Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Chemical composition, biological activities and product development of *Gastrodia elata*: a review

Liankui Wen[a,1], Yuchen Jiang[a,1], Wenqi Wang[a], Rongchen Zhu[a], Jiahua Liu[a], Yang He[a,*], Fei Zheng[b,*], Yuzhu Wu[c,*]

[a] *Department of Food Science and Engineering, Jilin Agricultural University, Changchun 130118, China*
[b] *Jilin Ginseng Academy, Changchun University of Chinese Medicine, Changchun 130117, China.*
[c] *National Engineering Research Center for Wheat and Corn Deep Processing, Changchun 130118, China*

ARTICLE INFO

Article history:
Received 13 December 2023
Received in revised form 4 February 2024
Accepted 26 March 2024

Keywords:
Gastrodia elata Blume
Chemical components
Biological activities
Product analysis

ABSTRACT

Gastrodia elata Blume has a rich history of use in Asian. However, there is still a need for systematic analysis regarding the relationship and in-depth development between its components and functions. Through comprehensive analysis utilizing databases such as PubMed, Web of Science, and Google Scholar, the practical components, biological activities, and product development of *G. elata* have been investigated. It has been found that the main active components of *G. elata*, such as gastrodin and *G. elata* polysaccharides, possess functionalities in improving conditions such as epilepsy, hypertension, and osteoporosis. These active components exhibit phenolic hydroxyl groups, molecular weight, conformation, and spatial arrangement, contributing to their enhanced ability to scavenge free radicals. Additionally, *G. elata* is known to have organic acids and esters, which exhibit potential immune regulatory and antiviral properties. Compounds with multiple acidic functional groups exhibit even more vigorous activity. Steroidal compounds like β-sitosterol, due to their presence of alcohol and ketone groups, along with a multi-ring structure, exhibit superior cholesterol-lowering activity. *G. elata* has already been recognized in the traditional chinese medicine and food homology list, showcasing its potential for development in line with the health demands of the current era. However, challenges regarding quality evaluation, peculiar odor, and the extraction process of the practical components still require immediate attention. Constructing a robust evaluation system and optimizing product processing techniques will be crucial for the future advancement of the *G. elata* industry.

1. Introduction

Gastrodia elata Blume, commonly known as Tianma, belongs to the Orchidaceae family. Historically, various names have been used to refer to *G. elata* in traditional herbal texts, such as Chijian and Dingfengcao[1-2]. As a heterotrophic plant, *G. elata* undergoes growth and development in a symbiotic relationship with the fungus *Armillaria*[3-4]. Indeed, *G. elata* is primarily distributed throughout Eastern Asia, encompassing regions such as China, Korea, Japan, and Siberia[5]. As a result of its exceptional growth characteristics and the unsustainable practices of resource extraction, wild populations of *G. elata* have been depleted in certain regions. Nevertheless, the cultivation of *G. elata* has expanded significantly in numerous areas across China, satisfying the prevailing market demand[6]. *G. elata* has a long history of traditional application in traditional Chinese medicine. Ancient literature mainly records its effects of calming the

* Corresponding authors.
E-mail address: heyang200704@jlau.edu.cn (Y. He); zhengfei@ccucm.edu.cn (F. Zheng); wo_shiwuyuzhu@jlau.edu.cn (Y.Z. Wu)
Peer review under responsibility of Beijing Academy of Food Sciences.

SciOpen Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2024.9250226

liver and restraining wind, activating blood circulation, and removing blood stasis. Typically, *G. elata* is widely used to relieve symptoms such as dizziness, headache, and epilepsy. These traditional uses were based on experience and practices passed down from generation to generation. Ancient Chinese medical theory focuses more on the overall efficacy of herbs but has a limited understanding of the specific chemical composition of *G. elata*.

With advancements in modern analytical technologies, a new era has been ushered in for exploring the medicinal properties of *G. elata*. *G. elata* has been extensively studied, and various compounds have been identified and isolated, including phenols, polysaccharides, organic acids and esters, and sterols[7]. Extensive research has been dedicated to unraveling the intricate properties of gastrodin, the principal medicinal constituent extracted from *G. elata*[8]. Esteemed since antiquity, it has long been revered for its remarkable impact on the central nervous system. Modern scientific investigation has unveiled its extraordinary efficacy at the intricate molecular level. A multitude of studies have elucidated the potent anti-inflammatory[7,9-11], antioxidant[12-16], and neuroprotective[17-23] effects attributed to gastrodin. At the same time, recent forays have shed light on its potential to inhibit ferroptosis[24] and safeguard against COVID-19[25]. Although preliminary research yields encouraging results regarding the role of *G. elata*, many future clinical trials are imperative to authenticate its efficacy and ensure its safety.

The noteworthy point is that *G. elata* has a dual history of medicinal use and consumption as food. In 2023, China officially recognized *G. elata* as a plant with both medicinal and food applications[26], providing a solid foundation for its integration into food production and consumption. Indeed, as *G. elata* transitions into the industrialization phase, there will be a specific focus on the development of food products and the corresponding technological challenges. This will involve addressing issues such as standardizing quality criteria and optimizing processing techniques. The pursuit of innovative strategies and approaches is imperative in order to overcome these multifaceted obstacles effectively. Despite the growing interest in *G. elata*, previous articles have focused more on its medicinal value[27-28]. As *G. elata* enters a new phase in its history, researchers have not thoroughly explored its value and potential as a foodstuff. This review aims to broaden the perspective of *G. elata* as a health food by discussing its chemical composition, pharmacological effects, and clinical applications and translating this information into practical guidelines for food development. We hope to enrich the understanding of the value of *G. elata* and promote its development and advancement in the food sector.

This review searched the relevant literature published up to November 2023 from electronic databases such as PubMed, Web of Science, Google Scholar, Wanfang database, and CNKI. We utilized keywords to explore *G. elata*, including chemical composition, pharmacological activity, safety and toxicity, clinical and food applications, and processing. The inclusion criteria were as follows: 1) studies should include, but not limited to, clinical studies, animal model studies, *in vitro* experiments, pharmacodynamic evaluations, toxicological assessments, as well as reviews and meta-analyses; 2) literature should provide sufficient data to support its findings, including experimental methods, statistical analyses, and discussion of the results; 3) the literature must be accessible in full text through public databases or library resources. The exclusion criteria were as follows: 1) literature not directly related to *G. elata*; 2) studies with duplicated studies, substandard outcome measures, or incomplete data; 3) purely conceptual, predictive, or hypothetical discussions. Finally, 179 research papers were included in this review, as shown in the flow chart (Fig. 1).

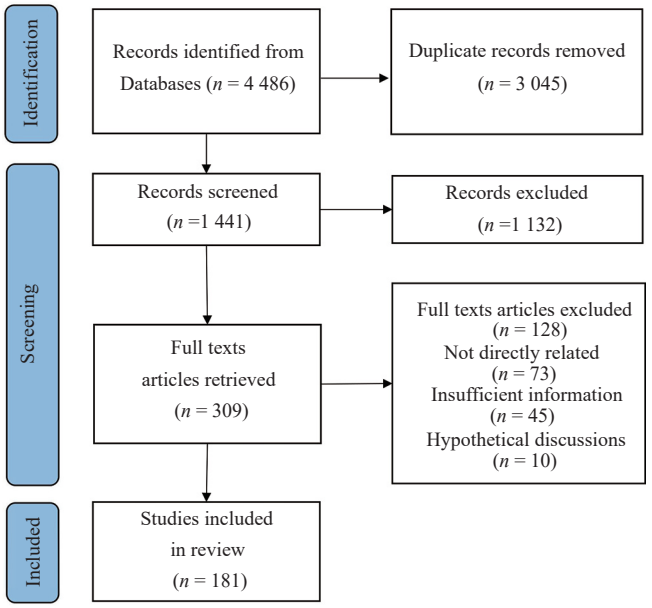


Fig. 1 The PRISMA flowchart of the selection procedures for the included studies.

2. Chemical composition

Extensive research has explored the chemical composition of *G. elata*, including phenols, polysaccharides, organic acids and esters, sterols, and other compounds (Table 1). We thoroughly analyzed the study, focusing on exploring the relationship between the structures of these components and their corresponding activities. Additionally, we investigated the names, molecular formulas, relative molecular weights, and other relevant information about these components.

2.1 Phenols

While phenolic compounds are indeed the most abundant among the known chemical components of *G. elata*, it is noteworthy that the total phenolic content in this plant is relatively modest (approximately 0.273%–0.805%)[27]. Phenolic compounds with benzene ring structures are widely recognized for their significant antioxidant properties, primarily attributed to hydroxyl and aldehyde groups on the benzene ring[28]. The phenolic hydroxyl groups on the benzene ring mainly provide the antioxidant activity of these compounds. Specifically, positioning the substituents at the para position of the phenolic hydroxyl group seems to enhance the stability of the compound and facilitate the reaction process. This enhanced stability is likely due to the conjugation effect between the substituents at the para position and the phenolic hydroxyl group, which helps stabilize the structure of the compound and thereby enhances its antioxidant capacity[29-30]. Therefore, we can infer that these characteristics make phenolic compounds highly promising in preventing and treating chronic diseases related to oxidative stress, particularly in the context of central nervous system-related disorders, showing great therapeutic potential.

Table 1
Chemical composition of *G. elata.*

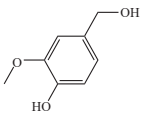
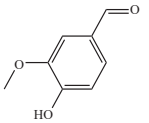
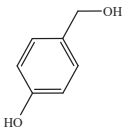
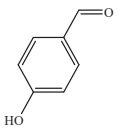
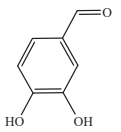
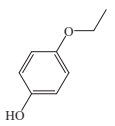
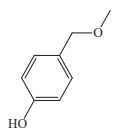
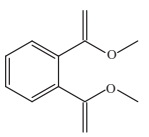
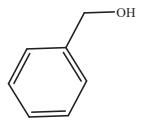
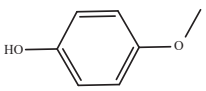
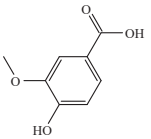
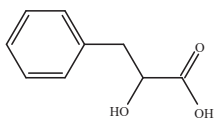
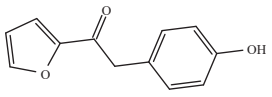
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
				Phenolic compounds		
1.	Vanillyl alcohol	$C_8H_{10}O_3$	154.16		498-00-0	[146]
2.	Vanilline	$C_8H_8O_3$	152.15		63253-24-7	[147]
3.	4-Hydroxybenzyl alcohol	$C_7H_8O_2$	124.14		623-05-2	[148]
4.	4-Hydroxybenzaldehyde	$C_7H_6O_2$	122.12		123-08-0	[149]
5.	3,4-Dihydroxybenzaldehyde	$C_7H_6O_3$	138.12		139-85-5	[150]
6.	*p*-Hydroxybenzyl ethyl ether	$C_8H_{10}O_2$	138.17		57726-26-8	[151]
7.	4-Hydroxybenzyl methyl ether	$C_8H_{10}O_2$	138.17		5355-17-9	[152]
8.	Dimethyl phthalate	$C_{12}H_{14}O_2$	190.24		131-11-3	[153]
9.	Benzyl alcohol	C_7H_8O	108.14		100-51-6	[154]
10.	Anisic alcohol	$C_7H_8O_2$	124.14		1331-81-3	[155]
11.	Vanillic acid	$C_8H_8O_4$	168.15		121-34-6	[155]
12.	*L*-Phenyllactic acid	$C_9H1_0O_3$	166.18		7622-30-2	[152]
13.	1-Furan-2-yl-2-(4-hydroxyphenyl)-ethanone	$C_{12}H_{10}O_3$	202.21		–	[156]

Table 1 (*Continued*)

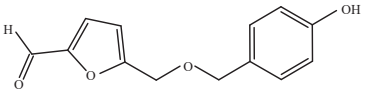
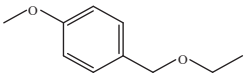
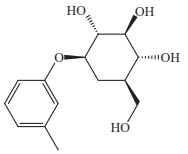
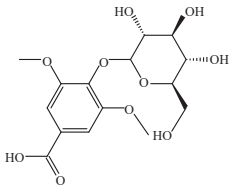
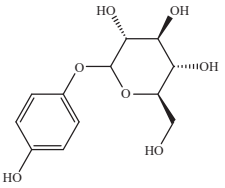
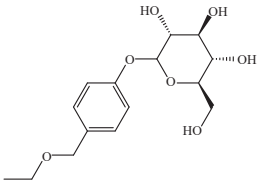
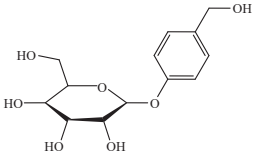
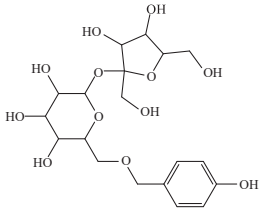
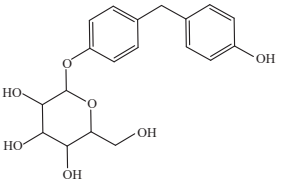
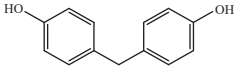
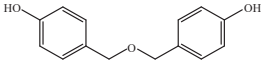
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
14.	5-(4-Hydroxylbenzyloxymethyl)-furan-2-carbaldehyde	$C_{13}H_{12}O_4$	232.24		–	[156]
15.	*p*-Methoxybenyl ethyl ether	$C_{10}H_{14}O_2$	166.22		–	[157]
16.	*p*-Methylphenyl-1-*O*-*D*-glucopyranoside	$C_{14}H_{20}O_5$	268.31		–	[97]
17.	3,5-Dimethoxybenzoic acid-4-*O*-*β*-*D*-glucopyranoside	$C_{15}H_{20}O_{10}$	360.31		–	[17]
18.	4-Hydroxybenzyl-*β*-*D*-glucopyranoside	$C_{12}H_{16}O_7$	272.25		–	[158]
19.	*p*-Ethoxymethylphenyl-1-*O*-*β*-*D*-glucopyranoside	$C_{15}H_{22}O_7$	314.33		–	[153]
20.	Gastrodin	$C_{13}H_{18}O_7$	286.28		62499-27-8	[32]
21.	Gastrodin A	$C_{19}H_{28}O_{12}$	448.42		–	[159]
22.	Gastrodin B	$C_{19}H_{22}O_7$	362.38		–	[160]
23.	4,4′-Dihydroxydiphenyl methane	$C_{13}H_{12}O_2$	200.24		620-92-8	[153]
24.	4-Hydroxybenzyl ether	$C_{14}H_{14}O_3$	230.26		–	[161]

Table 1 (*Continued*)

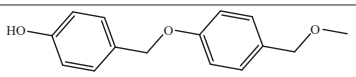
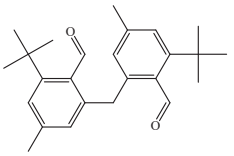
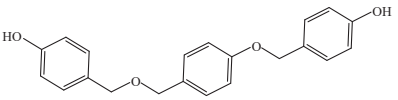
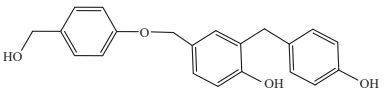
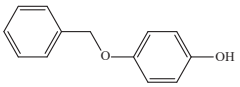
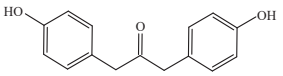
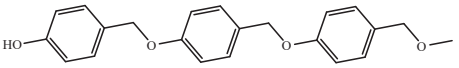
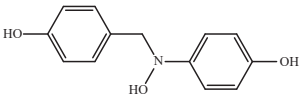
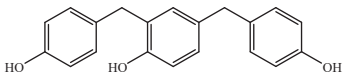
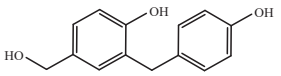
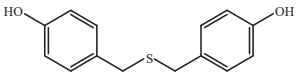
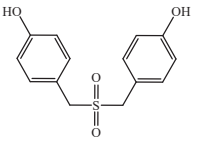
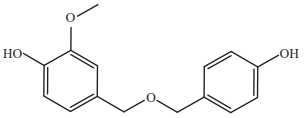
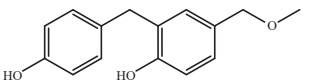
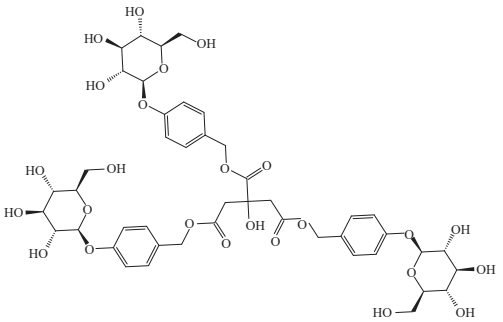
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
25.	4-(4′-Hydroxybenzyl-oxy) benzyl methyl ether	$C_{15}H_{16}O_3$	244.29		–	[9]
26.	2,2′-Methylene-bis(6-tert-butyl-4-methylphenl)	$C_{25}H_{32}O_2$	364.53		–	[162]
27.	Gastrol A	$C_{21}H_{20}O_4$	336.39		66644-99-3	[159]
28.	Gastrol B	$C_{21}H_{20}O_4$	336.39		–	[160]
29.	*p*-Hydroxybenyloxy benzlalcohol	$C_{13}H_{12}O_2$	200.24		–	[162]
30.	4,4′-Dihydroxybenzyl sulfoxide	$C_{15}H_{14}O_3$	242.27		–	[163]
31.	4-[4′-(4″-Hydroxybenzyloxy) benzyloxy]benzyl methyl ether	$C_{22}H_{22}O_4$	350.41		–	[164]
32.	Gastrodamine	$C_{13}H_{13}O_3N$	231.25		245428-10-8	[43]
33.	2,4-bis(4-Hydroxybenzyl) phenol	$C_{20}H_{18}O_3$	306.36		34826-64-7	[155]
34.	4-Hydroxy-3-(4′-hydroxybenzyl) benzyl alcohol	$C_{14}H_{14}O_3$	230.26		–	[165]
35.	bis-(4-Hydroxybenzyl)sulfide	$C_{14}H_{14}O_2S$	246.32		–	[166]
36.	4,4′-Dihydroxybenzyl sulfone	$C_{14}H_{14}O_4S$	278.32		–	[163]
37.	4-Hydroxybenzyl vanillyl ether	$C_{15}H_{16}O_4$	260.29		–	[167]
38.	4-Hydroxy-3-(4-hydroxybenzyl) benzylmethyl ether	$C_{15}H_{16}O_3$	244.29		–	[168]
39.	Parishin	$C_{45}H_{56}O_{25}$	996.92		62499-28-9	[169]

