[Short title + Author Name - P&H title] 18 (2025) 106086

Contents lists available at ScienceDirect

Arabian Journal of Chemistry

journal homepage: www.ksu.edu.sa

The traditional uses, phytochemistry and pharmacology of *Gastrodia elata* Blume: A comprehensive review

Yingfeng Zhong [a,b], Jieqing Li [a], Honggao Liu [c,*], Yuanzhong Wang [b,*]

[a] College of Agronomy and Biotechnology, Yunnan Agricultural University, Kunming, 650201, China
[b] Medicinal Plants Research Institute, Yunnan Academy of Agricultural Sciences, Kunming 650200, China
[c] Yunnan Key Laboratory of Gastrodia and Fungi Symbiotic Biology, Zhaotong University, Zhaotong 657000, Yunnan China

ARTICLE INFO

Keywords:
G. elata
Botanical characteristics
Traditional and folk uses
Chemical compounds
Pharmacological activities

ABSTRACT

As a rare medicinal plant, *Gastrodia elata* Blume (*G. elata*)as a medicinal use history of more than 2,000 years. In order to offer scientific references for developing and applying *G. elata*, the research gathered range of related publications through employing different electronic databases, including PubMed, Web of Science, Google Scholar and CNKI. Through conducting a comprehensive search, the research progress on *G. elata* was explored systematically from such aspects as folk and traditional uses, botany, phytochemistry, pharmacology, and toxicology. This genus, involves about 67 species, 9 varieties, nearly 700 classical formulations, and 630 metabolites, among which metabolites contain 360 chemical constituents, 243 volatile constituents, and 27 trace elements. Besides, in the analysis of modern pharmacology, it is found that *G. elata* has many different functions, such as anti-anxiety and anti-depressant activity, neurodegenerative diseases treatment, anti-convulsive activity, and improvement of memory activities, anti-cancer, and 25 other pharmacological activities. It was previously found that *G. elata* serves a possibly medicinal and edible plant that has abundant, chemical constituents and pharmacological activities, which can be broadly used in the pharmaceutical and food industry. At present, the clinical and food research on *G. elata* expanding. However, the utilization of *Gastrodia* resources remains suboptimal, with many traditional formulas receiving insufficient attention in research and development. Meanwhile, few studies have focused on non-medicinal parts and the characterization of polysaccharide structures. This implies that to provide a theoretical basis for the development and reasonable uses of *Gastrodia* resources, it is essential to further conduct comprehensive research on the genus, classical formulas, non-medicinal parts and the characterization of polysaccharide structures of *Gastrodia*.

1. Introduction

As the benefits of traditional Chinese medicine (TCM) in treating diseases are becoming increasingly obvious, Chinese drugs have taken the lead in clinical practice because of their multi-component, multi-target action, multifunctionality and low side effects. *Gastrodia*, a genus under the angiosperm phylum Orchidaceae, primarily features decaying herbs with inflated bulbs (Shi et al., 2021). To date, about 100 species of *G. elata* have been recorded worldwide (Kenji, 2022). It is mainly found in East Asia, Southeast Asia and Oceania. Among them, 13 species of the *Gastrodia* genus have been identified in China, such as *G. elata* Bl., *G. javanica* (Bl.) Lindl., and *G. gracilis* Bl., *G. angusta* S. Chow & S.C. (Dian et al., 2017). However, only the dried tubers of *G. elata* are listed in the Chinese Pharmacopoeia (Committee, 2020) (Fig. 1). Furthermore, *G. elata* is described as uniformly yellow or brownish-yellow, translucent and vitreous, with a horny texture and a hard fracture in the Japanese Pharmacopoeia, the Korean Pharmacopoeia, and the European Pharmacopoeia.

G. elata, commonly called "*Tianma*" in Chinese, is an obligate mycoheterotrophic plant also referred to as "*Chi Jian*", "*Du Yao Zhi*", or "*Ding Feng Cao*". *G. elata* is the most widely distributed species of the *Gastrodia* genus in both China and globally and is one of China's rare medicinal herbs, with a long history of edible and medicinal use (Chen Hong et al., 2022). Dominating traditional Asian medicine, *G. elata* has a usage of over 2,000 years and was first recorded in Shennong Bencaojing, described as having a pungent and warm flavor. Its long-term consumption is beneficial for energy, strength, weight loss, longevity, and life extension (Yun et al., 2016). TCM theory suggests that it has the

* Corresponding authors.
E-mail addresses: honggaoliu@126.com (H. Liu), boletus@126.com (Y. Wang).

https://doi.org/10.1016/j.arabjc.2024.106086
Received 9 May 2024; Accepted 10 December 2024
Available online 16 December 2024

effect of calming the liver and sinking yang, quenching wind and stopping spasms. In clinical applications, it is primarily used to treat various diseases, including depression, insomnia, dizziness, neurasthenia, Alzheimer's disease, hypertension, etc (Hou and Fang, 2012; Zhou et al., 2024). According to the "Dictionary of Chinese Ethnic Medicine", it is an effective method in folk herbal medicine for high blood pressure, limb numbness, hemiplegia, stomach pain, stroke, rheumatic paralysis. With the development of modern chemical composition and pharmacological research, its applications and efficacies are constantly expanding, including a wide range of application scenarios in cosmetics and nutraceuticals (Duan et al., 2023; Shim et al., 2017). It is used as an aphrodisiac and tonic and a functional food, added to porridge or alcoholic beverages, to prevent abortions and improve eyesight and sexual performance (Zhan et al., 2016). Furthermore, it was officially listed as a functional food material by the China Food and Drug Administration on November 15, 2021 (China 2021). Since the medicinal and edible value of *G. elata* continues to increase, the research and development of *G. elata* health varieties is receiving increasing attention.

In the present review, the phytochemical studies summarized 630 chemical constituents isolated and identified from the *G. elata*, including aromatics, saccharides and their glycosides, volatile constituents, etc., laying the foundation for its modern pharmacology. Studies have demonstrated that *G. elata* has various effects, such as the treatment of neurodegenerative diseases, hepatic and renal protective effects, improvement of memory, neuroprotection, etc. (Ahmad et al., 2019; Liu et al., 2018b; Zhou et al., 2018). *G. elata* tubers have been the focus of research both at home and abroad, whereas literature indicates that some *G. elata* stems involve chemical components similar to those of tubers and are rich in gastrodin (Jiang et al., 2012). For example, extracts from the stalks of *G. elata* have been demonstrated to have anticonvulsant and bacteriostatic effects (Jia et al., 2018; Wang et al., 2020). Regarding the above descriptions, wild *G. elata* presented more abundant activity than cultivated *G. elata* (Zhan et al., 2016). Wild *G. elata* is widely distributed across *China*, with high-quality *G. elata* growing in western Guizhou, northeastern Yunnan, southern Sichuan, and the Changbai mountain region (Zhan et al., 2016). As TCM continues to modernize and market demands for the quality of PCM, high-quality wild *G.elata* has always been favored by consumers. Because this phenomenon has caused over-exploitation of wild resources, the wild resources of *G. elata* have become increasingly endangered. Hence, emergency conservation measures should be conducted to conserve the natural habitats of *G. elata*, ensuring the sustainability and long-term growth of the *G. elata* industry.

Since ancient times, *G. elata* has been considered a precious herb. Due to its high medicinal value and large market demands, *G. elata* has been researched by many researchers in the past. A review of the traditional uses, biological activities and chemical composition of *G. elata* is beneficial for guiding the rational utilization of *G. elata* plants. Through observing the present research base, it is found that no systematic review has been conducted on *Gastrodia* genus plants. Therefore, this article presents a comprehensive review of the distribution, growth habits, traditional and folk uses, botany, phytochemistry, and pharmacology of 67 species and 9 varieties of the *Gastridia* genus, with the aims of providing a reference for further in-depth understanding and development of *G. elata*.

2. Material and methods

Literature on the genus *Gastrodia* is available online at Google Scholar, Web of Science, Baidu Scholar, PubMed, SciFinder database, Springer research and KNCI. In the research progress, the keywords

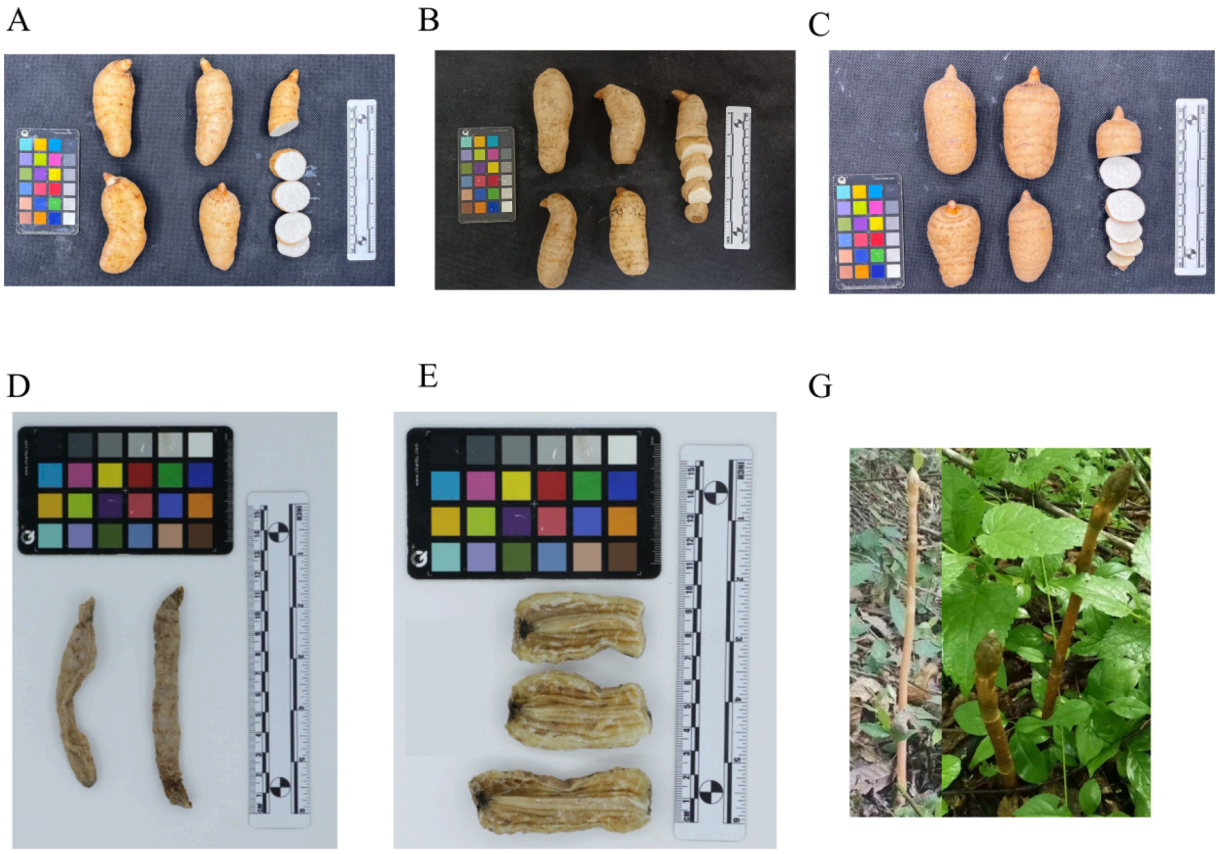


Fig. 1. *Gastrodia elata* Bl. A: *Gastrodia elata* Bl. *f. viridis* (Makino). B: *Gastrodia elata* Bl. *f. elata*. C: *Gastrodia elata* Bl. *f. glauca* S. Chow. D: Dried *Gastrodia elata* Bl. E: Decoction pieces of *Gastrodia elata* Bl. F: Stem of *Gastrodia elata* Bl.

include species of asparagus, herbal medicine, pharmacological properties, chemical composition and toxicity evaluation, etc. Use the "Dictionary of Chinese Ethnic Medicine" to find out the folk uses of Tianma in ethnic minorities. The scientific database of Chinese plant species (DCP) (https://db.kib.ac.cn/Default.aspx) was used to search for scientific names, species, varieties, and distributions of the genus *Gastrodia*. The research information of Amanita spp. was also accessed online through the Flora of China (https://www.iplant.cn). The molecular structures of the compounds shown in the text were generated by ChemBioDraw Ultra 14.0 software.

3. Botany studies

This study shows that the genus *Gastrodia* includes about 67 species and 9 varieties, and 34 species and 7 varieties were recorded in China, of which Taiwan province is very widely distributed with 22 species and 2 varieties (Table S1). It is characterized by a fleshy tuber, without leaves, with fused sepals and petals and two mealy pollinia without caudicles. It is widely distributed from southern China to Japan and eastern Siberia, northeast India to the eastern Himalayas, southeast Asia to eastern Australia and the southwest Pacific Islands, and tropical Africa, Madagascar, and the Mascarene Islands (Suetsugu, 2017; Suetsugu et al., 2018). They, like most other heterotrophic fungi, occur in small colonies and only appear on the ground during the breeding season, so the plant is rarely found (Suetsugu, 2017). Among them, *G. elata* is mainly distributed in most parts of China, such as Yunnan, Sichuan and Taiwan. About 9–24 species in Yunnan and Taiwan, 5–8 species in Sichuan (Fig. 2A). Secondly, it is also distributed abroad in Japan, Russia, South

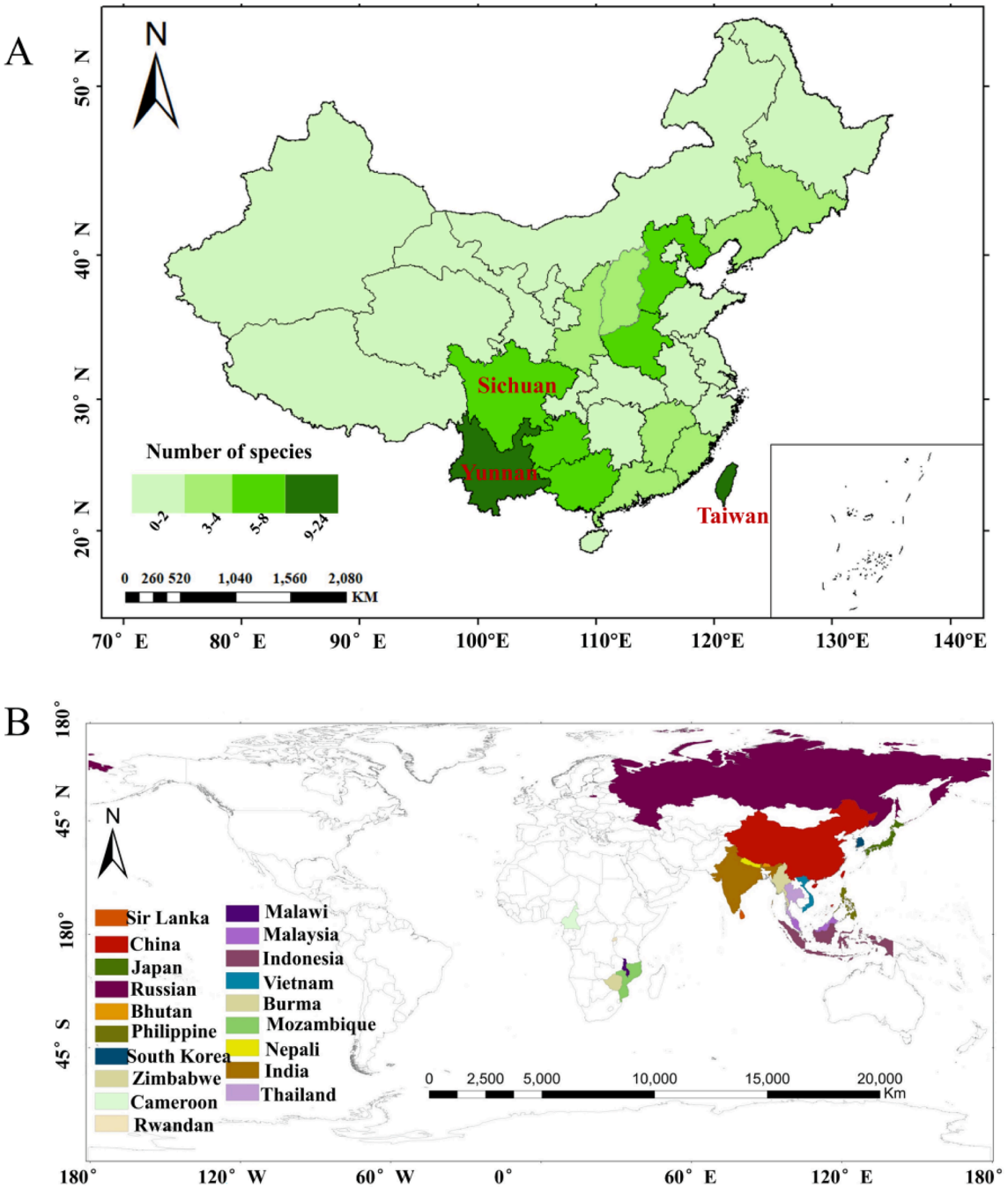


Fig. 2. (A)The distribution of the genus *Gastrodia* in China. (B) The distribution of *Gastrodia* in the world.

Korea, northeast India, and 18 other countries (Fig. 2B).

