-inflammatory cytokine expression, and apoptosis to relieve dextran sodium sulfate-induced colitis	[91]
ASP	Anti-inflammatory and immunomodulatory	Enhances activation of immune cells and cytokine secretion, acting as an immune enhancer	[92]
Angelica polysaccharide	Anti-inflammatory and immunomodulatory	Upregulates immune cell and enhances immune response through STAT1 and STAT3 signaling pathways	[93]
ASP	Anti-inflammatory and immunomodulatory	Stimulates strong immune responses when encapsulated with OVA in nanoparticle carriers as vaccine adjuvant	[94]
ASP	Anti-tumor	Repress tumorigenesis of neuroblastoma cell line SH-SY5Y cells through miR-675-mediated inactivation of the PI3K/AKT and JAK/STAT pathways	[95]
ASP	Anti-tumor	Decrease hepcidin expression, which can reduce iron burden and inhibit tumor proliferation through JAK/STAT and bone morphogenetic protein (BMP)-mothers against decapentaplegic homolog (SMAD) pathways	[96]
ASP	Anti-tumor	Promote apoptosis of leukemia cells	[19]
ASP	Anti-tumor	Serves as a targeted drug delivery carrier, to improve tumor microenvironment and enhance immune function, resulting in synergistic antitumor effect with chemotherapy drugs	[97]
ASP	Anti-tumor	Serves as a drug delivery carrier targeting liver cancer, generates superior antitumor activity	[98]
Z-LIG	Anti-tumor	Induce ovarian cancer cell death by inducing oxidative stress	[99]
Z-LIG	Anti-tumor	Enhances tamoxifen therapy in resistant breast cancer by inhibiting autophagy.	[100]
ASP	Hematopoietic	Prevent the JAK, SMAD and ERK pathways to down-regulate hepcidin	[101]
ASP	Hematopoietic	Restore erythropoietin (EPO) production and improve iron availability by blocking GATA-binding factor 2 (GATA2) and NF-κB activation	[102]
ASP	Hematopoietic	Delay oxidative stress-induced premature senescence of 5-fluorouracil-treated feeder co-cultured hematopoietic cells via down-regulation of over-activated Wnt/*β*-catenin signaling	[103]
ASP	Hematopoietic	Promote the expression of *cyclinD2* mRNA, downregulate the surface content of CD44 and CD49d on mononuclear cells in the bone marrow	[104-106]
ASP	Hematopoietic	Regulate mitochondrial function to reduce ROS, MDA, and MAO levels, and inhibit excessive apoptosis of hematopoietic stem cells	[107]
ASP	Hematopoietic	Reduce oxidative stress and apoptosis via reactivation of nuclear factor erythroid 2-related factor 2 (Nrf2) and PI3K/AKT pathways	[108]
Volatile oil	Vasodilation and antihypertensive	Inhibit the release of calcium ions and the influx of external calcium, reduce ET-1, and increase NO to relax blood vessels	[109-110]
Volatile oil	Vasodilation and antihypertensive	Inhibit inflammatory and oxidative pathways, suppress the generation of VCAM-1 and C-reactive protein, and enhance the levels of SOD and CAT	[111]
Volatile oil	Vasodilation and antihypertensive	Downregulate the expression of AT1R and the vascular endothelial tissue SLC7A1 through miR122, antagonizing the renin-angiotensin system to regulate vascular endothelial signaling factors	[112-113]
A. sinensis injection	Vasodilation and antihypertensive	Inhibit the overexpression of transforming growth factor-beta 1 (TGF-β1)/PI3K pathway in liver tissue, reduce portal vein pressure, and regulate changes in portal vein hemodynamics	[114]
Volatile oil	Vasodilation and antihypertensive	Regulate the PI3K/Akt/endothelial nitric oxide synthase (eNOS) signaling pathway to reduce blood pressure	[115]
A. sinensis	Anticoagulation and anti-thrombotic	Inhibit adenosine diphosphate- or arachidonic acid-induced platelet aggregation	[116]
A. sinensis extract	Neuroprotective	Activate p38 MAPK-mediated p90 ribosomal S6 kinase (p90RSK)/phosphorylated Bcl-2-associated death promoter (p-Bad)-induced anti-apoptotic-Cytc/caspase-3-related and p90RSK/ cAMP-response element binding protein (CREB)/brain-derived neurotrophic factor (BDNF) survival signaling pathways	[117]
A. sinensis extract	Neuroprotective	activation of p38 MAPK-mediated CREB/BDNF, glial cell line-derived neurotrophic factor (GDNF), and VEGF-A signaling pathways	[118]
LIG	Neuroprotective	Penetrates blood-brain barrier, providing potential protective effects on the nervous system	[119]
LIG	Neuroprotective	Induct *α*-processing of APP and Klotho and potential Aβ clearance	[120]
Z-LIG	Neuroprotective	Inhibit p38 and activation of PI3K/Akt signaling pathways concurrently to improve Aβ fibrils-induced neurotoxicity	[121]

