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REVIEW

Homeopathy for Heteropathy: FSS and Its Components for the Treatment of Alzheimer's Disease and Endometriosis

Yang Yu[1], Tiantian Sun[2], Jingyu Zhang[2], Songquan Wu[1], Xin Tong[3], Fazheng Zhao[3], Xin Fu[1]

[1]School of Medicine, Lishui University, Lishui, 323000, Zhejiang Province, People's Republic of China; [2]School of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin, 150040, Heilongjiang Province, People's Republic of China; [3]Zhejiang University of Traditional Chinese Medicine, Hangzhou, 310000, Zhejiang Province, People's Republic of China

Correspondence: Xin Fu, Email fu19511317872@sina.com

Abstract: Foshou San (FSS), which is a traditional Chinese compound formula. So far, a variety of components have been isolated and identified from its complex composition. These findings endow it with diverse pharmacological activities. According to a number of studies, FSS has significant efficacy in treating cognitive impairment in Alzheimer's disease (AD) and gynecological diseases like Endometriosis (EMs). Behind these curative effects, the specific chemical components of FSS play a crucial role. In this paper, the research progress of FSS in phytochemistry, pharmacology and pharmacokinetics are reviewed. Through comprehensive analysis of apoptosis regulation, oxidative stress and inflammation, ferroptosis, bile acid and intestinal flora, we further demonstrate the feasibility and potential of FSS in treating of AD and EMs. This not only reveals the potential mechanism of FSS, but also provides valuable experience and enlightenment for future research and application in related fields.

Keywords: Foshou San, component, alzheimer's disease, endometriosis, homeopathy for heteropathy

Introduction

Foshou San (FSS), also called Guixiong Tang (GXT), is a classic prescription in the ancient medical work "Pu-ji-beng-shi-fang", with the function of promoting blood circulation and removing blood stasis. It is composed of *Angelica sinensis* (AS) [Apiaceae; *Angelica sinensis* root] and *Ligusticum chuanxiong* (CX) [Apiaceae; *Ligusticum chuanxiong* rhizome] in a ratio of 2:1. AS is mainly planted in Gansu, China, with some also distributed in Yunnan, Sichuan, Shaanxi, and Hubei; CX is mainly planted in Sichuan, China, with some distribution in Yunnan, Guizhou, and Shaanxi. Their botanical characteristics are shown in Table 1. As a traditional Chinese compound formula, FSS is widely used in traditional medicine for gynecological and obstetric diseases such as fetal restlessness, postpartum lochia, abdominal pain, dysmenorrhea, as well as blood deficiency and blood stasis induced yellowing, dizziness, and body pain in regulating qi and blood. It has a long history of application and diverse practical experience.[1] In recent years, its efficacy in treating Alzheimer's disease (AD) has been discovered. AS is warm, sweet and pungent, nourishing blood and activating blood, regulating menstruation and relieving pain; CX is pungent and warm in nature, promoting blood circulation, removing blood stasis, promoting qi circulation and relieving pain, and is a qi medicine in blood. Both of them are commonly used drugs for enriching blood and promoting blood circulation in traditional Chinese medicine (TCM), which have the effects of promoting blood circulation, nourishing blood and promoting qi circulation. Therefore, taking both botanical drugs at the same time can enrich blood and dissipate blood stasis.

AD, a neurodegenerative disorder, can damage memory, cognition, and behavior, manifesting as dementia.[2,3] According to TCM theory, it is caused by stagnation of liver qi and blood stasis. Endometriosis (EMs) refers to the disease caused by endometrial glands or stromal cells outside the inner wall of uterine cavity, which usually occurs in women of reproductive age.[4] Hormone synthesis, immune inflammatory reaction, angiogenesis, invasion and metastasis,

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Table 1 The Botanical Characteristics of Angelica Sinensis and Ligusticum Chuanxiong

	Angelica sinensis	**Ligusticum chuanxiong**
Root et rhizome	The main root is thick and fleshy, cylindrical or conical in shape, with a surface ranging from yellow brown to dark brown, and roots have a strong aroma.	The rhizome is an irregular nodular fist shaped mass, with a surface ranging from yellow brown to dark brown, densely covered with circular nodes, and a concave stem mark at the top.
Stem	Upright, hollow, with longitudinal edges on the surface, usually purple in color.	Upright, cylindrical, hollow, with longitudinal edges on the surface and distinct nodes.
Leaves	The basal and stem leaves are both compound leaves with two to three lobes and three lobes, and the leaves are ovate to broadly ovate with serrated edges.	Basal leaves and stem leaves are two to three lobed compound leaves, with 3–5 pairs of leaflets. The leaves are ovate lanceolate in shape, and the edges are deeply lobed or entire.
Flower	Umbelliferae inflorescence terminal or lateral, inflorescence diameter 5–15 cm, small flowers white or light green	Umbelliferae inflorescence grows at the top or side, with small white flowers and 5 petals. The top is curled inward.

Note: The information comes from Zhiwu Zhi(www.iplant.cn).

and apoptosis are all considered as important pathogenesis.[5–7] According to the theory of TCM, "blood is unfavorable, water is produced", which is believed to be caused by blood stasis blocking the circulation of qi and blood. Therefore, TCM believes that AD and EMs have common symptoms such as "blood stasis" and "qi stagnation", which suggests that they can be treated with FSS. This reflects the multi-component, multi-target, and multi-therapeutic effects of TCM.

Emerging studies demonstrate that the combination of AS and CX in FSS exhibits significant synergistic effects in preventing and treating neurological disorders.[8] Experimental evidence indicates that FSS decoction ameliorates neurobehavioral deficits, reduces cerebral edema severity, and decreases infarct volume in rat models of cerebral ischemia.[9] Furthermore, FSS modulates the gut-liver-brain axis in APP/PS1 transgenic mice, rectifying intestinal dysbiosis while regulating alkaline phosphatase activity, lipopolysaccharide levels, and malondialdehyde concentrations, ultimately improving cognitive function in AD models.[10] In addition, studies have found that FSS has the effect of promoting blood circulation and removing blood stasis,[11–13] which can be used to treat AD and EMS. For example, verified through animal experiments and network pharmacology has[14] found that a new Chinese medicine formula "improved FSS", derived from FSS, can treat EMs by reducing angiogenesis, inhibiting invasion and metastasis, and regulating immunity.[15,16] At present, our research on the treatment of diseases with TCM prescriptions is more in-depth. We found that Chinese medicine has the advantages of multi-target and multi-channel in treating diseases. After summarizing many literatures, we found that there are many common KEGG and GO enrichment pathways in the network pharmacological search and treatment of AD and EMs by FSS, such as cancer pathway, biological regulation, stimulation response cell projection pathway, and chromium binding pathway.[17,18] In addition, a large number of clinical trials have shown that the main components of FSS, such as Ferulic acid (FA)[19] and Ligustrazine[20] have significant therapeutic effects on AD and EMs.[21,22] FSS was originally developed for gynecological conditions, its recent experimental validation in AD therapeutics prompted our multidimensional analysis. We hope to use this to comprehensively elucidate the pharmacological mechanism of FSS and to establish a translational framework connecting traditional therapeutic uses with novel neurological applications. This dual perspective not only enhances our understanding of FSS's polypharmacological effects but also provides methodological references for expanding TCM applications in modern medicine. About how FSS and its active components affect both AD and EMs, we drew Figure 1 to explain and summarize.

Phytochemistry

Components of FSS

Due to the inherent complexity of TCM and its formulations, a multimodal analytical approach is required to comprehensive quality assessment. As an integrative identification technology, chromatographic fingerprinting has become pivotal in TCM quality control. This technique not only provides comprehensive chemical profiling but also enables quantitative analysis of