G. elata plant is 30–100 cm tall, the fruit period is 5–7 months. It usually grows in the forest at an altitude of 400–3200 m and shows a complex symbiotic association relationship with the fungus Armillaria. So far, 9 varieties of the genus *Gastrodia* have been recorded (Li et al., 2016; Suetsugu, 2022). *G. elata* has plump rhizomes often elliptic to sub-dumbbell-shaped, 8–12 cm long, 3–5(−7) cm in diameter, densely packed nodes covered by numerous triangular broadly ovate sheaths. In addition, the ovary and pedicel are 7–12 mm long, slightly shorter than the bracts. *G. elata* growing to 30–100 cm tall, rarely to 200 cm. Floral tube capitate, 5–7 mm in diam. With a deep concavity between lateral sepals, the base is dilated, and outer surface is smooth. The capsule is obovate-elliptic, 1.4–1.8 cm long, 8–9 mm in diam. Racemes are 5–30 (−50) cm long, often with 30–50 flowers, and the bracts are shown to be oblong-lanceolate, 1.5 cm long. Ovary and pedicel 7–12 mm long, slightly shorter than bracts. In addition, the *G.elata* peduncle is orange, yellow, grayish-brown, or blue-green, without green leaves, as well as covered by several membranous sheaths in the lower part. The flowers are suberect, brightly colored, weakly opened, orange, pale yellow, blue-green, or yellowish-white, and the bulb is (or is not) hairy (https://www.iplant.cn/frps). Based on the morphological characteristics of the flowers, stalks and bulbs, *G. elata* is classified as *Gastrodia elata* Bl. *f. glauca* S.Chow (grayish-aura-colored flower stalks, larger plants), *Gastrodia elata* Bl. *f. elaata* (reddish flowers, orange-red flower stalks, bulbs often dumbbell-shaped), *Gastrodia elata* Bl. *f. flavida* S. Chow (yellowish-green flowers, yellow flower stems, bulbs ellipsoid or compressed cylindrical), *Gastrodia elata* Bl. *f. Pilifera* Tuyama (bulbs hairy), *Gastrodia elata* Bl. *f. Viridis* Mak (bluish-green flower stems, smaller plants), *Gastrodia elata* Bl. *f. alba* S. Chow (flowers grayish yellowish white, adult bulb pike-shaped), *Gastrodia elata* var. above ata Y. J. Zhang (flowers spirally arranged, fruit short conical oblique), *Gastrodia pubilabiata f. viridis* (ovary of the flower and pedicel has hairy), *Gastrodia elata* Bl. *f. Viridis* Mak (flower stem blue-green, plant smaller), *Gastrodia pubilabiata. f. viridis* (ovary of the flower and pedicel has dark green features), *Gastrodia pubilabiata f. castanea* (with 1–12 reddish-brown flowers and reddish-brown fruits), and 9 varieties (Table S1). Currently, four varieties of *G. elata, G. elata* Bl. *f. Viridis* Mak, *G. elata* Bl. *f. elata, G. elata* Bl. *f. flavida* S.chow and *G. elata* Bl. *f. glauca* S. chow, are widely cultivated, mainly in southern China and Korea (Lee et al., 2014) (Fig. 1). Among them, *Gastrodia* elata Bl. *f. glauca* S. Chow is characterized by sweet taste and high quality (Du et al., 2022; Zeng et al., 2023), and *Gastrodia elata* Bl. *f. Viridis* Mak is relatively high in fat, starch, polysaccharides and flavonoids (Ji et al., 2022). At the same time, a brief description of other gastrodia species is also given (Table S1).

4. Folk and traditional and clinical uses of *G. Elata*

4.1. Folk uses

G. elata is very popular for folk consumption. *G. elata* medicinal diet, such as "Tianma stewed black chicken", "Tianma sleeping porridge" "Tianma boiled pig brain" and so on. These medicinal diets taste delicious and with the effect of replenishing qi and nourishing blood, liver, and kidney deficiencies, enhancing immunity, nourishing yin and strengthening yang, etc. They are used for treating numbness of the limbs, hypertension, arteriosclerosis and neurasthenia, and have extremely high nutritional value (Shan et al., 2021; Yang et al., 2013a). In folk formulas, *G. elata* is often combined with *Ziziphi Spinosae Semen*, *Schisandre Chinensis Fructus*, *Puerariae Lobatae Radix*, *Lych Fructus,* and *Ginseng Radix Et Rhizoma* as a companion ingredient, which aids sleep, improves lowering of blood pressure, strengthens immunity and relieves physical fatigue (Jia Xin et al., 2022). In a related study on *G. elata* health food products, the total number of products reached 114. The clearly stated health functions included assisting in lowering blood pressure, improving sleep, assisting in improving memory, antioxidants, assisting in the protection of chemical liver damage, and so on, with a total of 10 functions (Jia Xin et al., 2022).

In the "*Dictionary of Chinese Ethnomedicine*", it was recorded that the treatment of headaches, migraine, and numbness of the limbs using *G. elata* is commonly in 18 ethnic minority areas. Among them, the *Yao* ethnic group refers to the *G.elata* as "*Chijian*", and the whole herb can be used as medicine for the treatment of hypertension, vertigo, sores, boils, swellings and pains (Jia and Li, 2005). The *Miao*, *Hani*, *Gelao* and *Maonan* ethnic groups call *G. elata* "*Yangyuyou*", "*Chijian*", "*Tianma*", "*Kelei*", and "*Longbunong*", which is used to treat stomach pain (Jia and Li, 2005). Above-ground stems of Hmong *G. elata* are used to treat high blood pressure, headaches, convulsions and dizziness, and tubers are used to treat convulsive spasms, acute and chronic convulsions, and stomach pains (Jia and Li, 2005) (Table S2).

4.2. Traditional and clinical uses

As a valuable medicinal herb, *G. elata* has been used in China for thousands of years, and its economic and medicinal value is extremely high. It is traditionally believed that *G. elata* relieves liver urgency and restores liver wind, thus calming the liver and subduing yang, tinnitus, adverse speech, lumbar and knee pain and weakness (Cheng, 2019). In clinical practice, *G. elata* is often used in epilepsy, numbness of the limbs and dizziness. Its earliest application can be traced back to "*Shen nong ben cao jing*", in which *G. elata* is recorded as "*Chi Jian*", classified as a "superior" drug with rejuvenating effects, non-toxic, and harmless to the body when taken over a long time. The medicinal records in ancient books describe killing Gui Jing Wu (ghost essence), cure Gu Du (poison produced by venomous insects), "treating pediatric wind-eclampsia and palpitations", "stopping panic and trance", "curing good fright and loss of will", and other utility descriptions find that *G. elata* is a traditional medicine for the treatment of mental illness in China. Later, in the "*Xin Xiu Ben Cao*" of the Song Dynasty, the dried rhizome (tuber) of *G. elata* was widely used as a useful part in the treatment of carbuncles, hand and foot disorders, and numbness of the limbs. In the *Song* and *Jin* dynasties, the "*Precious Drugs in Rhyme; Classified According to Nature to Drug*" had a medicinal fugue of *G. elata* the main head of vertigo, the medicine that dispels wind (Li, 2019). The *Ming* Dynasty "*Lei Gong Pao Zhi Yao Xing Jie*" concluded that *G. elata* has the efficacy of mastering paralysis and speech impediment, revitalizing the blood vessels and strengthening the tendons (Li, 2013). In Chinese medicine monographs such as the "*Ben Cao Gan Mu*", which is known as a miracle medicine for enhancing the liver meridian and curing diseases attacked by wind and evil, and is known as "*Ding feng cao*".

Additionally, in the "*Pharmacopoeia of the People's Republic of China*", *G. elata* has the efficacy of calming liver yang, restraining wind and stopping spasms, dispelling wind and clearing collaterals (Committee, 2015). Due to its various medicinal values, anapproximately 700 formulas have been formed by combining with *G. elata* and other medicinal plants (https://db.yaozh.com), which have been clinically verified for hundreds of years and have been handed down to the present day. Among them, *Tianma Gouteng* decoction (TGD) and Banxia Baizhu Tianma decoction (BBTD) ranked among the top 10 in terms of medications used. TGD is used to treat the neurodegenerative anti-hypertension effect, brain injury, parkinson's disease (PD) and alzheimer's disease (AD) because of its compounds such as alkaloids, carotenoids, flavonoids and natural phenols (Chik et al., 2013; Deng et al., 2022). Recently, attention has been given to the mechanism of action of the *G. elata* formulae on cases. Another study demonstrated for the first time that Tianma Hooker Tang can exert anti-oxidative stress and anti-inflammatory effects through up-regulation of transcription factor EB (TFEB), thereby reducing blood pressure (Deng et al., 2022). Meta-analysis results indicate that its combination with nifedipine is more effective in treating hypertension. It also has a protective effect on preeclampsia in pregnancy by modulating oxidative stress and nitric oxide (NO) signaling pathways (Dong et al., 2020; Wu et al., 2023). BBTD is used for curing spontaneous hypertension, vertigo, migraine,

and epilepsy, and its combination with Wen Gao Tang can improve the clinical efficacy of treating hypertension combined with hyperlipidemia without increasing the adverse effects of conventional drugs (Zhou et al., 2023). Thus, the classical formulations provide ideas for developing new modern Tianma compounds and new dosage forms.

Nowadays, many formulas containing *G. elata* have been applied in the form of capsules, injections, pills, tablets, granules, extracts, and other combinations of prescription (Table S3). For instance, Shi Yi Wei Shen Qi Pian is widely used in the treatment of different types of cancers, including breast cancer, and is considered a potential tumor neoantigen (Wan et al., 2021). The clinical and positive effects of Tianma injection are better than *Ginkgo Folium* extract injection in treating patients with dizziness or vertigo ($P < 0.01$), and the combination with anti-anxiety medication is more effective in treating menopausal hypertension (Lai et al., 2022; Zhong et al., 2016). Quan Tianma capsule is used for calming the liver, calming the wind and relieving spasms. Its main therapeutic function is vertigo, headache, numbness of limbs epilepsy caused by the upward disturbance of liver wind, etc. It combined with nourishing blood and clearing rain Granules can significantly treat chronic cerebral insufficiency of blood supply, it makes the patients' hemorheological indexes and cognitive functions improve, and is safe with no side effects (Qin, 2018). In addition, the combination of Quan Tianma Capsule and gastrodin with carbamazepine could attenuate the damage to hippocampal neurons, reduce the high expression of the multidrug resistance-associated protein 1 (mrp1) gene, and effectively improve its antiepileptic effect in mice (Dang et al., 2017). The therapeutic use of KCHO-1 (a novel mixture comprised of 30 % ethanol extracts obtained from nine natural products) for neurodegenerative diseases may be achieved by preventing Hydrogen peroxide (H_2O_2) or glutamate-induced oxidative damage (Lee et al., 2016a). Qingda Granules gavage experiments in mice showed its therapeutic effects and mechanisms on vascular smooth muscle cell proliferation, vascular dysfunction, and hypertension (Wu et al., 2023). Moreover, these traditional formulas are widely used in other herbal countries such as Japan, Korea, India and Nepal (Qin et al., 2017). It can be seen that the traditional formulas of *G. elata* have a wide range of clinical applications. In conclusion, a summary of *G. elata* formulas is necessary to facilitate the development of new formulas.

The basic features of the traditional usage of Chinese medicine are mainly to summarize the theoretical basis of the Chinese medicine study, and modern pharmacological research on the chemical composition of *G. elata* is hot topic. As we all know, the chemical composition of *G. elata* serves as a bridge connecting the different pharmacological activities of *G. elata* (Wang et al., 2019). Thus, it is of great significance to review the chemical constituents and pharmacological activities of *G. elata*.

5. Chemical compounds of *G. Elata*

G. elata is rich in alkaloids, flavonoids, fatty phenylpropanoids and terpenoids, and its major lipid metabolites are classified as sterols, fatty acyls, and polyketide (Zeng et al., 2023). Many of the metabolites in the metabolomics dataset were identified as carbohydrates, amino acids, benzenes, phenols and peptides. The present review describes 360 chemical constituents, 243 volatile constituents and 27 trace elements of *G. elata* (Table S4, Table S5). The chemical composition of these is mainly divided into aromatics (227) steroids (13), organic acids and esters (19), saccharides and their glycosides (65), amino acids and polypeptides (17), and others (19). Among these aromatics are subdivided into monobenzyl compounds (45), parishins (28), aromatic substituted glycosides (19), polybenzyl ethers (19), polybenzyls (41), heteroatom aromatics (53), aromatic furans (7) and others (15). Its volatile chemical components mainly include hydrocarbons, aldehydes, acids, alcohols, esters, phenols, ketones, ethers and others. This shows that the chemical composition of *G. elata* is rich, which provides a basis for modern pharmacological research, as well as a possibility for its development in healthcare products, cosmetics and functional foods.

5.1. Aromatics

Phytochemical, quality control and structural studies of the compounds in *G. elata* are abundant at home and abroad *G. elata* polysaccharides and phenolic compounds are widely recognized as typical bioactive constituents (Shan et al., 2021a). Compounds in which the molecule contains at least one benzene ring structure with an off-domain bond are known as aromatic compounds (Yu et al., 2022). The aromatic analogs in *G. elata* are diverse and can be classified into eight subgroups totaling 227 compounds based on nucleophilic structure, subgroup function and connectivity **(1–227)**. These aromatic compounds are considered to be the active ingredients of this phytomedicine and the properties and biological activities of the different subgroups are described below.

5.1.1. Monobenzyl compounds

Monobenzyl analogs contain a benzyl nucleus in the molecule, most of them contain phenolic hydroxyl groups and often form glycosides with mono-or disaccharides. 45 monobenzyl compounds **(1–45)** have been isolated from *G. elata* and characterized (Table S4, Fig. 3). 4-HBA and gastrodin, a variant of 4-HBA, as the main active ingredients that existed in *G. elata* give play to many pharmacological effects and unique mechanisms. The standard depended on them for assessing the quality of *G. elata* preparations (Committee, 2020). Xu et al. (2019) discovered 9 new gastrodin derivatives, including seven p-hydroxybenzyl-modified gastrodin ethers **(60–64, 75, 76)**, 6′-O-acetylgastrodin **(29)**, and 4-[α-d-glucopyranosyl-(1 → 6)-β-d-glucopyranosyloxy]benzyl alcohol **(30)**, were isolated from an aqueous extract of *G. elata* rhizomes. These compounds are readily absorbed by the small intestinal epithelium, and therein, glycosides and aminoglycosides with small relative molecular mass can cross the blood–brain barrier to exert a variety of pharmacological effects (Yu et al., 2022). For example, Vanillin **(2)**, gastrodin **(10)**, and 4-HBA **(12)** have anxiolytic and antidepressant effects similarly, which also existed neuronal protection and regeneration (Chen et al., 2016; Liu et al., 2018). P-methoxybenzyl alcohol **(9)** and gastrodin **(10)** have anti-inflammatory analgesic and adjunctive memory improvement effects (Liu and Mori, 1993; Xiang et al., 2018).

5.1.2. Parishins compounds

The parishin analogs are ester compounds formed when 1–3 carboxyl groups in citric acid are combined with the alcohol hydroxyl group of 4-HBA and its derivatives. A total of 28 parishin-like compounds **(46–73)** were isolated as shown in Table S4 of the chemical composition of *G. elata* and Fig. 4. According to a relative study, 189 possible parishin-like compounds were identified from *G. elata* by predictive characterization such as LCMS/MS, and 6 analogs containing substituents different from those of the traditional parishin-like substituents were predicted by characterization (Zhu et al., 2021). It is abundant that parishin-like compounds, and many of its components have not yet been isolated and identified.