chondrocyte apoptosis. ASP can enhance autophagy by activating the extracellular signal-regulated protein kinase pathway, inhibiting SNP-induced chondrocyte apoptosis, making it a potential alternative for the treatment of osteoarthritis (OA). Cheng et al.[91] demonstrated that ASP can reduce the activity of myeloperoxidase in colonic tissue, regulate the expression of pro-inflammatory cytokines and related proteins, thereby inhibiting experimental colitis induced by dextran sulfate sodium in mice.

The immunomodulatory activity of *A. sinensis* is mainly reflected through ASP, whose regulatory mechanisms include promoting the activation of immune cells, regulating the secretion of cytokines, affecting the function of immune organs, promoting antibody production, and intervening in immune cell signaling pathways. The immune function of the body is closely related to the production and activation of T/B cells, natural killer cells, macrophages, and cytokines. ASP has the function of promoting the activation of various immune cells and enhancing the secretion of cytokines, and is considered an immune enhancer[8]. Wang et al.[92] compared the *in vitro* immunomodulatory activities of 5 ASPs and found that they have different immune-enhancing activities, all of which can cause lymphocyte proliferation and upregulate the secretion of interferon-γ, IL-2, IL-6, and TNF-α in peripheral blood lymphocytes. Shen et al.[93] showed that ASP can upregulate the number of immune cells such as peripheral blood and splenic myeloid suppressor cells to varying degrees, enhancing the immune function of the body. ASP can bind to various receptors on the surface of immune cells, activate different signaling pathways, enhance the protective immune response mediated by cellular and humoral immunity, and can be used as a vaccine adjuvant to enhance the immune effect of vaccines[94]. Studies have encapsulated ASP and ovalbumin (OVA) in poly(lactic-co-glycolic acid) (PLGA) to create a new type of nanoparticle vaccine carrier (ASP-PLGA/OVA) as a vaccine delivery system and adjuvant system for OVA, finding that ASP-PLGA/OVA can stimulate a strong humoral and cellular immune response, induce a strong and long-lasting Th1 and Th2 mixed immune response, and upregulate the levels of Th-related cytokines, suggesting that ASP can be used as an effective and safe adjuvant for vaccine delivery and treatment of infectious diseases. In addition, ASP was encapsulated into PLGA nanoparticles to develop an ASP-PLGA drug delivery system[123]. Compared with blank PLGA, ASP-PLGA significantly promoted lymphocyte proliferation and increased the ratio of $CD4^+$ T to $CD8^+$ T cells, indicating enhanced immune activity of ASP in the PLGA delivery system[124].

The effectiveness of ASP as an immunomodulator provides directional guidance for the development of *A. sinensis*-related immune regulation function products, but the mechanism of action of its specific components needs further evaluation and research.

4.3 The anti-tumor activity

The anti-cancer effects of *A. sinensis* are primarily manifested through ASP and *Z*-LIG, with related anti-tumor mechanisms including anti-proliferation, induction of tumor cell apoptosis, anti-metastasis, inhibition of tumor angiogenesis, and immune regulation through multiple molecular and signaling pathways[95,125]. Ren et al.[96] explored the impact of ASP on tumor growth and iron metabolism, discovering that ASP regulates the expression of hepcidin in the liver and serum, reducing the iron load in the liver, spleen, and transplanted tumors of tumor-bearing mice, thereby inhibiting the growth of tumor cells and transplanted tumors. This finding is of great significance for the treatment of cancer in patients with iron overload. Liu et al.[19] found that ASP-21 can activate the intrinsic apoptotic pathway to induce leukemia cell apoptosis, providing an effective basis for the mechanism of action against leukemia.