Table 1 (*Continued*)

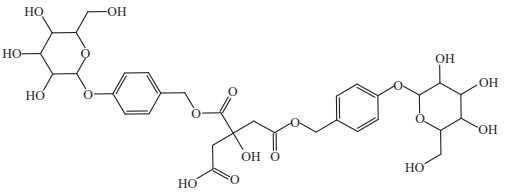
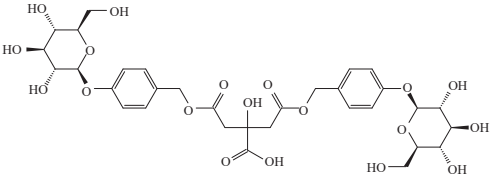
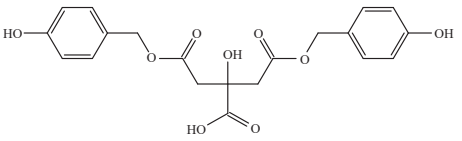
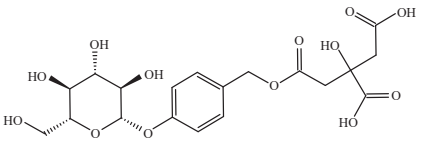
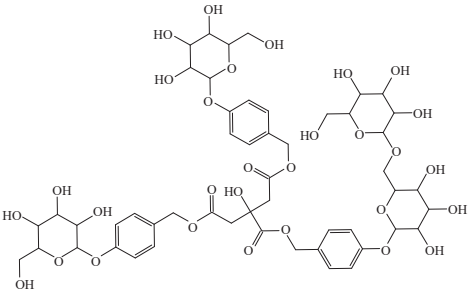
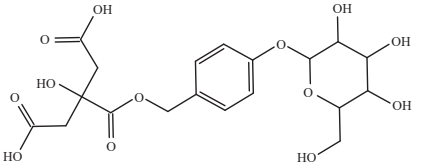
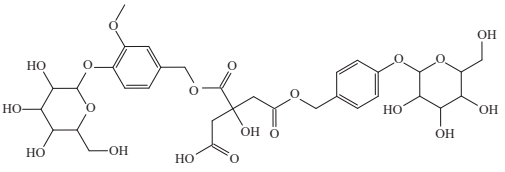
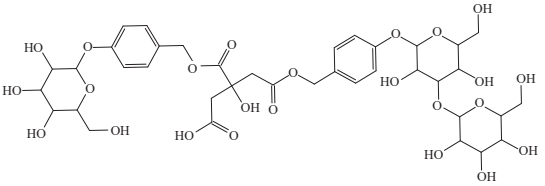
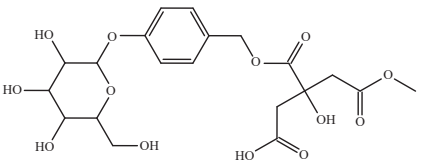
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
40.	Parishin B	$C_{32}H_{40}O_{19}$	728.65		174972-79-3	[169]
41.	Parishin C	$C_{32}H_{40}O_{19}$	728.65		174972-80-6	[169]
42.	Parishin D	$C_{20}H_{20}O_{9}$	404.37		952068-64-3	[149]
43.	Parishin E	$C_{19}H_{24}O_{13}$	460.39		952068-57-4	[169]
44.	Parishin F	$C_{51}H_{66}O_{30}$	1 159.06		–	[152]
45.	Parishin G	$C_{19}H_{24}O_{13}$	460.39		952283-93-1	[152]
46.	Parishin H	$C_{33}H_{42}O_{20}$	758.68		–	[55]
47.	Parishin I	$C_{38}H_{50}O_{24}$	890.79		–	[55]
48.	Parishin J	$C_{20}H_{26}O_{13}$	474.42		–	[55]

Table 1 (*Continued*)

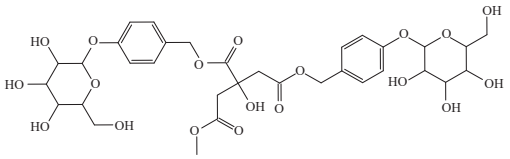
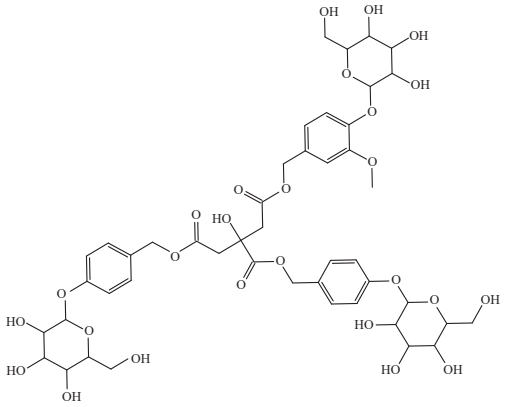
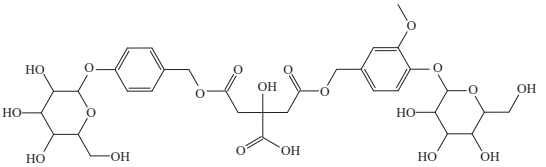
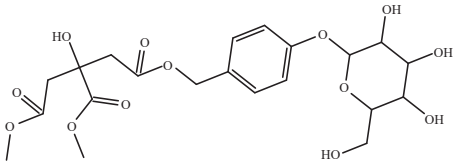
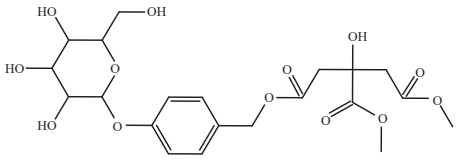
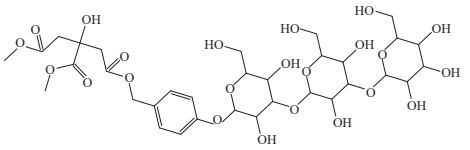
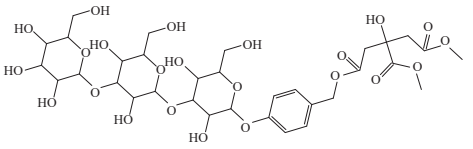
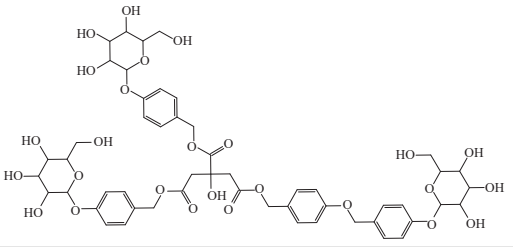
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
49.	Parishin K	$C_{33}H_{42}O_{19}$	742.68		–	[55]
50.	Parishin L	$C_{46}H_{58}O_{26}$	1 026.94		–	[55]
51.	Parishin M	$C_{33}H_{42}O_{20}$	758.23		–	[55]
52.	Parishin N	$C_{21}H_{28}O_{13}$	488.44		–	[55]
53.	Parishin O	$C_{21}H_{28}O_{13}$	488.44		–	[55]
54.	Parishin P	$C_{33}H_{48}O_{23}$	812.72		–	[55]
55.	Parishin Q	$C_{33}H_{48}O_{23}$	812.72		–	[55]
56.	Parishin R	$C_{52}H_{62}O_{26}$	1 103.04		–	[55]

Table 1 (*Continued*)

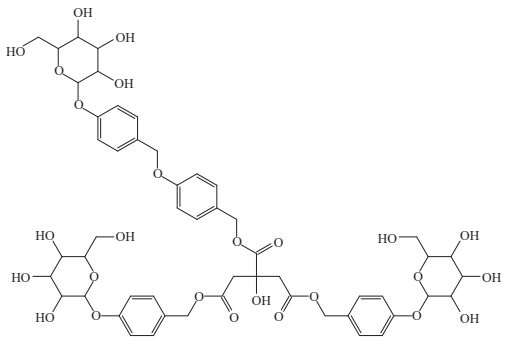
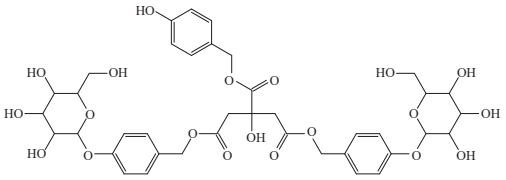
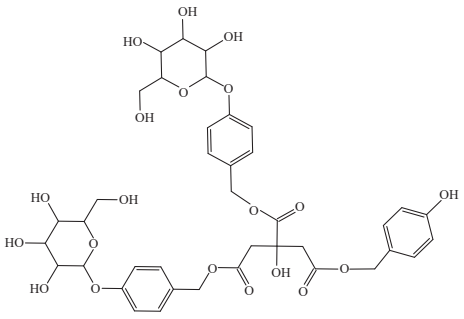
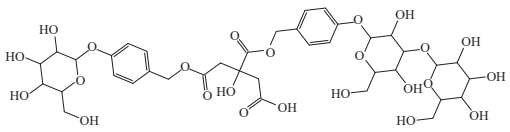
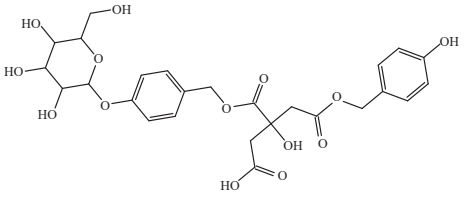
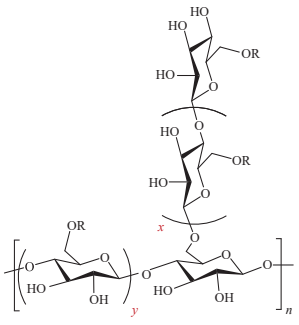
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
57.	Parishin S	$C_{52}H_{62}O_{26}$	1 103.04		–	[55]
58.	Parishin T	$C_{39}H_{46}O_{20}$	834.78		–	[55]
59.	Parishin U	$C_{39}H_{46}O_{20}$	834.78		–	[55]
60.	Parishin V	$C_{38}H_{50}O_{24}$	890.79		–	[55]
61.	Parishin W	$C_{26}H_{30}O_{14}$	566.51		–	[55]
				Polysaccharide compounds		
62.	WGEW	–	2.8×10^5	 R = H ($x + y = 16$)	–	[170]

Table 1 (*Continued*)

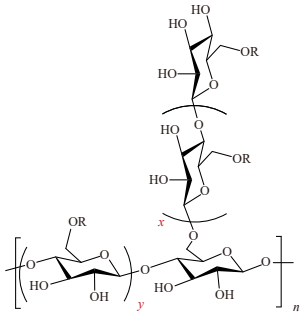
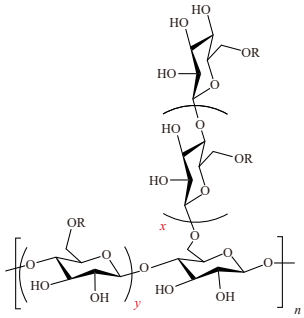
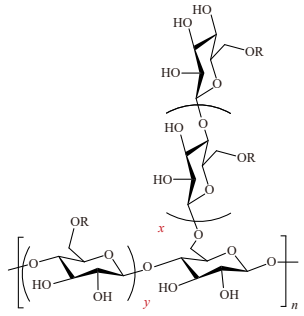
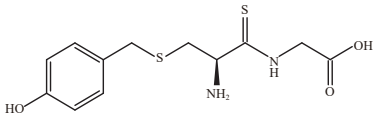
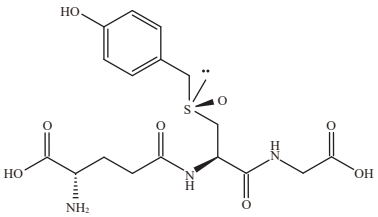
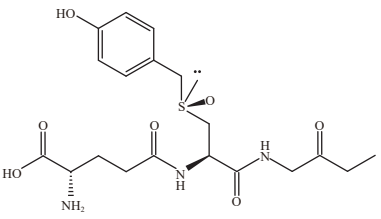
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
63.	AGEW	–	1.0×10^5	 R = H ($x + y = 14$)	–	[170]
64.	WTMA	–	7.0×10^5	 R = H ($x + y = 15$)	–	[171]
65.	PGE	–	1.54×10^6	 R = H ($x + y = 20$)	402760-82-1	[172]
				Organic acids and ester compounds		
66.	(+)-*L*-*S*-(4-Hydroxybenzyl) cysteinylglycine	$C_{12}H_{16}O_3N_2S_2$	300.39		–	[173]
67.	(−)-(*SS*)-*γ*-*L*-glutamyl-*L*-[*S*-(4-hydroxybenzyl)] cysteinylglycine sulfoxide	$C_{18}H_{24}N_3O_8S_2$•	444.48		1290191-64-8	[173]
68.	Ethyl(−)-(*SS*)-*γ*-*L*-glutamyl-*L*-[*S*-(4-hydroxybenzyl)] cysteinylglycinatesulfoxide	$C_{20}H_{28}N_3O_8S_2$•	456.53		1220036-04-3	[173]

Table 1 (*Continued*)

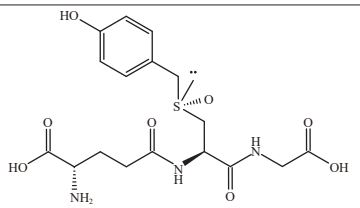
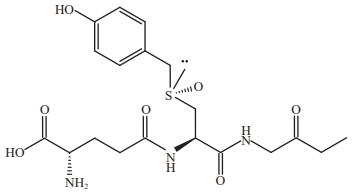
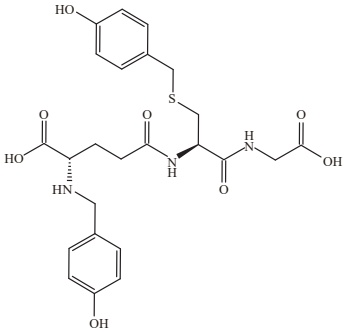
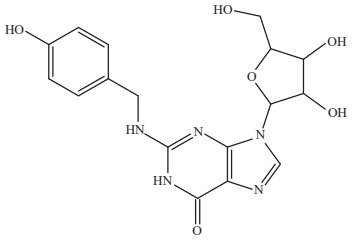
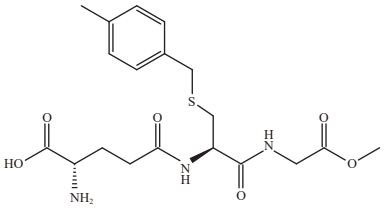
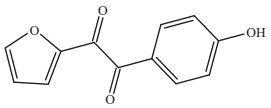
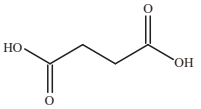
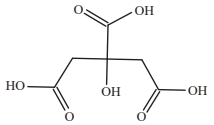
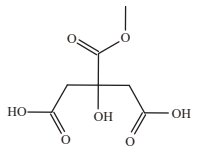
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
69.	(−)-(*RS*)-*γ*-*L*-Glutamyl-*L*-[*S*-(4-hydroxybenzyl)]cysteinylglycine sulfoxide	$C_{18}H_{24}N_3O_8S_2$•	444.48		1290191-64-8	[173]
70.	Ethyl(−)-(*RS*)-g-*L*-glutamyl-*L*-[*S*-(4-hydroxybenzyl)] cysteinylglycinate sulfoxide	$C_{20}H_{28}N_3O_8S_2$•	456.53		1220036-04-3	[173]
71.	(−)-*γ*-*L*-[*N*-(4-Hydroxybenzyl)] glutamyl-*L*-[*S*-(4-hydroxybenzyl)] cysteinylglycine	$C_{24}H_{29}N_3O_8S$	535.61		1290191-64-8	[173]
72.	Gastronucleoside	$C_{17}H_{19}O_6N_5$	389.37		–	[174]
73.	Methyl(−)-*γ*-*L*-glutamyl-*L*-*S*-(4-hydroxybenzyl) cysteinylgly cinate	$C_{19}H_{27}O_6N_3S$	425.50		772-65-6	[173]
74.	1-Furan-2-yl-2-(4-hydroxy-phenyl)-ethane-1,2-dione	$C_{12}H_8O_4$	216.19		–	[175]
75.	Succinic acid	$C_4H_6O_4$	118.09		618-57-5	[173]
76.	Citric acid	$C_6H_8O_7$	192.12		3676-85-5	[176]
77.	6-Methyl citrate	$C_7H_{10}O_7$	206.15		–	[177]