5.1.3. Aromatic substituted glycosides compounds

These compounds are derivatives of gastrodin in which more than 2 hydroxyl groups in the monosaccharides are replaced by aromatic groups and form glycosidic bonds with the hydroxyl groups of the aromatic groups. Furthermore, other hydroxyl groups are alternatives in the monosaccharides, which are usually replaced by acetoxy groups, monosaccharides, and aromatic groups. Totally 19 compounds **(74–92)** were isolated (Table S4, Fig. 5). Wang et al., (2018) used HR-ESI-MS to isolate four new gastrodin derivatives containing a *trans*-cinnamoyl unit from *G. elata* **(74–77)**. Xu et al., (2019) identified nine new gastrodin derivatives using spectroscopic and single crystal X-ray methods, which included seven p-hydroxybenzyl-modified gastrodin ethers **(78–84)**, 6′-O-acetylgastrodin **(85)** and 4-(α-D-glucopyranosyl-(16)-β-D-

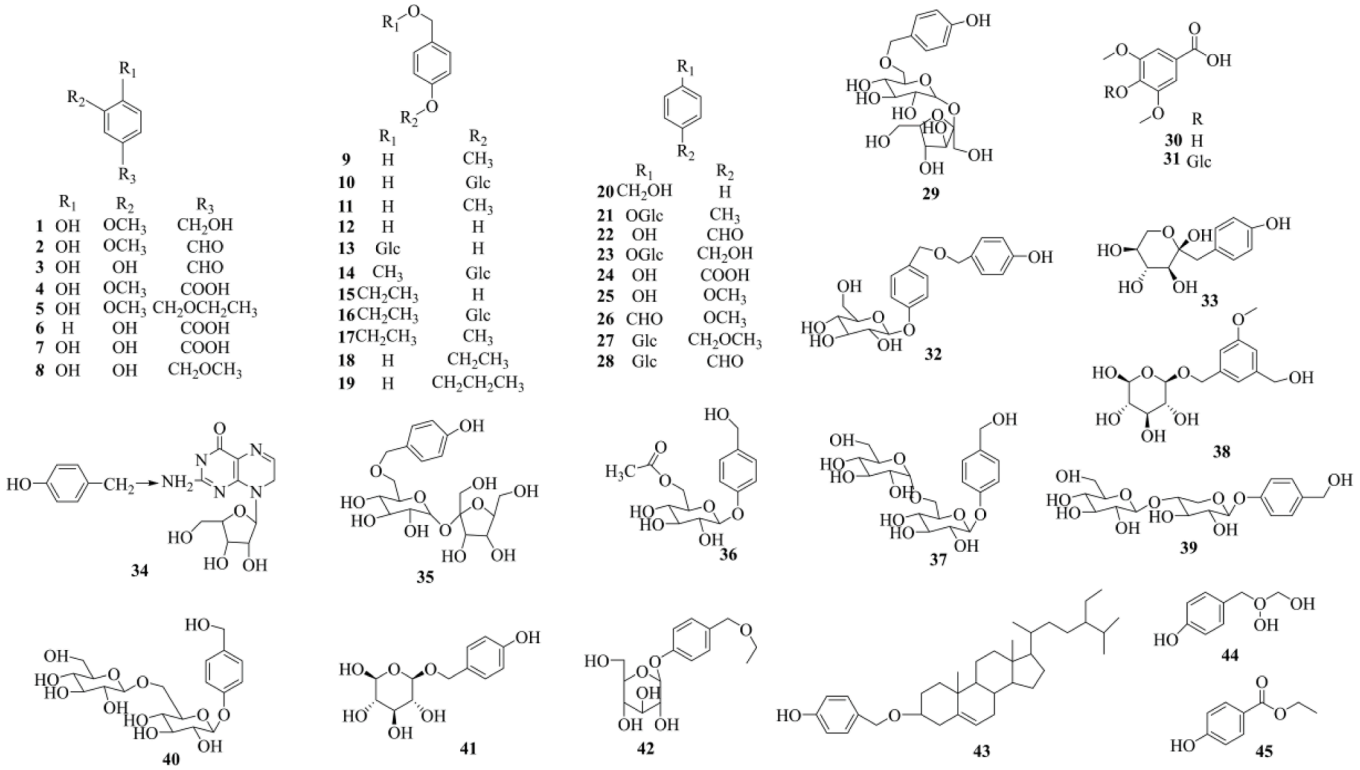


Fig. 3. Monobenzyl compounds of *G. elata*.

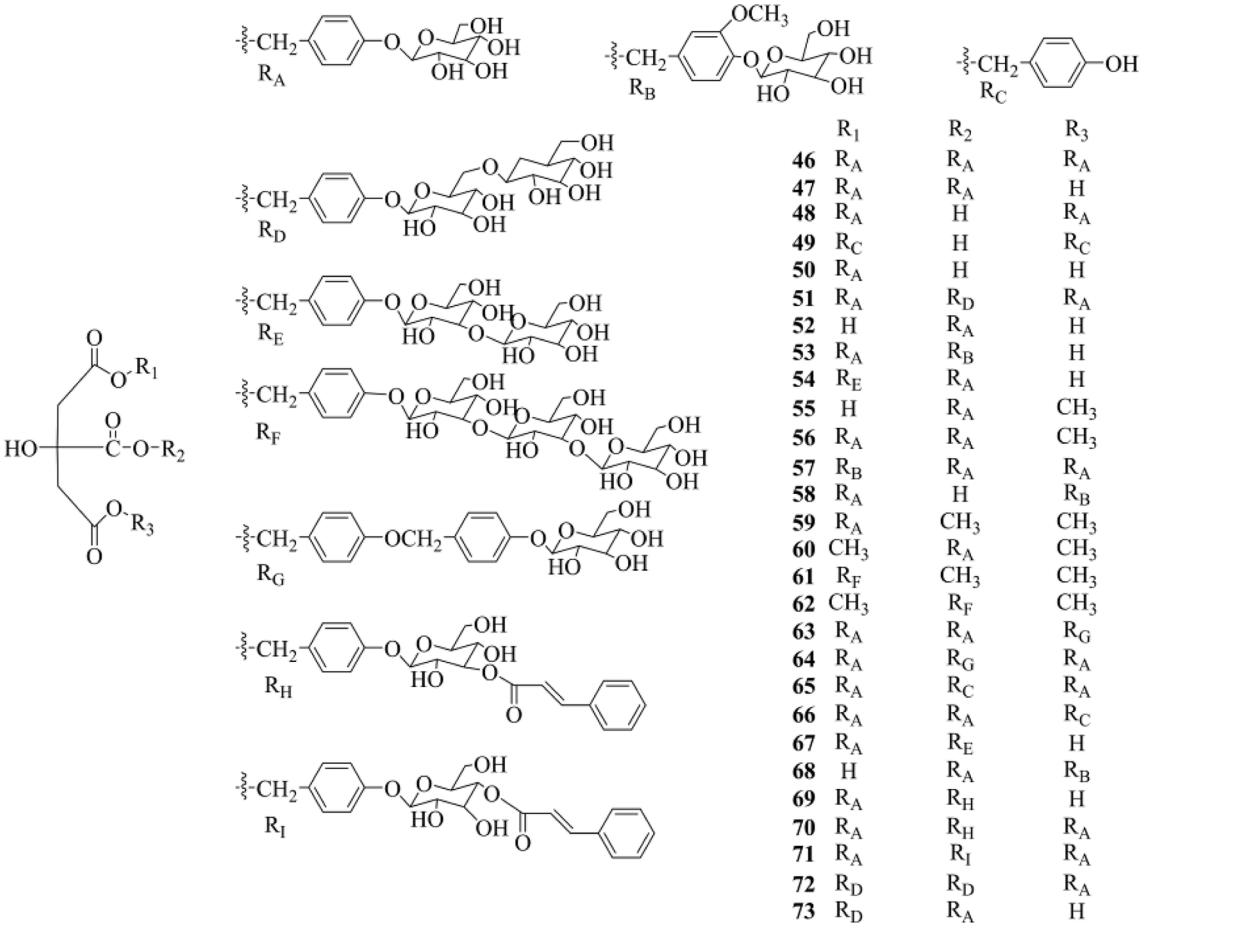
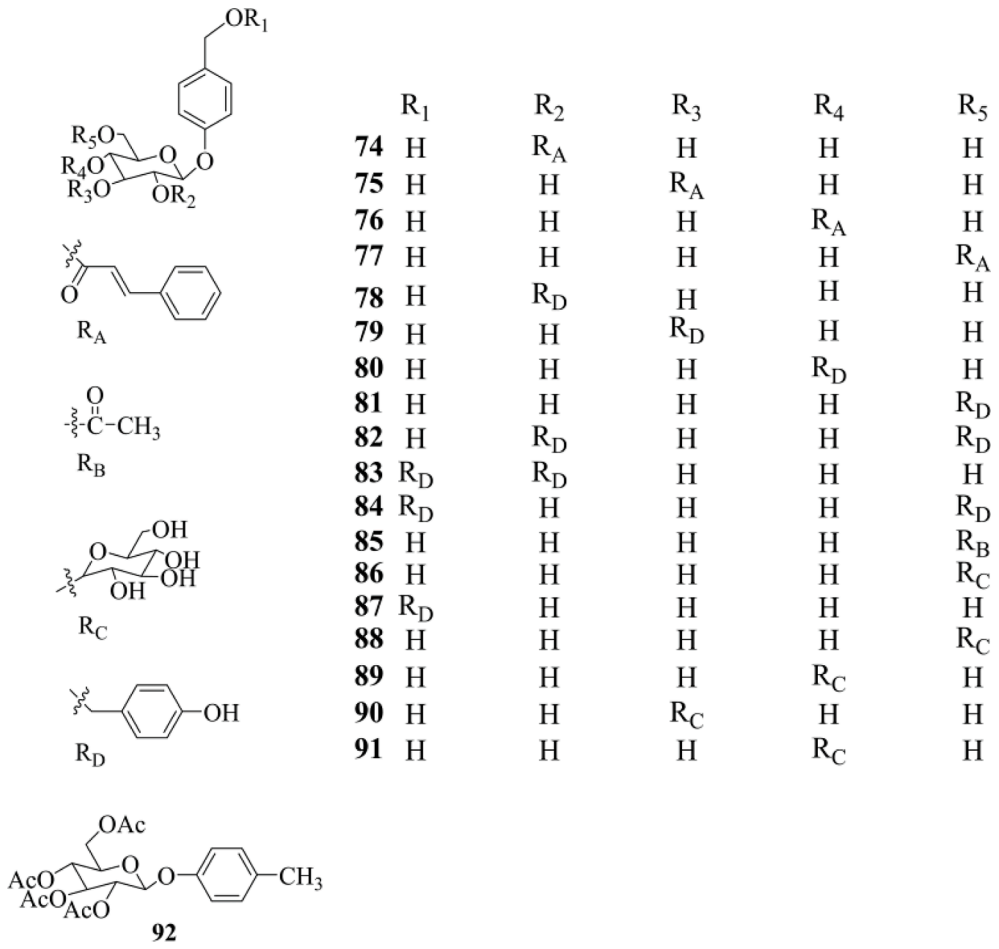


Fig. 4. Parishins compounds of *G. elata*.



	R_1	R_2	R_3	R_4	R_5
74	H	R_A	H	H	H
75	H	H	R_A	H	H
76	H	H	H	R_A	H
77	H	H	H	H	R_A
78	H	R_D	H	H	H
79	H	H	R_D	H	H
80	H	H	H	R_D	H
81	H	H	H	H	R_D
82	H	R_D	H	H	R_D
83	R_D	R_D	H	H	H
84	R_D	H	H	H	R_D
85	H	H	H	H	R_B
86	H	H	H	H	R_C
87	R_D	H	H	H	H
88	H	H	H	H	R_C
89	H	H	H	R_C	H
90	H	H	R_C	H	H
91	H	H	H	R_C	H

Fig. 5. Aromatic substituted glycosides compounds in *G. elata*.

glucopyranosyloxy) benzyl alcohol **(86).** Unfortunately, no reports on the pharmacology of such compounds have been seen so far.

5.1.4. *Polybenzyl ethers compounds*

As shown in Table S4 of the chemical composition of *G. elata* and Figs. 6, 19 compounds **(93–111)** of polybenzyl ethers compounds have been identified and isolated, which are compounds in which 2 or more benzyl units are formed through oxygen atoms linked end to end or phase to phase, and the phenolic hydroxyl group on the phenyl unit often forms glycosides with monosaccharides and can also be substituted with alkoxy groups. One of the bis(4-hydroxybenzyl) ethers **(97)** was identified as the first polybenzyl ether in *Gastrodia* (Taguchi et al., 1981). 4-(((4-ethoxybenzyl)oxy) methyl)-phenol **(102)** is a recently discovered polybenzyl ether (Gao et al., 2023).

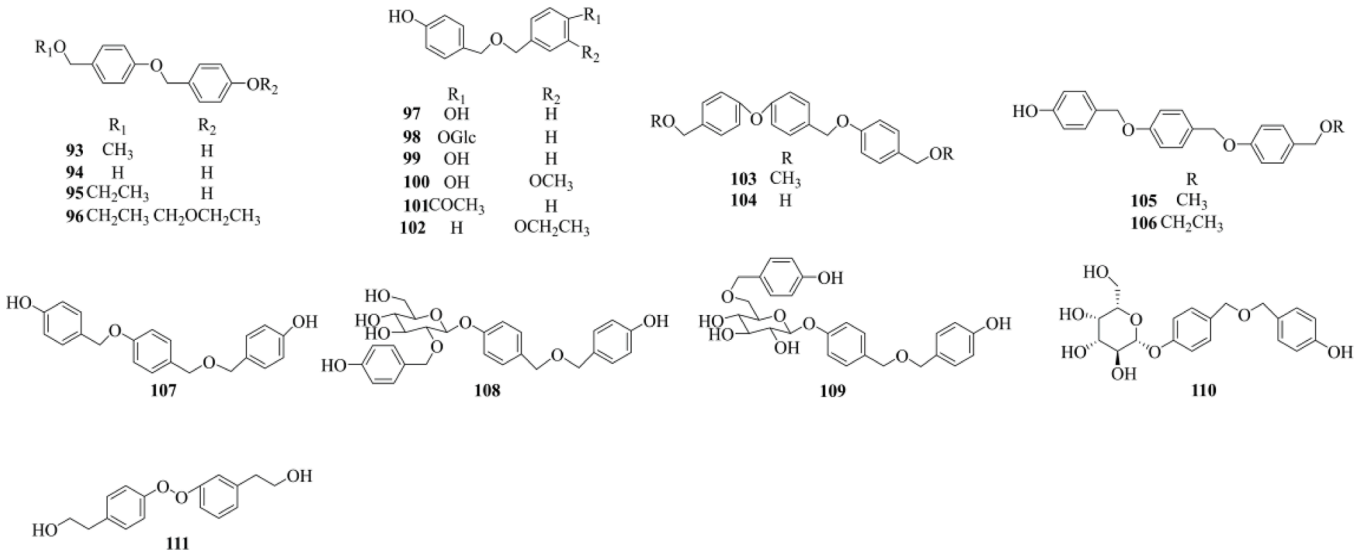


Fig. 6. Polybenzyl ethers compounds in *G. elata*.

Gastropolybenzylol I **(101)** and gastropolybenzylol H **(99)** have antagonistic effects on melatonin receptors MT1 and MT2, which are hypothesized to have potential pharmacological effects in improving sleep, immunomodulation, and anti-aging (Chen et al., 2019). In addition bis (4-hydroxybenzyl) ether mono-β-L-galactopyranoside **(110)** exhibited significant antioxidant and anti-aging effect (Farooq et al., 2019). However, the pharmacological activity of these compounds has been less studied and further research is needed.

5.1.5. *Polybenzyl compounds*

Polybenzyl compounds, with at least 2 benzyl groups directly linked by carbon–carbon single bonds or sharing a common methylene group, and whose benzene rings, and phenolic hydroxyl groups are usually replaced by alcohols, ethers, aldehydes and alkoxyl groups, are a special class of biphenyl compounds. 41 compounds **(112–152)** of this compound have been isolated and characterized by *G.elata* (Table S4, Fig. 7). This biphenyl analog has antidiabetic and antitumor effects and has great potential in the treatment of PA and AD (Li et al., 2020a). Most of these compounds also have antithrombotic, anti-inflammatory, neuroprotective, and antioxidant effects, with the bis(4-hydroxyphenyl) methane **(117)**, Gastrol B **(128)** and gastrotribenzins A **(129)** compounds being more prominent (Su et al., 2023; Zhang et al., 2013). Compounds such as 4,4′-methylenediphenol **(113)**, gastropolybenzylol B **(116)** and gastropolybenzylol C **(120)** exert agonistic impacts on the activation of melatonin MT1 and MT2, which may be associated with the efficacy of enhancing sleep and regulating immunity (Chen et al., 2019; Chen et al., 2019a). This group of compounds is rich in pharmacological effects and provides the foundation for the different medicinal effects of *G. elata*.

5.1.6. *Heteroatom aromatics compounds*

At present, 54 heteroatom aromatics compounds **(153–205)** have been identified from *G. elata* (Table S4, Fig. 8). In which, most of compounds consist of the substitution of the alcohol hydroxyl group of the benzyl unit by heteroatom-containing groups such as amino acids, amine groups, nucleosides, etc., or by heteroatoms to each other, and a few compounds have substitutions at the terminal positions of the phenyl or benzene rings. Guo et al. 2015 and Shao et al. (2021) isolated 7 such compounds **(160–162, 165, 166, 180 191)** from aqueous extracts of *G. elata* and determined their structures using spectroscopic and chemical methods. Among them (−)-(R, S)-γ-L-glutamyl-L-(S-(4-hydroxybenzyl)) cysteinylglycine sulfoxide **(167)** counteracts serum deprivation-induced damage to PC12 cells with ischaemic injury, divanillyl sulfone **(188)** has anti-inflammatory and analgesic effects. It is worth noting that the class of compounds has pharmacological effects such as antiplatelet and neuroprotection and that S-containing aromatic compounds have been associated with anticancer or antimicrobial activity (Pyo et al., 2004; Zeng et al., 2023). So the subsequent research and development of heteroatom compounds isolated from *G. elata* is a highlight.