Regarding cancer treatment, a new therapeutic strategy combining chemotherapy with immunonano drug delivery is a promising approach to cancer treatment. ASP has specific tissue targeting properties, and during the drug delivery process as a drug carrier, it not only enhances immune function but also targets the corresponding pathological sites. This makes it a potential carrier for targeted drug delivery in cancer treatment, improving the tumor microenvironment, enhancing the body's immune function, and coordinating with chemotherapeutic drugs to exert anti-tumor effects[97]. Zhang et al.[98] studied ASP nanoparticles as targeted drug delivery for liver cancer and found that ASP nanoparticles internalize into liver cancer cells through receptor-mediated endocytosis, significantly inhibiting tumor growth, making it a good choice for cancer treatment. In addition, *Z*-LIG in *A. sinensis* also plays an anti-tumor role. Lang et al.[99] found that *Z*-LIG promotes apoptosis of ovarian cancer cells by inducing oxidative stress; Qi et al.[100] found that *Z*-LIG inhibits autophagy in tamoxifen-resistant breast cancer cells, thereby enhancing the therapeutic effect of tamoxifen *in vitro*, providing a new perspective for overcoming chemotherapeutic drug resistance.

A. sinensis has a promising application prospect in the treatment and prognosis of cancer patients. Developing new effective therapeutic drugs in a targeted manner provides a new strategy for the selection of chemotherapeutic and prognostic drugs, reducing the toxic side effects of chemotherapeutic drugs, improving chemosensitivity, reducing drug resistance, and improving prognosis.

4.4 The regulation of blood circulation

A. sinensis is widely used in traditional Chinese medicine for its blood-nourishing and blood-activating effects, which aligns with the modern medical research focus on regulating blood circulation. Circulatory disorders may lead to diseases such as hypertension, coronary heart disease, thrombosis, and atherosclerosis. These disorders are related to factors such as reduced blood volume, vascular stenosis, thrombus formation, and microcirculatory disturbances. The following discussion will focus on how *A. sinensis* regulates blood circulation by affecting these factors.

4.4.1 Improvement of hematopoietic function

ASP are the main active components of *A. sinensis* for improving hematopoietic function, used in the treatment of diseases related to blood deficiency, with significant therapeutic effects on anemia due to ischemia, chronic diseases, and kidney diseases[126]. The mechanism of action includes inhibiting the expression of hepcidin, regulating iron metabolism, promoting the synthesis of erythropoietin, and increasing the levels of red blood cells and hemoglobin[101]; inhibiting the expression of hepatic hepcidin, mobilizing iron from the spleen and liver to increase serum iron levels, restoring erythropoietin

production, improving iron utilization rate, and inducing anti-anemia effects[102]; inhibiting premature aging of hematopoietic cells induced by oxidative stress, delaying bone marrow suppression[103]. Zhang et al.[104], Rui et al.[105] and Wu et al.[106] found that ASP can promote the expression of *cyclinD2* mRNA, downregulate the surface content of CD44 and CD49d on mononuclear cells in the bone marrow to restore the hematopoietic function of irradiated mice. Zhang et al.[107] used polysaccharides from *A. sinensis* to intervene in a myelodysplastic anemia model in mice and found that it could reduce the levels of reactive oxygen species (ROS), malondialdehyde (MDA), and monoamine oxidase (MAO), increase the mitochondrial content in bone marrow cells, improve the mitochondrial membrane potential, enhance the stability of the mitochondrial membrane, repair the blood environment, and inhibit excessive apoptosis of hematopoietic stem cells. ASP also suppresses oxidative stress in the hematopoietic microenvironment, delaying the senescence of hematopoietic and bone marrow mesenchymal cells and slowing the degradation of hematopoietic function, which is closely linked to the treatment of chronic anemia[127]. The spleen, an important organ for human haematopoietic function, can produce red blood cells and plays a crucial role in maintaining normal haematopoiesis during severe ischaemia or certain diseases[128]. Du et al.[108] studied the antagonistic effect of ASP on 5-fluorouracil-induced injury and dysfunction of the spleen and splenocytes in mice and the possible mechanisms, finding that ASP could inhibit splenic injury and dysfunction by inhibiting oxidative stress and cell apoptosis, suggesting that ASP could be a potential alternative therapy for the treatment or adjunctive treatment of anemia.

Apart from ASP, there are relatively few studies on the effects of other components of *A. sinensis* on hematopoietic function. However, some studies have found through *in vivo* and *in vitro* experiments that FA, astragaloside (AST), formononetin (FRM), calycosin (CAL) and calycosin-7-*O*-*β*-glucoside (CLG) in *A. sinensis* can significantly increase the numbers of red blood cells, white blood cells, platelets and hemoglobin in peripheral blood as well as the area of bone marrow hematopoietic tissue, promote the proliferation of aging hematopoietic stem cells, reduce the positive rate and the proportion of cells in G0/G1 phase, increase the proportion of cells in G2/M + S phase and the expressions of cyclin D1 and CDK4 proteins, and the combination of these 5 components has the best effect[129-130].