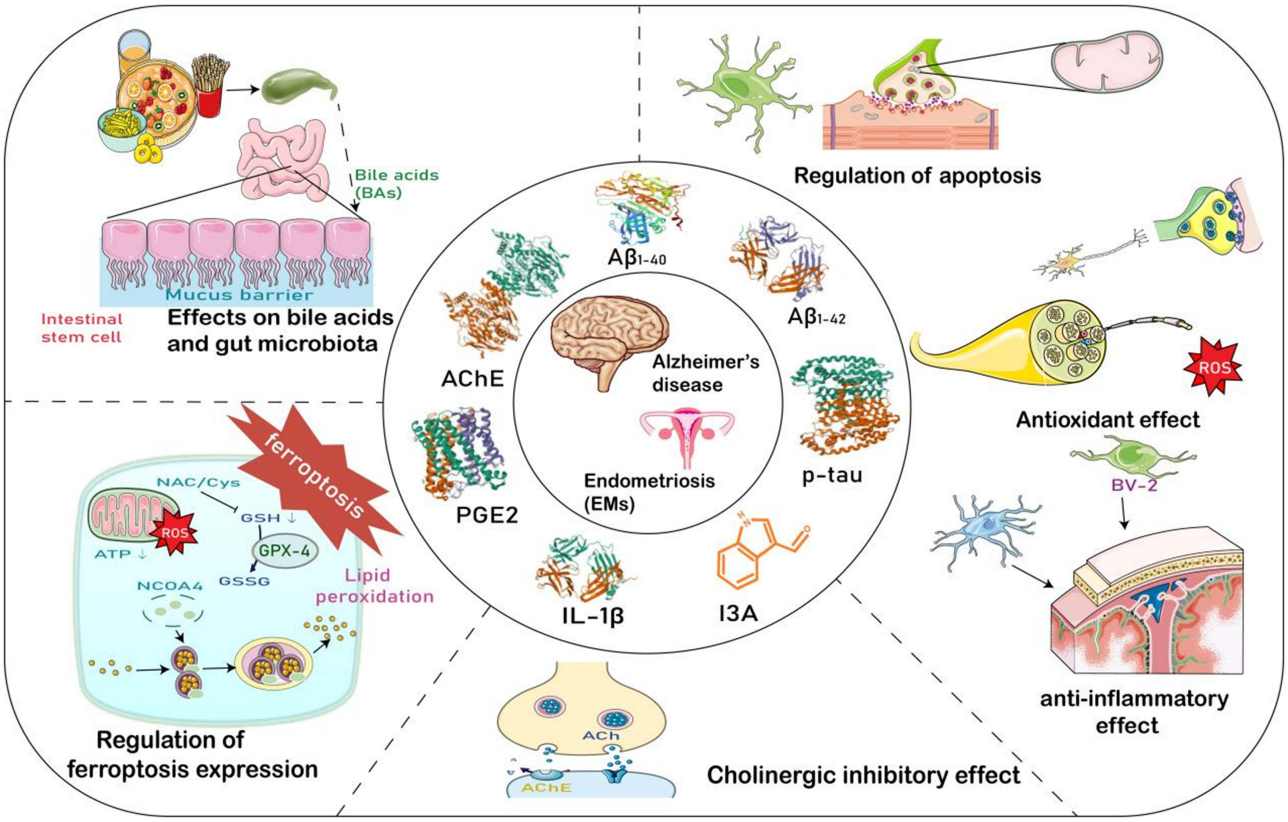

Figure 1 How FSS and its active components affect both AD and EMs.

characteristic components, thereby ensuring the authenticity, superior quality, and batch-to-batch consistency of crude drugs and their intermediate products. Additionally, research has found that compared to a single decoction of AS or CX, FSS does not produce any new components, but it helps to dissolve the active ingredients[23] Therefore, we screened literature from the recent years on PubMed and CNKI using "Angelica sinensis (Danggui)", "Ligusticum chuanxiong (Chuanxiong)", "Foushou San", and "component", as the keywords. A total of 167 relevant components were collected, including Phthalides, Organic acids, Phenols (excluding phenolic acids), Nitrogen-containing components, etc. Then, we associated different types of components with AD and EMs to discover their roles in these diseases.

Phthalides

Phthalides, widely present in Apiaceae plants, are a class of organic components with special structures and properties. A total of 58 components were identified, including common FSS phthalide components such as N - butylphthalide, Ligustilide, and Senkyunolide. Research has found that phthalides have vasodilatory effects,[24] which may be related to the blood activating and stasis removing effects of FSS. This suggests that phthalides are an important component of FSS in the treatment of AD. For example, Zhu et al found that Ligustilide can improve memory impairment in mice.[25] N-butylphthalide can improve learning and memory in cognitively impaired rats, and can be used to treat cognitive dysfunction in neurodegenerative diseases, such as AD.[26] Senkyunolide has the effects of improving inflammation, ischemic stroke, neuroprotection, and improving AD.[27,28] The relevant components are listed in Table 2, and the corresponding structures are shown in Figure 2.

Organic Acids

Organic acids refer to certain organic components that are acidic, and the organic acids in FSS are mainly phenolic acids. It is known that the phenolic acids isolated from FSS include FA, Chlorogenic acid (CGA), Caffeic acid (CA) etc. They are believed to have analgesic, anti-inflammatory, antioxidant, and platelet aggregation inhibiting effects,[32] among which FA has been proven to improve the symptoms of AD by preventing neurodegeneration in several brain regions, inhibiting

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Table 2 Phthalides in FSS

NO.	Component	Category	Ref
1	(3′Z)-(3S,8S,3a′S,6′R)-4,5-dehydro-3.3′a,8.6′-diligustilide	Phthalides	[29]
2	(3′Z)-(3S, 8R, 3a′S, 6′R)-4,5-dehydro-3.3a′,8.6′-diligustilide	Phthalides	[29]
3	Z-senkyunolide E	Phthalides	[24]
4	(Z, Z')-6,8',7,3'-diligustilide	Phthalides	[24]
5	3,8-Dihydrodiligustilide	Phthalides	[24]
6	3-Butyl-4-hydroxyphthalide	Phthalides	[24]
7	3-Butylidene-6-hydroxy-5,6-dihydrophthalide	Phthalides	[24]
8	3-Butylidene-7-hydroxyphthalide	Phthalides	[24]
9	3-Butylidenephthalide	Phthalides	[24]
10	3-Carboxyethyl-phthalide.	Phthalides	[24]
11	E-senkyunolide E	Phthalides	[24]
12	4,5-Dihydro-3-butylidenephthalide	Phthalides	[24]
13	4,5-Dihydro-3-butylphthalide	Phthalides	[24]
14	4,7-Dihydroxy-3-butylphthalide	Phthalides	[24,30]
15	4-Hydroxy-3-butylphthalide	Phthalides	[30]
16	Angelicide	Phthalides	[24,30]
17	Ansaspirolide	Phthalides	[24]
18	2-(1-Oxopentyl)-benzoic acid methyl ester	Phthalides	[24]
19 20	Chuanxiongnolide A Chuanxiongnolide B	Phthalides	[24]
21	Cnidilide	Phthalides	[24]
22	Teylusticolactone D	Phthalides	[30]
23	Ligusticolactone epoxide	Phthalides	[30]
24	E-Ligustilide	Phthalides	[24,30,31]
25	Levistolide A	Phthalides	[24,30]
26	Ligusticoside A	Phthalides	[24]
27	N-butylphthalide	Phthalides	[24,30]
28	Z-ligustilide dimer E-232	Phthalides	[24]
29	Neocnidilide	Phthalides	[24,30]
30	5-Hydroxy-3-butenylphthalein	Phthalides	[30]
31	Riligustilide	Phthalides	[24]
32	Senkyunolide A	Phthalides	[24,30,31]
33	Senkyunolide B	Phthalides	[24,30]
34	Senkyunolide C	Phthalides	[24]

(*Continued*)

Table 2 (Continued).

NO.	Component	Category	Ref
35	Senkyunolide D	Phthalides	[24,30]
36	Senkyunolide E	Phthalides	[24,29]
37	Senkyunolide F	Phthalides	[24,30]
38	Senkyunolide G	Phthalides	[24,30]
39 40	Senkyunolide H Senkyunolide I	Phthalides	[24,30]
41	Senkyunolide J	Phthalides	[24,30]
42	Senkyunolide K	Phthalides	[24,30]
43	Senkyunolide L	Phthalides	[24]
44	Senkyunolide M	Phthalides	[24,30]
45	Senkyunolide N	Phthalides	[24,30]
46	Senkyunolide O	Phthalides	[24]
47	Senkyunolide P	Phthalides	[24]
48	Senkyunolide Q	Phthalides	[24,30]
49 50	Senkyunolide R Senkyunolide S	Phthalides	[24,30]
51	Tokinolide B	Phthalides	[24]
52	Wallichilide	Phthalides	[24]
53	Z-6-hydroxy-7-methoxy-ligustilide	Phthalides	[30]
54	Z, Z'-3,3',8,8'-diligustilide	Phthalides	[24]
55	(Z)-3-butylidenephthalide	Phthalides	[29]
56	Z-6,7-epoxyligustilide	Phthalides	[24]
57	Z-Butenylphthalide	Phthalides	[32]
58	Z-Ligustilide	Phthalides	[24,30]

the aggregation of Aβ oligomers, and exerting antioxidant, anti-inflammatory and anti-apoptotic effects.[33] The relevant components are listed in Table 3, and the corresponding structures are shown in Figure 3.

Phenols (Excluding Phenolic Acids)

Phenol components refer to substances with natural plant hormone activity, including phenolic aldehydes, phenolic esters, coumarins, flavonoids etc. Coumarin components are an important class of organic components. More than 10 kinds of coumarins, including Umbelliferone, Umbelliferone 6-carboxylic acid, Nodakeninand Nodakenetin, were isolated from AS, which have antihypertensive, neuroprotective, anti-amnesic, antioxidant, anti-diabetic and anti-AD effects.[34] Flavonoids are a class of components that are widely found in plants and have a variety of biological activities, including antioxidant, anti-cancer, anti-inflammatory, hypolipidemic, cardiovascular, and cerebrovascular protection and other effects. The relevant components are listed in Table 4, and the corresponding structures are shown in Figure 4.