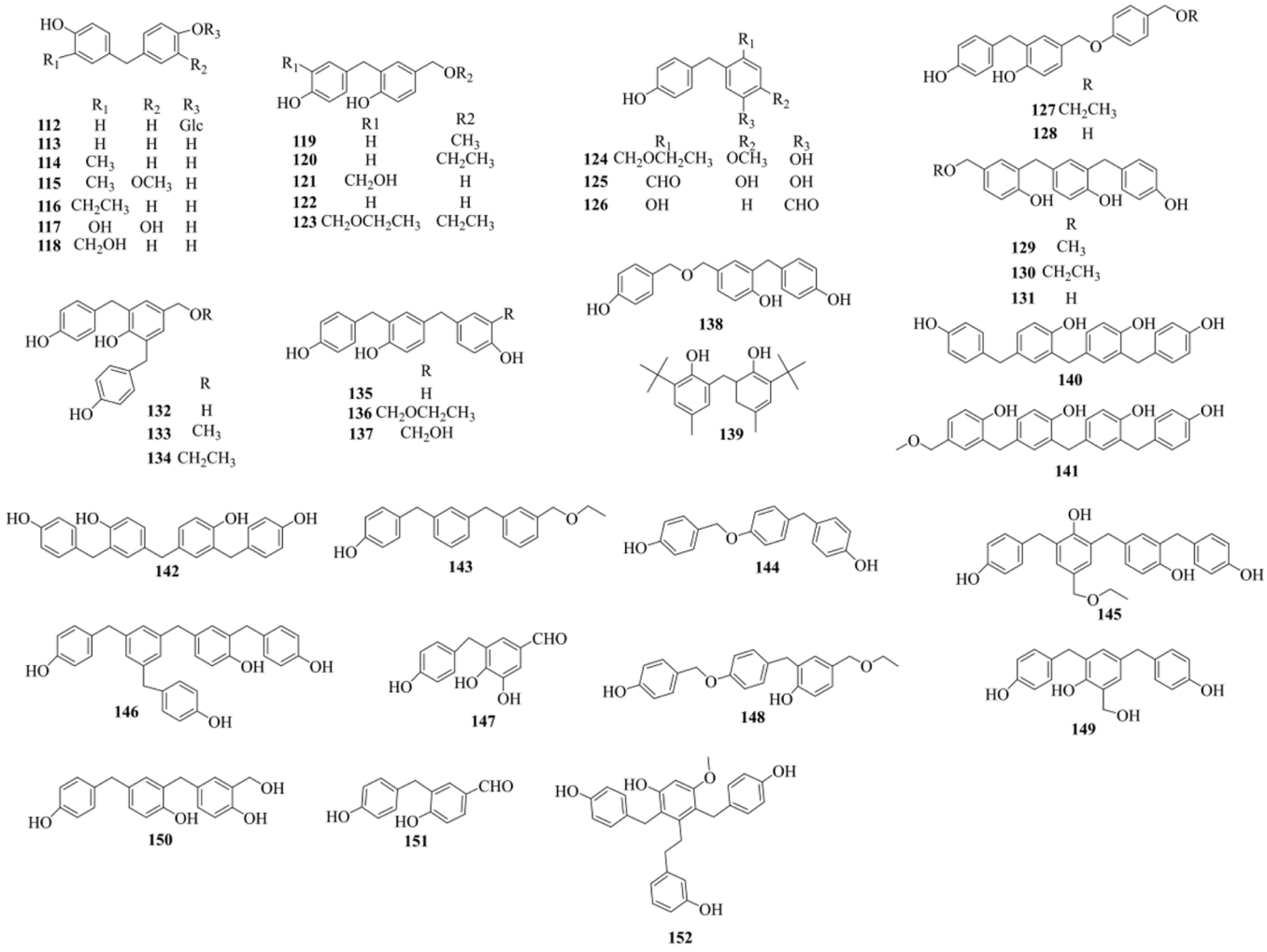


Fig. 7. Polybenzyl compounds in *G. elata*.

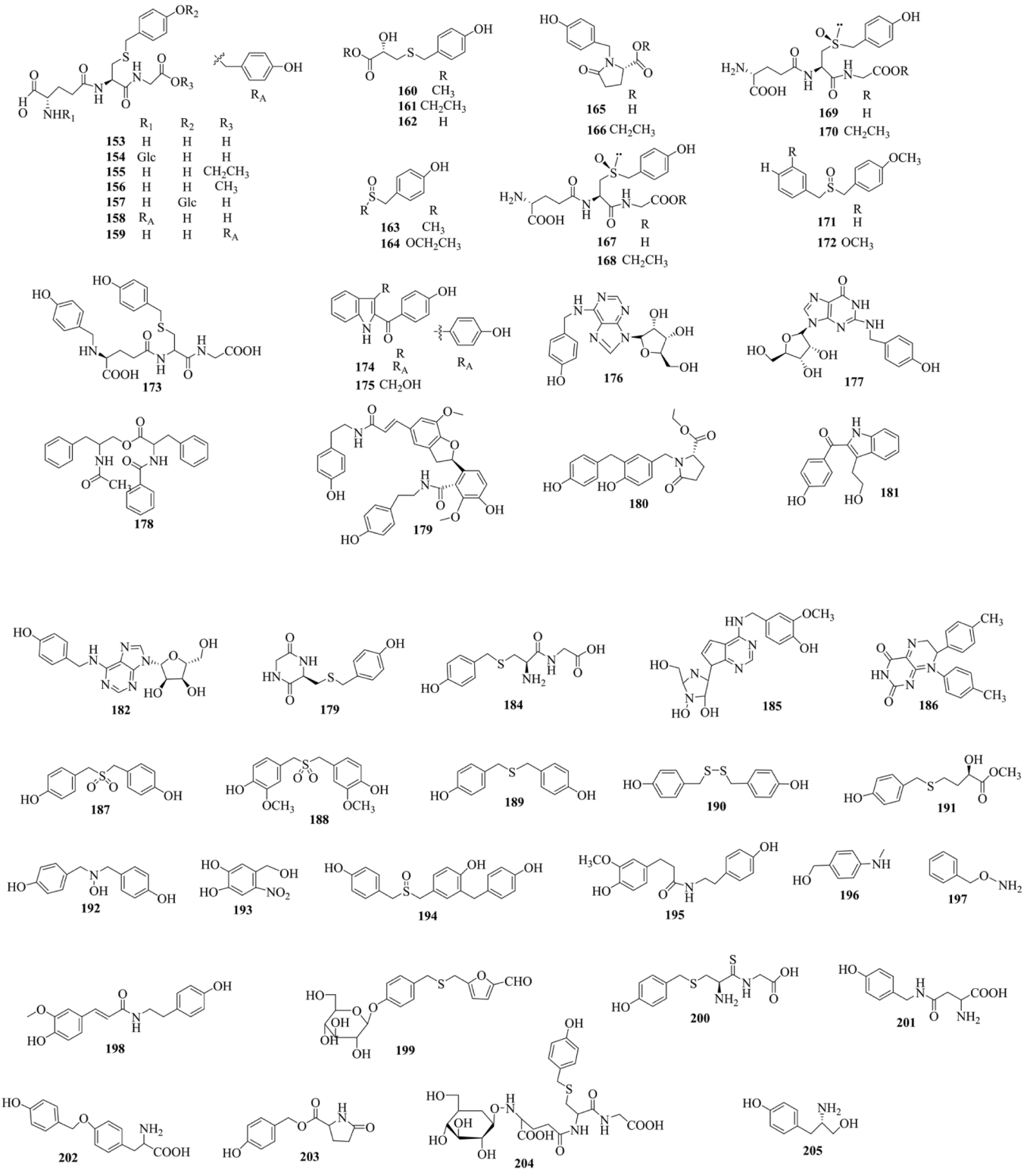


Fig. 8. Heteroatom aromatics compounds in *G. elata*.

5.1.7. Aromatic furans compounds

The benzene ring of this class of compounds is connected to the furan ring through a carbon chain or oxygen atom. 7 aromatic furans compounds **(206–212)** have been isolated from *G. elata* (Table S4, Fig. 9). These compounds have been manifested shown to inhibit human liver cancer cell lines, colon cancer cell lines, and human breast cancer cell lines as well as have anti-tumor effects (Huang et al., 2015; Kim et al., 2017; Lee et al., 2007).

5.1.8. Others compounds

As shown in Table S4 of the chemical compositions of *G. elata* and Fig. 10, there are other aromatics different from those mentioned above, and 15 such compounds were isolated from *G. elata* **(213–227)**. Among them, gastrodinol **(224)** revealed significant cytotoxicity (IC_{50} of 2.5 ~

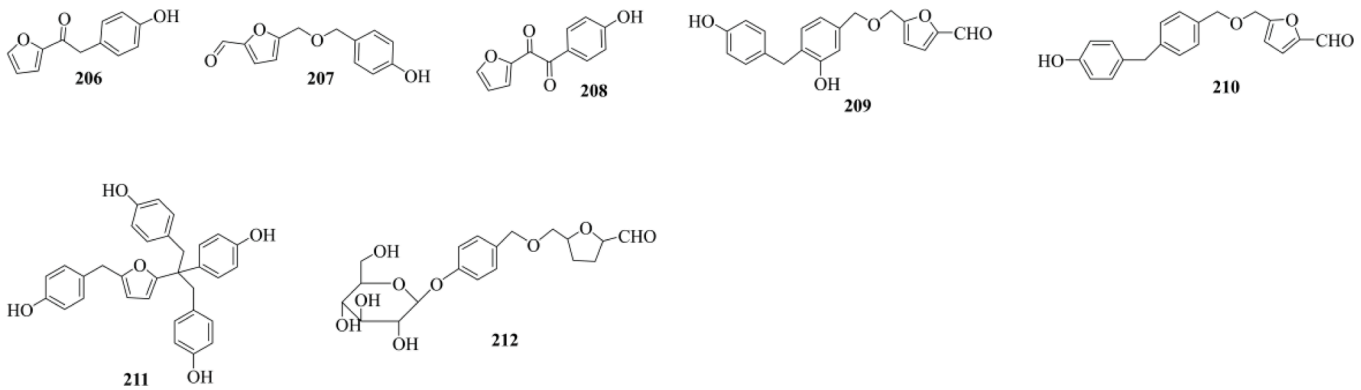


Fig. 9. Aromatic furans compounds in *G. elata*.

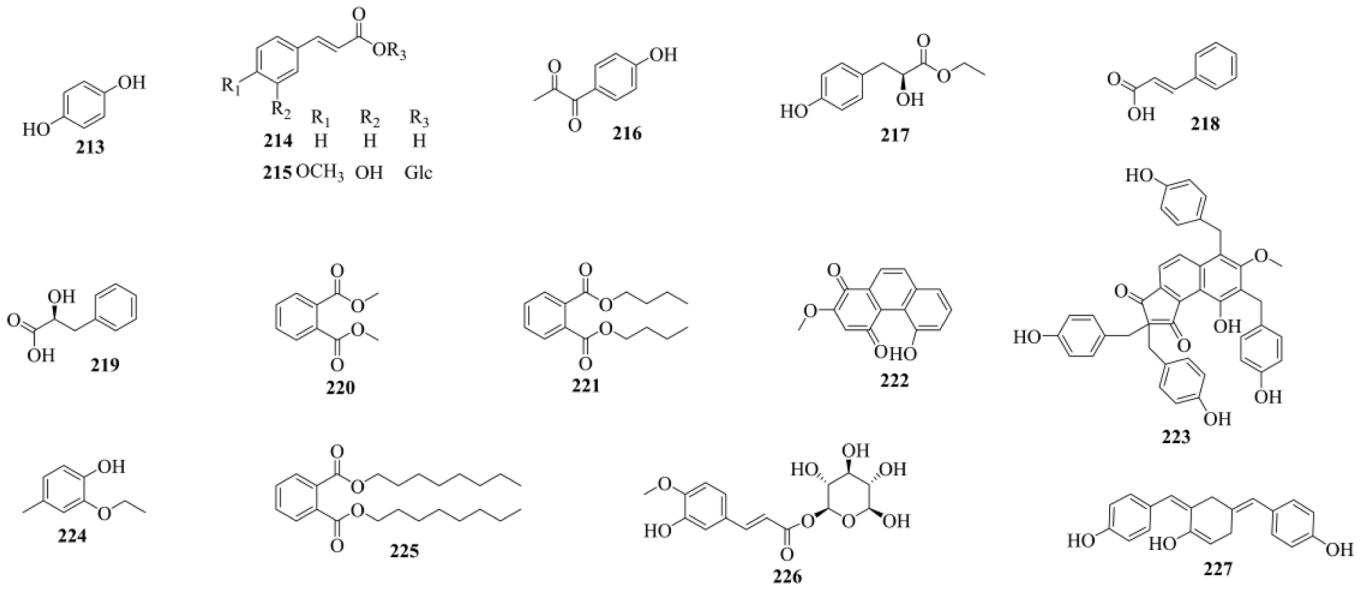


Fig. 10. Others compounds in *G. elata*.

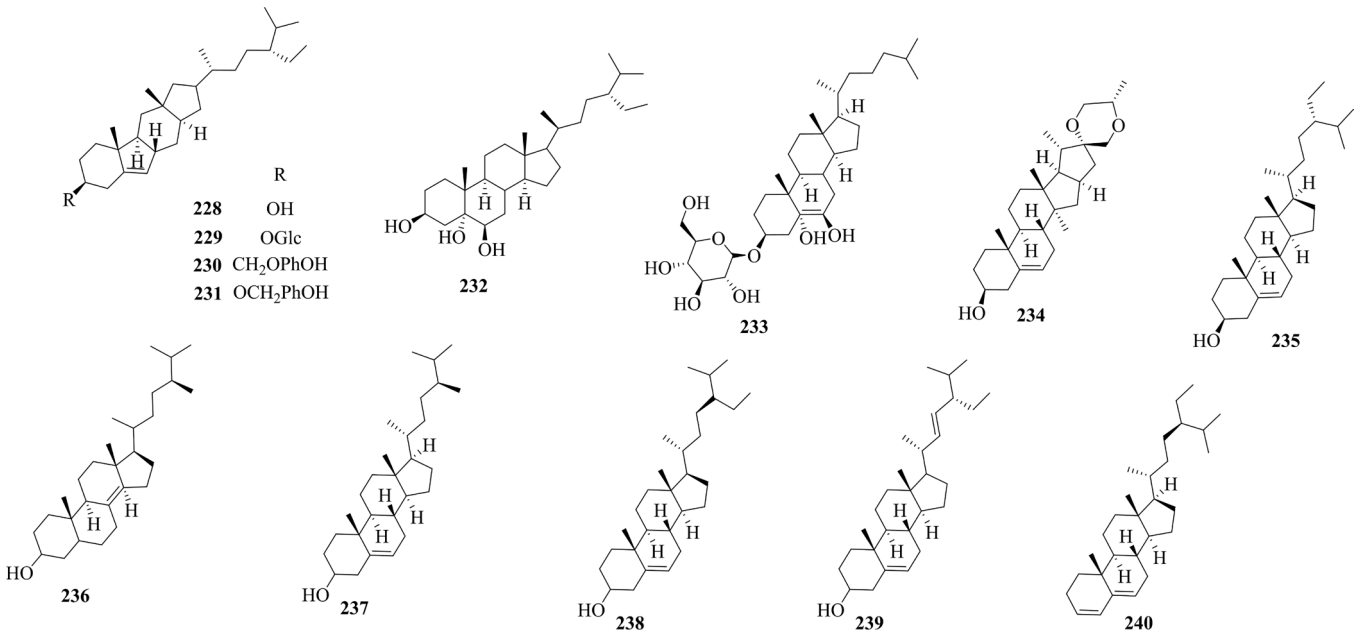


Fig. 11. Steroid compounds in *G. elata*.

3.8 μM) against five *in vitro* human cancer cell lines (Yang et al., 2020). Cymbinodin A **(223)** is cytotoxic (IC_{50} = 3.73 mM) against human small cell lung cancer (NCI-H187) cell line (Lertnitikul et al., 2020).

5.2. Steroid compounds

Steroids are a class of compounds containing the basic backbone structure of cyclopentane polyhydrophenanthrene with two horn methyl groups and C-17 side chains. 13 Steroids compounds **(228–240)** have been identified from *G. elata* (Table S4, Fig. 11). Various steroids such as β-daucosterol **(234)**, Diosgenin **(235)**, and Stigmasterol **(236)** have been shown to possess obvious significant activities such as anti-oxidative stress damage, inhibition of inflammatory factor expression in brain tissue, and inhibition of neurogenic senescence (Liang et al., 2020; Shiu-Min Cheng et al., 2020). Most steroids can penetrate the blood–brain barrier and have anti-inflammatory effects on the peripheral and central nervous system (Yang et al., 2019). This class of compounds is known to be one of the material bases for the neuropharmacological effects of *G. elata.*

5.3. Organic acids and esters

19 organic acids and esters compounds **(241–259)** have been identified from G. elata (Table S4, Fig. 12). Among them, trimethylcitryl-β-D-galactopyranoside **(245)** inhibited gamma-aminobutyric acid (GABA) aminotransferase activity by 56.8 % at a concentration of 10 mg/ml, with latent neuroprotective effects (Choi et al., 2006). In addition, citric acid **(241)**, an *in vivo* hydrolyzed product of the parish in a class of *G. elata* and a highly abundant organic acid with auxiliary neuroprotective which can lower lipopolysaccharide-induced oxidative stress damage in brain and liver tissues (Abdel Salam et al., 2014). It is used as a chelating agent and as an acidifier and flavoring agent in the pharmaceutical industry and foodstuffs (Lambros et al., 2022). Notably *trans*-3-phenylacrylic acid **(253)** has represented therapeutic effects against bacterial infections, in the treatment of neurological disorders, cancer and diabetes (Ruwizhi and Aderibigbe, 2020).