In summary, ASP play a crucial role in improving hematopoietic function via multiple demonstrated mechanisms. This underlines its significance in hematopoietic disorder treatment and sets the stage for further exploration of its clinical potential.

4.4.2 Vasodilation and antihypertensive effects

Impaired vasodilation or hypertension can give rise to circulatory disturbances. Extensive studies have revealed that *A. sinensis* can regulate vascular-related factors, such as inhibiting the release of calcium ions and the influx of external calcium, reducing the content of endothelin-1 (ET-1) which has a vasoconstrictive effect, and increasing the content of nitric oxide to relax blood vessels[109-110]. It can also exert vasodilatory and antihypertensive effects by inhibiting inflammatory and oxidative pathways, suppressing vascular inflammatory responses, such as inhibiting the generation of vascular cell adhesion molecules (VCAM-1) and C-reactive protein, and enhancing the levels of superoxide dismutase (SOD) and catalase (CAT) in the body[111]. In addition, microRNA can regulate the expression of genes closely related to endothelial cell function, thereby modulating endothelial cells and vascular function, participating in the occurrence and development of hypertension[131]. Qu et al.[112-113] studied the pharmacodynamic mechanism of *A. sinensis* extract in treating hypertensive rats and found that the extract downregulated the expression of angiotensin II type 1 receptor (AT1R) and the vascular endothelial tissue SLC7A1 through miR122, antagonizing the renin-angiotensin system to regulate vascular endothelial signaling factors and exert vasodilatory effects. Additionally, it has been shown that LIG could regulate vasoconstriction by affecting the level of vasoactive substances such as ET-1, prostacyclin (PGI2), vascular endothelial growth factor (VEGF), renin, angiotensin II (AngII) level in serum, and regulate the ERK signaling pathway to lower blood pressure by activating the myocardial tissue AT1R target site[132]. Experimental studies have also found that *A. sinensis* can act on numerous signaling pathways involved in the process of vasodilation or blood pressure reduction, such as by increasing nitric oxide synthase (NOS), regulating extracellular protein kinases extracellular signal-regulated kinase 1/2 (ERK1/2), phosphatidylinositol 3-kinase (PI3K), and protein kinase B (Akt) signaling pathways, reducing blood flow resistance, enhancing the oxygen-carrying capacity of blood cells, regulating hemodynamic changes, and playing a role in lowering blood pressure[114-115].

4.4.3 Anticoagulation and anti-thrombotic effects

Antithrombotic therapy has emerged as a crucial objective in the treatment of ischemic disorders, such as cerebral ischemia. By reducing platelet aggregation, inhibiting the formation of new blood vessels within plaques, and facilitating fibrinolysis, the state of vascular infarction can be improved, thereby effectively preventing thrombosis. *A. sinensis* demonstrates a remarkable ability to bidirectionally regulate the body's coagulation system, possessing both anticoagulant and hemostatic effects. Recent investigations have revealed that *Z*-LIG exhibits significant neuroprotective effects against cerebral ischaemic injury in multiple animal models[133]. Orther studies have demonstrated that *Z*-LIG can dose-dependently reduce the weight of arterial thrombus in arteriovenous shunt thrombosis and suppress adenosine diphosphate-induced platelet aggregation in rats *in vivo*[134]. Moreover, FA in *A. sinensis* serves as an important marker for evaluating anti-platelet aggregation ability; it can inhibit the release of serotonin (5-HT) and thromboxane A2 (TXA2)-like substances, increase the PGI2/TXA2 ratio, and prevent platelet aggregation, thereby preventing thrombosis[116]. Additional activities about FA include inhibiting hepatic cholesterol synthesis, reducing lipid levels, and lowering cardiovascular disease risk factors[35,135-137].

4.5 Neuroprotective activity

The diverse bioactive components within *A. sinensis* play a crucial role in safeguarding the nervous system, as they possess significant potential for protective and therapeutic functions, especially in the context of cerebral ischemic injury[138-139]. The significance of these components in neuroprotection is underpinned by their ability to act through multiple pathways that target key aspects of neuronal health.