Table 1 (*Continued*)

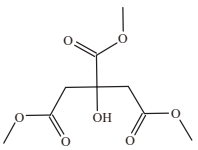
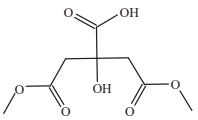
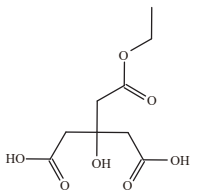
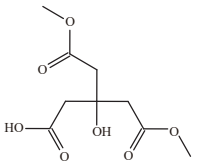
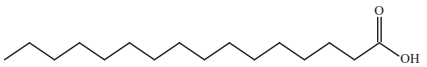
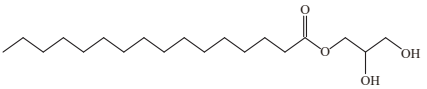
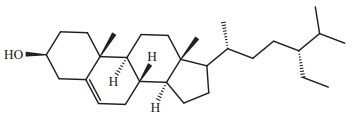
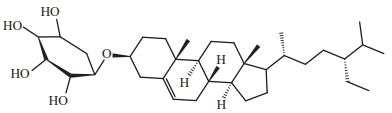
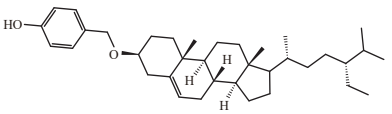
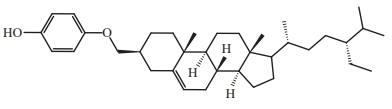
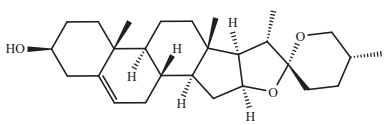
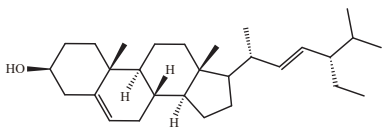
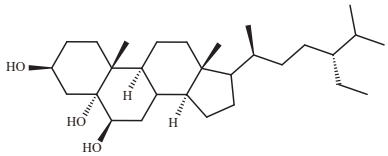
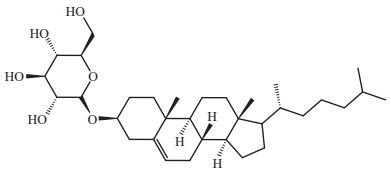
No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
78.	Trimethyl citrate	$C_9H_{14}O_7$	234.20		1587-20-8	[178]
79.	1,5-Dimethyl citrate ester	$C_8H_{12}O_7$	220.18		–	[177]
80.	Citric acid monoethyl citrate	$C_9H_{14}O_7$	234.20		–	[43]
81.	Dimethyl citrate	$C_9H_{14}O_7$	234.20		53798-97-3	[43]
82.	Palmitic acid	$C_{16}H_{32}O_2$	256.43		31678-63-4	[176]
83.	Glyceryl monopalmitate	$C_{19}H_{38}O_4$	330.51		26657-96-5	[179]
				Steroidal compounds		
84.	*β*-Sitosterol	$C_{29}H_{50}O$	414.72		19044-06-5	[155]
85.	*β*-Sitosterol glucoside	$C_{35}H_{60}O_5$	560.86		–	[9]
86.	4-Hydroxybenzyl *β*-sitosterol ether	$C_{36}H_{56}O_2$	520.84		–	[166]
87.	3-*O*-(4′-Hydroxybenzyl)-*β*-sitosterol	$C_{36}H_{56}O_2$	520.84		–	[164]
88.	Diosgenin	$C_{27}H_{42}O_3$	414.63		89299-45-6	[157]
89.	Stigmasterol	$C_{29}H_{48}O$	412.70		125636-86-4	[164]

Table 1 (*Continued*)

No.	Chemical component	Chemical formula	Molecular weight (Da)	Constitutional formulas	CAS	References
90.	Stigmastane-3*β*,5*α*,6*β*-triol	$C_{29}H_{52}O_3$	448.73		20835-91-0	[162]
91.	*β*-Daucosterol	$C_{33}H_{56}O_6$	548.80		474-58-8	[176]

Note: — represents not studied.

4-Hydroxybenzyl alcohol (4-HBA) is a phenolic compound found in *G. elata*. A hydroxyl group at the para position increases the molecule's polarity and reduces its affinity for lipids, affecting its ability to traverse biological membranes. Therefore, under physiological conditions, hydroxybenzyl alcohol can relatively easily penetrate the blood-brain barrier, bind to benzodiazepine receptors on cell membranes, enhance the affinity of *γ*-aminobutyric acid (GABA) receptors, and exert inhibitory effects on the central nervous system[31]. Gastrodin, a small molecular phenolic glycoside, is derived from the partial substitution of glucose in 4-HBA, constituting around 0.025% of *G. elata*[32-33]. Due to the presence of the glucose moiety, gastrodin has a lower permeability than 4-HBA. Gastrodin can be hydrolyzed in the body to generate 4-HBA. Therefore, it is speculated that their mechanism of action may involve the hydrolysis of gastrodin into 4-HBA in the body, followed by the combined effects on benzodiazepine receptors after crossing the blood-brain barrier. 4-HBA and gastrodin can induce sleep waveforms in the average adult electroencephalogram, and their sedative-hypnotic effects may be related to the shared structural characteristics with the non-polar hydrophobic plane and charge centers located at both ends of the plane, with a distance of 0.7 nm[34]. Hence, both 4-HBA and gastrodin can serve as significant material foundations for the anti-epileptic, anti-depressant, and supportive effects of *G. elata* on the central nervous system.

Due to the minimal quantities and low economic efficiency of extracting 4-HBA and gastrodin directly from *G. elata*, chemical synthesis has become the preferred approach. One approach involves the Koenigs-Knorr reaction, where brominated tetraacetyl glucose reacts with *p*-hydroxybenzaldehyde (or 3-methoxy-4-hydroxybenzaldehyde) in acetone solution to obtain glycoside products, which are then subjected to reduction, acetylation, saponification, and other reactions to obtain gastrodin and its analogs[35]. Xiang et al.[36] have also synthesized sugar moieties and 1,3-*cis*-retinoic acid conjugates to obtain more potent retinoic acid derivatives, the study used vanillyl alcohol, 4-HBA, and *m*-hydroxybenzyl alcohol as sugar moieties linked to retinoic acid and successfully synthesized 4 compounds, and pharmacological experiments have demonstrated that these compounds exhibit strong anticancer and antibacterial effects. In addition to chemical modifications, enzymatic reactions can be explored for structural modifications. Enzymatic esterification or etherification reactions of hydroxyl groups can improve the solubility and bioavailability of gastrodin. This approach can enhance the stability and activity of the compounds, thereby improving their clinical efficacy. Enzymatic modifications present a promising area that can provide new pathways and opportunities for the further development of gastrodin and other phenolic compounds.

2.2 Polysaccharides

G. elata polysaccharide content ranges from about 3% to 26%[37-38], comprising monosaccharides like glucose, mannose, rhamnose, and galactose. Its backbone is primarily *α*-(1→4)-glucan, with side chains formed of 1→4,6-linked glucose, 1→3-linked glucose, and 1→6-linked glucose[39]. The specific functional activities of polysaccharides are primarily determined by their physicochemical properties and structural characteristics, such as molecular weight, glycosidic linkage type, and ionic acid content, all of which influence their bioactivity.

From the perspective of molecular weight, higher molecular weight polysaccharides may have more vigorous biological activities, such as anti-tumor and immune activities[40]. However, reports show a reverse correlation between polysaccharide molecular weight and biological activities[41]. According to current research, it can be inferred that there is a specific relationship between the molecular weight of polysaccharides and their biological activity within a specific range. Moderate molecular weight polysaccharides can exhibit significant biological activity, while excessively large polysaccharides may have limited effectiveness in interacting with target molecules. Conversely, very low molecular weight polysaccharides may be unstable and have restricted molecule interactions, resulting in weaker biological activity. Therefore, the influence of molecular weight on the biological activity of plant polysaccharides is complex and requires a comprehensive understanding of factors such as structural characteristics and spatial conformation.

Regarding glycosidic bond types, the leading chains of starch and *G. elata* polysaccharide are primarily composed of *α*-(1→4) bonds[42]. Despite playing an essential role in physiological metabolism, starch has relatively low biological activity. In contrast, *G. elata* polysaccharide exhibits significant biological activity, suggesting the presence of factors other than the main chain glycosidic bonds. The (1→3) side chain glycosidic bonds in *G. elata* polysaccharide may be a critical factor in enhancing activity, similar to the well-known (1→3) and (1→6) bonds in *Ganoderma lucidum* polysaccharide with anticancer effects[43]. Adding ionic acids, which introduce carboxyl groups with negative charge and acidic characteristics, can increase polysaccharides' solubility and

biological activity. For example, low molecular weight polysaccharides from seaweed rich in uronic acids have shown anti-obesity effects in mouse experiments[44], suggesting that studying the relationship between uronic acid content in *G. elata* polysaccharide and its biological activity can provide new insights for the development of polysaccharide derivatives with specific health benefits.

Due to the incomplete characterization of the structure of *G. elata* polysaccharides, our current understanding of their structure-function relationship primarily relies on studies of polysaccharides from other plants. Therefore, future research should focus on unraveling the composition of *G. elata* polysaccharides and their related bioactivities. By elucidating the link between their structure and activity, hypotheses regarding the impact of *G. elata* polysaccharide structures on biological activities can be validated. These in-depth investigations will expand our knowledge of *G. elata* polysaccharides, providing valuable information and guidance for their further development and applications.

2.3 Organic acids and esters

The organic acid content in *G. elata* is approximately 0.026%–0.056%[45-46]. *G. elata* contains some small molecule organic acids, including citric acid, palmitic acid, and *L*-glutamic acid. These acids can undergo esterification reactions with alcohols to form esters. In addition, *G. elata* also contains several small molecular esters, such as a 6-methyl ester of citric acid, 1-ethyl ester of citric acid, 1,5-dimethyl ester of citric acid, and glycerol-1-stearate[47], among others. Organic acids and their esters have pharmacological effects such as hepatoprotection, antioxidant activity, immune modulation, antiviral properties, and antimicrobial effects. The dehydration polymerization of one molecule of citric acid and one molecule of gastrodin produces parishin, which may have an auxiliary role in the neuroprotective effect of *G. elata*. It can reduce oxidative stress damage in brain and liver tissues induced by lipopolysaccharides[48]. In addition, citric acid is an essential metabolite in the tricarboxylic acid cycle. It promotes the generation of adenosine triphosphate (ATP) in the body, playing a role in energy supplementation and fatigue relief[49].

There is limited research on the efficacy assessment of organic acids and their esters in *G. elata*. However, information from relevant herbal medicine reports suggests that their activity is significantly reduced. When phenolic acids have hydroxyl groups on the ortho positions (positions 3 and 4) of the benzene ring. For example, compared to hydroxybenzoic acid and meta-hydroxybenzoic acid, protocatechuic acid, which has one more hydroxyl group, exhibits a decreased inhibition rate on platelet aggregation by 10.15% and 1.45%, respectively. On the other hand, phenolic acids with methoxy substitutions show increased activity. For instance, compared to caffeic acid, ferulic acid, which has a methoxy substitution at position 3, shows a 28.06% higher inhibition rate. Danshensu, with a methoxy substitution in its structure, exhibits a 27.63% higher inhibition on platelet aggregation compared to trimethoxybenzene[50]. Based on these observations, we can infer that phenolic acids with methoxy substitutions may have better efficacy.

G. elata is widely distributed in China and demonstrates reliable clinical efficacy with minimal adverse reactions, indicating promising prospects for development and application. However, previous pharmacological research on similar traditional Chinese medicines has primarily concentrated on phenols and polysaccharides, neglecting organic acids and esters with lower content. The research mentioned above indicates that organic acids hold significant potential in treating cardiovascular diseases. Therefore, it is significant to emphasize scientific research on organic acids and esters in *G. elata* to understand the pharmacological basis of traditional Chinese medicine and provide new insights into preventing and treating cardiovascular diseases.

2.4 Steroids

Steroids are organic compounds sharing a common structural core known as the steroid nucleus, consisting of a cycle arrangement of 3 six-carbon rings and 1 five-carbon ring, forming a 17-carbon tetracyclic framework, with the 4 rings designated as A, B, C, and D[51]. The diversity of steroidal compounds arises from functional group modifications on the steroid nucleus. Functional groups such as hydroxyls and ketones are typically found at specific carbon atoms, like C-3 on ring A and C-17 on ring D. The addition of functional groups alters the chemical properties of steroids, such as solubility and reactivity, which in turn influences their biological functionality through interactions with other molecules. For instance, cholesterol features a hydroxyl group at the C-3 position and an 8-carbon alkyl chain at C-17, critical for its role in cellular membranes, providing essential stability and fluidity[52]. *G. elata* contains several steroid compounds, including *β*-sitosterol, *γ*-sitosterol, and stigmasterol[53]. *β*-Sitosterol, structurally similar to cholesterol, possesses a hydrophilic hydroxyl group at C-3 and a hydrophobic straight alkyl chain with ten carbon atoms at C-17. This configuration enables *β*-sitosterol to embed its hydrophobic side chain into lipid bilayers while the hydroxyl group interacts with the hydrophilic head groups on the membrane surface. Such structural attributes allow *β*-sitosterol to stabilize cell membranes, modulate membrane protein functions, and regulate cellular signaling, substance transport, and metabolism. Due to its structural similarity, it competes with cholesterol for absorption sites in the small intestine, aiding in the reduction of cholesterol absorption and lowering blood cholesterol levels.

Although there are limited reports on the steroidal components of *G. elata*, they may still be considered one of the active substances responsible for its pharmacological effects. In the future, it is possible to enhance the bioavailability of *G. elata* sterols through structural modifications or improve the content and purity of sterols through more cost-effective purification processes. These advancements would further enhance the application value of *G. elata* sterols in various industries. *G. elata* contains adenine, nucleosides (such as AmD2-9, AmD2-20, and AmD2-28), several amino acids, and trace elements (including Fe, Cr, Zn, Mn, Cu, and Se)[54]. These essential trace elements have anti-aging, disease prevention, and control effects[55-56]. Further research and development may uncover additional potential applications and utilization methods in the future.

3. Biological activity

In traditional Chinese medicine theory, *G. elata* is believed to have calming effects on the liver, relieve wind, and promote blood circulation. This herb has been used throughout history to treat various conditions such as pediatric febrile convulsions, tetanus, limb paralysis, numbness, rheumatoid arthritis, and epileptic-like seizures. Modern research has deepened the understanding of pharmacological

effects on *G. elata*, revealing its potential to benefit multiple body systems. Classifying its effects based on different body systems and summarizing each system's underlying pathological processes and improvement pathways enhances our understanding and guides clinical applications.

3.1 Nervous system protective effect

Nervous system diseases primarily affect the central nervous system and peripheral nervous system, giving rise to conditions like epilepsy, Parkinson's disease, Alzheimer's disease, and others. The underlying pathology of most neurological disorders involves neuronal damage resulting from factors such as ischemia, hypoxia, toxins, and infections. Extensive research has revealed that the significant mechanisms of nervous system damage include the excessive release of excitatory amino acids, calcium ion overload, oxidative stress, and immune-inflammatory responses (Fig. 2)

Neuronal metabolism is highly active within brain tissue. Under ischemic and hypoxic conditions, energy metabolism disorders and ATP deficits can occur, impairing sodium-potassium pump activity. This impairs intracellular and extracellular ionic concentration balance, depolarizing cell membranes. Depolarization, in turn, activates voltage-dependent calcium channels, prompting a significant influx of Ca^{2+} and subsequent excitatory amino acid glutamate (Glu) release, resulting in extracellular Glu accumulation[57]. Excessive Glu can overstimulate postsynaptic *N*-methyl-*D*-aspartate receptors, causing neurotoxicity. This toxicity prompts further Ca^{2+} influx, causing mitochondrial oxidative phosphorylation uncoupling and cellular respiration inhibition, resulting in irreversible neuronal damage and death[58].

Additionally, elevated Ca^{2+} activates intracellular nitric oxide synthase (NOS), producing nitro compounds and oxygen free radicals[59], and activates NADPH oxidase, generating superoxide anions, causing further oxidative stress damage[60-61]. This process generates reactive oxygen and nitrogen oxide compounds, triggering matrix metalloproteinase (MMP) released from various cells, damaging the blood-brain barrier and triggering neuroinflammatory responses[62]. In early inflammation stages, microglial cells are activated, and the damaged blood-brain barrier allows neutrophil infiltration into ischemic brain regions. These activated immune cells generate numerous oxygen-free radicals, such as nitric oxide (NO) and reactive oxygen species (ROS), setting up a vicious cycle with oxidative stress and exacerbating brain tissue damage[63].