5.4. Saccharides and their glycosides

Polysaccharides are polymeric macromolecular compounds consisting of multiple monosaccharides linked by glycosidic bonds, which are very abundant up to 21.6 % (Zhan et al., 2016). At present, sixty-five polysaccharide compounds **(260–324)** have been identified from *G. elata* (Table S4, Fig. 13). The main structure of most of the compounds of *G. elata* polysaccharide is a 1 → 6 keyed branched chain of α-(1 → 4)-glucan (Wang et al., 2022; Zhan et al., 2016). For example: WTM-1 **(277)**, WTM-2 **(279)**, WTM-3 **(280)**, GBI-1 **(297)**, GBI-II **(298)**, GB II **(300)** etc. Additionally, *G. elata* polysaccharides PGEB-3H **(288)** with (1 → 4)-α-D-glucose as the main chain has a hypolipidemic effect (Ming et al., 2012). *G. elata* polysaccharide PGE **(283)** is an α-glucopyranose ring structure, mainly with 1 → 4-linked glucose as the main chain, with branches that may be 1 → 6-linked glucose terminals, 1 → 4, 6 or 1 → 3-linked glucose, with angiotensin-converting enzyme (ACE) inhibitory activity and antitumor activity (Chen, 2019). Notably, based on the conformational relationship of sulfated polysaccharides with anti-angiogenic target proteins (Id1 and HS) (Hong et al., 2010). It was confirmed that the sulfated derivative of the *G. elata* polysaccharide WGEW, WSS25 **(270)**, blocked the BMP2/Smad/Id1 signaling pathway and inhibited Id1 expression in HMEC-1 cells and liver tumor cells. Another molecular mechanism by which WSS25 inhibits angiogenesis is by suppressing HMEC-1 cells through the inhibition of dicer, a key enzyme in miRNA biosynthesis (Xiao et al., 2013) (Fig. 14), which suggests that the anti-angiogenic mechanism of WSS25 has been studied clearly, but its conformational relationship is still complex. Therefore, the conformational relationship of the sulfated polysaccharide derivatives of *G. elata* is to be further investigated.

5.5. Amino acids and polypeptides

17 amino acids and polymorphic compounds **(325–341)** have been identified from *G. elata* as shown in the *G. elata* chemical composition Table S4 and Fig. 15 **(325–341)**. This includes 9 non-essential amino acids and 7 essential amino acids, which are very abundant (Shao et al., 1994). It is worth mentioning that amino acids are not only beneficial for improving sleep quality, boosting immunity, and treating Inflammatory bowel disease they can also alleviate wrinkles and keep skin fine and hydrated (He et al., 2018; Zhang et al., 2022). Among them, arginine **(340)** can alleviate immune damage and play an important role in anti-inflammatory, mucosal barrier repairing, and mucosal healing, while histidine **(339)** inhibits oxidative stress in intestinal epithelial cells (He et al., 2018; Lori A. Coburn et al., 2016; Zhang et al., 2022).

5.6. Others

19 other compounds **(342–360)** such as adenosine, vitamins, and aldehydes were found in *G. elata* (Table S4, Fig. 16). Some of them, adenosine and its analogs, especially N_6-bis(4-hydroxybenzyl) adenosine **(358)** and N6 −(4-hydroxybenzyl) adenosine **(357)**, have antiviral, sedative, neuron-protective, and immunomodulatory activities (Huang et al., 2007; Wang et al., 2018; Zhang et al., 2012). Vitamins **(350–353)** play an important role in the nervous system, heart activity and vision.

5.7. Volatile components

As shown in Table S5 of the Chemical Composition of *G. elata* and Fig. 17. Plant volatiles in *G. elata* include hydrocarbons (e.g.

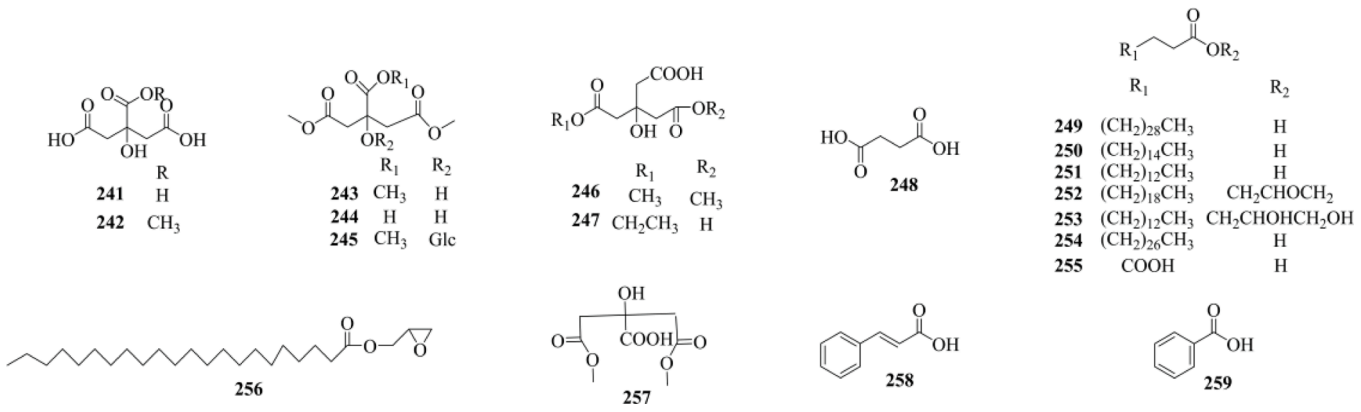


Fig. 12. Organic acids and esters in *G. elata*.

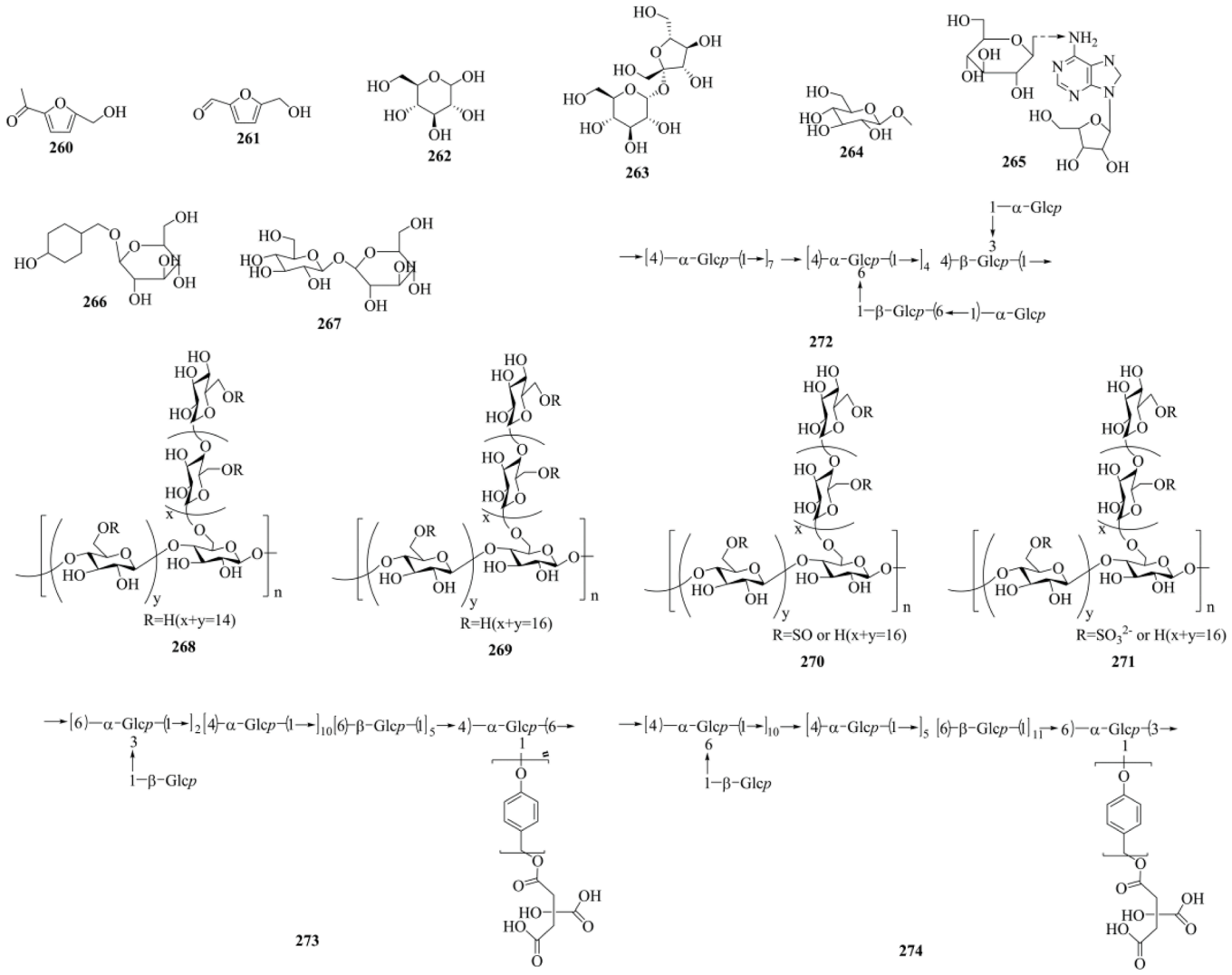


Fig. 13. Saccharides and their glycosides in *G. elata*.

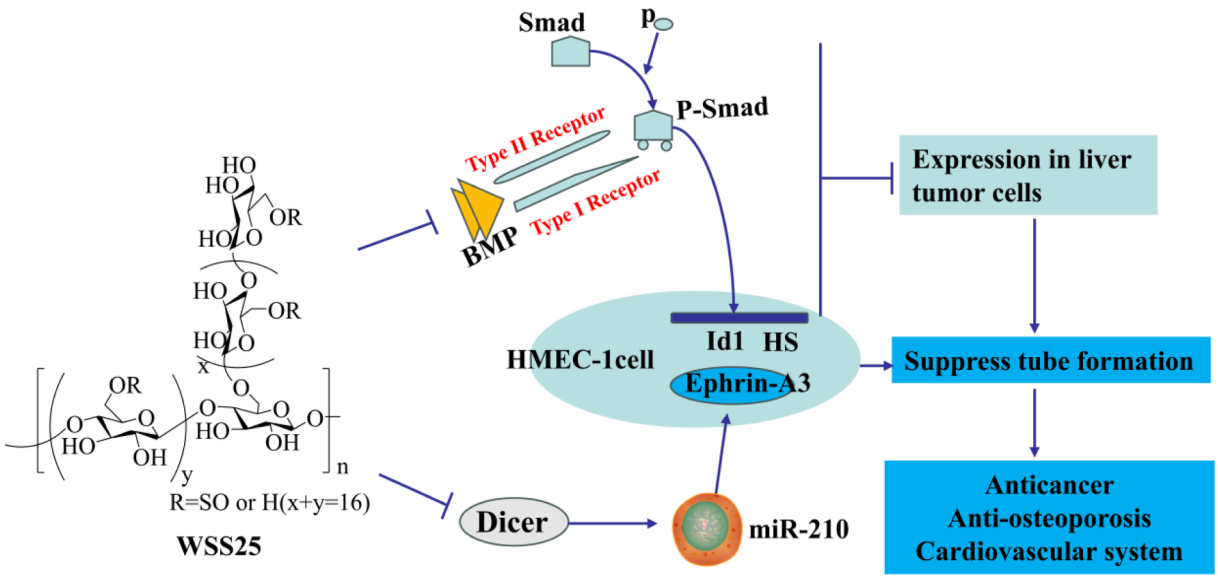


Fig. 14. The pathway of tube formation suppression by the sulfated polysaccharides WSS25 from *G. elata*.

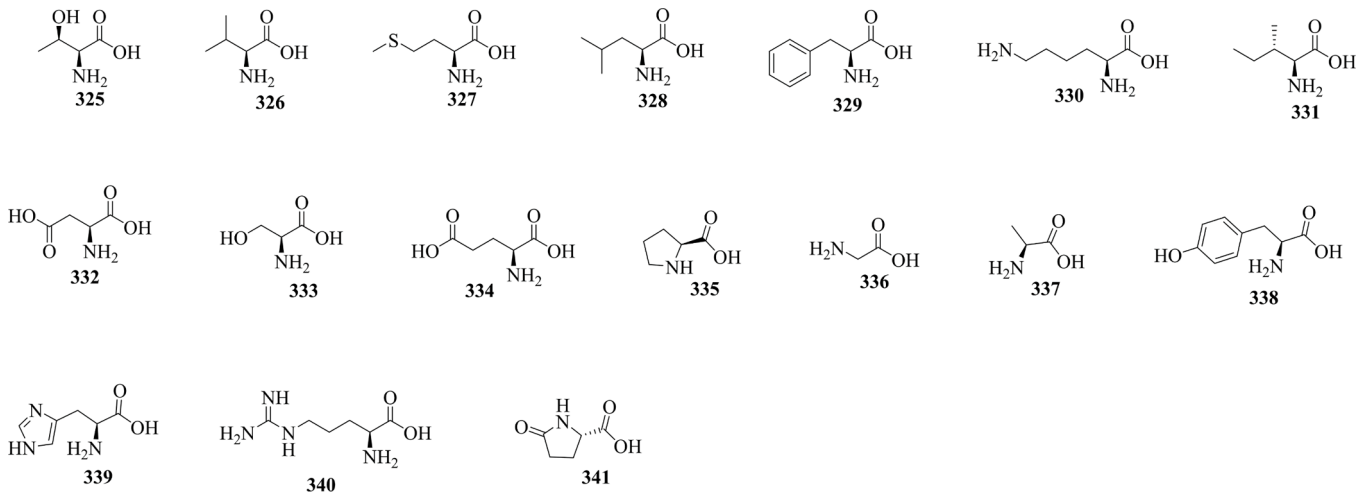


Fig. 15. Amino acids and polypeptides in *G. elata*.

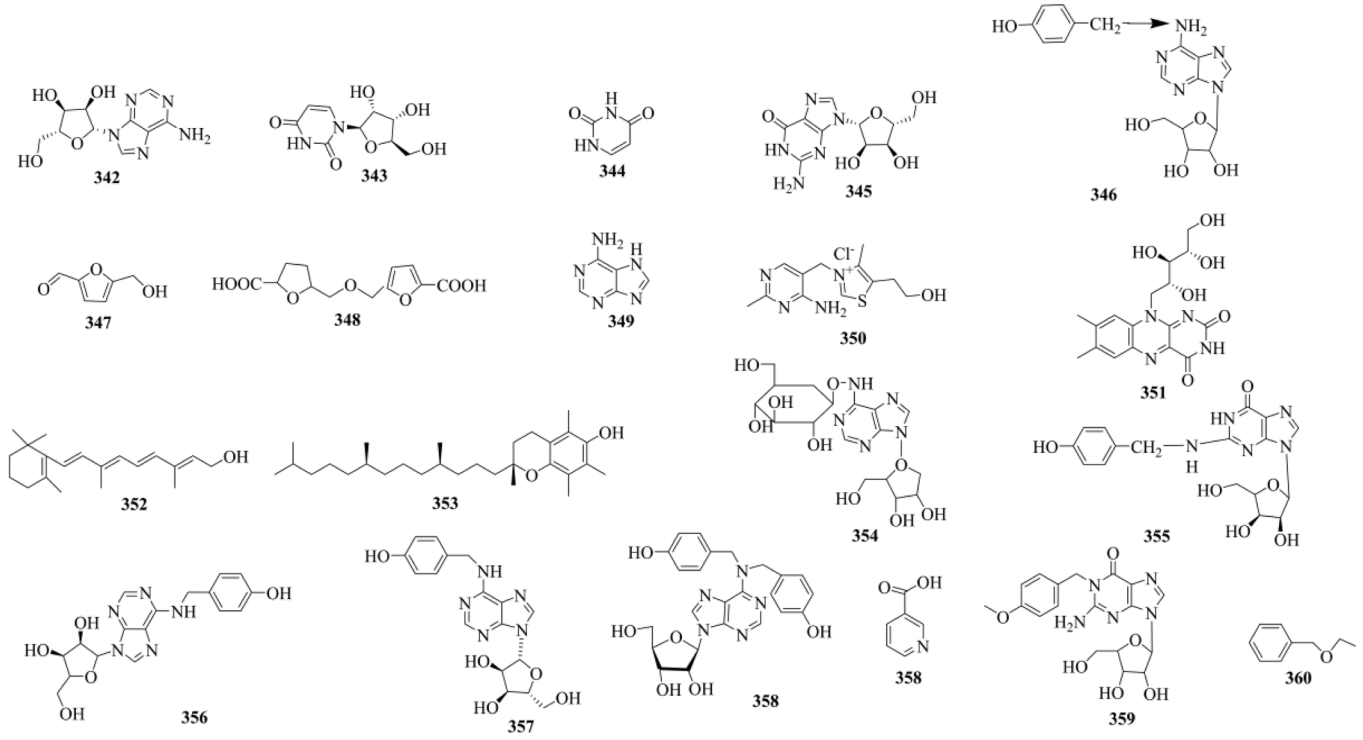


Fig. 16. Other compounds in *G. elata*.