Among these pathways, the antioxidant activities and the inhibition of neuronal necrosis and apoptosis are particularly prominent in manifesting the neuroprotective effects of *A. sinensis*[140-141]. Cheng et al.[117] found that extracts of *A. sinensis* can activate the p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway, significantly increasing the survival rate of neurons in the hippocampal CA1 region, inhibiting their apoptosis, and protecting the hippocampus from ischemia-reperfusion injury. Furthermore, Cheng et al.[118] discovered that extracts of *A. sinensis* promote neuronal survival by enhancing p38 MAPK-mediated neurogenesis and dendritic growth in the hippocampus. Collectively, these findings vividly illustrate the multifaceted nature of the neuroprotective efficacy of the extracts of *A. sinensis*.

Despite its relatively low bioavailability due to the liver's first-pass effect, the volatile oil of *A. sinensis* has a unique brain protection advantage. It can easily penetrate the blood-brain barrier and enter the cerebrospinal fluid outside brain cells, with high selectivity in the cerebellum, thus playing a valuable role in safeguarding neurological health[119,142]. Specifically, LIG can exert neuroprotective effects against stroke through its antioxidant, anti-apoptotic, and anti-neuroinflammatory actions, making it a valuable therapeutic option for neurological disorders[143-144]. Its specific distribution in brain tissue allows for exploration of its potential applications in treating brain diseases. In addition, *Z*-LIG can induce the clearance of amyloid precursor protein, inhibit neurotoxicity, and has neuroprotective effects on Alzheimer's disease[120-121]. Moreover, FA contributes to its brain-protective and therapeutic profile through its ability to exhibit antidepressant effects by promoting energy metabolism activity[145].

In summary, the brain-protective activity of *A. sinensis* is multi-faceted, with different pharmacological activities being applicable to the treatment of various neurological diseases. This showcases the diverse and important pharmacological effects that *A. sinensis* can bring to bear in modern medicine.

5. Summary and future perspectives

A. sinensis (Oliv.) Diels has manifested remarkable potential within the realms of functional foods, pharmaceuticals, and cosmetics, owing to its diverse bioactivities and multi-component nature. Presently, research endeavors have predominantly centered on ASP, along with specific compounds such as FA and LIG. While these components have exhibited promising anti-tumor, antioxidant, and anti-apoptotic properties in the context of food product development, a considerable number of other constituents within *A. sinensis* remain relatively unexplored.

Regarding the biosynthetic pathways, there has been some progress in understanding those of certain active components such as phenolic acids, flavonoids, and coumarins. However, investigations into the key genes involved in these pathways have often been fragmented, lacking a holistic and systematic approach. In particular, for the more complex and unstable components like polysaccharides and FA derivatives, research is rather limited, both in terms of exploring their biosynthetic pathways and analyzing the functions of key genes. Additionally, it has been found that factors like early bolting and habitat conditions play a role in regulating the synthesis and accumulation of important active components in *A. sinensis* by influencing gene expression within the biosynthetic pathways, thereby impacting the content of these components.

Looking forward, given the pivotal role that natural products play in the development of novel functional foods, nutraceutical products, and drugs, *A. sinensis* is favorably positioned for further exploration. To fully unlock its potential, several aspects warrant focused attention. Firstly, optimizing the preparation procedures of *A. sinensis* extracts is of utmost importance for augmenting production efficiency and ensuring stringent quality control, thereby facilitating its broader application in functional foods. Secondly, a more in-depth exploration of the pharmacodynamics and bioavailability of its active components, particularly ASP, is indispensable for formulating more efficacious pharmaceutical products. The high biocompatibility and beneficial pharmacological effects of ASP render nanoparticles derived from it a promising candidate for drug delivery systems. Future studies should strive to further enhance their targeting capabilities and pharmacological activities, enabling precise targeting of affected areas in a variety of diseases, such as cancers and cardiovascular diseases, with the aim of maximizing therapeutic efficacy while minimizing adverse effects.

Furthermore, comprehensive research on the regulatory mechanisms governing the synthesis and accumulation of all active components, especially those of polysaccharides and FA derivatives, is urgently required. By understanding how environmental factors interact with these regulatory mechanisms, it will be possible to optimize cultivation and production practices, thereby harnessing the full potential of *A. sinensis* in practical applications. Overall, continued research in these directions will not only expand our understanding of this valuable traditional Chinese medicinal material but also create new opportunities for its utilization across diverse industries.

Conflict of interest

The authors of this manuscript declare that there is no conflict of interests regarding of the publication of this manuscript.

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