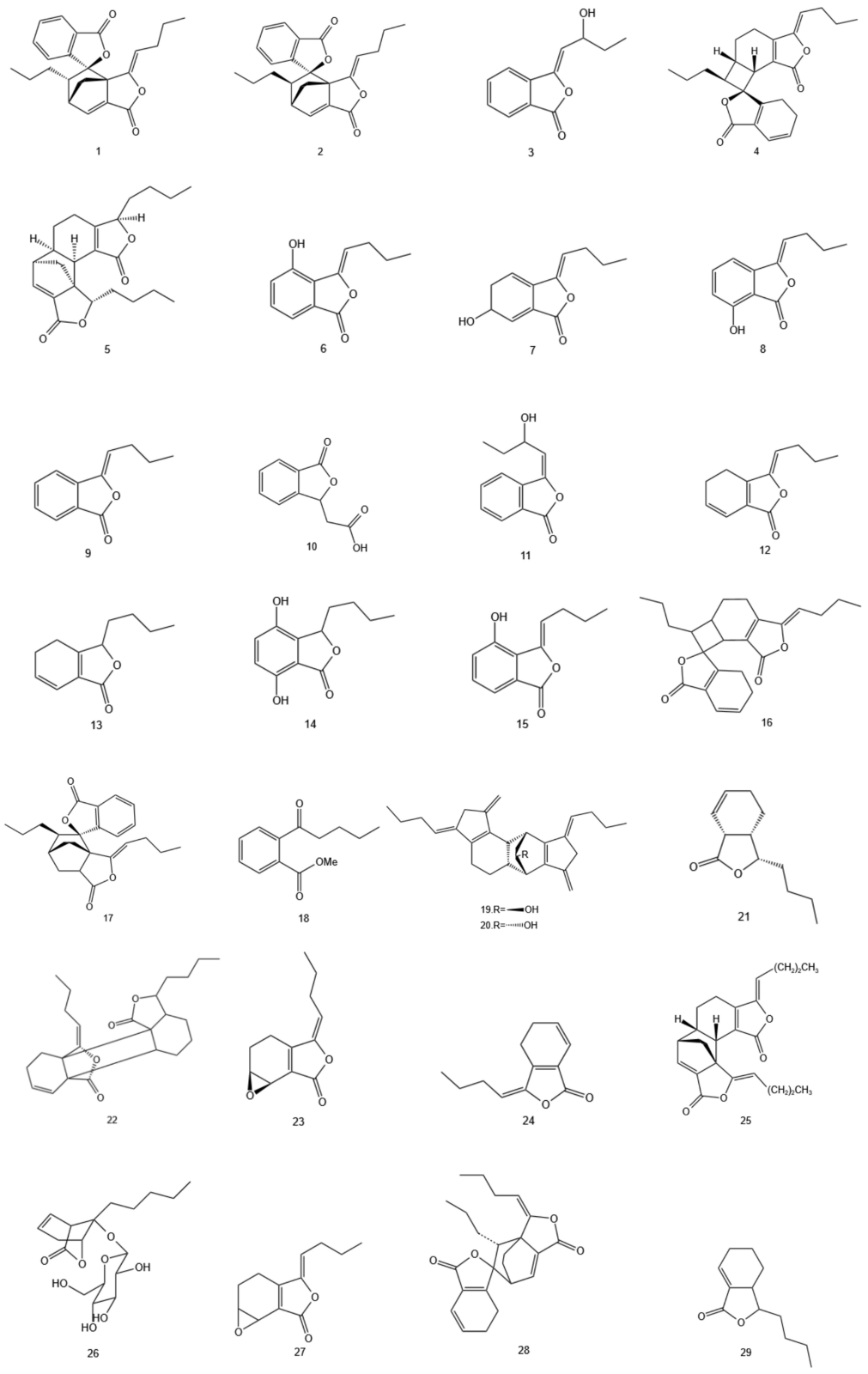

Figure 2 Continued.

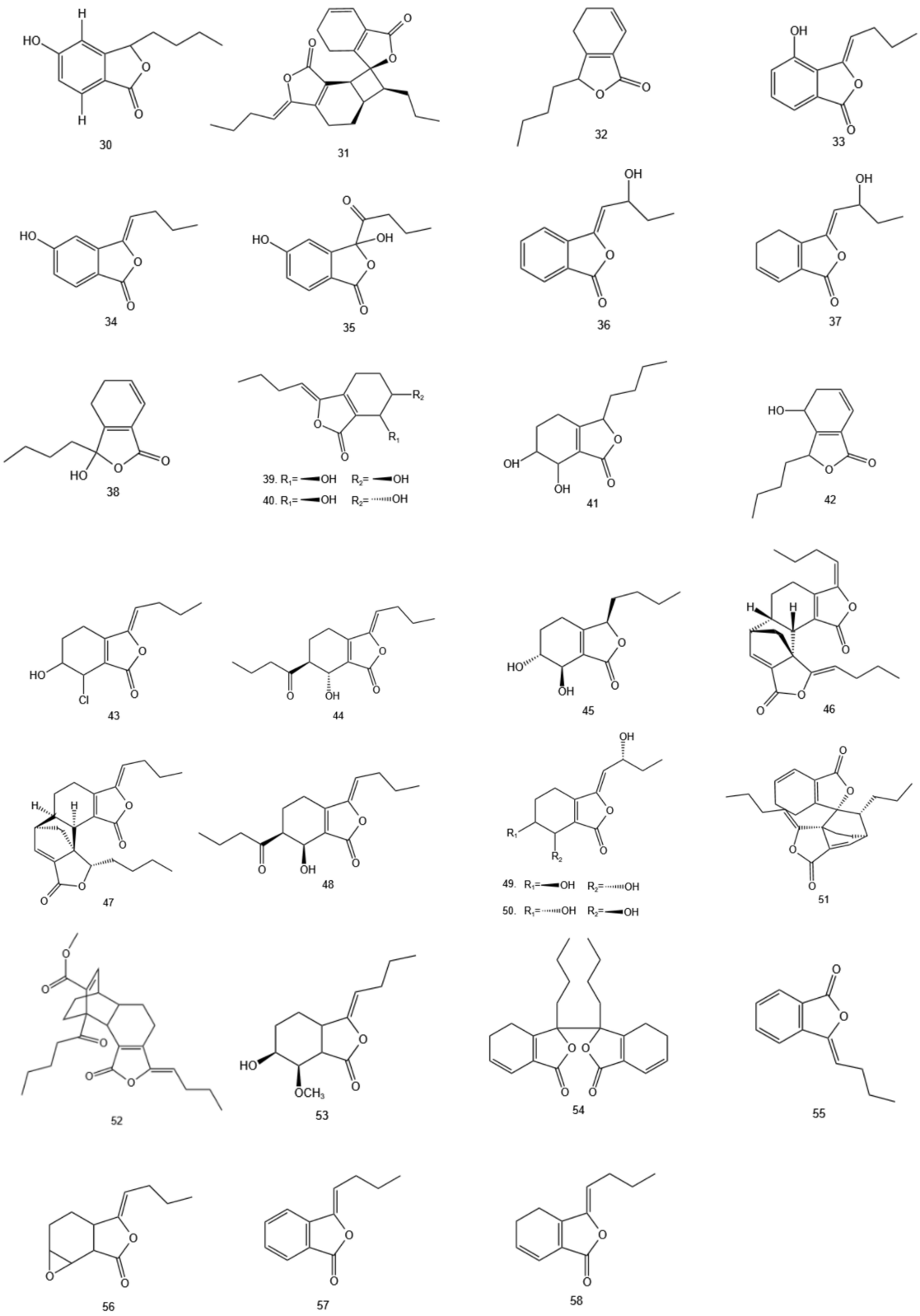

Figure 2 Structure of Phthalide components.

Nitrogen Components

This section includes Alkaloids, Amino acids, Amides etc. Alkaloids are a class of nitrogen-containing organic components primarily derived from plants, and Alkaloids have a cyclic structure with nitrogen atoms mostly embedded

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Table 3 Organic Acids in FSS

NO.	Component	Category	Ref
1	Azelaic acid	Dicarboxylic acid	[30,31]
2	Suberic acid	Dicarboxylic acid	[30]
3	Citric acid	Hydroxycarboxylic acid	[30]
4	L-Malic acid	Hydroxycarboxylic acid	[30]
5	13-Hydroxy-9,11-octadecadienoic acid	Hydroxy fatty acid	[30]
6	P-anisic acid	Aromatic carboxylic acids	[31]
7	Veratric acid	Aromatic carboxylic acids	[31]
8	Quinic acid	Cyclohexanecarboxylic acid	[30]
9	Sedanonic acid	Cyclohexanecarboxylic acid	[24]
10	Caffeic acid	Phenolic acid	[24,30]
11	Chlorogenic acid	Phenolic acid	[30]
12	Ferulic acid	Phenolic acid	[24,30]
13	Gallic acid	Phenolic acid	[24,30]
14	Isochlorogenic acid	Phenolic acid	[32]
15	Isoferulic acid	Phenolic acid	[30]
16	Isovanillic acid	Phenolic acid	[31]
17	Neochlorogenic acid	Phenolic acid	[30]
18	P-coumaric acid	Phenolic acid	[30]
19	Phydroxybenzoic acid	Phenolic acid	[24]
20	Salicylic acid	Phenolic acid	[30]
21	Vanillic acid	Phenolic acid	[24, 30, 31, 34]
22	1,3-Dicaffeoylquinic acid	Phenolic acid	[30]
23	1,4-Dicaffeoylquinic acid	Phenolic acid	[30]
24	1,5-Dicaffeoylquinic acid	Phenolic acid	[30]
25	3-O-Feruloylquinic acid	Phenolic acid	[30]
26	Cryptochlorogenic acid	Phenolic acid	[30]
27	Protocatechuic acid	Phenolic acid	[24,30]
28	Sinapic acid	Phenolic acid	[24]
29	Palmitic acid	Saturated fatty acids	[24]
30	Lignoceric acid	Saturated fatty acids	[24]
31	Linoleic acid	Unsaturated fatty acid	[24]
32	10,12-Octadecadienoic acid	Unsaturated fatty acid	[32]
33	8,11,14-Eicosatrienoic acid	Unsaturated fatty acid	[32]

(*Continued*)

Table 3 (Continued).