hydrocarbons, terpenes) and their oxygenated compounds (e.g. alcohols, aldehydes, ketones, acids, esters, lactones, ethers, phenols, etc.). They are broadly divided into fatty acid derivatives, monoterpenes and sesquiterpenes, aromatic compounds, and some nitrogen-containing (n-phenyl-benzenamine) and sulfur-containing (acetyl sulfide) compounds **(361-603)** . Studies have shown that 2,3,5,6-tetramethylpyrazine **(577)** can treat arsenic-induced nephrotoxicity, improve microcirculation, dilate small arteries, anti-platelet aggregation and cerebral blood flow (Gong et al., 2016; Jin et al., 2021). Armiloid A **(521)**, armilliphatics A **(530)**, armilliphatics B **(531)** armilliphatics C **(532)**, and 14-hydroxydihydromelleolide **(533)** all inhibited acetylcholinesterase inhibitory activity, but armiloid A **(521)** was more inhibitory (IC_{50} = 4.91 μM) (Li et al., 2019; Li et al., 2020c). 13-hydroxymelleolide K **(534)** showed moderate *in vitro* cytotoxic activity against five human cancer cells (HL-60, A549, MCF-7, SMMC-7721, and SW480) with IC_{50} values ranging from 15.80-23.03 μM (Li et al., 2020c). It is significant that 1-hexen-3-ol **(484)** can be used both as a pharmaceutical intermediate and as a flavouring (Liu et al., 2018). In addition, squalene **(382)** is hepatoprotective and improves human immune function, and penctrimertone **(465)** has moderate cytotoxicity and significant bacteriostatic activity (Li et al., 2020b; Liu et al., 2015). Due to the antimicrobial and bactericidal properties of the volatile components (Guan et al., 2008). Therefore, this class of compounds is considered to be a promising alternative to conventional chemical preservation, especially botanical volatile organic compounds with biocompatibility, practicability and accessibility, which are found versatile in defending both foodborne pathogens and spoilage organisms (Quan et al., 2022). So, the focus of subsequent research could be on the antibacterial mechanism and biosynthesis of the volatile components of *G. elata,* aiming to study safer preservatives and other practical applications. This is very

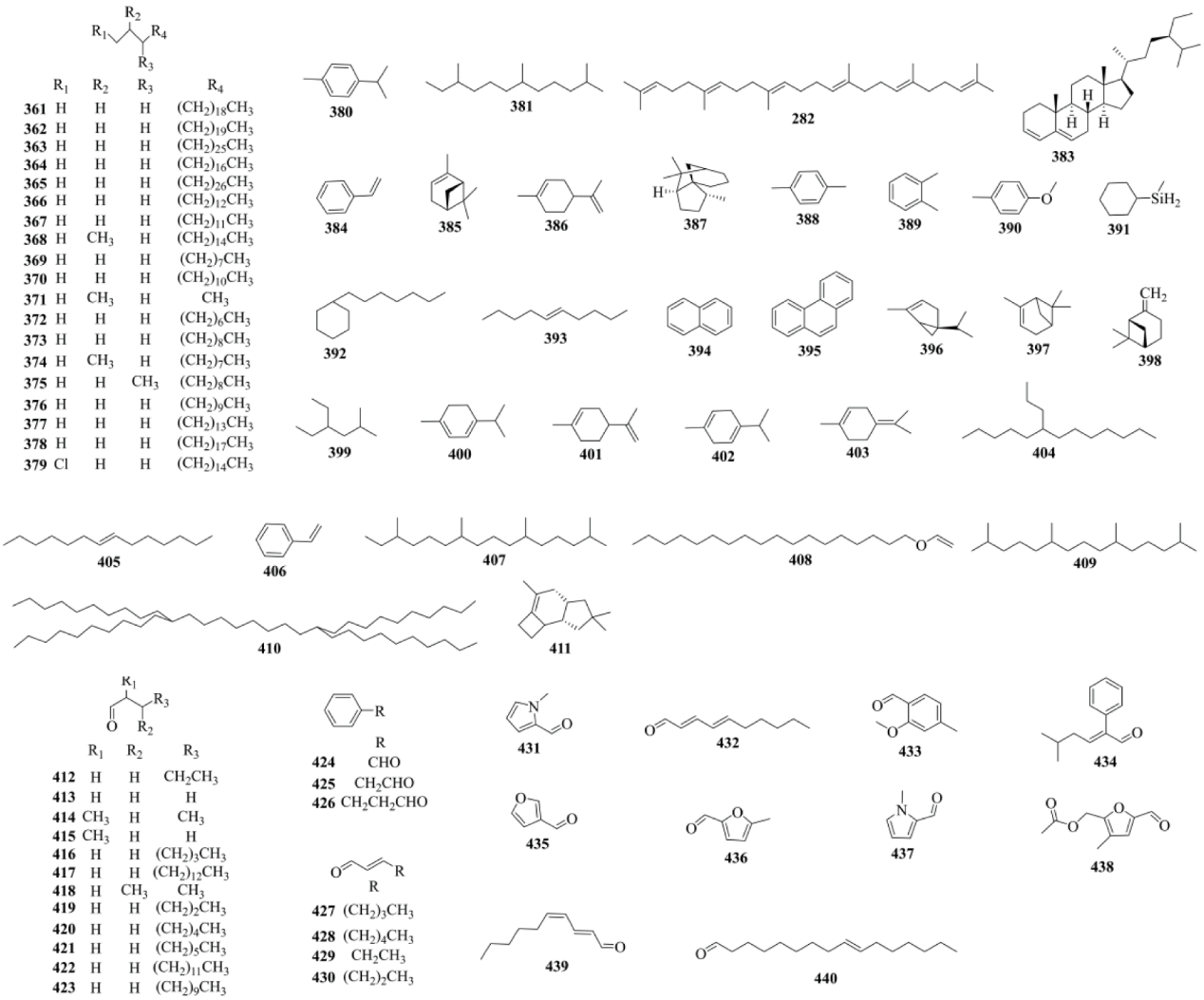


Fig. 17. Volatile components in *G. elata*.

necessary for domestic for the current status of *G. elata* research.

5.8. Trace elements

G. elata is full of in trace elements (including 27 types) **(604–630)** such as Zn, Fe, Mn, Cu, Ni, Mg, Sn, etc (Table S5). However, trace elements are very much associated with a variety of functions in the human body, and they have a positive effect on the health of the human body (Himoto and Masaki, 2020). Among them, Zn **(604)**, Fe **(606)**, Mn **(607)**, etc. are essential trace elements for the human body (Li et al., 2020a). The elements Zn **(604)**, Cu **(605)**, Fe **(606)**, and Se **(630)** can improve chronic liver diseases, including chronic hepatitis, liver cirrhosis, nonalcoholic fatty liver disease, and autoimmune liver diseases (Himoto and Masaki, 2020). As a result, research on trace elements of *G. elata* is also necessary.

5.9. Swot-based analysis of G. elata activities

SWOT analysis is a situation analysis method based on internal and external competitive environment and competitive conditions, and the research object is compared from four aspects: S (advantages), W (disadvantages), O (opportunities) and T (challenges). Based on SWOT analysis method, this paper analyzed the separation and application of bioactivity of calamus flavus. The rich range of active ingredients identified from *G. elata* so far has opened up possibilities for developing elata in formulations, clinical, modern pharmacology, cosmetics, health products and foods. However, studies of its pharmacological activity have mostly focused on monobenzyl and sugars such as gastrodin, 4-HBA, and parishins. Pharmacological studies of other compounds, such as aromatic compounds and volatile compounds (such S-containing heteroatom), are less, and the application of aromatic substitution of glycoside compounds has not been reported so far. In addition, parishins in aromatics have not been fully discovered, and the structure of many polysaccharides has not been determined. *G. elata* is included in the list of medicinal and edible plants in China, which has led to the increasing attention of researchers on the application of active ingredients of asparagus, which is the opportunity that asparagus exists at present. However, there are still many challenges, such as the conformational relationship between agave polysaccharide components and activity is not clear, and more pharmacological activities need to be further explored and improved. The application of trace elements and volatile components should be paid more attention.

6. Pharmacological activities

G. elata is effective in the treatment of diseases and the improvement of bodily functions, particularly in the regulation of the nervous and cardiovascular systems. The various pharmacological effects of *G. elata*

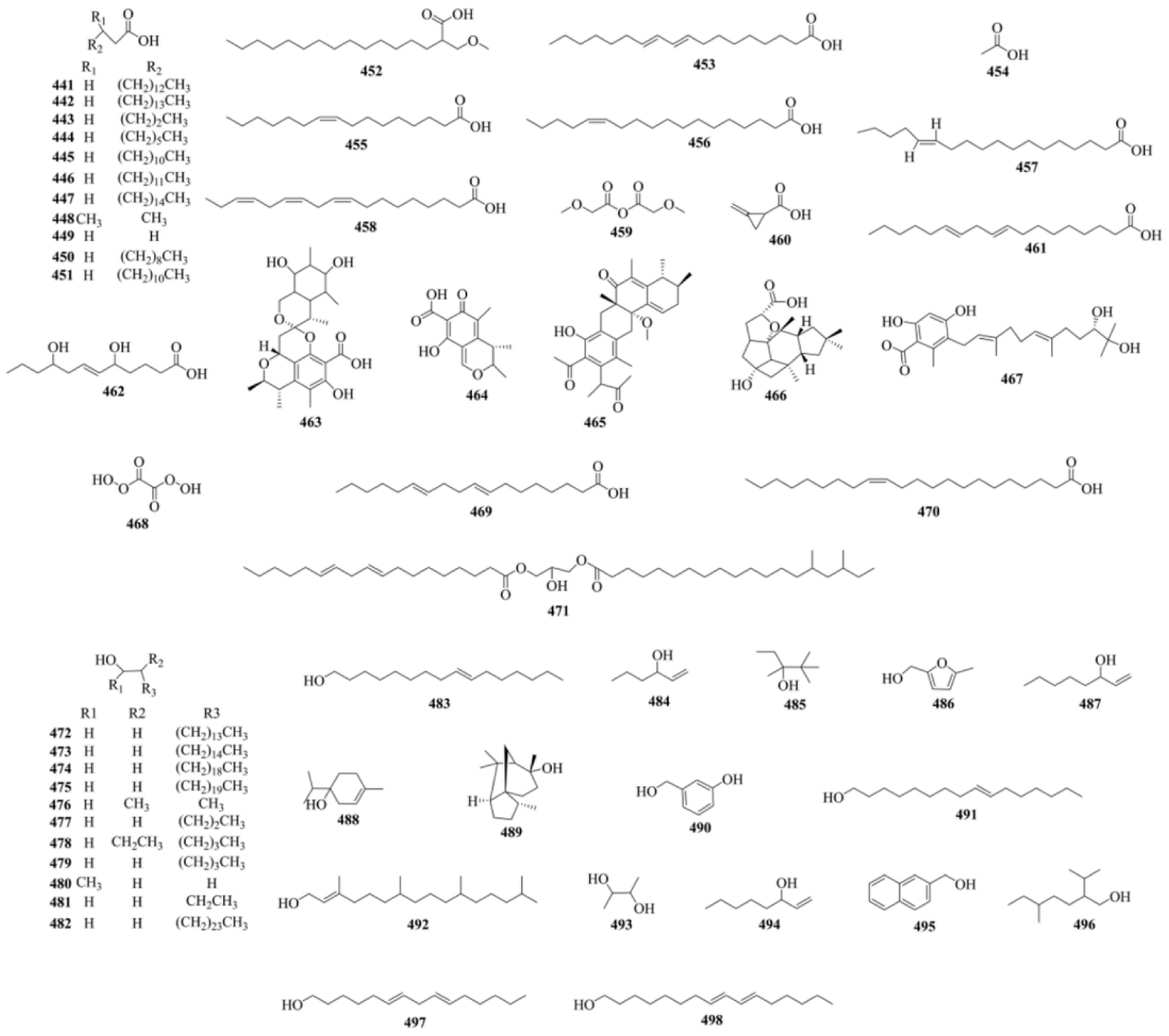


Fig. 17. (*continued*).

active substances based on *in vitro* and *in vivo* studies are listed in Table S6. The results demonstrated that *G. elata* exhibits anti-anxiety and anti-depressant properties, neuroprotective and regenerative effects, antioxidant and anti-ageing capabilities, the capacity to treat neurodegenerative diseases, sedative and hypnotic properties, anti-hypertensive effects, anti-MIRI activity, memory-enhancing properties, and an anti-osteoporosis effect, in addition to other pharmacological effects (Fig. 18).

6.1. Neuroprotective activities

6.1.1. Neuron protection and regeneration

From PC12 cell ischemic/hypoxic model, Huang et al. (2007) analyzed by MTT assay pointed out the active components N6-(4-hydroxybenzyl) adenine riboside (NHBA) **(185)** and bis(4-hydroxybenzyl) sulfide (BIS) **(189)**, preventing serum deprivation induced apoptosis in a concentration-dependent manner and bound to the adenosine A_{2A} receptor (A_{2A}-r) gene, which is abundantly expressed in γ-aminobutyric acid striatal neurons and regulates different regions of the brain. In the meanwhile, Wang et al. (2018) conducted the same experiment and indicated that N_6-(4-hydroxybenzyl) adenosine **(357)** and grossamide **(179)** actives had a significant neuroprotective impact on 6-hydroxydopamine-induced cell death, in which IC_{50} was 10 and 10.2 μM, separately.*G. elata*'s role in neurotoxicity treatment or serving as a neuroprotective agent is presented in certain approaches. After the phosphatidylinositol 3-kinase (PI3K) signaling pathway concerning brain-derived neurotrophic factor (BDNF) went through up-regulation, it was found that *G. elata* exerted a neuroprotective influence on the glutamate-induced HT22 hippocampal cytotoxicity in an efficient manner (Han et al., 2014). Additionally, the 5-((4-O-β-d-glucopyranosylbenzyloxy) methyl)-furan-2-carbaldehyde **(212)** and 5-((4-O-β-D-glucopyranosylbenzylsulfide) methyl)-furan-2-carbaldehyde **(199)**, which served as *G. elata*'s active ingredients,preventde PC12 cells from MPP^+ toxicity at the separate 30 mM and 100 mM concentrations separately to the largest extent (Li et al., 2016a). In addition, this research also applied western blotting, flow cytometry, and qRT-PCR in order to analyse the influence of gastrodin on male ICR mice, glutamate-induced HT22 and human dopaminergic cells-treated with MPP^+. The results was that gastrodin **(10)** not only prevented the dopamine depletion but also attenuated a variety of neuronal damages through the use of the oxidative stress (OS), extracellular regulated protein kinases (EPK1/2-P38), and Nrf2/HO-1 and Wnt/Nrf2 signaling pathways as well as apoptosis. At the same time, heme oxygenase-1 (HO-1) expression was also triggered through activating the activation of the p38 mitogen-activated protein kinases/nuclear factor-E2-related factor 2 (p38 MAPK/Nrf2) signaling pathway (Jiang et al., 2014; Jiang et al., 2020; Liu et al., 2020). After the sirtuin1/toll-like receptor 4/Nuclear factor κB (SIRT1/TLR4/NF-κBp65) signaling pathway was modulated

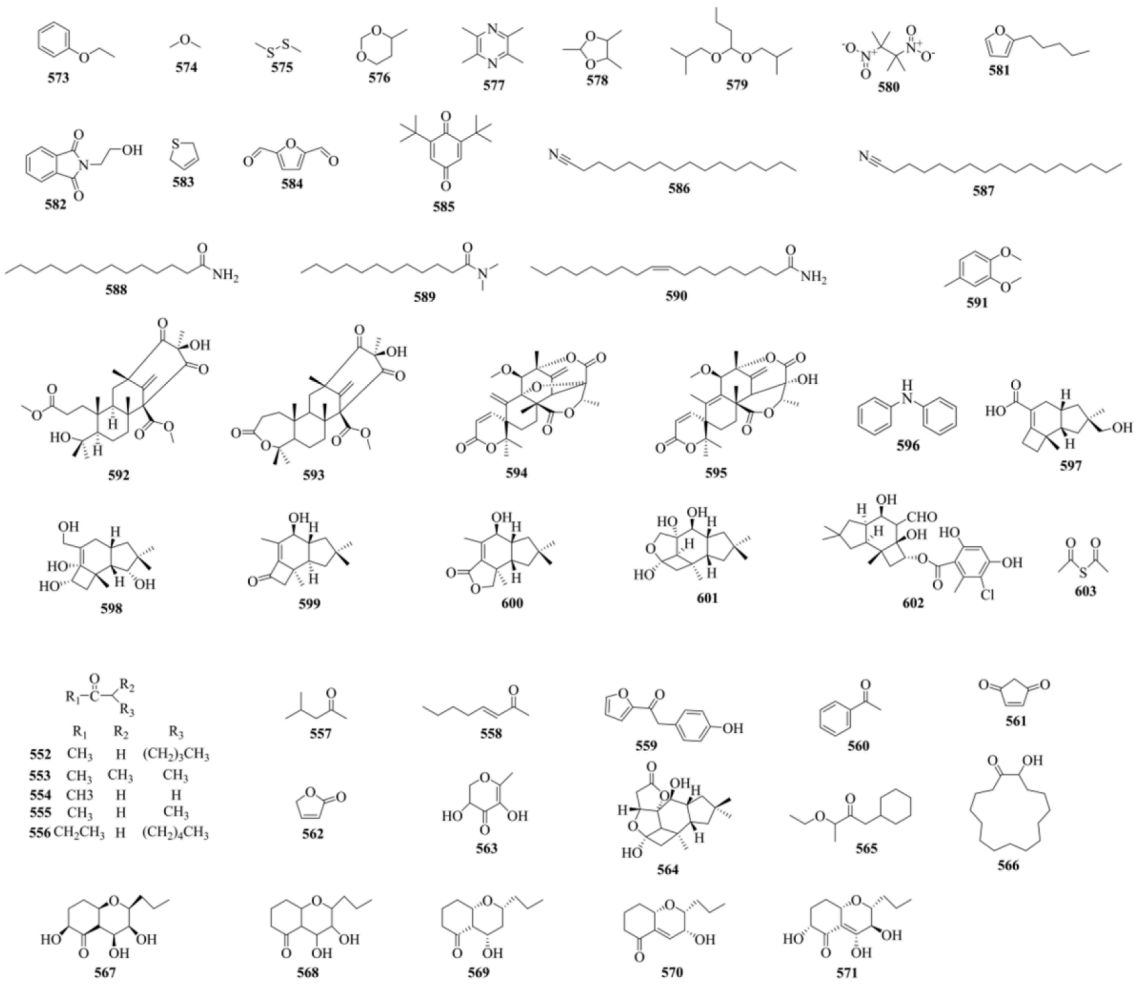


Fig. 17. (*continued*).

and oxidative stress was attenuated, there were damages on the high glucose (HG)-induced apoptosis within human retinal endothelial cells (HRECs), and it is likely to be a new drug tthat can be used for the diabetic retinopathy (DR) treatment (Zhang et al., 2018). At the same time, gastrodin **(10)** served as the neuroprotective against autophagy in SH-SY5Y cells due to that it not only down-regulated the LC3B and Beclin-1 expression but also inhibited the AKT/mTOR signaling pathway (Yang et al., 2019). Also, it can Schwann cells' (SCs) proliferation and growth is affected since the EPK1/2/AKt pathway is inhibited or the PI3K/MAPK pathway is activated (Li et al., 2022; Zuo et al., 2016). Interestingly, Li et al., (2022) administered gastrodin **(10)** intravenously at a dose of 20 mg/kg/d to a PNI rat model for a fortnight and explored it by utilizing the dual-luciferase reporter gene, qRT-PCR, and western blotting. The findings implied that gastrodin could promote note only the expressionof neurofilament-200 (NF-200) and myelin basic protein (MBP), but also nerve regeneration and myelin formation by inhibiting oxidative stress and regulating the miR-497/BDNF axis.