GABA is a primary inhibitory amino acid in the brain, which can counteract neurotoxic damage from excitatory amino acids. Studies indicated that gastrodin enhances GABA activity in the hippocampus within a gerbil epilepsy model. Further investigation revealed that gastrodin influences key GABA synthesis enzymes, glutamic acid decarboxylase 65 (GAD65) and GAD67, but does not affect the GABA transporter. However, it reduces GABA-transaminase, succinic semialdehyde dehydrogenase, and succinic semialdehyde reductase activities, GABA-degrading enzymes, thereby raising GABA concentration in the synaptic cleft[64-65]. Gastrodin modulates middle cerebral arterial occlusion (MCAO) mice by downregulating MMP2 and MMP9, repairing the blood-brain barrier, inhibiting neuronal death, and obstructing inflammation-induced neurotoxicity[66]. Chen et al.[67] showed in a mouse epilepsy model provoked by pentylenetetrazole that gastrodin can suppress M1 microglia marker levels of interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) and can reverse the M2 microglia marker IL-10 levels. It also suggested that gastrodin can inhibit the expression of mitogen-activated protein kinase (MAPK), cAMP response element binding protein (CREB), and nuclear factor-κB (NF-κB), indicating that gastrodin reduces epileptic seizures by inhibiting the microglia-mediated inflammatory response associated with MAPK[67].

3.2 Cardiovascular system protective effect

Hypertension, a significant cardiovascular risk[68], is linked to the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, and ion transport[69]. RAAS controls blood pressure and electrolyte homeostasis, which is essential in hypertension pathogenesis[70]. Renin is

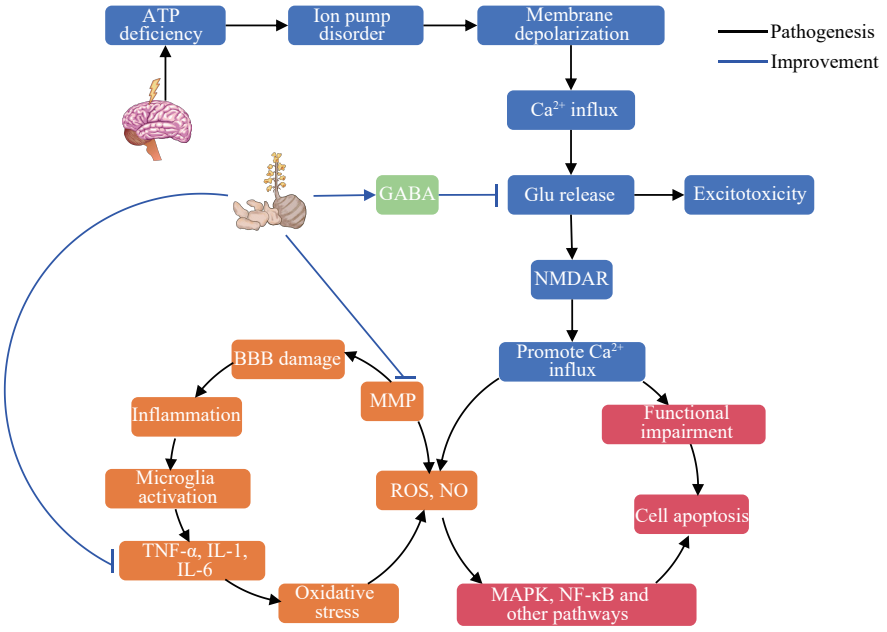


Fig. 2 The main mechanism of *G. elata* improving the nervous system. →, activation; ⊣, inhibition; BBB, blood-brain barrier; NMDAR, *N*-methyl-*D*-aspartate receptors.

released from the kidneys in response to decreased blood flow, initiating a cascade converting angiotensinogen to angiotensin I (Ang I) and Ang II, with the latter causing vasoconstriction and aldosterone release, culminating in increased blood pressure[71-72]. Endothelial dysfunction underlies essential hypertension, with vascular homeostasis maintained by a balance of endothelial vasoactive agents[73]. Endothelin (ET), a potent vasoconstrictor, heightens vascular resistance and blood pressure, while NO acts as a primary vasodilator[74-75]. Ang II enhances endothelin release, influencing the ET-Ang II synergism, whereas NO downregulates endothelin and renin, reducing Ang II synthesis[76] (Fig. 3).

Peroxisome proliferator-activated receptor gamma (PPARγ), a nutrient-sensitive nuclear transcription factor, can downregulate the expression of angiotensin-converting enzyme and Ang II type 1 receptor (AT1R), counteracting the effects of Ang II and inhibiting the synthesis and secretion of adrenal aldosterone[77-78]. Liu et al.[79] conducted experimental studies and found that gastrodin upregulates the expression of *PPARγ* mRNA and protein in myocardial tissue, reduces the levels of Ang II and aldosterone in serum, and downregulates the expression levels of *AT1R* mRNA and protein. Studies have shown that *G. elata* polysaccharide increases NO levels in rat serum, reduces plasma Ang II and ET levels, and exhibits vasodilation and blood pressure-lowering effects[80]. These findings indicate that *G. elata* polysaccharide promotes the production of endogenous vasodilators, inhibits the release of endogenous vasoconstrictors, restores the balance between them, and lowers blood pressure. Dai et al.[81] isolated 4 phenolic compounds from *G. elata* using ethyl acetate and demonstrated their ability to induce aortic vasodilation in rats.

3.3 Skeletal system protective effect

Osteoporosis, a systemic metabolic bone disease, occurs when bone resorption by osteoclasts surpasses bone formation by osteoblasts, resulting in an imbalance in bone homeostasis[82]. Osteoclasts, derived from the monocyte/macrophage cell line (RAW264.7 cells), is crucial in bone tissue resorption. It releases hydrochloric acid and lysozyme to dissolve surrounding bone tissue. The process of bone resorption by osteoclasts involves 4 stages: preparation, initiation, maturation, and termination. In osteoporosis, inflammation, and immune responses trigger the release of cytokines like TNF and IL-1 from immune cells such as macrophages and T cells. These cytokines stimulate the production of macrophage colony-stimulating factor and receptor activator of NF-κB ligand (RANKL), activating osteoclasts precursor cells and attracting them to the bone surface[83]. Factors like aging, lack of exercise, and malnutrition can also increase osteoclast activity. During the initiation stage, RANKL binds to the receptor activator of NF-κB (RANK) on osteoclasts precursor cells, activating signaling pathways such as NF-κB and MAPK, ultimately leading to the activation of nuclear factor of activated T cells cytoplasmic 1 (NFATc1). NFATc1, a transcription factor, triggers the expression of genes involved in osteoclast differentiation and activation[84], promoting the maturation of osteoclasts. precursor cells into mature osteoclasts cells. Mature osteoclasts cells degrade the bone matrix by secreting enzymes like acid phosphatase (ACP), tartrate-resistant acid phosphatase (TRAP), cathepsin K (CTSK), and matrix MMP9[85]. Typically, osteoclasts cells undergo programmed death (apoptosis) after completing bone resorption. However, osteoclasts tend to have a

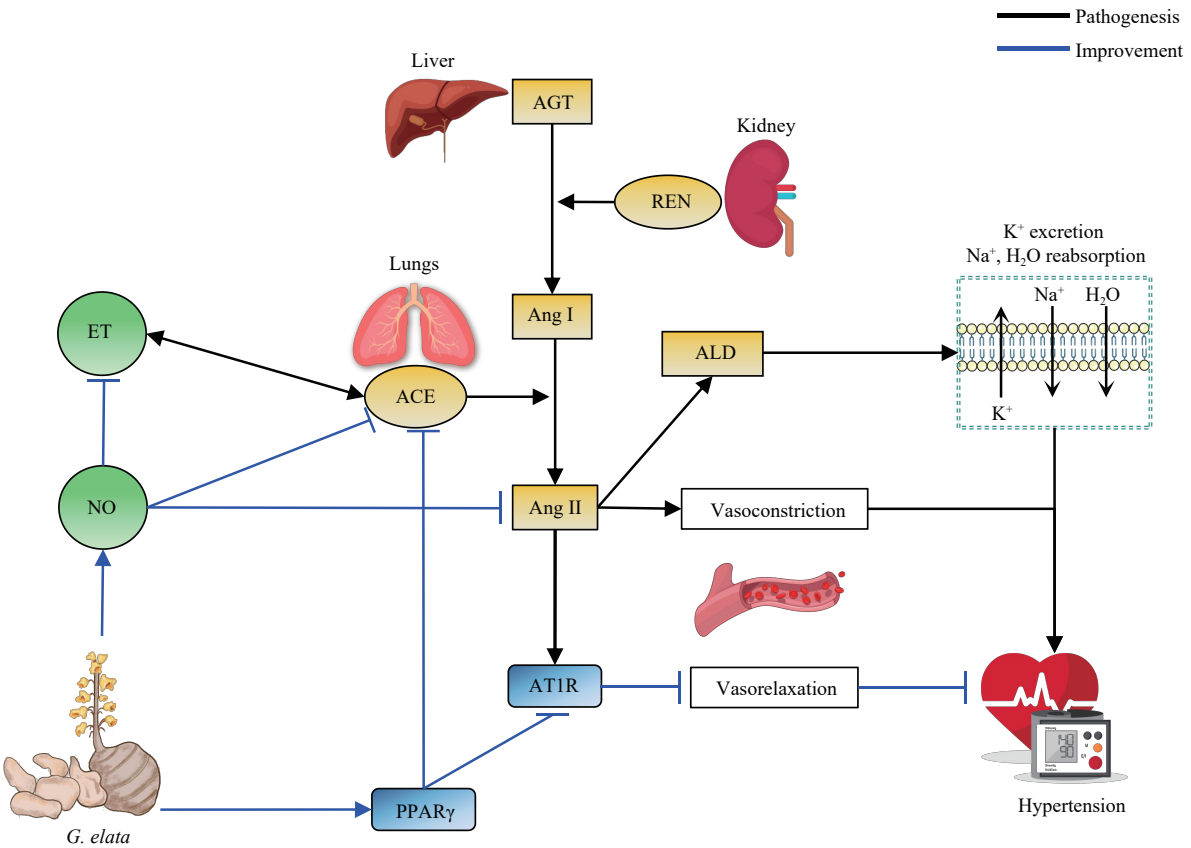


Fig. 3 The main mechanism of *G. elata* improving hypertension. →, activation; ⊣, inhibition; AGT, angiotensinogen; REN, renin; ACE, angiotensin-converting enzyme; ALD, aldosterone.

prolonged lifespan in osteoporosis, leading to excessive bone resorption[86] (Fig. 4).

ROS plays a crucial role in osteoclast differentiation[87]. Osteoclasts require higher ROS levels than other bone cells[88]. However, excessive ROS can disrupt normal biological functions, cause an imbalance in cellular redox reactions, and lead to oxidative stress[89]. Gastrodin has been shown to reduce ROS levels in RAW264.7 cells under oxidative stress, inhibit the H_2O_2-induced expression of osteoclast-specific genes *NFATc1*, *CTSK* and *TRAP*, and reduce the number of osteoclasts. This suggests that gastrodin has potential anti-osteoporotic effects by inhibiting osteoclast differentiation[90]. Similarly, WSS25, a sulfated derivative of *G. elata* polysaccharide, has been found to dose-dependently inhibit osteoclast differentiation and the expression of osteoclast formation-specific genes *NFATc1*, *CTSK*, *TRAP* and *MMP9* in RANKL-induced RAW264.7 cells[91]. The inhibitory effects of gastrodin and *G. elata* polysaccharide on osteoclasts may be attributed to their structural similarity, as both compounds contain glucose molecules. However, further research is required to explore the mechanisms of action of gastrodin and *G. elata* polysaccharide on osteoclasts and determine the significance of their structural similarities in inhibiting osteoclast function. NF-κB signaling is a crucial intracellular pathway regulating inflammation and proinflammatory stress responses[91]. Proinflammatory cytokines stimulate osteoclast differentiation and bone resorption by inducing RANKL expression[92]. In experiments using IL-1β-induced rat chondrocyte inflammation, gastrodin inhibited the NF-κB pathway, decreased the release of inflammatory mediators IL-6 and TNF-α, reduced matrix catabolism in IL-1β-treated chondrocytes, and maintained cellular homeostasis in chondrocytes[93].

3.4 Other protective effect

Apart from impacting the systems mentioned above, stress and unhealthy lifestyle habits can also result in disorders in the digestive, endocrine, urinary, respiratory, and other systems, leading to conditions such as gastritis, diabetes, nephritis, asthma, and other diseases. *G. elata* and its active ingredients exhibit preventive and therapeutic effects on these diseases. The main mechanisms involve the inhibition of oxidative stress and the regulation of immune inflammation.

Chronic atrophic gastritis is a digestive system disease characterized by gastric mucosal atrophy and intestinal metaplasia resulting from long-term chronic inflammation of the gastric mucosa. Its pathogenesis involves various factors, including prolonged gastric mucosal inflammatory response, *Helicobacter pylori* infection, autoimmune response, and environmental factors, leading to damage to the gastric mucosa[92]. Animal studies using rat models have demonstrated that *G. elata* can ameliorate chronic atrophic gastritis by modulating energy and purine metabolism and exerting antioxidant and anti-inflammatory effects. *G. elata* restores the dysfunction of the citric acid cycle (TCA) by increasing ATP levels, thereby improving gastric mucosal function. Additionally, *G. elata* reduces hypoxanthine levels, thereby mitigating damage to the gastric mucosa caused by oxidative stress. Moreover, *G. elata* enhances the activity of superoxide dismutase (SOD),

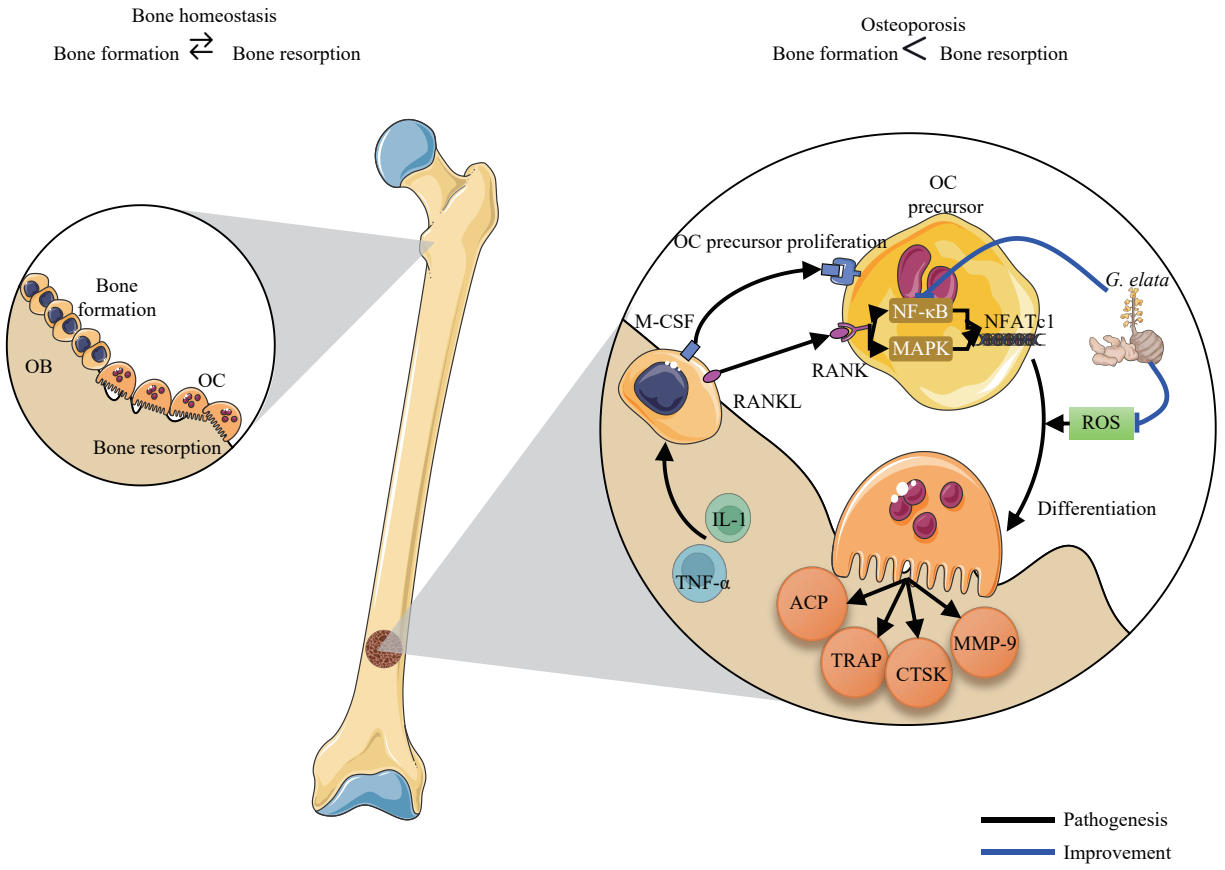


Fig. 4 The main mechanism of *G. elata* improving osteoporosis. →, activation; ⊣ , inhibition; OB,osteoblast; OC, osteoclast; M-CSF, macrophage colony-stimulating factor.

leading to increased levels of endogenous antioxidants such as glutathione (GSH) and ascorbic acid, effectively reducing the damage inflicted by oxygen free radicals on the gastric mucosa. Furthermore, *G. elata* diminishes the levels of inflammatory mediators like NO and histamine, significantly attenuating the inflammatory response of the gastric mucosa[93].