NO.	Component	Category	Ref
34	Succinic acid	Dicarboxylic acid	[24]
35	Fumaric acid	Dicarboxylic acid	[31]

in the ring. They have significant physiological activity and are active components in Chinese botanical drugs. Alkaloids represented by Ligustrazine have significant effects in the treatment of AD and EMs.[35,36] In addition, Amino acids and Amides are also believed to have a protective effect on blood vessels.[25,26] The relevant components are listed in Table 5, and the corresponding structures are shown in Figure 5.

Other Components

The components include Terpenes and their derivatives, Vitamins, Polysaccharides etc. Terpenes are volatile and aromatic oily components, and studies have found that terpenes can improve vascular function.[29] Vitamins are a class of trace organic substances that humans and animals must obtain from food in order to maintain normal physiological functions, which play an important role in the process of human growth, metabolism and development, and can improve the body's immunity. Recent studies have found that folic acid can alleviate symptoms of AD by reducing inflammation.[37] It is worth noting that Polysaccharides, which are polymerized carbohydrates formed by the condensation and dehydration of multiple monosaccharide molecules, and their molecular structure is complex and large. Polysaccharides are widely distributed in nature, some of which constitute the components of animal and plant cell walls, such as cellulose; some are nutrients stored by animals and plants, such as glycogen and starch, and some have special biological activities. For example, *Angelica sinensis* polysaccharides (ASP) is considered to have unique effects in improving anemia, anti-inflammatory, antioxidant, immune regulation, and other aspects[38] and Ligusticum chuanxiong polysaccharides have various biological activities such as promoting immunity.[39] The relevant components are listed in Table 6, and the corresponding structures are shown in Figure 6.

The Main Active Components and Chemical Structure of FSS

AS and CX, both belonging to the Apiaceae family, exhibit significant phytochemical similarities that underlie their frequent combination in TCM formulations. Literature analysis reveals that 16 common characteristic peaks in the FSS fingerprint predominantly originate from these two botanical drugs, corroborating their component consistency. Shared bioactive components include phenolic acids (CGA, CA, FA) and phthalide derivatives (Butylphthalide, Ligustilide, and Senkyunolide).[41] Notably, CX possesses distinctive marker components such as Ligustrazine, which may contribute to its unique pharmacological properties. These phthalide derivatives and alkaloids demonstrate significant pharmacological activities in TCM preparations, playing crucial roles in ensuring therapeutic efficacy and medication safety. Particularly, the characteristic components Ligustrazine and Senkyunolide series are considered as key biomarkers underlying CX's specific medicinal actions. The common components after FSS extraction are shown in Figure 7.

Based on the above content, we believe that the most essential active ingredients are phthalides and organic acid compounds, as they are the most abundant and diverse in FSS. Therefore, we have included these two categories of compounds in Tables 2 and 3. Some of their components, such as CGA, CA, FA, and Butylphthalide, have been proven to play a key role in the treatment of AD and EMs. Additionally, emerging evidence highlights the indispensable role of polysaccharides in FSS-mediated therapeutic effects.

CGA regulates lysosomal function in SH-SY5Y cells derived from APP/PS1 AD model mice. This regulatory process inhibits the autophagy induced by Aβ25-35, thereby alleviating CA1 neuronal loss and cognitive deficits in vivo, providing a new idea for the treatment of AD.[42] It is worth mentioning that CGA not only has a protective effect on the nervous system, but also has been found to have a targeted therapeutic effect on EMs. Through complex network analysis, scientists further confirmed the beneficial effect of CGA on EMs, opening up a new way for the treatment of this common gynecological disease.[43] Similarly, CA can reduce cellular dysfunction, oxidative stress damage and

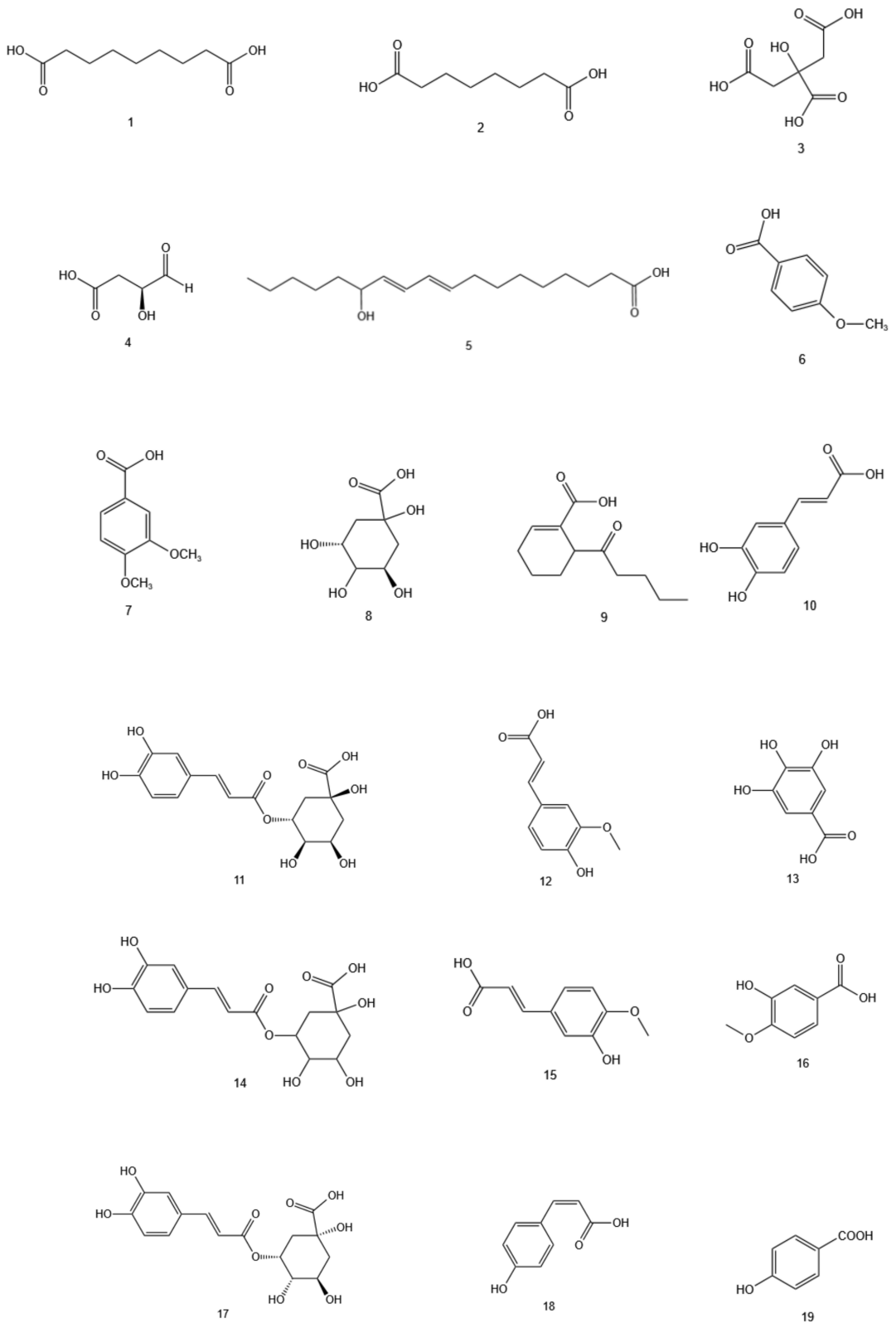

Figure 3 Continued.