6.1.2. *Antioxidant and antiaging*

G. elata polysaccharides have been found to exert the impacts of 1,1-diphenyl-2-picryl hydrazyl (DPPH), hydroxyl radical (OH·), ABTS radical (ABTS·), and superoxide anion radical (O_2^-) scavenging (Hou and Hou, 2018; Zhou et al., 2017). According to the studies, 4-(hydroxymethyl)-5-nitrobenzene-1, 2-diol **(193)**, which was *G. elata*'s active ingredient, inhibited linoleic acid peroxidation and Fe2þ-cysteine-induced lipid in rat liver microsomes with the IC_{50} of 9.99x10^{-6} mol/L (Guo et al. 2015. Based on the treatment with the compound vanillin **(2)**, 4-hydroxybenzyl aldehyde (4-HBAL) **(22)** and 4-HBA **(12)** in *G. elata* blocked oxidative damage within PC12 cells. The order of antioxidant capacity of the phenolic compounds in its *G. elata* was 4-HBA > vanillyl alcohol > vanillin > 4-HBAL (Jung et al., 2007).

As we all know, silent information regulator 2 (Sir2) and Uth1 are key genes associated with longevity. However, the anti-aging effect of *G. elata* was shown to reduce Uth1 gene expression, oxygen species significantly (ROS) and malondialdehyde (MDA) levels, and significantly increase Sir2 gene expression in yeast strains, catalase (CAT) and glutathione peroxidase (GPx) activities (Farooq et al., 2019). This suggested that there is a strong strong correlation between the effects of anti-aging and antioxidant stress in *G.elata*. Parishin was found to exert anti-aging effects through modulating the Sir2/uth1/TOR signaling pathway (Lin et al., 2016). Significantly, *G. elata* polysaccharides were also able to increase the activities of superoxide dismutase SOD, glutathione peroxidase (GSH-Px) and CAT in serum and organ tissues of senescent mice, inhibits MDA and 8-hydroxydeoxyguanosine (8-OHdG) as well as mRNA expression of apoptotic factors Caspase-3, mMAFbX and MuRF-1 (Wang and Liu, 2019). In addition, 4-HBA **(12)** activated the forkhead box O (FOXO)/DAF-16, SKN-1, and HSF-1 pathways, regulated various pathways such as stress response pathways in mitochondria and endoplasmic reticulum, protein homeostasis and autophagy, and enhanced resilience against senescence and aging-associated neurodegenerative diseases (Liu et al., 2022). Recent studies had implide that N6-(4-hydroxybenzyl)adenine riboside (T1-11) **(357)** , the active component of tensin, activates A2AR (Hsu et al., 2020). TM-2 (T1-11) **(357)**, parishins A **(46)**, parishins B **(47)**) attenuates D-galactose (D-gal-) and $BeSO_4$-induced SH-SY5Y through inhibition of oxidative stress and reduction of senescence-associated β-galactosidase (SA-β-gal) activity.

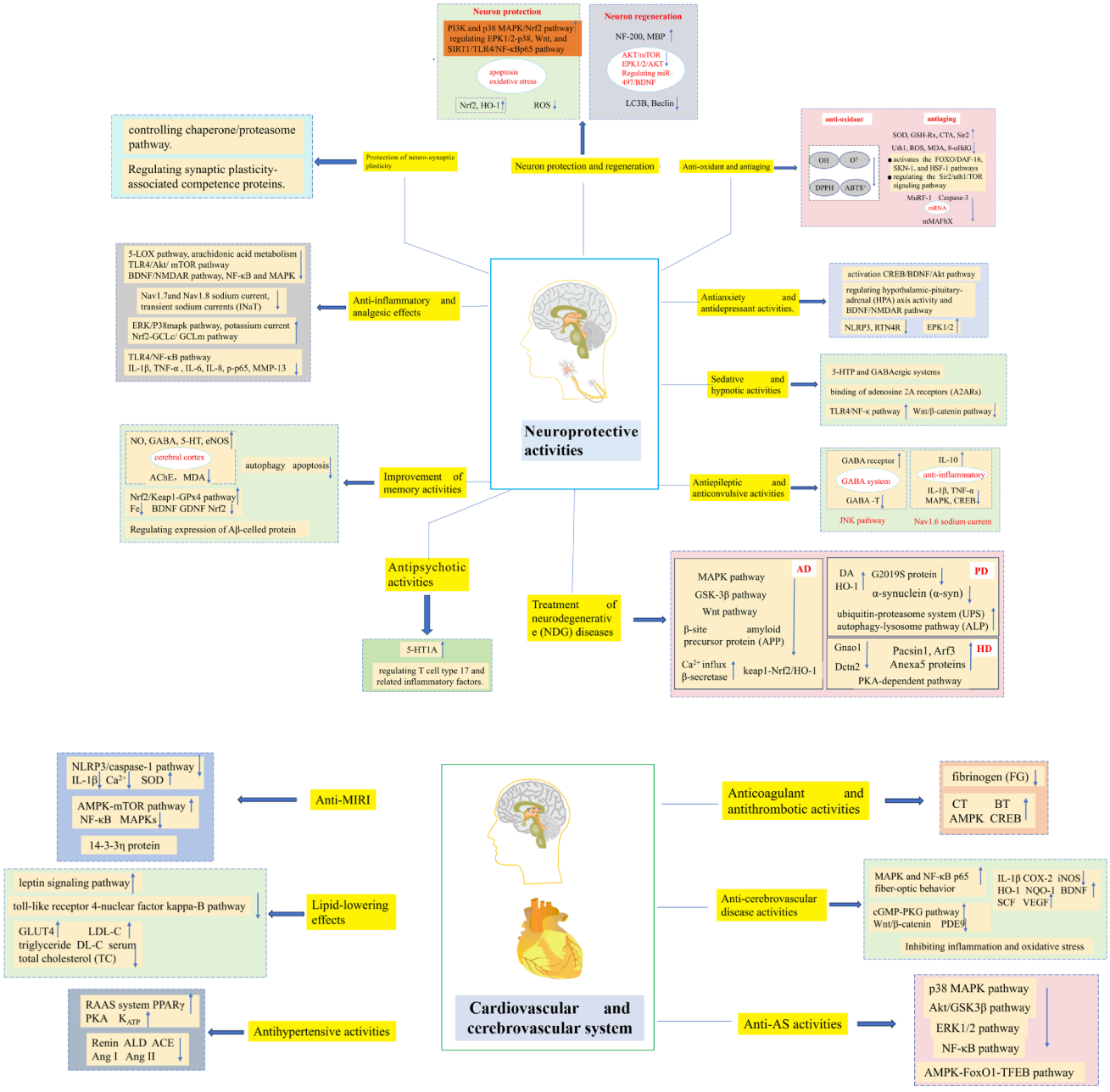


Fig. 18. The pharmacological activities and underlying molecular mechanisms of *G. elata*.

Simultaneously, it also regulates the SH2B1-Akt pathway and EPK-/akt-related pathways to induce neural neogenesis (Hsu et al., 2021). These findings demonstrate that *G. elata* is an effective herbal remedy for delaying aging and preventing aging-related neuroinflammation and neurodegeneration.

6.1.3. *Protection of neuro-synaptic plasticity*

In the isobaric tags for the relative and absolute quantitation (iTRAQ)-based proteomics method, *G. elata* was seen to drive neuro-regeneration by inhibiting stress-related proteins by promoting the neurodegenerative process, and through controlling AIP5 and other neuroprotective genes, the chaperone/proteasome degradation pathways (e.g. CALR, FKBP3/4, and HSP70/90), synaptic plasticity-associated competence proteins such as RTN1/4, NCAM, and PACSIN2 (Manavalan et al., 2012a; Ramachandran et al., 2012). In a study on lead exposure-induced synaptic plasticity injury, a reparative effect was exerted on lead-induced synaptic plasticity impairments within the hippocampal CA1 region, due to that gastrodin mitigated the decreased input/output (I/O), paired-pulse facilitation (PPF), and field excitatory postsynaptic potential (fEPSP) long-term potentiation (LTP) impairments in rats after the lead exposure (Yong et al., 2009).

6.1.4. *Treatment of neurodegenerative (NDG) diseases*

G. elata prevents neurodegenerative diseases such as AD, HD, and PD and the resulting cognitive deficits (Wang et al., 2021a). In the AD brain, counteracting Aβ-induced neurotoxicity and restoring the occurrence of NPCs is an effective strategy for treating AD (Percario et al., 2020). PD is primarily caused by the fact that 80 % of nigrostriatal dopamine (DA) neurons is lost and α-synuclein is excessively accumulated (Fasina et al., 2022). Besides, HD is defined as neurodegenerative disorder which is dominated by autosomal caused by the CAG trinucleotide repeat sequence is unstably amplified in the Huntington's protein (Htt) gene

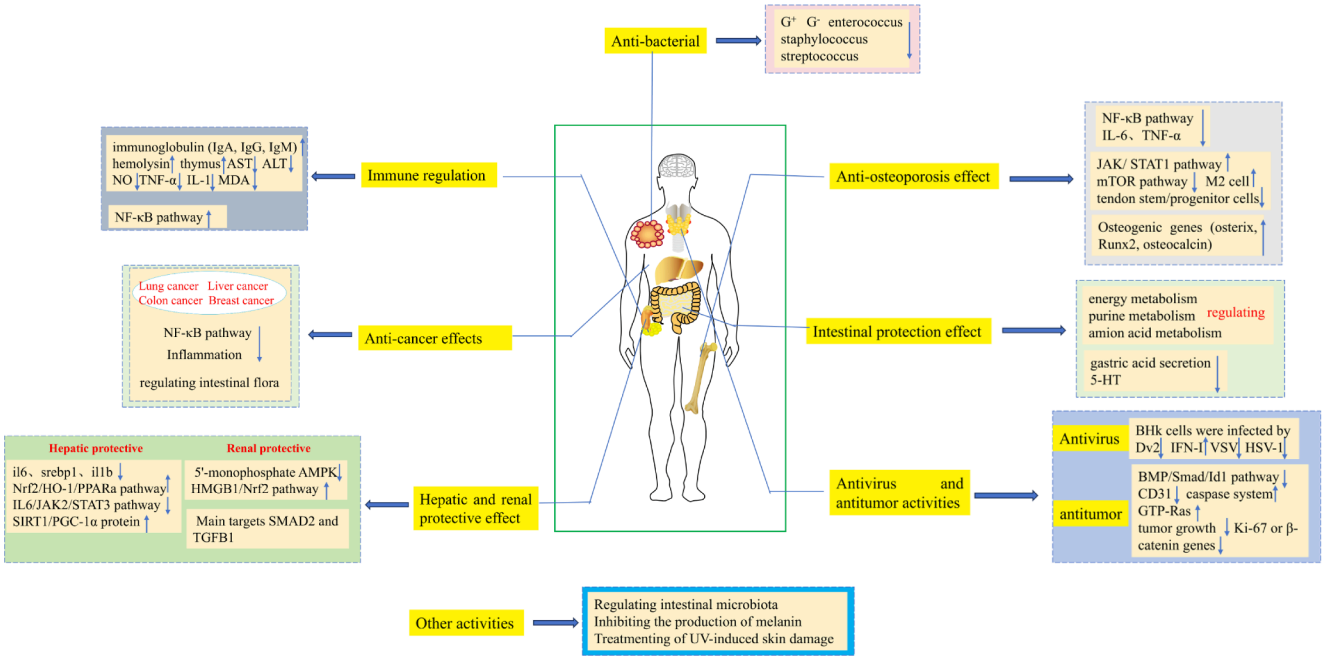


Fig. 18. (*continued*).

that has cognitive decline, mental retardation, involuntary movements, chorea, and some other characteristic phenotypes (Bates et al., 2015).

Upon the glycogen synthase kinase 3β (GSK-3β), the microbe-gut-brain axis, and the keap1-Nrf2/HO-1 went through partially targeting, the AD mouse models' memory was enhanced and the amyloid β-peptide production was also blocked due to that Gastrodin **(10)** drives the non-amyloidosis processing of the α-secretase mediated β-site amyloid precursor protein (APP) (Fasina et al., 2022; Mishra et al., 2011). Interestingly the combination of Focused Ultrasound and gastrodin to open the blood–brain barrier may be a desirable strategy for the treatment of AD (Luo et al., 2022). On the other hand, Yan et al. (2019) acted on strains of C. elegans with different concentrations of gastrodin **(10)** and showed that gastrodin relies on the insulin-like DAF-2/DAF-16 signaling pathway to reduce the accumulation of α-synuclein (α-syn). In addition, He et al (2021) gavaged drosophila melanogaster model with different concentrations of gastrodin **(10)** and revealed by lifespan analysis, and RT-PCR analysis, gastrodin, protecting dopaminergic neurons and increased dopamine levels, restoring the original posterior cerebral dopaminergic neurons that were gradually lost in the lateral 1 area of the original brain for achieving protective effect against PD (He et al., 2021). Thus, showing a protective effect against PD. Meanwhile, gastrodin **(10)** and 4-HBA **(12)** prevented neuronal loss in a Drosophila PD model by preventing G2019S protein overactivation through the glial Nrf2/Mad fiber signaling pathway (Lin et al., 2021). In addition, Peng et al. (2023) raised that 20C is a drug candidate for the treatment of PD. 20C not only significantly reduces the amount of α-synuclein inclusions, but also enables A53 T α-Syn transgenic mice to significantly reduce toxic α-synuclein levels. 20C also improved mitochondrial dynamics, thereby protecting mitochondrial morphology and function from α-synuclein-induced degeneration. However, gastrodin **(10)** can promote the degradation of mHtt by activating the ubiquitin–proteasome system (UPS) and the autophagy-lysosome pathway (ALP) making it a potential therapeutic agent for PD (Sun et al., 2024). Manavalan et al. 2012 proposed that the supernatant of *G. elata* powder substance exerted anti-HD effects through down-regulation of Gnao1 and Dctn2, and up-regulation of molecular chaperones and proteins associated with misfolded protein response (e.g., Anexa5), as well as other HD-related proteins (e.g., Pacsin1 and Arf3). Thus, *G. elata* could beapplied in treat neurodegenerative diseases by modulating the brain proteome.

6.1.5. *Antianxiety and antidepressant activities*

Depression is a dangerous psychological disorder that can cause serious economic damage and social problems. Major depression (MOD) patients and animals exhibiting depression-like behaviors suffer from delayed neuroplasticity and neurotransmitter dysregulation, even life-threatening (Pittenger and Duman, 2008). The results of Zhou et al. (2024) demonstrated that *G. elata* plays a critical role in treating depression and insomnia. This is attributed to its multi-targeting action and the relatively low incidence of side effects.