Type 2 diabetes is an endocrine system disorder characterized by insulin resistance and impaired secretion. *G. elata* contains several small molecule compounds, such as gastrodin, 4-hydroxybenzyl alcohol, 4-hydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, and vanillin, which have been found to penetrate the blood-brain barrier and exert effects in the brain, particularly in the hypothalamus, responsible for regulating energy and glucose metabolism. These compounds modulate energy and glucose metabolism by influencing neuronal activity and signaling pathways[94]. In a rat model of type 2 diabetes, gastrodin improved insulin sensitivity by enhancing hypothalamic insulin signaling and reducing hepatic glycogen output during hyperinsulinemic states. Studies have demonstrated that gastrodin reduces the expression of inflammatory cytokines and markers of oxidative stress in the hypothalamus while increasing the expression of proteins related to insulin signaling pathways, ultimately improving insulin sensitivity and glucose metabolism[95]. Additionally, *G. elata* extract has been shown to enhance glucose-stimulated insulin secretion by increasing the number of pancreatic islet β-cells, thus improving type 2 diabetes[96].

Gastrodin has shown potential in improving renal damage caused by CCl_4, inhibiting renal fibrosis, collagen deposition, and α-smooth muscle actin (α-SMA) accumulation, as well as reducing renal tissue inflammation[97]. Its effects are mediated by the inactivation of the receptor for advanced glycation end products (RAGE) and high mobility group protein B1 (HMGB1) pathways, as well as the inhibition of Toll-like receptors (TLR), NF-κB, and transforming growth factor (TGF)-β[98]. RAGE and HMGB1 are pivotal mediators of inflammation and oxidative stress in various diseases, including renal fibrosis[99]. TLRs are pattern recognition receptors involved in the innate immune response, and their activation can trigger the production of proinflammatory cytokines and chemokines[100]. TGF-β is a cytokine that promotes fibrosis development by facilitating fibroblast differentiation into myofibroblasts and the accumulation of extracellular matrix proteins[101]. These findings indicate that gastrodin can potentially treat renal fibrosis by inhibiting renal inflammation and oxidative stress through the inactivation of RAGE and HMGB1 pathways and the inhibition of TLR, NF-κB, and TGF-β. However, further research is necessary to fully elucidate the underlying mechanisms and ascertain the clinical potential of gastrodin in treating renal fibrosis.

Bronchial asthma is a chronic respiratory disease primarily characterized by immune response, airway inflammation, and airway structure changes. In an animal model of IgE-mediated asthma in guinea pigs, phenolic compounds derived from *G. elata* demonstrate significant inhibition of airway resistance during asthma's acute and remission phases. Additionally, these compounds effectively suppress leukocyte recruitment, histamine release, eosinophil peroxidase activity, and phospholipase A_2 activity[102].

In summary, it is evident that gastrodin, as the main active ingredient in *G. elata*, plays a crucial role in maintaining the health of various body systems. However, limited research on other components of *G. elata* hinders a comprehensive understanding of its efficacy. Therefore, there is an urgent need for comprehensive research on *G. elata*, including the study of the pharmacological effects of its various components, exploration of the mechanisms of action, evaluation in disease models, conducting clinical trials, and comprehensive assessment of its use alone or in combination with other traditional Chinese medicines. In-depth research will enhance our understanding of *G. elata* and its components in preventing and improving various diseases, facilitating new drug development, promoting industrial progress, and enhancing traditional Chinese medicine's competitiveness in the global pharmaceutical market.

4. Product development and limiting factors

4.1 Safety and toxicity of G. elata

References have demonstrated the safety of *G. elata* extracts, specifically gastrodin, and 4-HBA, in acute and subacute toxicity studies[103-104], with no significant adverse reactions observed. Acute oral toxicity assays have revealed that the maximal tolerable dosage surpasses 5 000 mg/kg, thereby categorizing it within the realm of non-toxic substances, in alignment with entries documented in the Chinese Pharmacopoeia[105-106]. Following the evaluation of the safety of *G. elata* wine in the late 20th century[107], a series of toxicological tests were carried out on compound preparations and functional food products associated with *G. elata*[108-113] (in China, although both medicine and food homology substances and functional food belong to the category of food, they must be treated differently), the results of these studies have shown that *G. elata* products have a very high safety profile. While *G. elata* has a long history of use in traditional medicine and is classified as a medicine and food homology substance, it is essential to acknowledge that its use in modern food products does not come without risks. Processed *G. elata* products may change bioactive components, potentially impacting their safety and effectiveness. However, toxicological studies related to *G. elata* remain relatively limited, with a primary focus on acute and genotoxicity tests and less available data on subacute and chronic toxicity. This limited research contributes to the uncertainty surrounding the safety assessment of *G. elata* products and can impact their development. Therefore, it is imperative to prioritize safety assessment and conduct clinical trials while developing *G. elata* products to ensure their safety and efficacy in human usage. The manuscript proposes that forthcoming endeavors should establish threshold standards rooted in the typical pollutant residues or toxic elements inherent in *G. elata*. Guided by risk assessment and synergized with toxicological evaluation and scrutiny of dietary configurations. A preliminary summary of the above studies is presented and a complete evaluation strategy for medicine and food homology substances is proposed, as shown in Fig. 5. These efforts should cultivate a scientific and bespoke safety assessment study of *G. elata* as a dietary item. This evaluation should align with its distinctive beneficial properties, thus providing a foundational safety platform for the forward march in developing *G. elata*.

4.2 Clinical application of G. elata

Due to its non-toxic and practical nature, *G. elata* is often combined with other medicinal herbs in traditional Chinese medicine formulas, such as Tian Ma Gou Teng Yin and Ban Xia Bai Zhu Tian Ma Tang[114-115].

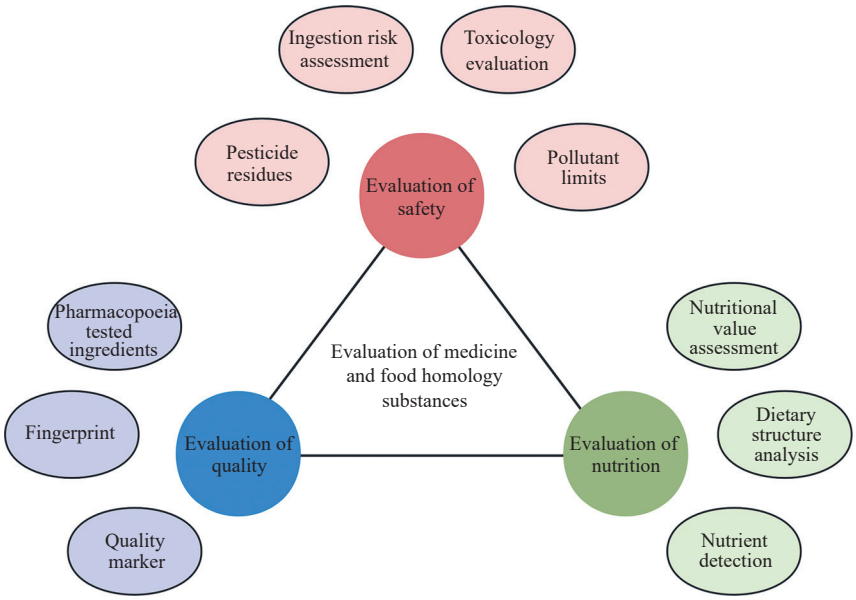


Fig. 5 Evaluation of medicine and food homology substance.

In modern clinical practice, significant progress has been made in integrating the concepts of traditional Chinese and Western medicine to improve the diagnosis and treatment of patients. The simultaneous use of Western medicine and *G. elata* as an adjunct therapy has shown superior efficacy compared to monotherapy, particularly in treating conditions such as depression, insomnia, and cardiovascular diseases[116-119]. Previous studies have primarily focused on the neuroregulatory effects of *G. elata*. However, pharmacological analysis of *G. elata* has found that many other pharmacological functions have not been fully utilized in clinical practice. Therefore, research should focus on more detailed investigations into these pharmacological activities. Such exploration can reveal new potentials of *G. elata* in clinical applications and further expand its value in food development.

While traditional *G. elata* products are known for their therapeutic effectiveness, they face specific issues regarding convenience and stability. With the advancement of modern drug preparation technology, the primary dosage forms of *G. elata* now encompass injections, pills, tablets, and mixtures[120]. These dosage forms can deliver the active ingredients directly into the body, enhancing the therapeutic effect and facilitating daily administration and dosage control. This reveals that care also needs to be taken in developing *G. elata* food products to maintain the efficacy and stability of the product and that new food types can be explored, drawing on previous experience in the development of pharmaceutical agents. By combining the pharm-targeted drug delivery method elata and modern food processes, we can develop more convenient and easy-to-use *G. elata* food products, such as granules, oral liquids, functional beverages, etc., which are convenient for users to carry and use. In addition, the stability and bioavailability of the active ingredients of *G. elata* can be improved by microencapsulation, nanochemistry, or other technical means. The future *G. elata* food can be more diversified, portable, and based on ensuring efficacy and stability to meet the needs of modern consumers for health products, providing them with more convenient and effective health solutions.

4.3 Food application of G. elata

In China, the folk consumption of *G. elata* has a long history. In the Tang Dynasty, *G. elata* was harvested immediately after taking advantage of the fresh raw food. In the Song Dynasty, in addition to raw food, *G. elata* also used brown sugar or honey pickled and processed into candied fruit for consumption[121]. However, due to the scarcity of wild asparagus resources in ancient times, edible and therapeutic efficacy had not been developed and popularized. With the emergence of artificial cultivation, the scarcity of asparagus has been improved, the edible and nutritional value has gradually come to the fore, and the related health food and therapeutic methods have also been developed rapidly. During the pilot work on medicinal food, *G. elata* edible products were created in various forms, such as rice powder, punch, drinking tea, freeze-dried granules, dried fruits, and oral liquid[122]. Meanwhile, health food products developed with *G. elata*, especially those that improve sleep, maintain healthy blood pressure, and enhance immunity, have been very popular among the public. The fact that *G. elata* will be officially recognized as a medicinal substance in China in 2023 indicates that innovations in the product development of *G. elata* and other medicinal substances will become an important driving force in the health food sector. Indeed, there are several challenges to be addressed during the development and commercialization process. These include establishing quality assessment standards, addressing the unique odor of *G. elata*, refining extraction techniques for active ingredients, and overcoming a series of other obstacles that may arise. We shall expound upon these issues with greater specificity in the ensuing discourse.

4.4 Quality evaluation

The empirical judgment of medicinal materials based on their appearance has long been a convenient and standard method for quality evaluation. In the case of *G. elata*, a good-quality product is characterized by its larger size, heavier weight, solid texture, yellow and white color, and translucent leathery cross-section without hollows.

Modern qualitative identification technology has made assessing the quality of *G. elata* products easier. By analyzing the characteristic attributes of its key components, such as hydroxybenzyl alcohols and gastrodin, using methods like UV absorption, mass spectrometry, and nuclear magnetic resonance, the purity and active ingredient content of *Gastrodia* products can be determined and certified. However, it should be noted that the grade of *G. elata* products cannot be solely established based on chemical composition. Studies have shown no correlation between product grade and gastrodin content, and different seasons may affect the content of gastrodin, adenosine, and polysaccharides in *G. elata*[123-124]. Therefore, relying solely on chemical composition as a screening index for product grading is not reasonable.

The World Health Organization (WHO) guidelines for evaluating herbal medicines require chromatographic fingerprint identification if the active ingredients cannot be identified. This ensures consistency in product quality[125]. In recent years, Chinese pharmaceutical workers have proposed the concept of fingerprints to control the quality of traditional Chinese medicines effectively. The fingerprint refers to the ability of Chinese medicinal materials to identify the authenticity or origin of a sample through proper analysis. The relative stability of product quality can be ensured by analyzing the area or proportion of the prominent characteristic peaks in the fingerprint. Some studies have also utilized a technology called one-measurement-multiple-evaluation to simultaneously measure the contents of various active ingredients in *G. elata*, such as gastrodin, *p*-hydroxybenzyl alcohol, parishin A, and parishin B[126]. This approach aligns with the concept of "multi-component, multi-target, overall regulation" and the need to establish a new model for multi-index quality evaluation specific to traditional Chinese medicine. While fingerprint technology comprehensively displays the characteristics of traditional Chinese medicine ingredients, the practical application may be limited by difficulties in determining each ingredient's peak value and content. On the other hand, the one-measurement-multiple-evaluation method overcomes the lack of reference substances and simplifies quantitative analysis. By combining the 2 approaches, the overall control provided by fingerprints can be complemented by quantitative measurement of representative compounds, allowing for a better understanding of the amounts of individual components and providing multiple indicators for quality evaluation of traditional Chinese medicine[127].

4.5 Special smell treatment

The distinct odor of *G. elata* is commonly called "horse urine smell"[128]. Analysis of *G. elata* juice's volatile components indicates that ether compounds are abundant and serve as the main volatile substances. Ethers typically possess smoky and pungent odors, which may contribute to the horse urine-like smell in *G. elata* juice. Researchers have conducted preliminary investigations into the specific odor components. Some studies suggest that dimethyl disulfide, a sulfide compound reminiscent of horse urine, may be responsible for this smell[129]. It is difficult for the general population to accept this taste, so they find it difficult to insist on or even refuse to eat *G. elata* food. Therefore, when developing *G. elata* food and functional food, it is imperative to take reasonable measures to deal with foul odors to obtain good sensory properties.

To develop *G. elata* products, it is crucial to mitigate the unfavorable sensory effects of its distinct odor while preserving its functional ingredients. Various techniques, including honey processing, steaming, and fermentation, have been employed to reduce or mask the unpleasant taste of *G. elata*, creating sensory-friendly and nutritious food products[130]. Stir-frying with honey bran enhances its taste and wind-dispelling effects, while honey processing involves coating, steaming, and drying to impart a sweet taste and prevent oxidation[131]. High-pressure steam treatment eliminates off-flavors and increases the content of gastrodin, the main component of *G. elata*[132]. In 2019, a South Korean patent introduced fermentation technology using lactic acid bacteria to ameliorate the unpleasant odor of *G. elata*. This method effectively weakens the special odor while enhancing antioxidant effects and significantly increasing the content of active ingredients like gastrodin[133-134].

Nevertheless, these methods have their drawbacks. Honey treatment can remove off-flavors but is complex and unsuitable for people with diabetes due to its high sugar content. Traditional high-temperature steaming may degrade thermosensitive components, affecting activity. While capable of generating new active compounds, fermentation is challenging to control and subject to environmental variation, leading to inconsistent product quality[135].

Technological advancements have revolutionized the modern processing of Chinese medicinal herbs like *G. elata*, making the process more scientific and standardized. Flash streaming technology has proven superior to traditional high-temperature boiling methods. Its ability to rapidly heat and cool significantly reduces the loss of heat-sensitive components, thereby better preserving the active ingredients[136]. The controllability of flash steaming ensures consistent product quality across batches[137]. Furthermore, artificial intelligence transforms traditional fermentation processes by enabling real-time monitoring and dynamic optimization[138]. This precise control of environmental conditions and nutrient supply enhances the quality and yield of fermented products. Such refined management also helps increase the medicinal component content and functional properties in the post-processing of *G. elata*. These technological advancements enhance product quality and production efficiency and reduce resource waste. With further research and practical applications, these advanced technologies are expected to find broader usage in processing *G. elata* and other Chinese medicinal herbs, driving continuous innovation and progress in the traditional Chinese medicine industry.

4.6 Functional ingredient purification process

In order to enhance product efficacy, convenience of consumption, portability, and process requirements, it is expected to extract and concentrate raw materials before processing them into the final product. Traditional methods, such as soaking[139] and thermal reflux extraction[140], have limitations such as long extraction time, low efficiency, and toxic solvents like methanol. Enzyme extraction also has limitations in temperature and pH adaptability.

Modern extraction and purification technologies offer diverse solutions to improve the efficiency and quality of active ingredient extraction from *G. elata* and other medicinal plants. Supercritical fluid extraction (SFE) is widely applied to extract active ingredients from traditional Chinese medicines. It is effective for compounds such as terpenes, essential oils, alkaloids, and flavonoids, including phenolics

from *G. elata*[141]. The technique entails an extraction phase using supercritical fluid, followed by a separation stage where parameters are tuned to recover the constituents, allowing for collection and solvent reuse. This method guarantees a green and efficient extraction[142]. Ultra-high pressure extraction achieves equilibrium between intracellular and extracellular fluids by mixing raw materials with solvents and subjecting them to pressures above 100 MPa, followed by rapid decompression that results in a substantial osmotic pressure differential to release active compounds[143]. This technique has effectively isolated polysaccharides, flavonoids, saponins, alkaloids, and organic acids in traditional Chinese medicine studies[144]. Chromatographic separation technology, particularly preparative liquid chromatography (Prep-LC), is gaining attention for its ability to purify biologically active substances with high purity. Its high separation efficiency, recovery, and capacity for processing high-value compounds like phenols, terpenes, and organosulfides[145]. Future advancements may investigate Prep-LC integrated with SFE and ultra-high pressure extraction for even more efficient extraction and purification from complex mixtures.