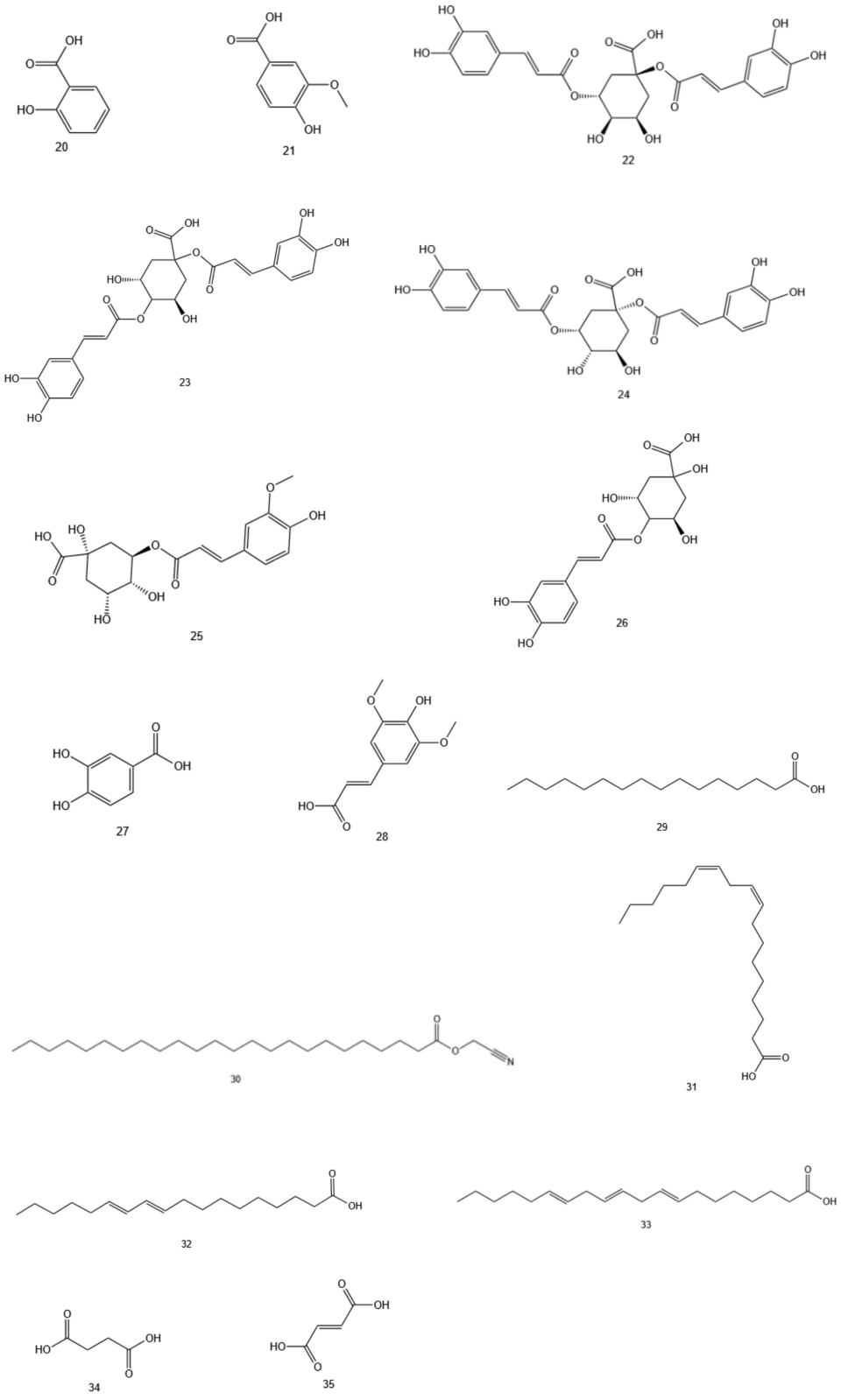

Figure 3 Structure of Organic Acids components.

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Table 4 Phenols (Excluding Phenolic Acids) in FSS

NO.	Component	Category	Ref
1	1-Hydroxy-1-(3-methoxy-4-hydroxyphenyl)-ethane	Phenolic derivatives	[24]
2	3-Methoxy-4-hydroxystyrene	Phenolic derivatives	[24]
3	5-Hydroxymethyl-6-endo-3-methoxy-4-hydroxyphenyl-8-oxa-bicyclo(3.2.1)-oct-3-one	Phenolic derivatives	[24]
4	Butylparaben	Phenolic esters	[30]
5	Coniferyl ferulate	Phenolic esters	[30]
6	Vanillin	Phenol aldehyde	[24,30,31]
7	Chrysophanol	Anthraquinones	[24]
8	Ethyl ferulate	Phenolic esters	[31]
9	Scopoletin	Coumarins	[24,30]
10	Nodakenin	Coumarins	[34]
11 12 13 14	Pd-C-I Pd-C-II Pd-C-III Decursidin	Coumarins	[34]
15	2′-Isopropyl psoralen	Coumarins	[34]
16	3′(R)-O-acetyl-4′ (S)-O-tigloylkhellactone	Coumarins	[34]
17	Cis-3′-acetyl-4′-angeloylkhellactone	Coumarins	[34]
18	Decursinol	Coumarins	[34]
19 20 21	4′-Hydroxy Pd-C-III (+)-Trans-decursidinol 4′-Methoxy Pd-C-I	Coumarins	[34]
22 23	Nodakenetin Isorutarine	Coumarins	[34]
24 25	Umbelliferone Umbelliferone 6-carboxylic acid	Coumarins	[34]
26	Coumarin	Coumarins	[30]
27	6-Methoxycoumarin	Coumarins	[30]
28	Isofraxidin	Coumarins	[30,31]
29	Secoisolariciresinol	Lignan	[30]
30	Apiole	Phenylpropanoids	[31]
31	Astragalin	Flavonoids	[24]
32	Daidzein	Flavonoids	[24]
33	Rutin	Flavonoids	[30]
34	Flavokawain A	Flavonoids	[31]

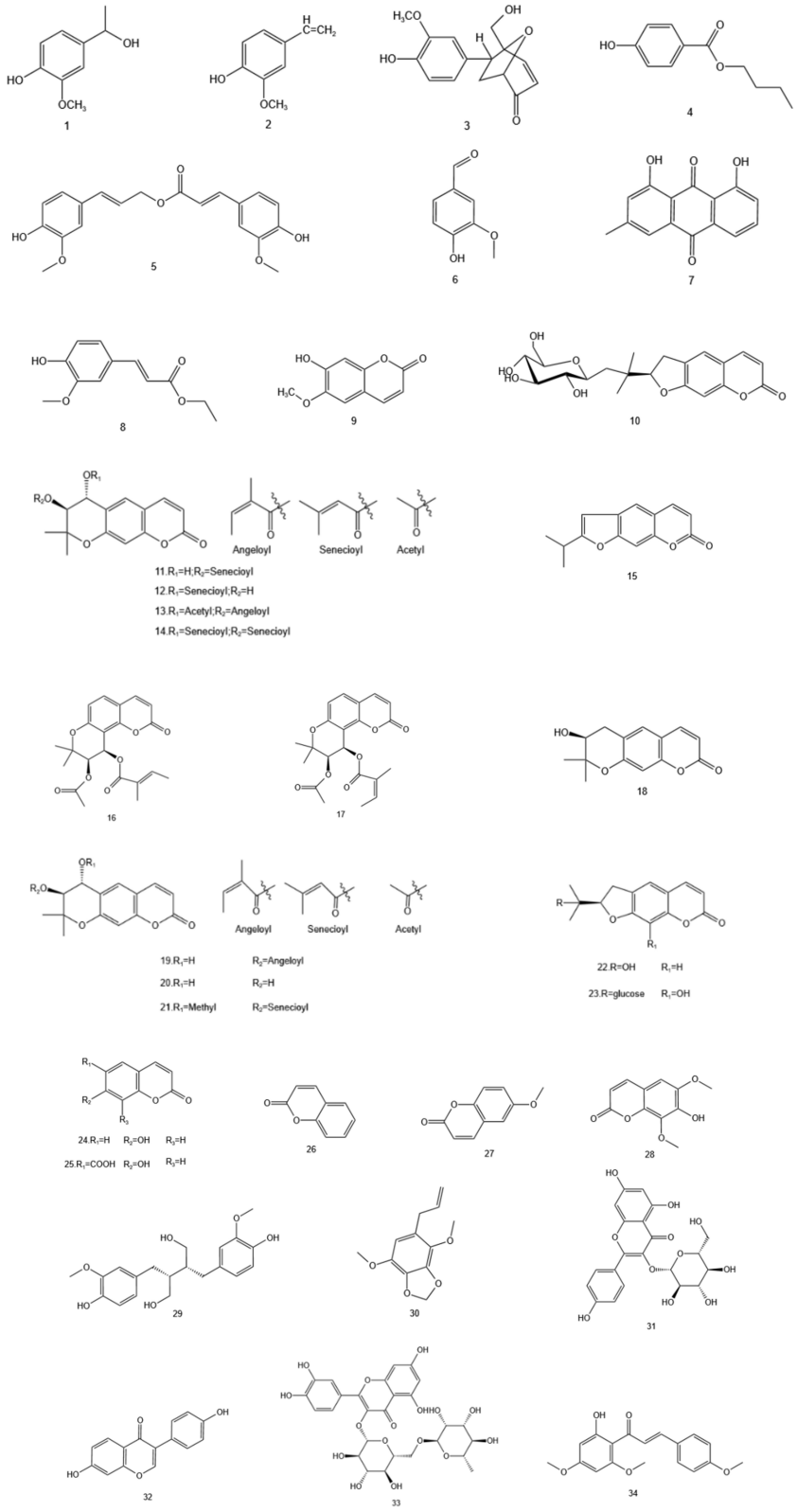

Figure 4 Structure of Phenols (excluding phenolic acids) components.

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Table 5 Nitrogen Components in FSS

NO.	Component	Category	Ref
1	L-isobutyl-L-valine anhydride	Amino acid derivatives	[24]
2	L-valine-L-valine anhydride	Amino acid derivatives	[24]
3	Pyroglutamic acid	Amino acid derivatives	[30,31]
4	Ligustrazine	Alkaloids	[24]
5	1-Acetyl-β-carboline	Alkaloids	[24]
6	1-β-Ethyl acrylate-7-aldehydo-β-carboline	Alkaloids	[24]
7	Pelolyrine	Alkaloids	[24,30]
8	Uracil	Nucleotide base	[24,30]
9	Adenine	Nucleotide base	[24,30]
10	Adenosine.	Nucleosides	[24,30,31]
11	Trimethylamine	Amine	[24]
12	(2R)-2-hydroxy-N-[(2S,3S,4R,8E)-1,3,4-trihydroxypentadec-8-en-2-yl]heptacosanamide	Amides	[24]
13	(2R)-2-hydroxy-N-{(3S,4S,5S)-4-hydroxy-5-[(4E)-undec-4-en-1-yl]tetrahydrofuran-3-yl} heptacosanamide	Amides	[24]
14	(2R)-2-hydroxy-N-[(2S,3S,4R,8E)-1,3,4-trihydroxyicos-8-en-2-yl]tetracosanamide	Amides	[24]
15	Aurantiamide acetate	Amides	[24]
16	Isoleucine	Amino acids	[30]
17	Leucine	Amino acids	[30,31]
18	Phenylalanine	Amino acids	[30]
19	L-Glutamic acid	Amino acids	[31]
20	Valine	Amino acids	[32]
21	Tyrosine	Amino acids	[30]
22	Arginine	Amino acids	[30]
23	Proline	Amino acids	[30]
24	Spermidine	Polyamine	[30]

transcriptional regulation in rat cortex, and has a significant therapeutic effect on AD.[44] The mechanism of CA's antioxidant activity may be related to the increase in the nuclear translocation of Nrf2 and the expression of the antioxidant enzymes glutathione peroxidase (GPx) and glutathione reductase (GR), which together reduce oxidative stress levels and protect the nervous system from damage.[45] In addition, FA is believed to have anti AD effects through anti amyloidosis, anti-inflammatory, antioxidant, mitochondrial protection, and inhibition of cell apoptosis,[46] and it can be used in combination with Ligustrazine and Fumarate to inhibit the invasion and metastasis of EMs through MMP/TIMP signaling pathway.[47] Furthermore, Butylphthalide can regulate the level of inflammation in the body, and for patients with acute cerebral infarction, it can significantly improve neurological function, alleviate stroke symptoms, and improves prognosis in patients.[48]

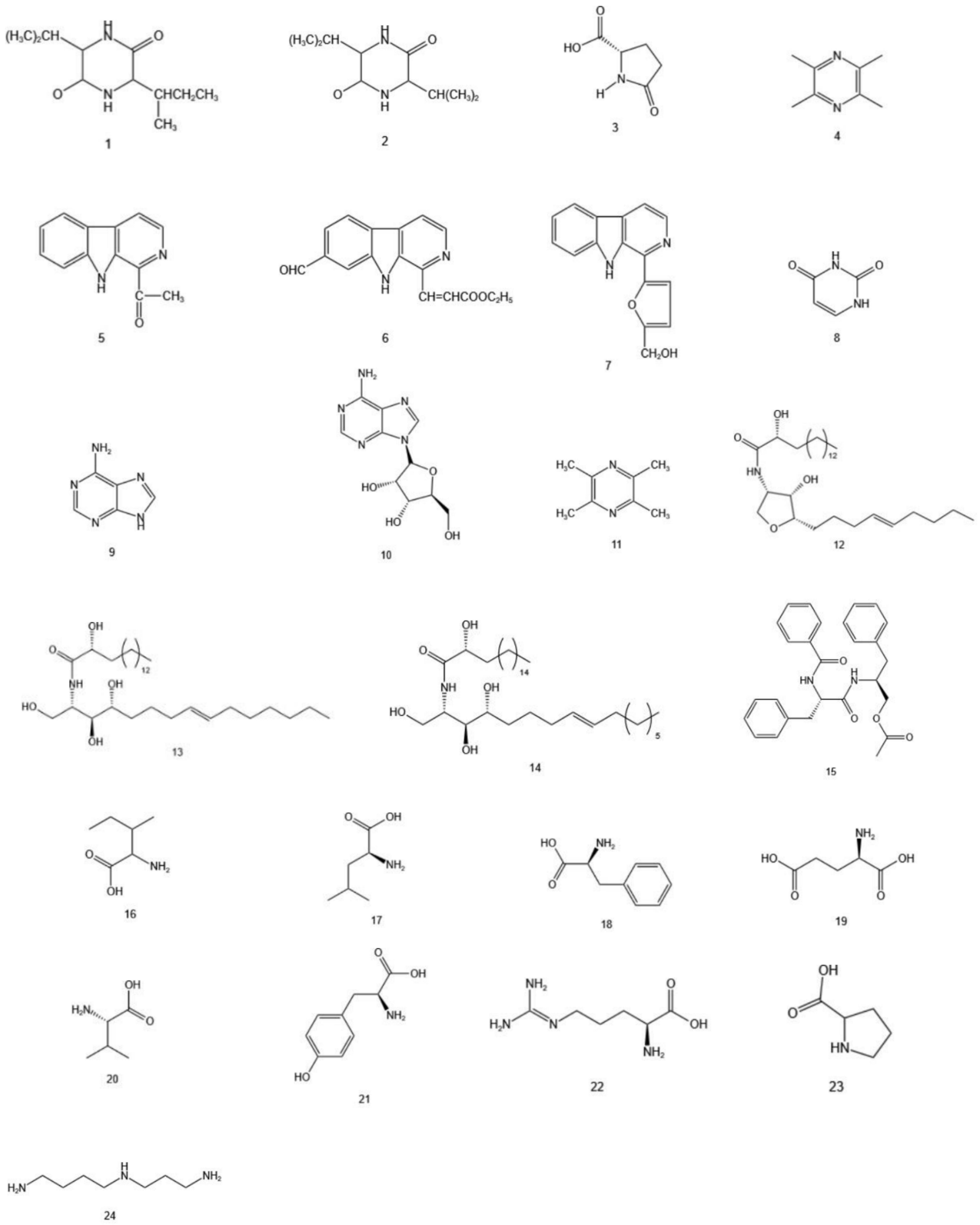

Figure 5 Structure of Nitrogen components.

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Table 6 Other Components in FSS

NO.	Component	Category	Ref
1	Geranial	Terpenes and their derivatives	[31]
2	Isocitral	Terpenes and their derivatives	[31]
3	Cuminyl alcohol	Terpenes and their derivatives	[31]
4	Ginkgolide A	Terpenes and their derivatives	[31]
5	Ginkgolide J	Terpenes and their derivatives	[31]
6	Ginkgolide B	Terpenes and their derivatives	[31]
7	Acorenone	Terpenes and their derivatives	[31]
8	Ergosterol peroxide	Sterols	[24]
9	Campest-4-en-3-one	Sterols	[24]
10	Folic acid	Vitamins	[24]
11	Choline	Vitamins	[24,30]
12	Nicotinic acid	Vitamins	[30]
13	(2R)-N-[(2S,3R,4E,8E)-1-(β-D-glucopyranosyloxy)-3-hydroxy-dodeca-4,8-dien-2-yl]-2-hydroxydocosanamide	Cerebroside	[24]
14	(2R)-N-[(2R,3S,4R,8E)-1-(β-D-gluco-pyranosyloxy)-3,4-dihydroxyoctadec-8-en-2-yl]-2-hydroxyhexadecanamide	Cerebroside	[24]
15	*Angelica sinensis* polysaccharides	Polysaccharide	[38,40]
16	*Ligusticum chuanxiong* polysaccharides	Polysaccharide	[24]

Pharmacology

Regulation of Apoptosis

The normal human body maintains the stability of its internal environment by precisely regulating apoptosis. However, in neurodegenerative, endocrine, and metabolic diseases, improper activation of apoptosis can lead to cell loss and tissue damage,[49] resulting in neuronal degeneration[50] and endocrine imbalances. Fortunately, FSS and its active components have demonstrated significant therapeutic potential in modulating apoptosis. These effects are mediated through multiple mechanisms, including enhancing cellular antioxidant levels. For instance, FSS exerts neuroprotective effects by reducing reactive oxygen species (ROS), caspase-3, and Bax protein expression,[51] thereby alleviating pathological damage in AD and EMs.

Among FSS components, ASP is particularly noteworthy. ASP alleviates AD and EMs pathology by regulating apoptosis through the Bcl-2, Caspase, and IAP protein families. It also exhibits diverse pharmacological effects, including anti-anemia, hepatoprotective, hypoglycemic, lipid-lowering, anti-inflammatory, anti-tumor, and antiviral properties. In AD models, ASP improves spatial learning and memory deficits by modulating apoptotic pathways, it suppresses pro-apoptotic Bax/Bad heterodimers, upregulates the anti-apoptotic Bcl-2/Bax ratio, and reduces caspase-3