5. Conclusion and future research

This study delves into the relationship between the structural characteristics of active components in *G. elata* and their diverse biological functions, highlighting how phenols, polysaccharides, organic acids, esters, and steroids impact neuroprotection, hypertension management, and bone health. The research also notes shortcomings, such as the pharmacological focus on phenols and polysaccharides. At the same time, other potential active components are less explored, and the mechanisms behind their effects remain largely unelucidated. Many studies have only characterized bioactivity without a deep understanding of molecular mechanisms. Future research should employ multi-omics approaches to investigate these active components' specific mechanisms of action thoroughly.

With the advancement of modern cultivation techniques, the yield of *G. elata* is expected to increase significantly, presenting opportunities for economic growth and challenges in ensuring product quality and standardization for industrialization. The current quality assessment system fails to comprehensively evaluate the efficacy of *G. elata* due to its oversimplified nature and lack of consideration for all efficacy-influencing factors. A more comprehensive quality evaluation system is urgently needed, incorporating chemical component analysis and an integrated assessment of pharmacological activity and biological effectiveness. Additionally, the unique odor of *G. elata* and limitations in extraction techniques pose barriers to its large-scale application. Fortunately, advanced extraction technologies such as flash evaporation and ultra-high-pressure extraction can efficiently isolate active components while eliminating undesirable odors without compromising their activity. The future application of these technologies promises to enhance product quality and market acceptance significantly. To maximize *G. elata*'s industrial potential, we must refine the quality assessment system, adopt advanced extraction techniques, and conduct comprehensive research. This will help fully exploit the value of *G. elata*, develop innovative products meeting modern health needs, and advance human health endeavors.

Conflict of interest

There is no conflict of interest.

Acknowledgements

We thank the Laboratory of Agricultural Products Processing and Storage Engineering for their support. This work was supported by the Jilin Scientific and Technological Development Program (20230202047NC).

References

[1] Y. Liu, J. Gao, M. Peng, et al., A review on central nervous system effects of gastrodin, Front. Pharmacol. 9 (2018) 24. http://doi.org/10.3389/fphar.2018.00024.

[2] J. Hu, J. Yang, L. Yang, et al., Medicinal orchids: *Dendrobium* species and *Gastrodia elata* blume, CRC Press, 2021, pp. 165-192.

[3] T. Liu, Z. Hua, P. Han, et al., Mycorrhizosphere bacteria, *Rahnella* sp. Hpda25 promotes the growth of *Armillaria gallica* and its parasitic host *Gastrodia elata*, Front. Microbiol. 13 (2022) 842893. http://doi.org/10.3389/fmicb.2022.842893.

[4] J. Cai, I. Muhammad, B. Chen, et al., Whole genome sequencing and analysis of armillaria gallica jzi34 symbiotic with *Gastrodia elata*, BMC Genomics 1(24) (2023) 275. http://doi.org/10.1186/s12864-023-09384-4.

[5] M.J. Kim, H.J. Yang, B.R. Moon, et al., *Gastrodia elata* blume rhizome aqueous extract improves arterial thrombosis, dyslipidemia, and insulin response in testosterone-deficient rats, Evid.-Based Complement Altern. Med. 2017 (2017) 1-11. http://doi.org/10.1155/2017/2848570.

[6] L. Min, Plant data center of Chinese Academy of Sciences. (2021). https://www.plantplus.cn/.

[7] P. He, Y. Hu, C. Huang, et al., *N*-Butanol extract *of Gastrodia elata s*uppresses inflammatory responses in lipopolysaccharide-stimulated macrophages and complete freund's adjuvant-(CFA-) induced arthritis rats *via* inhibition of MAPK signaling pathway, Evid.-Based Complement Altern. Med. 2020 (2020) 1-11. http://doi.org/10.1155/2020/1658618.

[8] H. Zhu, D. Zhang, Q. Zhang, et al., 4-Hydroxybenzyl alcohol derivatives and their sedative-hypnotic activities, Rsc Adv. 35(8) (2018) 19539-19550. http://doi.org/10.1039/C8RA01972J.

[9] J.Y. Lee, Y.W. Jang, H.S. Kang, et al., Anti-inflammatory action of phenolic compounds from *Gastrodia elata* root, Arch. Pharm. Res. 10(29) (2006) 849-858. http://doi.org/10.1007/BF02973905.

[10] E.K. Ahn, H.J. Jeon, E.J. Lim, et al., Anti-inflammatory and anti-angiogenic activities of *Gastrodia elata* blume, J. Ethnopharmacol. 3(110) (2007) 476-482. http://doi.org/10.1016/j.jep.2006.10.006.

[11] S.M. Hwang, Y.J. Lee, D.G. Kang, et al., Anti-inflammatory effect of *Gastrodia elata* rhizome in human umbilical vein endothelial cells, Am. J. Chin. Med. 2(37) (2009) 395-406. http://doi.org/10.1142/S0192415X09006916.

[12] J. Liu, A. Mori, Antioxidant and free radical scavenging activities of *Gastrodia elata* Bl. and *Uncaria rhynchophylla* (Miq.) Jacks, Neuropharmacology 12(31) (1992) 1287-1298. http://doi.org/10.1016/0028-3908(92)90058-w.

[13] S.J. Yu, J.R. Kim, C.K. Lee, et al., *Gastrodia elata* blume and an active component, *p*-hydroxybenzyl alcohol reduce focal ischemic brain injury through antioxidant related gene expressions, Biol. Pharm. Bull. 6(28) (2005) 1016-1020. http://doi.org/10.1248/bpb.28.1016.

[14] E. Song, H. Chung, E. Shim, et al., *Gastrodia elata* blume extract modulates antioxidant activity and ultraviolet a-irradiated skin aging in human dermal fibroblast cells, J. Med. Food 11(19) (2016) 1057-1064. http://doi.org/10.1089/jmf.2016.3722.

[15] J.W. Xian, A.Y. Choi, C.B. Lau, et al., *Gastrodia* and *Uncaria* (Tianma Gouteng) water extract exerts antioxidative and antiapoptotic effects against cerebral ischemia *in vitro* and *in vivo*, Chin. Med. 11 (2016) 27. http://doi.org/10.1186/s13020-016-0097-6.

[16] W. Tan, Q. Zheng, K. Feng, et al., Neuroprotection of *gastrodia elata* polyphenols against H_2O_2-induced pc12 cell cytotoxicity by reducing oxidative stress, Front. Pharmacol. 13 (2022) 1050775. http://doi.org/10.3389/fphar.2022.1050775.

[17] Z.B. Huang, Z. Wu, F.K. Chen, et al., The protective effects of phenolic constituents from *Gastrodia elata* on the cytotoxicity induced by KCl and

glutamate, Arch. Pharm. Res. 11(29) (2006) 963-968. http://doi.org/10.1007/BF02969279.

[18] T.Y. Jung, S.I. Suh, H. Lee, et al., Protective effects of several components of *Gastrodia elata* on lipid peroxidation in gerbil brain homogenates, Phytother. Res. 10(21) (2007) 960-964. http://doi.org/10.1002/ptr.2193.

[19] H. An, I.S. Kim, S. Koppula, et al., Protective effects of *Gastrodia elata* blume on MPP^+-induced cytotoxicity in human dopaminergic SH-SY5Y cells, J. Ethnopharmacol. 2(130) (2010) 290-298. http://doi.org/10.1016/j.jep.2010.05.006.

[20] Q. Ma, Q. Wan, S. Huang, et al., Phenolic constituents with inhibitory activities on acetylcholinesterase from the rhizomes of *Gastrodia elata*, Chem. Nat. Compd. 1(51) (2015) 158-160. http://doi.org/10.1007/s10600-015-1228-5.

[21] J.Y. Huang, Y.H. Yuan, J.Q. Yan, et al., 20C, a bibenzyl compound isolated from *Gastrodia elata*, protects pc12 cells against rotenone-induced apoptosis *via* activation of the Nrf2/ARE/HO-1 signaling pathway, Acta Pharmacol. Sin. 6(37) (2016) 731-740. http://doi.org/10.1038/aps.2015.154.

[22] W.Z. Liang, C.R. Jan, S.S. Hsu, Cytotoxic effects of gastrodin extracted from the rhizome of *Gastrodia elata* blume in glioblastoma cells, but not in normal astrocytes, *via* the induction of oxidative stress-associated apoptosis that involved cell cycle arrest and p53 activation, Food Chem. Toxicol. Pt A 107 (2017) 280-292. http://doi.org/10.1016/j.fct.2017.07.013.

[23] C. Lu, S. Qu, Z. Zhong, et al., The effects of bioactive components from the rhizome of *Gastrodia elata* blume (Tianma) on the characteristics of parkinson's disease, Front. Pharmacol. 13 (2022) 963327. http://doi.org/10.3389/fphar.2022.963327.

[24] Y.L. Wang, S.S. Li, M. Wang, et al., Gastrodin inhibits H_2O_2-induced ferroptosis of pc12 cells, Chinese Journal of Clinical Pharmacology and Therapeutics 5(26) (2021) 532-538. http://doi.org/10.12092/j.issn.1009-2501.2021.05.009.

[25] Y. Li, Y. Ji, F. Li, A review: mechanism and prospect of gastrodin in prevention and treatment of T2DM and COVID-19, Heliyon 11(9) (2023) e21218. http://doi.org/10.1016/j.heliyon.2023.e21218.

[26] National Health Commission of the People's Republic of China & State Administration for Market Regulation, Announcement on 9 new substances such as codonopsis pilosula that are both food and traditional Chinese medicinal materials according to tradition, (2023). http://www.nhc.gov.cn/sps/s7892/202311/f0d6ef3033b54333a882e3d009ff49bf.shtml.

[27] H.B. Zhou, S.Z. Lu, Z.S. Yu, et al. Mechanisms for the biological activity of *Gastrodia elata* blume and its constituents: a comprehensive review on sedative-hypnotic, and antidepressant properties, Phytomedicine 123 (2024) 155251. https://doi.org/10.1016/j.phymed.2023.155251.

[28] M.Q. Gong, F.F. Lai, J.Z. Chen, et al. Traditional uses, phytochemistry, pharmacology, applications, and quality control of *Gastrodia elata* blume: a comprehensive review, J. Ethnopharmacol. 319(Pt 1) (2024) 319. https://doi.org/10.1016/j.jep.2023.117128.

[29] Q. Wang, D.D. Li, A.M. Chen, et al., Comparison on main chemical composition contents in three variants of *Gastrodia elata* from southwest China, Chinese Traditional and Herbal Drugs 11(49) (2018) 2646-2652. http://doi.org/10.7501/j.issn.0253-2670.2018.11.025.

[30] A. Zeb, Phenolic antioxidants in foods: chemistry, biochemistry and analysis, Springer International Publishing, Cham, (2021) 25-87. https://link.springer.com/book/10.1007/978-3-030-74768-8.

[31] C.X. Li, F.R. Wang, B. Zhang, et al., Stability and antioxidant activity of phenolic compounds during *in vitro* digestion, J. Food Sci. 2(88) (2023) 696-716. http://doi.org/10.1111/1750-3841.16440.

[32] K. Ichikawa, R. Sasada, K. Chiba, et al., Effect of side chain functional groups on the DPPH radical scavenging activity of bisabolene-type phenols, Antioxidants 3(8) (2019) 65. http://doi.org/10.3390/antiox8030065.

[33] C. Tsai, K. Wu, T. Chiang, et al., Comparative transcriptome analysis of *Gastrodia elata* (orchidaceae) in response to fungus symbiosis to identify gastrodin biosynthesis-related genes, BMC Genomics 1(17) (2016) 212. http://doi.org/10.1186/s12864-016-2508-6.

[34] Y.G. Zhang, Q.J. Peng, H.Y. Zhang, et al., Synthesis and anticonvulsive activity of gastrodigenin homologues and analogues, Journal of Sichuan University (Medical Sciences) 1 (1984) 17-22.

[35] A. Alves, M. Correia-da-Silva, C. Nunes, et al., Discovery of a new xanthone against glioma: synthesis and development of (pro)liposome formulations, Molecules 3(24) (2019) 409. http://doi.org/10.3390/molecules24030409.

[36] J.N. Xiang, L.H. Jiang, C.Y. Chen, et al., Studies on the synthesis and antiproliferative activities of 13-*cis*-retinyl sugar derivatives, J. Carbohydr. Chem. 7(25) (2006) 595-614. http://doi.org/10.1080/07328300600966497.

[37] W. Gang, Q. Minjian, K. Jichuan, et al., Determination of gastrodins and polysaccharides in rhizoma gastrodia, Research and Practice on Chinese Medicines 1 (2007) 40-43. http://doi.org/10.3969/j.issn.1673-6427.2007.01.016.

[38] Y.K. Xang, X.Y. Li, C. Chen, et al., Effects of steam and water blanching on drying characteristics, water distribution, microstructure, and bioactive components of *Gastrodia elata*, Plants 6(12) (2023) 1372. http://doi.org/10.3390/plants12061372.

[39] Z. Zhu, C. Chen, H. Sun, et al., Structural characterization and ACE-inhibitory activities of polysaccharide from *Gastrodia elata* blume, Nat. Prod. Res. 12(33) (2019) 1721-1726. http://doi.org/10.1080/14786419.2018.1434643.

[40] J. Li, L. Fan, S. Ding, Isolation, purification and structure of a new water-soluble polysaccharide from *Zizyphus jujuba* cv. Jinsixiaozao, Carbohydr. Polym. 2(83) (2011) 477-482. http://doi.org/10.1016/j.carbpol.2010.08.014.

[41] J. Qu, P. Huang, L. Zhang, et al., Hepatoprotective effect of plant polysaccharides from natural resources: a review of the mechanisms and structure-activity relationship, Int. J. Biol. Macromol. 161 (2020) 24-34. http://doi.org/10.1016/j.ijbiomac.2020.05.196.

[42] A. Takada, J. Kadokawa, Fabrication and characterization of polysaccharide ion gels with ionic liquids and their further conversion into value-added sustainable materials, Biomolecules 1(5) (2015) 244-262. http://doi.org/10.3390/biom5010244.

[43] Y. Zhang, S. Li, X. Wang, et al., Advances in lentinan: isolation, structure, chain conformation and bioactivities, Food Hydrocoll. 2(25) (2011) 196-206. http://doi.org/10.1016/j.foodhyd.2010.02.001.

[44] N. Li, X. Fu, M. Xiao, et al., Enzymatic preparation of a low-molecular-weight polysaccharide rich in uronic acid from the seaweed *Laminaria japonica* and evaluation of its hypolipidemic effect in mice, Food Funct. 3(11) (2020) 2395-2405. http://doi.org/10.1039/C9FO02994J.

[45] G.Y. Duan, M. Zhang, X.J. Tang, et al., Study on quality evaluation of hybrid *Gastrodia*, Journal of Food Science and Technology 42(5) (2024) 157-167. http://doi.org/10.12301/spxb202200919.

[46] X. Zeng, J. Li, T. Chen, et al., Global metabolic profile and multiple phytometabolites in the different varieties of *Gastrodia elata* blume, Front. Plant Sci. 14 (2023) 1249456. http://doi.org/10.3389/fpls.2023.1249456.

[47] T. Wang, H. Chen, S. Xia, et al., Ameliorative effect of parishin C against cerebral ischemia-induced brain tissue injury by reducing oxidative stress and inflammatory responses in rat model, Neuropsychiatr. Dis. Treat. 17 (2021) 1811-1823. http://doi.org/10.2147/NDT.S309065.

[48] O.M.E. Abdel-Salam, E.R. Youness, N.A. Mohammed, et al., Citric acid effects on brain and liver oxidative stress in lipopolysaccharide-treated mice, J. Med. Food 5(17) (2014) 588-598. http://doi.org/10.1089/jmf.2013.0065.

[49] J. Qiao, Z. Shang, X. Liu, et al., Regulatory effects of combined dietary supplementation with essential oils and organic acids on microbial communities of cobb broilers, Front. Microbiol. 12 (2022) 814626. http://doi.org/10.3389/fmicb.2021.814626.

[50] D.L. Liu, G.R. Ding, N. Chen, et al., An inquiry of activities of phenolic acids against the aggregation of rabbit platelet *in vitro*, Journal of Shenyang Pharmaceutical University 15 (1998) 25-28. http://doi.org/10.14066/j.cnki.cn21-1349/r.1998.01.007.

[51] X. Jiang, Recent advances in the critical role of the sterol efflux transporters abcg5/g8 in health and disease, Springer Singapore Pte. Limited, Singapore, (2020) 105-136.

[52] B. He, L. Dai, L. Jin, et al., Bioactive components, pharmacological effects, and drug development of traditional herbal medicine *Rubus chingii* Hu (fu-pen-zi), Front. Nutr. 9 (2023) 1052504. http://doi.org/10.3389/fnut.2022.1052504.

[53] A.A. Jovanovic, B.D. Balanc, V.B. Djordjevic, et al., Effect of gentisic acid on the structural-functional properties of liposomes incorporating beta-sitosterol, Colloid Surf. B-Biointerfaces 183 (2019) 110422. http://doi.org/10.1016/j.colsurfb.2019.110422.

[54] X.T. Xie, H.Y. LI, Q. Wang, et al., The studys of chemical constituents in *Gastrodia elata* blume, Journal of Yunnan Normal University (natural sciences edition) 3(24) (2004) 22-25. http://doi.org/10.3969/j.issn.1007-9793.2004.03.008.