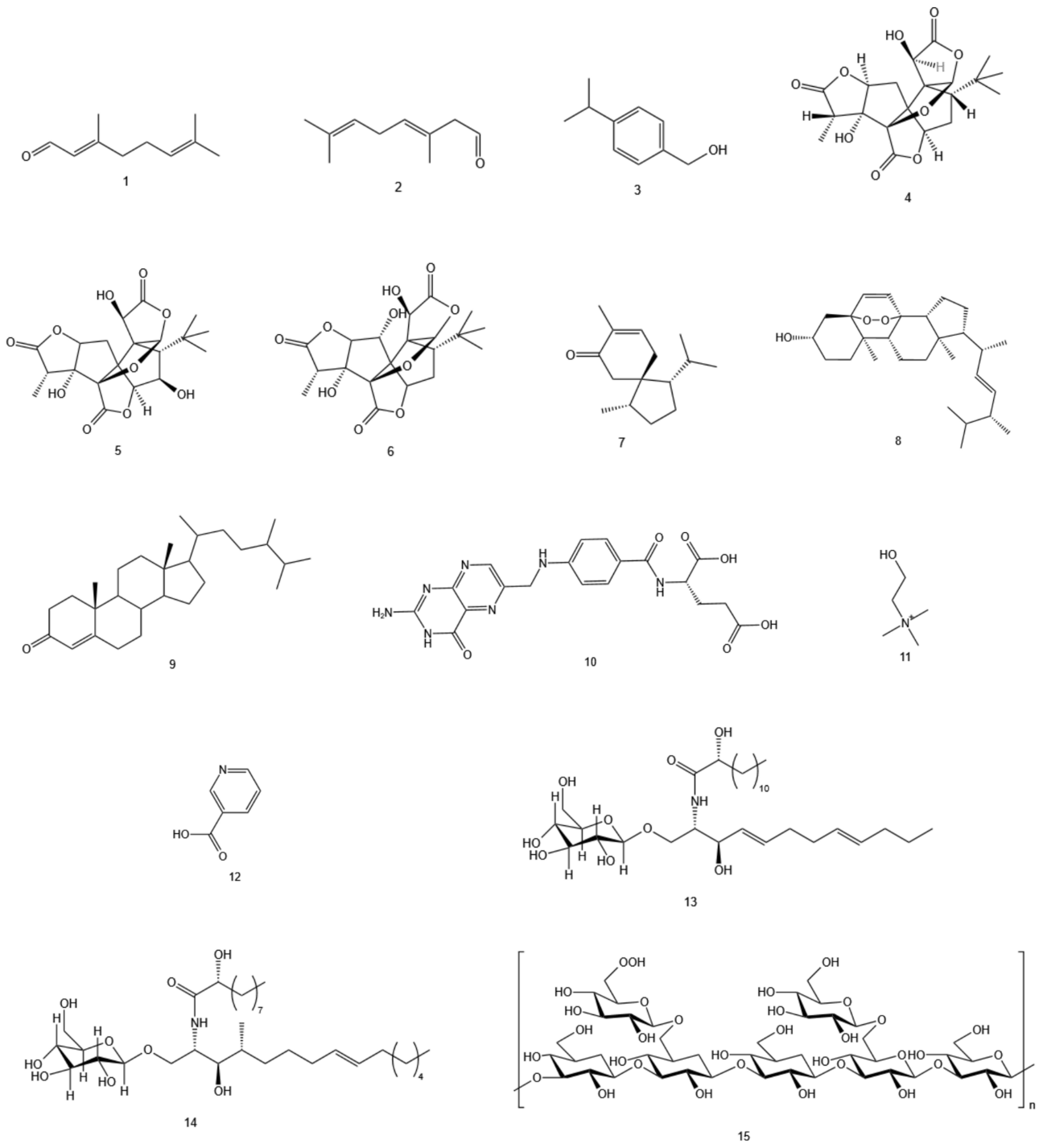

Figure 6 Structure of Other components.The structure of Ligusticum chuanxiong polysaccharides are unclear, so they are not listed.

and caspase-9 expression, thereby inhibiting mitochondrial apoptosis. Additionally, ASP enhances antioxidant activity, such as superoxide dismutase (SOD) and catalase (CAT) while lowering malondialdehyde (MDA) levels, further reducing neuronal apoptosis. Histological improvements in hippocampal CA1, CA3, and DG regions further support its neuroprotective role. Collectively, ASP inhibits Aβ 25–35 induced neuronal apoptosis in AD rats by downregulating caspase-3 and Bax, achieving therapeutic effects comparable to donepezil HCl.[52]

ASP also promotes hematopoiesis via the PI3K/Akt pathway, stimulating hematopoietic cell proliferation and differentiation.[53] It enhances erythropoietin (EPO) production by stabilizing HIF-2α in the kidneys and liver, increasing

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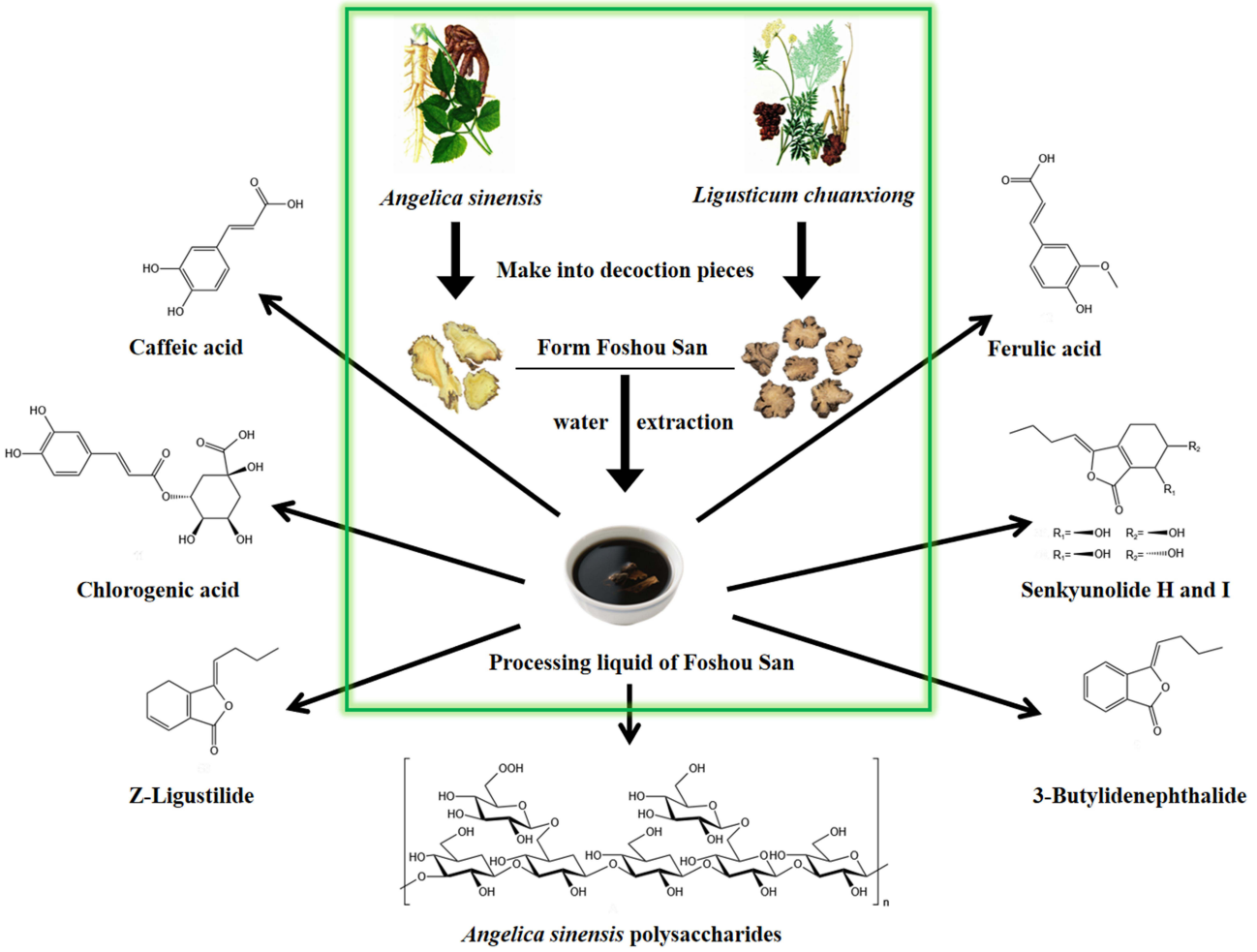

Figure 7 Common components and chemical structures of FSS botanical drugs.

serum EPO levels.[54] Subsequent EPOR/JAK2/STAT5 and PI3K/Akt signaling upregulates Bcl-XL, Fam132b, and TFRC genes, while elevating the Bcl-2/Bax ratio in bone marrow-derived monocytes. This ratio correlates with anti-apoptotic capacity, enabling enhanced hematopoietic differentiation and mitigating EMs-associated bleeding complications.[55]

Notably, in addition to ASP, other active components in FSS also exhibited regulatory effects on apoptosis. For example, Ligustilide improves mitochondrial apoptosis in AD mouse model through PKA/AKAP1 signaling pathway[56] and Butylphthalide inhibits neuronal apoptosis in mice by activating the Akt/mTOP and GDNF/GFRα1/Ret signaling pathway.[57,58] Regarding EMs, CA, an important active ingredient in FSS, has been found to reduce ROS levels in ectopic endometrial cells and alleviate endometrial cell damage.[59] In summary, FSS and its bioactive components regulate apoptosis through multiple pathways, offering novel therapeutic strategies for AD and EMs.