[55] Z. Li, Y. Wang, H. Ouyang, et al., A novel dereplication strategy for the identification of two new trace compounds in the extract of *Gastrodia elata*

using uhplc/q-tof-ms/ms, J. Chromatogr. B 988 (2015) 45-52. http://doi.org/10.1016/j.jchromb.2015.02.020.

[56] J.L. Li, Z. Zhao, H.C. Liu, et al., Content of mineral elements of *Gastrodia elata* by principal components analysis, China Journal of Chinese Materia Medica 6 (40) (2015) 1123-1128. http://doi.org/10.4268/cjcmm20150626.

[57] J. Kriska, Z. Hermanova, T. Knotek, et al., On the common journey of neural cells through ischemic brain injury and alzheimer's disease, International Journal of Molecular Sciences 18(22) (2021) 9689. http://doi.org/10.3390/ijms22189689.

[58] X. Song, Y. Zhang, Z. Tang, et al., Advantages of nanocarriers for basic research in the field of traumatic brain injury, Neural Regen. Res. 2(19) (2024) 237-245. http://doi.org/10.4103/1673-5374.379041.

[59] M. Faizan, I. Jahan, M. Ishaq, et al., Neuroprotective effects of trigonelline in kainic acid-induced epilepsy: behavioral, biochemical, and functional insights, Saudi Pharm. J. 12(31) (2023) 101843. http://doi.org/10.1016/j.jsps.2023.101843.

[60] Z. Han, L. Gao, Y. Lin, et al., Neuroprotection of taurine against reactive oxygen species is associated with inhibiting NADPH oxidases, Eur. J. Pharmacol. 777 (2016) 129-135. http://doi.org/10.1016/j.ejphar.2016.03.006.

[61] I. Azarova, E. Klyosova, A. Polonikov, Single nucleotide polymorphisms of the rac1 gene as novel susceptibility markers for neuropathy and microvascular complications in type 2 diabetes, Biomedicines 3(11) (2023) 981. http://doi.org/10.3390/biomedicines11030981.

[62] S.M. Stamatovic, C.M. Phillips, G. Martinez-Revollar, et al., Involvement of epigenetic mechanisms and non-coding RNAs in blood-brain barrier and neurovascular unit injury and recovery after stroke, Front. Neurosci. 13 (2019) 864. http://doi.org/10.3389/fnins.2019.00864.

[63] M. Frinchi, G. Morici, G. Mudó, et al., Beneficial role of exercise in the modulation of mdx muscle plastic remodeling and oxidative stress, Antioxidants 4(10) (2021) 558. http://doi.org/10.3390/antiox10040558.

[64] S.J. An, S.K. Park, I.K. Hwang, et al., Gastrodin decreases immunoreactivities of γ-aminobutyric acid shunt enzymes in the hippocampus of seizure-sensitive gerbils, J. Neurosci. Res. 4(71) (2003) 534-543. http://doi.org/10.1002/jnr.10502.

[65] M. Matias, S. Silvestre, A. Falcao, et al., *Gastrodia elata* and epilepsy: rationale and therapeutic potential, Phytomedicine 12(23) (2016) 1511-1526. http://doi.org/10.1016/j.phymed.2016.09.001.

[66] S. Wang, Y. Nan, W. Zhu, et al., Gastrodin improves the neurological score in mcao rats by inhibiting inflammation and apoptosis, promoting revascularization, Int. J. Clin. Exp. Pathol. 11(11) (2018) 5343-5350.

[67] L. Chen, X. Liu, H. Wang, et al., Gastrodin attenuates pentylenetetrazole-induced seizures by modulating the mitogen-activated protein kinase-associated inflammatory responses in mice, Neurosci. Bull. 3(33) (2017) 264-272. http://doi.org/10.1007/s12264-016-0084-z.

[68] L.G. Douma, M.L. Gumz, Circadian clock-mediated regulation of blood pressure, Free Radical Biol. Med. 119 (2018) 108-114. http://doi.org/10.1016/j.freeradbiomed.2017.11.024.

[69] K. Wu, H. Zheng, W. Wu, et al., Temporal relationship between triglyceride-glucose index and blood pressure and their joint cumulative effect on cardiovascular disease risk: a longitudinal cohort study, Cardiovasc. Diabetol. 1(22) (2023) 332. http://doi.org/10.1186/s12933-023-02058-1.

[70] A.F. Valookaran, J. Bouchard, B.M. Aloud, et al., Therapeutic potential of select dietary compounds in the management of hypertension and its cardiovascular complications, Molecules 21(27) (2022) 7222. http://doi.org/10.3390/molecules27217222.

[71] S. Kumar, N. Dietrich, K. Kornfeld, Angiotensin converting enzyme (ACE) inhibitor extends *Caenorhabditis elegans* life span, Plos Genet. 2(12) (2016) e1005866. http://doi.org/10.1371/journal.pgen.1005866.

[72] T. Xiao, J. Lu, J. Zhang, et al., A trimeric human angiotensin-converting enzyme 2 as an anti-SARS-cov-2 agent, Nat. Struct. Mol. Biol. 2(28) (2021) 202-209. http://doi.org/10.1038/s41594-020-00549-3.

[73] C.H. Leo, H.H. Ng, S.A. Marshall, et al., Relaxin reduces endothelium-derived vasoconstriction in hypertension: revealing new therapeutic insights, Br. J. Pharmacol. 1(177) (2020) 217-233. http://doi.org/10.1111/bph.14858.

[74] O.M. Ruberti, B. Rodrigues, Estrogen deprivation and myocardial infarction: role of aerobic exercise training, inflammation and metabolomics, Curr. Cardiol. Rev. 4(16) (2021) 292-305. http://doi.org/10.2174/1573403X15666190729153026.

[75] K.P. Cunningham, L.H. Clapp, A. Mathie, et al., The prostacyclin analogue, treprostinil, used in the treatment of pulmonary arterial hypertension, is a potent antagonist of TREK-1 and TREK-2 potassium channels, Front. Pharmacol. 12 (2021) 705421. http://doi.org/10.3389/fphar.2021.705421.

[76] S. Adiarto, S. Heiden, N. Vignon-Zellweger, et al., Et-1 from endothelial cells is required for complete angiotensin II-induced cardiac fibrosis and hypertrophy, Life Sci. 13-14(91) (2012) 651-657. http://doi.org/10.1016/j.lfs.2012.02.006.

[77] S.Z. Duan, C.Y. Ivashchenko, M.G. Usher, et al., PPAR-γ in the cardiovascular system, PPAR Res. 2008 (2008) 1-10. http://doi.org/10.1155/2008/745804.

[78] P. Sarafidis, A. Lasaridis, Actions of peroxisome proliferator-activated receptors-γ agonists explaining a possible blood pressure-lowering effect, Am. J. Hypertens. 6(19) (2006) 646-653. http://doi.org/10.1016/j.amjhyper.2005.12.017.

[79] W. Liu, L. Wang, J. Yu, et al., Gastrodin reduces blood pressure by intervening with raas and PPARγ in SHRs, Evid.-Based Complement Altern. Med. 2015 (2015) 1-8. http://doi.org/10.1155/2015/828427.

[80] H.C. Liao, Y.S. Shen, Antihypertensive effect of polysaccharides substracted from *Gastrodia elata* blume, Chinese Journal of Hypertension 7(14) (2006) 531-534. http://doi.org/10.16439/j.cnki.1673-7245.2006.07.007.

[81] R. Dai, T. Wang, X. Si, et al., Vasodilatory effects and underlying mechanisms of the ethyl acetate extracts from *Gastrodia elata*, Can. J. Physiol. Pharmacol. 5(95) (2017) 564-571. http://doi.org/10.1139/cjpp-2016-0407.

[82] S.S. Lei, J. Su, Y. Zhang, et al., Benefits and mechanisms of polysaccharides from chinese medicinal herbs for anti-osteoporosis therapy: a review, Int. J. Biol. Macromol. Pt B(193) (2021) 1996-2005. http://doi.org/10.1016/j.ijbiomac.2021.11.030.

[83] J.H. Park, Y.J. Son, C.H. Lee, et al., *Circaea mollis* Siebold & Zucc. *A*lleviates postmenopausal osteoporosis in a mouse model *via* the BMP-2/4/Runx2 pathway, BMC Complement. Med. Ther. 1(20) (2020) 1-11. http://doi.org/10.1186/s12906-020-02914-7.

[84] T. Noguchi, K. Ebina, M. Hirao, et al., Apolipoprotein E plays crucial roles in maintaining bone mass by promoting osteoblast differentiation *via* ERK1/2 pathway and by suppressing osteoclast differentiation *via* c-Fos, NFATc1, and NF-κB pathway, Biochem. Biophys. Res. Commun. 2(503) (2018) 644-650. http://doi.org/10.1016/j.bbrc.2018.06.055.

[85] L. Mei, W. Sang, Z. Chen, et al., Small molecule inhibitor repsox prevented ovariectomy-induced osteoporosis by suppressing osteoclast differentiation and bone resorption, J. Cell. Physiol. 12(233) (2018) 9724-9738. http://doi.org/10.1002/jcp.26914.

[86] Y. Zhang, S. Zhang, Y. Wang, et al., ULK1 suppresses osteoclast differentiation and bone resorption *via* inhibiting Syk-JNK through DOK3, Oxidative Med. Cell. Longev. 2021 (2021) 2896674. http://doi.org/10.1155/2021/2896674.

[87] N.K. Lee, Y.G. Choi, J.Y. Baik, et al., A crucial role for reactive oxygen species in rankl-induced osteoclast differentiation, Blood 3(106) (2005) 852-859. http://doi.org/10.1182/blood-2004-09-3662.

[88] J. Zhang, The osteoprotective effects of artemisinin compounds and the possible mechanisms associated with intracellular iron: a review of *in vivo* and *in vitro* studies, Environ. Toxicol. Pharmacol. 76 (2020) 103358. http://doi.org/10.1016/j.etap.2020.103358.

[89] T. S. Agidigbi, C. Kim, Reactive oxygen species in osteoclast differentiation and possible pharmaceutical targets of ROS-mediated osteoclast diseases, Int. J. Mol. Sci. 14(20) (2019) 3576. http://doi.org/10.3390/ijms20143576.

[90] Q. Huang, J. Shi, B. Gao, et al., Gastrodin: an ancient chinese herbal medicine as a source for anti-osteoporosis agents *via* reducing reactive oxygen species, Bone 73 (2015) 132-144. http://doi.org/10.1016/j.bone.2014.12.059.

[91] C. Chen, Y. Qin, J. Fang, et al., WSS25, a sulfated polysaccharide, inhibits RANKL-induced mouse osteoclast formation by blocking SMAD/ID1 signaling, Acta Pharmacol. Sin. 9(36) (2015) 1053-1064. http://doi.org/10.1038/aps.2015.65.

[92] L. Yu, G. Zhou, Z. Shi, et al., Interleukin-8 regulates the autophagy and apoptosis in gastric cancer cells *via* regulating PI3K/Akt signaling pathway, Dis. Markers 2022 (2022) 7300987. http://doi.org/10.1155/2022/7300987.

[93] C. Chen, Y. Fu, M. Li, et al., Nuclear magnetic resonance-based metabolomics approach to evaluate preventive and therapeutic effects of *Gastrodia elata* blume on chronic atrophic gastritis, J. Pharm. Biomed. Anal. 164 (2019) 231-240. http://doi.org/10.1016/j.jpba.2018.10.035.

[94] Y. Zhang, B. Zhou, M. Wen, et al., ZG02 improved hepatic glucose metabolism and insulin sensitivity *via* activation of AMPK/SIRT1 signaling pathways in a high-fat diet/streptozotocin-induced type 2 diabetes model, Diabetes Metab. Syndr. Obes. 13 (2020) 4333-4339. http://doi.org/10.2147/DMSO.S275145.

[95] Y. Bai, K. Mo, G. Wang, et al., Intervention of gastrodin in type 2 diabetes mellitus and its mechanism, Front. Pharmacol. 12 (2021) 710722. http://doi.org/10.3389/fphar.2021.710722.

[96] H. Yang, M. Kim, D. Kwon, et al., Anti-diabetic activities of *Gastrodia elata* blume water extracts are mediated mainly by potentiating glucose-stimulated insulin secretion and increasing β-cell mass in non-obese type 2 diabetic animals, Nutrients 3(8) (2016) 161. http://doi.org/10.3390/nu8030161.

[97] J.Q. Ma, Y.Z. Sun, Q.L. Ming, et al., Effects of gastrodin against carbon tetrachloride induced kidney inflammation and fibrosis in mice associated with the AMPK/Nrf2/HMBG1 pathway, Food Funct. 5(11) (2020) 4615-4624. http://doi.org/10.1039/d0fo00711k.

[98] Y. Wu, S. Wen, W. Zhang, et al., *Gastrodia elata* Bl.: a comprehensive review of its traditional use, botany, phytochemistry, pharmacology, and pharmacokinetics, Evid.-Based Complement Altern. Med. 2023 (2023) 5606021. http://doi.org/10.1155/2023/5606021.

[99] J. Liang, J. He, Y. Gao, et al., Exploring the potential mechanism of tang-shen-ning decoction against diabetic nephropathy based on the combination of network pharmacology and experimental validation, Evid.-Based Complement Altern. Med. 2021 (2021) 1-16. http://doi.org/10.1155/2021/1025053.

[100] S. Iori, M. Pauletto, I. Bassan, et al., Deepening the whole transcriptomics of bovine liver cells exposed to AFB1: a spotlight on toll-like receptor 2, Toxins 7(14) (2022) 504. http://doi.org/10.3390/toxins14070504.

[101] X.Q. Tian, X.W. Ni, H.L. Xu, et al., Prevention of doxorubicin-induced cardiomyopathy using targeted MaFGF mediated by nanoparticles combined with ultrasound-targeted MB destruction, Int. J. Nanomed. 12 (2017) 7103-7119. http://doi.org/10.2147/IJN.S145799.

[102] Y.W. Jang, J.Y. Lee, C.J. Kim, Anti-asthmatic activity of phenolic compounds from the roots of Gastrodia elata Bl, Int. Immunopharmacol. 2(10) (2010) 147-154. http://doi.org/10.1016/j.intimp.2009.10.009.

[103] D. Shixian, Pharmacological studies on *Gastrodia elata* bluma. I. The sedative and anticonvulsant effects of synthetic gastrodin and its genin, Acta Botanica Yunnanica (1979).

[104] M. Yunjiang, D. Shixian, Pharmacological studies on *Gastrodia elata* blume. 2. Effects of synthetic gastrodin and its genin on the heart and small intestine, Acta Botanica Yunnanica (1980).

[105] L.M. Ojemann, W.L. Nelson, D.S. Shin, et al., Tian ma, an ancient Chinese herb, offers new options for the treatment of epilepsy and other conditions, Epilepsy Behav. 2(8) (2006) 376-383. https://doi.org/10.1016/j.yebeh.2005.12.009.

[106] Y. Zhu, Chinese materia medica: chemistry, pharmacology and applications, CRC Press (1998).

[107] G.Y. Zhan, J.Q. Sun, H.Q. Wang, Toxicological test of *Gastrodia elata* wine, Journal of Guiyang Medical College 4 (1994) 377-378. http://doi.org/10.19367/j.cnki.1000-2707.1994.04.031.

[108] D.C. Tang, F.Y. Mao, Y. Jiang, Study on acute toxicity and mutagenicity of Tianma Jianhao tea, Journal of Health Toxicology 1(13) (1999) 71. http://doi.org/10.3969/j.issn.1002-3127.1999.01.030.

[109] W.G. Huang, J.K. Tang, The main pharmacodynamics and acute toxicity experiments of renshen tianma capsule, Journal of Guiyang Medical College 2(26) (2001) 162-163. http://doi.org/10.3969/j.issn.1000-2707.2001.02.034.

[110] G.L. Yuan, L. Jiang, G. Yin., et al., Toxicological safety study of gastrodiae rhizoma-semen ziziphi spinosae capsule, Journal of Food Safety & Quality 5 (2013) 1408-1414. http://doi.org/10.19812/j.cnki.jfsq11-5956/ts.2013.05.023.

[111] X.F. Zhu, Q. Hu, C.X. Zhang, Food safety of Zaoren Tianma capsule and its effect on sleep in mice, Jiangsu Medical Journal 4(46) (2020) 332-336. http://doi.org/10.19460/j.cnki.0253-3685.2020.04.003.

[112] K.H. Lu, G.L. Ou, H.P. Chang, et al., Safety evaluation of water extract of *Gastrodia elata* blume: genotoxicity and 28-day oral toxicity studies, Regul. Toxicol. Pharmacol. 114 (2020) 104657. http://doi.org/10.1016/j.yrtph.2020.104657.

[113] X.N. Mao, H.J. Zhou, X.J. Yang, et al., Neuroprotective effect of a novel gastrodin derivative against ischemic brain injury: involvement of peroxiredoxin and tlr4 signaling inhibition, Oncotarget 53(8) (2017) 90979-90995. http://doi.org/10.18632/oncotarget.18773.

[114] M. Jin, B. Cao, C. Lin, et al., Tianma gouteng decoction exerts pregnancy-protective effects against preeclampsia *via* regulation of oxidative stress and no signaling, Front. Pharmacol. 13 (2022) 849074. http://doi. org/10.3389/fphar.2022.849074.

[115] J. Lin, Q. Wang, S. Xu, et al., Banxia baizhu tianma decoction, a Chinese herbal formula, for hypertension: integrating meta-analysis and network pharmacology, Front. Pharmacol. 13 (2022) 1025104. http://doi.org/10.3389/fphar.2022.1025104.

[116] N.I. Aihua, F. Di, J. Man, et al., Observation on curative effect of gastrodin injection combined with paroxetine on depression, Modern Journal of Integrated Traditional Chinese and Western Medicine 33(29) (2020) 3654-3657, 3692. http://doi.org/10.3969/j.issn.1008-8849.2020.33.002.

[117] H.U. Linyuan, C. Wei, W. Mingqing, et al., A randomized, double-blind, parallel controlled, multicenter clinical study of Tianma Xingnao capsule in the treatment of primary insomnia (liver and kidney deficiency, liver-wind disturbance), Journal of Tianjin University of Traditional Chinese Medicine 2(41) (2022) 188-194. http://doi.org/10.11656/j.issn.1673-9043.2022.02.14.

[118] L. Wei, S. Huang, Y. Zhu, Clinical study of Tianma Gouteng Yin combined with nimodipine in the treatment of mild to moderate vascular dementia, Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease 11(19) (2021) 1899-1901. http://doi.org/10.12102/j.issn.1672-1349.2021.11.027.

[119] J. Chen, Q. Huang, J. Li, et al., *Panax ginseng* against myocardial ischemia/reperfusion injury: a review of preclinical evidence and potential mechanisms, J. Ethnopharmacol. 300 (2023) 115715. http://doi.org/10.1016/j.jep.2022.115715.

[120] H. Duan, Y. Zhou, S. Zhou, et al., Application of *Gastrodia elata* in functional food in china, Science and Technology of Food Industry 9(44) (2023) 403-412. http://doi.org/10.13386/j.issn1002-0306.2022050051.

[121] S. Feng, Z. Liangyun, J. Changshun, et al., History of *Gastrodia elata* consumption and development proposals, China Food Drug Administration 3 (2021) 110-115. http://doi.org/10.3969/j.issn.1673-5390.2021.03.013.

[122] M.Q. Gong, F.F. Lai, J.Z. Chen, et al., Traditional uses, phytochemistry, pharmacology, applications, and quality control of *Gastrodia elata* blume: a comprehensive review, J. Ethnopharmacol. Pt 1(319) (2024) 117128. http://doi.org/10.1016/j.jep.2023.117128.

[123] Y. Lei, J. Li, J. Xiao, et al., Correlation between contents of gastrodin and polysaccharides with grade of *Gastrodia* tuber, Chinese Traditional and Herbal Drugs 3(46) (2015) 418-423. http://doi. org/10.7501/j. issn. 0253-2670.2015.03.021.

[124] J. Xiao, Y. Lei, T. Lin, et al., Comparison of bioactive compounds in winter tianma and spring tianma for quality assessment, World Chinese Medicine 5(11) (2016) 767-770, 776. http://doi.org/10.3969/j.issn.1673-7202.2016.01.004.

[125] W.H.O., Guidelines for the assessment of herbal medicines, 1991.

[126] W. Xin, W. Hui, Y. Fei, et al., Determination of six ingredients of gastrodin from *Gastrodia elata* with quantitative analysis of multi-components by single marker, Chinese Traditional and Herbal Drugs 3(49) (2018) 694-699. http://doi.org/10.7501/j.issn.0253-2670.2018.03.027.

[127] X.Y. Peng, Z.Y. Chen, B. Cui, et al., Establishment of HPLC fingerprints and determination of five constituents for Erlong capsules, Chinese Traditional Patent Medicine 3(44) (2022) 718-723. http://doi. org/10.3969/j.issn.1001-1528.2022.03.006.

[128] Q. Guo, Y. Wang, S. Lin, et al., 4-Hydroxybenzyl-substituted amino acid derivatives from *Gastrodia elata*, Acta Pharm. Sin. B 4(5) (2015) 350-357. http://doi.org/10.1016/j.apsb.2015.02.002.

[129] M. Moré, F. Soteras, A.C. Ibañez, et al., Floral scent evolution in the genus *Jaborosa* (Solanaceae): influence of ecological and environmental factors, Plants 8(10) (2021) 1512. http://doi.org/10.3390/plants10081512.

[130] Z. Su, Y. Yang, S. Chen, et al., The processing methods, phytochemistry and pharmacology of *Gastrodia elata* Bl.: a comprehensive review, J. Ethnopharmacol. 314 (2023) 116467. http://doi.org/10.1016/j.jep.2023.116467.

[131] W.W. Zhang, S.H. Zheng, Y.H. Wang, et al., Study on the quality of *Gastrodiae rhizoma* under different drying and processing methods, World Science and Technology-Modernization of Traditional Chinese Medicine 4(22) (2020) 1278-1284. http://doi.org/10.11842/wst.20191121003.

[132] Y. Xie, X. Li, Y. Zhang, et al., Effects of high-humidity hot air impingement steaming on *Gastrodia elata*: steaming degree, lossweight, texture, kineticsdrying, microstructure and active components, Food Bioprod. Process. 127 (2021) 255-265. http://doi.org/10.1016/j.fbp.2021.03.005.

[133] Y.E. Song, S.R. Choi, E.J. Song, et al., Method for fermented *Gastrodia elata* BL using lactic acid bacteria, 2018.

[134] P.S. Young, K.S. Young, C.Y. Sik, et al., Fermented *Gastrodia eleata* that improved taste and manufacturing method thereof, 2019.

[135] C. Jiang, M. Liu, X. Yan, et al., Lipase addition promoted the growth of proteus and the formation of volatile compounds in suanzhayu, a traditional fermented fish product, Foods 11(10) (2021) 2529. http://doi. org/10.3390/foods10112529.

[136] O. Zheng, Q. Sun, A. Dong, et al., Gelation process optimization of shrimp surimi induced by dense phase carbon dioxide and quality evaluation of gel, Foods 23(11) (2022) 3807. http://doi.org/10.3390/foods11233807.

[137] Y. Xie, L. Zhong, X. Xue, et al., Optimization of processing technology of braised rehmanniae radix based on multiple indexes and response surface technology and correlation between components and color, Zhongguo Zhongyao Zazhi 18(47) (2022) 4927-4937. http://doi. org/10.19540/j. cnki.cjcmm.20220128.306.

[138] N. Andersson, J. G. Fons, M. Isaksson, et al., Methodology for fast development of digital solutions in integrated continuous downstream processing, Biotechnol. Bioeng. 121 (2023) 2378-2387. http://doi.org/10.1002/bit.28501.

[139] S. Tan, T.X. Wu, H.W. Fu, Extraction process optimization of active ingreidient gastrodin in gastrodia, Food Sci. Technol. 9 (2012) 230-233. http://doi.org/10.13684/j.cnki.spkj.2012.09.006.

[140] H. Xue, J. Li, G. Wang, et al., Ultrasound-assisted extraction of flavonoids from *Potentilla fruticosa* L. Using natural deep eutectic solvents, Molecules 18(27) (2022) 5794. http://doi.org/10.3390/molecules27185794.

[141] P.A. Uwineza, A. Waśkiewicz, Recent advances in supercritical fluid extraction of natural bioactive compounds from natural plant materials, Molecules 17(25) (2020) 3847. http://doi.org/10.3390/molecules25173847.

[142] O. Basaar, A.N. Farhan, K. Al Mamari, et al., An overview on supercritical fluid extraction of herbal medicines: process and methodology, Abhath Journal of Basic and Applied Sciences 1(2) (2023) 1-8. http://doi.org/10.59846/ajbas.v2i1.448.

[143] C. Sang, Q. Bai, X. Feng, et al., Optimized extraction of camp from jujube by ultra-high pressure technology and the anti-allergic effect for peanut allergy mouse, Front. Nutr. 9 (2022) 862900. http://doi.org/10.3389/fnut.2022.862900.

[144] Y. Wang, X. Xiong, G. Huang, Ultrasound-assisted extraction and analysis of maidenhairtree polysaccharides, Ultrason. Sonochem. 95 (2023) 106395. http://doi.org/10.1016/j.ultsonch.2023.106395.

[145] O.A. Hernández-Aguirre, C. Muro, E. Hernández-Acosta, et al., Extraction and stabilization of betalains from beetroot (*Beta vulgaris*) wastes using deep eutectic solvents, Molecules 21(26) (2021) 6342. http://doi.org/10.3390/molecules26216342.

[146] Y.W. Jang, J.Y. Lee, C.J. Kim, Anti-asthmatic activity of phenolic compounds from the roots of *Gastrodia elata* Bl, Int. Immunopharmacol. 2(10) (2010) 147-154. http://doi.org/10.1016/j.intimp.2009.10.009.

[147] H.J. Kim, I.K. Hwang, M.H. Won, Vanillin, 4-Hydroxybenzyl aldehyde and 4-hydroxybenzyl alcohol prevent hippocampal ca1 cell death following global ischemia, Brain Res. 1181 (2007) 130-141. http://doi.org/10.1016/j.brainres.2007.08.066.

[148] J. Choi, D. Lee, A new citryl glycoside from *Gastrodia elata* and its inhibitory activity on gaba transaminase, Chem. Pharm. Bull. 12(54) (2006) 1720-1721. http://doi.org/10.1248/cpb.54.1720.

[149] X. Yang, J. Zhu, R. Yang, et al., Phenolic constituents from the rhizomes of *Gastrodia elata*, Nat. Prod. Res. 2(21) (2007) 180-186. http://doi.org/10.1080/14786410601081997.

[150] X. Li, B. Xiang, T. Shen, et al., Anti-neuroinflammatory effect of 3, 4-dihydroxybenzaldehyde in ischemic stroke, Int. Immunopharmacol. (82) (2020) 106353. http://doi.org/10.1016/j.intimp.2020.106353.

[151] J. Zheng, P.P. Sun, A.J. Hu, et al., Extraction of polysaccharide from *Gastrodia elata* blume and preparation of its drinks, Food Research and Development 4(39) (2018) 123-129. http://doi.org/10.3969/j.issn.1005-6521.2018.04.022.

[152] L. Wang, H. Xiao, L. Yang, et al., Two new phenolic glycosides from the rhizome of *Gastrodia elata*, J. Asian Nat. Prod. Res. 5(14) (2012) 457-462. http://doi.org/10.1080/10286020.2012.669755.

[153] Y.L. Wei, W. Cai, Z.C. Zhang, et al., Constituents in rat plasma after oral administration of the extract of *Gastrodia elata* BL, China Pharmaceuticals 21(24) (2015) 8-10.

[154] J.Y. Lee, Y.W. Jang, H.S. Kang, et al., Anti-inflammatory action of phenolic compounds from *Gastrodia elata* root, Arch. Pharm. Res. 10(29) (2006) 849-858. http://doi.org/10.1007/BF02973905.

[155] D. Xiaohua, L. Zilei, Y. Dasong, et al., Study on the chemical constituents of *Gastrodia elata*, Journal of Chinese Medicinal Materials 10(36) (2013) 1608-1611. http://doi.org/10.13863/j.issn1001-4454.2013.10.022.

[156] Y. Lee, M. Woo, C. Kim, et al., Two new benzofurans from *Gastrodia elata* and their DNA topoisomerases i and ii inhibitory activities, Planta Med. 12(73) (2007) 1287-1291. http://doi. org/10.1055/s-2007-981619.

[157] Y. Wang, S. Lin, M. Chen, et al., Chemical constituents from aqueous extract of *Gastrodia elata*, Zhongguo Zhong Yao Za Zhi 12(37) (2012) 1775-1781.

[158] L. Wang, Studies on chemical constituents and quality control of *Gastrodia elata*, 2007.

[159] N. Li, K.J. Wang, J.J. Chen, et al., Phenolic compounds from the rhizomes of *Gastrodia elata*, J. Asian Nat. Prod. Res. 9 (2007) 373-377. http://doi.org/10.1080/10286020600780979.

[160] Z. C. Zhang, G. Su, J. Li, et al., Two new neuroprotective phenolic compounds from *Gastrodia elata*, J. Asian Nat. Prod. Res. 6(15) (2013) 619-623. http://doi.org/10.1080/10286020.2013.791286.

[161] X.H. Zheng, W. Liu, L. Chen, et al., Study on chemical constituents of fresh *Gastrodia elata* bl. F. elata, Modern Chinese Medicine 5(20) (2018) 529-532. http://doi.org/10.13313/j.issn.1673-4890.20180102002.

[162] C.X. Ma, Study on chemical constituents and sleeping pharmacological activity of *Gastrodia elata* bl. Effective parts, Changchun University of Chinese Medicine, 2020.

[163] M.K. Pyo, J.L. Jin, Y.K. Koo, et al., Phenolic and furan type compounds isolated from *Gastrodia elata* and their anti-platelet effects, Arch. Pharm. Res. 4(27) (2004) 381-385. http://doi.org/10.1007/BF02980077.

[164] H.S. Yun-Choi, M.K. Pyo, K.M. Park, Isolation of 3-o-(4'-hydroxybenzyl)-beta-sitosterol and 4-[4'-(4"-hydroxybenzyloxy)benzyloxy]benzyl methyl ether from fresh tubers of *Gastrodia elata*, Arch. Pharm. Res. 3(21) (1998) 357-360. http://doi.org/10.1007/BF02975302.

[165] J. Hayashi, T. Sekine, S. Deguchi, et al., Phenolic compounds from *Gastrodia* rhizome and relaxant effects of related compounds on isolated smooth muscle preparation, Phytochemistry 5(59) (2002) 513-519. http://doi.org/10.1016/s0031-9422(02)00008-0.

[166] Y.Q. Xiao, L. Li, X.L. You, Studies on chemical constituents of effective part of *Gastrodia elata*, Zhongguo Zhong Yao Za Zhi 1(27) (2002) 35-36.

[167] A.R. Han, H.J. Shin, H.R. Jeon, et al., Two new phenolic compounds from the rhizomes of *Gastrodia elata* blume, Helv. Chim. Acta 7(94) (2011) 1310-1314. http://doi.org/10.1002/hlca.201000425.

[168] H. D. Zhan, H. Y. Zhou, Y. P. Sui, et al., The rhizome of *Gastrodia elata* blume-an ethnopharmacological review, J. Ethnopharmacol. 189 (2016) 361-385. http://doi.org/10.1016/j.jep.2016.06.057.

[169] J. H. Lin, Y. C. Liu, J. P. Hau, et al., Parishins B and C from rhizomes of *Gastrodia elata*., ChemInform 37(27) (1996) 549-551. http://doi.org/10.1002/chin.199637287.

[170] H. Qiu, W. Tang, X. Tong, et al., Structure elucidation and sulfated derivatives preparation of two alpha-*d*-glucans from *Gastrodia elata* BL. and their anti-dengue virus bioactivities, Carbohydr. Res. 15(342) (2007) 2230-2236. http://doi.org/10.1016/j.carres.2007.06.021.

[171] X. Chen, D. Cao, L. Zhou, Structure of a polysaccharide from *Gastrodia elata* Bl., and oligosaccharides prepared thereof with anti-pancreatic cancer cell growth activities, Carbohydrate Polymers: Scientific and Technological Aspects of Industrially Important Polysaccharides 3(86) (2011) 1300-1305. http://doi.org/l0.10l6/j.carbpol.20l 1.06.029.

[172] H. Zhu, C. Liu, J. Hou, et al., *Gastrodia elata* blume polysaccharides: a review of their acquisition, analysis, modification,

and pharmacological activities, Molecules 13(24) (2019). http://doi.org/10.3390/molecules24132436.

[173] Q.L. Guo, Y.N. Wang, C.G. Zhu, et al., 4-Hydroxybenzyl-substituted glutathione derivatives from *Gastrodia elata*, J. Asian Nat. Prod. Res. 5(17) (2015) 439-454. http://doi.org/10.1080/10286020.2015.1040000.

[174] L. Wang, H.B. Xiao, X.M. Liang, Chemical constituents from *Gastrodia elata* (iii), Chinese Traditional and Herbal Drugs 8(40) (2009) 1186-1189. http://doi.org/10.3321/j.issn:0253-2670.2009.08.003.

[175] Z.F. Li, Y.W. Wang, Q. Wang, et al., Chemical constituents from *Gastrodia elata* (ii), Chinese Traditional and Herbal Drugs 14(45) (2014) 1976-1979. http://doi.org/10.7501/j.issn.0253-2670.2014.14.002.

[176] H.C. Feng, Studies on the constituents of *Gastrodia elata*, Acta Chim Sin 37 (1979) 175.

[177] Z. Hao, Z. Wei, L. Wang, et al., Selective hydrogenation of ethyne on γ-Mo_2N, Applied Catalysis A: General 1(192) (2000) 81-84. http://doi.org/10.1016/S0926-860X(99)00328-2.

[178] N.K. Huang, Y. Chern, J.M. Fang, et al., Neuroprotective principles from *Gastrodia elata*, J. Nat. Prod. 4(70) (2007) 571-574. http://doi.org/10.1021/np0605182.

[179] Y. Xiao, L. Li, X. You, Studies on chemical constituents of effective part of *Gastrodia elata*, China Journal of Chinese Materia Medica (2002) 35-36. http://doi.org/10.3321/j.issn:1001-5302.2002.01.012.