Improve Oxidative Stress and Inflammation

Oxidative stress is dominated by ROS and reactive nitrogen species (RNS), while inflammation is a defense system of the body against damaged tissues. Studies have shown that inflammation and oxidative stress can interact with each other and are considered important factors in disease development.[60] Especially in AD and EMs, the occurrence of oxidative stress and inflammation plays a crucial role. In AD patients, the weaker the antioxidant system in the patient's body, the more susceptible neurons are to damage.[61] Studies have found that Dl-3-n-butylphthalamide can induce inflammation in APP/PS1 mice through the AGE-RAGE signaling pathway and Nrf2-TXNIP Trx axis.[62,63] In recent years, some studies have shown that ASP can reduce free radical metabolism and inflammatory factor expression levels in AD patients. Choi

M et al confirmed the ability of AS extract to alleviate cognitive deficits in mice injected with Aβ1-42 by increasing BDNF expression, ERK1/2 and CREB phosphorylation, inhibiting neuronal loss and neuroinflammatory responses, suggesting the therapeutic potential of AS in neurodegenerative diseases such as AD.[64] FA, a natural antioxidant that can also improve cognitive impairment, is a recognized neuroprotective component for AD that reverses Aβ oligomer-induced morphological defects and reduces oxidation levels including protein oxidation, lipid peroxidation, and ROS assays.[65] Vanillic acid, a FSS component, also has antioxidant and anti-inflammatory activities and can improve learning and memory disorders in AD rats,[66] and Ligustrazine can inhibit the inflammatory response of human endometrial stromal cells through the STAT3/IGF2BP1/RELA axis, which is expected to be used in the treatment of EMs.[35,67]

EMs is an estrogen-dependent inflammatory disease in which oxidative stress, inflammation, and immunity play an important role in the development of EMs.[68] In addition, TNF and IL-6 are inflammatory factors involved in the inflammatory response. High expression of TNF-α and IL-6 was detected in ectopic endometrium and ascites effusion.[69] A variety of active components in FSS, such as CA and FA, have good anti-inflammatory effects.[70,71] Z-ligustilide can attenuate lipopolysaccharide-induced inflammatory response by inhibiting the NF-κB pathway, inhibiting autophagy and accumulating DNA damage.[72,73] The active component ASP in FSS can reduce LPS-induced inflammation and apoptosis by downregulating COX-1, downregulating cyclooxygenase, reducing the synthesis of PGs to inhibit leukocyte chemotaxis,[74] reducing bradykinin production, inhibiting hyaluronidase, and achieving anti-inflammatory effects. Notably, Dai Y et al found that ovarian hyperoxidative stress in patients with EMs led to cumulus granulosa cell senescence.[75] Therefore, modulating oxidative stress in the body is considered as a promising approach for the treatment of EMs.[76,77] Navid Jamali's experiment showed that CA can show antioxidant activity by increasing the nuclear translocation of Nrf2 and the expression of antioxidant enzymes GPx and GR, and achieve the therapeutic effect of oxidative stress on EMs cells by reducing oxidative stress.[45]

Emerging evidence clearly links oxidative stress to AD pathogenesis.[78,79] In summary, FSS and its active components have demonstrated therapeutic potential for AD and EMs by inhibiting inflammatory factors and modulating oxidative stress responses.

Inhibit Ferroptosis

Iron overload in cells not only exacerbates the accumulation of toxic Aβ, leads to the formation of highly phosphorylated Tau protein, and directly induces oxidative damage in neurons,[80] but also damages ovarian granulosa cells, oocytes, and embryos, leading to EMs-related infertility.[81,82] Therefore, inhibition of ferroptosis can alleviate the symptoms of AD and EMs to some extent. Research has found that FSS can regulate ferroptosis to improve the symptoms of vascular dementia.[83] In addition, it has been confirmed that AS and CX play important roles in regulating ferroptosis.[84,85] For example, Ge et al found that CX can regulate ferroptosis through the JAK-STAT3 pathway.[86] Furthermore, the active component of FSS has shown significant effects in regulating iron metabolism and inhibiting ferroptosis. The most noteworthy among them is ASP. ASP, as one of the main components of FSS, has shown significant therapeutic effects in regulating iron metabolism disorders, and studies have shown that it may be related to the regulation of hemagglutinin and EPO. Wang et al established a rat model of renal anemia and found that ASP stimulates endogenous EPO synthesis and activates the downstream EPOR pathway, which jointly promotes erythropoiesis and improves iron utilization.[55] Inflammatory ferritin is an important cytokine that regulates iron balance in the body. It promotes iron release from cells into the extracellular space, thereby increasing iron ions in the plasma. At the same time, it decreases iron utilization by hematopoietic cells and decreases hematopoietic cell activity.[87] Acidic ASP inhibits inflammatory ferroportin by blocking the IL-6/STAT3 and BMP/Smad pathways. In addition, it can increase the expression of ferroportin, mobilize iron in the liver and spleen, and increase serum iron levels.[88] At the same time, too much hemagglutinin can lead to iron deposition in mononuclear macrophages, hindering the absorption of iron in the intestine. ASP has a strong inhibitory effect on the expression of hemagglutinin, and regulates iron homeostasis and increases pig iron supply. Similarly, Zhang et al and Liu et al further explored the molecular mechanism of ASP regulating ferritin and iron metabolism, and found that ASP could down-regulate the expression of ferritin by down-regulating C-EBP α, JAK/STAT, BMP/SMAD and ERK pathways, and by up-regulating the expression of transferrin, thereby promoting the transport of tissue iron to serum iron and further improving iron utilization.[89,90] Unfortunately, there are few reports on FSS improving EMs symptoms by regulating ferroptosis and this gap in research represents a direction worthy of attention.

Regulates Intestinal Gut Microbiota and Bile Acid Metabolism

Bile acids, as products of cholesterol metabolism and clearance, are produced in the liver and further metabolized by intestinal bacteria. Imbalance of gut microbiota and abnormal bile acid metabolism have been confirmed to be one of the common causes of AD[91,92] and EMs.[93–95] This means that FSS can treat different diseases through improving gut microbiota imbalance and bile acid metabolism. In fact, numerous studies have confirmed that FSS can treat AD by improving gut microbiota and bile acid metabolism. For example, FSS can regulate the intestinal microbiota balance of APP/PS1 double transgenic AD mice, increase the number of lactobacilli in the intestine, reduce the abundance of Escherichia coli, and reduce the lipid peroxidation level in the liver, serum, brain and intestine of mice, which indicates that FSS can improve the cognitive function of mice by reducing lipid peroxidation levels and improving neuroinflammatory damage.[96] In addition, animal experiments have shown that FA reduces non-alcoholic fatty liver disease (NAFLD) formation and lowers serum TC, TG, and LDL levels. It also alters gut microbiota composition particularly the Firmicutes/Bacteroidetes ratio—and decreases I3A production.[97] These findings suggested that FA regulates bile acid metabolism via gut microbiota modulation, thereby alleviating AD and EMs symptoms.[98] In summary, the improvement of gut microbiota imbalance and bile acid metabolism by FSS is a new direction for explaining the differential treatment of AD and EMs with FSS.

Pharmacokinetics

At present, there are relatively few reports on the pharmacokinetics of FSS components and flavorings in vivo, but research in this field is essential for a deeper understanding of the absorption, distribution, metabolism and excretion of FSS in living organisms. Pharmacokinetic studies can help us to predict the kinetic parameters of the main active components of drugs, such as bioavailability, apparent volume of distribution, half-life, clearance, etc., thus providing an important basis for drug screening and optimization.[99] Previous studies have shown that the pharmacokinetic parameters of related components in plasma were determined by high-performance liquid chromatography (HPLC) by means of intragastric administration, such as intragastric administration of FSS decoction to rats and rabbits, and it was found that the concentration of active components such as FA and Ligustrazine in plasma was high, and the elimination half-life time was significantly shortened.[100] Indicating that these components can be rapidly absorbed and exert their effects in the body. The pharmacokinetic study of Jiawei Foshou San in mice showed that the bioavailability of the formula in mice is generally high, and the absorption degree of each component in the pathological model of EMs is significantly better than that of normal rats, which provided strong evidence for the pharmacokinetic rationality of Jiawei FSS Capsule in the treatment of EMs.[101]

It is worth noting that Li et al discovered that AS extract, CX extract and AS-CX extract were administered to blood-deficient mice, and HPLC analysis showed that FA was well absorbed in blood-deficient rats and eliminated slowly. At the same time, CX can significantly prolong the distribution half-life of AS extract in blood-deficient rats, increase its partition volume and FA absorption, and prolong the half-life of FA in blood-deficient rats, which reveals the mutual promotion and auxiliary effect of AS and CX as a pair of botanical drugs.[102] This suggests that FSS can exhibit stronger therapeutic effects compared to AS or CX alone. These findings provide strong evidence for the use of FSS in the treatment of AD and EMs.

Conclusion

This article reviews a large number of literature and summarizes the therapeutic potential of FSS and its bioactive components in the treatment of AD and EMs. The identification of multiple active plant-derived components in FSS formulations has demonstrated remarkable therapeutic efficacy against both AD and EMs, offering novel insights into FSS's pharmacological mechanisms while exemplifying the TCM principle of treating diverse diseases through syndrome differentiation. The review further elucidates FSS's therapeutic mechanisms through its modulation of critical biological processes including cellular apoptosis regulation, oxidative stress mitigation, anti-inflammatory actions, iron deposition inhibition, bile acid metabolism optimization, and gut microbiota modulation. These findings suggest FSS exerts its therapeutic effects via multi-target, multi-pathway interventions. Notably, the article highlights FSS's potential influence on disease progression through gut microbiome regulation, proposing innovative perspectives for studying gut-brain-uterine axis disorders. As principal components of FSS, AS and CX demonstrate particular therapeutic significance. The abundant availability and wide distribution of these herbal constituents underscore TCM's unique value in managing

major diseases. Investigating the synergistic mechanisms of this classic botanical drug in treating AD and EMs not only enhances our understanding of TCM therapeutic principles, but also revitalizes the inheritance and development of traditional medicinal culture.

Although preliminary evidence supports FSS's potential in AD and EMs management, several research gaps persist. Current literature shows limited investigation into FSS's synergistic treatment of these comorbid conditions. Furthermore, the therapeutic contributions of numerous components of FSS is still uncharacterized, and requires systematic phytochemical analysis. Future research should prioritize well-designed pharmacological studies, comprehensive toxicological assessments, and randomized clinical trials to validate FSS's medical applications. This provides a theoretical basis for clinical medication safety and the development of Chinese patent medicines.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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