The injection of 4-HBA **(12)** (50 and 100 mg/kg) and 4-HB **(26)** (100 mg/kg) into male ICR mice significantly increased the time spent in the elevated plus maze and the percentage of time spent and arm entries into the open arms ($p < 0.05$) (Jung et al., 2006). Parshin C **(48)** can normalization of neurotransmitter and corticosterone levels, inhibition of NLRP3 inflammasome activation achieves antidepressant effects (Jiang et al., 2024). When the apoptosis and reticulon 4 receptors (RTN4R) was modulated, the depression within zebrafish and cellular models was extracted by *G.elata*'s ameliorative effect (Wang et al., 2022). In addition, there were certain antidepressant effects since the cAMP response element binding protein (CREB)/BDNF/Akt pathway was activated (Huang et al., 2021; Wang et al., 2022b). The antidepressant effect of gastrin could be mediated by attenuating single prolonged stress (SPS)-induced hypothalamic neuropeptide Y expression, enhancing the EPK1/2 phosphorylation level, and modulating inflammatory response-associated factors and tumor necrosis factor-α (TNF-α) and hypothalamic–pituitary–adrenal (HPA) axis activity (TNF-α) (Lee et al., 2016; Zhang et al., 2014, Liu et al., 2018; Wang et al., 2020). What's more, *G. elata* exerts potent antidepressant effects by alternating monoamine regulation and gut microbial composition and function and modulating the BDNF/NMDAR pathway (Gao et al., 2023). All these findings provide novel ideas for utilizing *G. elata* intreating depression and related neurological disorders.

6.1.6. *Sedative and hypnotic activities*

Insomnia refer to a very common condition featured by difficulty in maintaining sleep. Studies have exhibited that GABA and adenosine could be sleep-regulating substances (Kryger et al., 2006). Therefore, medications for sleep can work by activating GABAA receptors, inhibiting GABAergic neurons. And reducing adenosine levels in the basal

forebrain, hypothalamus, cortex, and brainstem. Researchers using Morris water maze assay and Western blotting assay on SD rats have shown that *G. elata* can improve sleep quality by regulating sleep-related substances.

N^6-(3-methoxyl-4-hydroxybenzyl) adenine rriboside (B2) **(182)** and NHBA **(185)**, which were isolated from *G. elata*, exerting significant sedative and hypnotic effects. It can both increase c-Fos's expression in GABAergic neurons in the ventral lateral preoptic area (VLPO) and activate sleep centers in the anterior hypothalamus (Li et al., 2014; Zhang et al., 2012). At the same time, through increasing cortical and hypothalamic GAD enzyme activity and GABA levels, it can significantly shorten the latency period of sleep and elevate the non-rapid eye movement (NREM) sleep time (Shi et al., 2014). Notably, it has been found that NHBA could mediate sleep-promoting effects by activating adenosine 2A receptors (A2ARs) in GABAergic neurons of the ventrolateral preoptic nucleus (VLPO), thereby potentially ameliorating polarity stress-related insomnia (Jou et al., 2021). Furthermore, 4-HBA **(12)** and its derivatives have demonstrated sedative-hypnotic activity. The synergistic effects of 4-HBA with 4-hydroxybenzyl alcohol 3-furancarboxylic acid diester (2FHBA) and 5-hydroxytryptophan (5-HTP) suggest that its anti-insomnia properties may be mediated through the 5-HTP and GABAergic systems (Zhu et al., 2018). It is significant that gastrodin **(10)** is viewed as a potential candidate for treating of REM sleep deprivation. It can improve both sleep quality and cognitive impairment associated with REM deprivation by activating the TLR4/NF-κB pathway and inhibiting the Wnt/β-catenin signaling pathway (Liu et al., 2023). It is noticeable that timethylcitryl-β-D galactopyranoside **(245)** and 4-HBA **(12)**, the other active ingredients of *G.elata*, inhibited GABA transaminase (GABA-T) activity by 56.8 % and 30.9 %, respectively (Choi et al., 2006). Gastropolybenzylol G **(146)** activates melatonin MT1 and MT2 receptors (Chen et al., 2019). There is also the compound 4,4′-methylenediphenol **(113)** considered as a potential candidate for melatonin agonist (Chen et al., 2019a). Although these compounds can modulate the sleep-related substance melatonin, whether these compounds can improve sleep and by what mechanism they act has not been reported.

6.1.7. Antiepileptic and anticonvulsive activities

Epilepsy is a complex neurobehavioural disorder caused by excessive neurons with a global prevalence of 1.2 % (Fiest et al., 2017). Therefore, the development of antiepileptic drugs is urgent. Administering aqueous extracts of *G. elata* (0.5, 1.0 g/kg/d) into KA-treated male SD rats for a fortnight,. resulting in *G. elata* could regulate kainic acid induced epilepsy-activating protein 1 (AP-1) expression (based on JNK signaling pathway) (Hsieh et al., 2007). Meanwhile, Yip et al., (2020) showed that water extract of *G. elata* inhibits acute exacerbations and attenuates pathological changes in pilocarpine-induced TLE mice providing preclinical evidence. This was accompanied by a reduction in mTOR and attenuation of astrogliosis. In addition, gastrodin **(10)** increases c-fos expression and seizure latency, inhibits MAPK, CREB, and NF-jB and reduces the levels of tumor necrosis factor-alpha (TNF-alpha) and pro-inflammatory cytokine interleukin-1 beta (1L-1β) to attenuate seizure-like behavior (Chen et al., 2017; Jin et al., 2018). After injecting gastrodin **(10)** at a concentration of 10 mM into male adult SD rats, Shao et al. (2017) utilized EEG/EMG recordings and immunohistochemistry and other methods for analysis and found that inhibition of the Navl.6 sodium current by gastrodin may become the mechanism of its anticonvulsant effect. Its pharmacological effects can be enhanced when *G. elata* is applied together with antiepileptic drugs, including VPA and PHT (Zhou et al., 2015). Its co-administration with VPA can promote the transport mechanism of VPA into the brain through the organic anion transporting polypeptide (OATP) transporter, increase VPA in the brain, exert anticonvulsant effects more effectively, and the severity of seizures (Yang et al., 2021; Yang and Tsai, 2022). Therefore, certain new insights are offered into the interaction between conventional drugs and conventional antiepileptic drugs within the animal models of status epilepticus. It lays a basis for the development of new drugs.

6.1.8. Anti-inflammatory and analgesic effects

G. elata both inhibits TNF-α-induced vascular inflammation and arachidonic acid metabolism in the 5-lipoxygenase (5-LOX) pathway by suppressing oxidative stress and NF-κB activation within human umbilical vein endothelial cells (HUVEC) and induces the expression of cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS) mRNAs (Ahn et al., 2007; Hwang et al., 2009). As indicated by these results, *G. elata* possesses anti-angiogenic, anti-inflammatory, and analgesic activities. Meanwhile, Ng et al. (2016) employed a water extract of *G. elata* (505, 1515 mg/kg) on SD rats with traumatic brain injury (TBI) by continuous gavage for one week, and found that its anti-inflammatory activity was achieved by suppressing TBI brain TNF-α and pro-inflammatory cytokine interleukin-6 (IL-6) levels in TBI brain. After applying the active ingredient 20C of *G. elata* to LPS-activated BV-2 cells, Shao et al. (2018) analysed *G. elata* through MTT, immunofluorescence and western blotting and identified that the anti-inflammatory activity of *G. elata* could also be regulated by inhibiting TLR4/Akt/ mTOR and regulating the ERK/p38MAPK signaling pathway. In addition, *G. elata* makes its anti-inflammatory effects mainly through hindering the activation of NF-κB and MAPK to regulate glial cell M1/M2 polarisation and reduce inflammatory mediators, or by significantly inhibiting COX-I and tt activity and silica-induced ROS generation (Lee et al., 2006; Xiang et al., 2018). Interestingly, gastrodin **(10)** can alleviate neuropathic pain by inhibiting microglia mitosis-induced NLRP3 inflammasome activation and inhibiting NaV1.7 and NaV1.8 sodium channels (Wang et al., 2021b). The significant analgesic therapeutic effect of gastrodin **(10)** on inflammatory pain is achieved by inhibiting spinal synaptic potentials between primary afferent fibers and neurons in layer 1 of the spinal cord in inflammatory states via Acid-sensing ion channels (ASIC) channels (Xiao et al., 2016). Peripheral analgesic effects in chronic pain can also be achieved by augmenting potassium current in small diabetic neurons and decreasing transient sodium currents (INaT), as in Painful diabetic neuropathy (PDN) (Sun et al., 2012).

It is worth reminding that *G. elata* can have therapeutic effects on some diseases and nerve pain protection through oxidative stress and anti-inflammatory effects. Research shows: that gastrodin **(10)** not only attenuates mRNA levels of IL-8, IL-6, IL-1β and TNF-α in the DRG, sciatic nerve, and spinal cord of Vininduced rats but was also able to promote recovery from spinal cord injury by enhancing the Nrf2-GCLc/ GCLm signaling pathway (Du et al., 2016; Xie et al., 2021). For the treatment of rheumatoid arthritis by inhibiting the NF-kB pathway signaling pathway in rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS), attenuating TNF-α-induced IL-6 and IL-8 production in RA-FLS, inhibiting p-p65, MMP-3 and MMP-13 expression and degradation of IkBa to achieve (Li et al., 2017).

6.1.9. Antipsychotic activities

The 5-HT1A receptor is considered an important target for the treatment of schizophrenia, and *G. elata* significantly attenuated the abnormal behavior induced by phencyclidine (1-(1 phenylcyclohexyl) piperidine hydrochloride (PCP)), which may act through activation of serotonin 5-HT1A in mice (Shin et al., 2011). Shin et al. (2010) showed in an 8-OH-DPA t-stimulated (35S) GTP-γS binding assay that Parishin C **(48)**, the active ingredient of *G. elata*, also activated 5-HT1A activity with a very high affinity to its receptor, suggesting an antipsychotic effect (Shin et al., 2010). In addition, gastrodin **(10)** can effectively regulate the expression level of its phase phasic helper T cell type 17 and related inflammatory factors, which is more effective in the treatment of schizophrenia (Song et al., 2019). However, there are few reports on this pharmacology and further studies are needed.

6.1.10. Anti-vertigo activities

According to the phenomenon manifested by labyrinth and platform

jumping assay, giving mice with *G. elata* polysaccharides (GEP) (50, 100, 200 mg/kg), is effective for anti-vertigo activity, which to be effective in shortening the time to avoid electric shock in vertigo model mice (Yu et al., 2006). Clinical investigations have shown gastrodin injection to be safe and effective in the treatment of vertigo (Jing et al., 2004), as well as useful in the treatment of acute vertigo by correcting blood flow to the brain and rapidly improving vertigo symptoms (Zhang and Xu, 2023).

6.1.11. Improvement of memory activities

G. elata polysaccharides exhibited some memory-improving effects by increasing NO, GABA, and 5-HT levels, and endothelial nitric oxide synthase (eNOS) expression, as well as decreasing AChE in the cerebral cortex and hippocampus, which elevated the acetylcholine (ACh) contents, and inhibited the level of MDA production (Ming et al., 2010; Shi et al., 2017). Liu et al., (2016a) injected Aβ1-42 oligomer-induced LTP male Wistar rats' model with Parishin C **(48)**, an active ingredient of *G. elata*, at 20 mg/mL, and demonstrated that Parishin C exerted a protective effect on soluble Aβ1-42 oligomer-induced LTP injury. Wu et al. (2016) and Liu et al. (1993) acted 4-HBA **(12)** on the brain tissues of mice and rats *in vivo* and *in vitro*, respectively, and the results showed that 4-HBA could reverse cycloheximide (CXM)-induced memory deficits in rats through activation of epinephrine and also inhibited brain oxidation. Concurrently, 4-HBA **(12)** blocked BDNF and glial cell line-derived neurotrophic factor (GDNF) mRNA and protein levels, as well as down-regulated hippocampal nucleus erythropoietic cell 2 p45-associated factor 2 (Nrf2) levels and up-regulated TNF-α and IL-1 expression to prevent A42-induced synaptic and cognitive deficits (Ding et al., 2019). In addition, *G. elata* may inhibit excessive autophagy by modulating the P38 MAPK signaling pathway, reducing Ab deposition, inhibiting apoptosis by lowering Beclin-1, LC3-II and p62 levels or by inhibiting aberrant phosphorylation of amyloid β (Aβ) and Tau as well as regulating the normalization of the GABAergic system without affecting Al levels in the brain (He et al., 2008; Liu et al., 2018). This demonstrated that gastrodin can ameliorate cognitive deficits and hippocampal neuronal damage in rats. It is interesting to note that gastrodin is also able to facilitate neurological damage and cognitive decline in VaD by inhibiting hippocampal neuronal Fe droop through activation of the Nrf2/Keap1-GPx4 signaling pathway, which provides a scientific rationale for the development of *G. elata* functional foods (Su et al., 2023).

Huang et al 2023 gavaged CRS-induced ICR mice with fresh 60% ethanol extract of *G. elata* (0.5, 1 g/kg), which was analyzed by Morris water, OLRT and NORT showed that it significantly inhibited chronic restraint stress (CRS)-induced BAX, Drp1 and CytC activation. The hippocampus in the brains of ICR mice, revealing the mechanism is to inhibit the levels of TNF-α and IL-1β in the hippocampus and increase the levels of AKT, p- AKT, CREB and p-CREB. *In vitro* and *in vivo* experiments showed that fresh *G. elata* attenuated CRS-induced cognitive deficits. Cheng et al. (2023) found that *G. elata* power + Huperzine A (Hup) significantly reversed learning and behavioral memory deficits induced by simulated weightlessness through activation of the BDNF pathway, anti-oxidative stress, and improvement of synaptic plasticity (Chen et al., 2023). This provides a basis for the application of *G. elata* to protect space from specific environmental stress damage and is expected to be developed into an aerospace health product.

6.2. Cardiovascular and cerebrovascular system

6.2.1. Anticoagulant and antithrombotic activities

Thrombophilia is a serious health risk, mainly due to excessive platelet aggregation in blood vessels, which can occur in arterial or venous circulation (Kuijpers et al., 2014). Currently, long-term use of new oral anticoagulants and antiplatelet agents for the prevention and treatment of thrombophilia may lead to coagulation abnormalities and cause cerebral, gastrointestinal and subcutaneous adverse effects (Wong et al., 2000). Therefore, reducing the side effects associated with long-term medication is a concern for most researchers.

Pyo et al., (2004) investigated the effects of 4,4′-dihydroxybenzyl sulfone **(187)** and 4,4′-dihydroxy-dibenzylether **(97)**, the active components of tensides, on platelet aggregation platelets in rats induced by epinephrine and prostaglandin-endoperoxide analog (U46619). The effect of these two compounds showed anti-platelet aggregation activity with IC_{50} of 83 μM and 3 μM, respectively. While polysaccharide 2–1 form *G. elata* (PEG2-1) **(324)** and gastrodin **(10)** were able to reduce fibrinogen (FG) levels and prolong coagulation time (CT) and bleeding time (BT) in mice, thereby reducing symptoms of thrombosis (Liu et al., 2006; Shi et al., 2007). Furthermore, Kim et al. (2017) showed the effects of orchiectomies (ORX) in 7-week-old male SD rats with 0.3 %, 1 % *G. elata* water extract. The results are appreciated, the extracts of *G. elata* could completely normalize the timing of arterial thrombosis and blood flow and reduce triglyceride accumulation in ORX rats by enhancing AMPK and CREB activities or attenuating hepatic insulin signaling (Kim et al., 2017). It was interesting to note that MJGE09 (mixed extract of *G. elata* and Zanthoxylum schinifolium (ZS)) was able to exhibit inhibition of collagen and ADP-induced platelet aggregation both *in vivo* and *in vitro* in mice. This suggested that MJGE09 can be used as a potential anticoagulant with improved antithrombotic effects (Jeon et al., 2021). This finding could provide a better idea for antithrombotics, facilitate the research of safer, reliable antithrombotic drugs, and require follow-up studies on MJGE09 effective dose concentration and other pharmacological mechanisms.

6.2.2. Anti-cerebrovascular disease activities

According to Zeng et al. (2006) reported by *in vivo/in vitro* experiments, the consequence indicated gastrodin (100 mg/kg) is effectiveness for reducing edema and infarct volume after MCAO. They also significantly inhibited OGD and glutamate-induced neuronal cell death and OGD-induced increases in Ca^{2+} and NO at concentrations of 15 ug/mL, 30 ug/mL. It also inhibits PDE9 activity and activates the cGMP-PKG pathway to promote hippocampal neurogenesis to ameliorate learning memory deficits in cerebral ischemia mice (Xiao et al., 2021). Meanwhile, gastrodin **(10)** inhibited ischemia–reperfusion (I/R) injury-induced up-regulation of the inflammatory cytokine IL-1β, as well as the expression of pro-oxidant enzymes COX-2 and iNOS in the ischemic brain, thereby ameliorating the subacute cerebral I/R injury (Liu et al., 2016). The neuroprotective effects of phenolic compounds of *G. elata* (PCGE) was found in the transient middle cerebral artery occlusion model in rats, which proved PCGE mechanism is to activate Nrf2 in brain cells, reduce H_2O_2-induced LDH release, and up-regulate the expression of HO-1, NQO-1, and BDNF by dehydrogenase and western blotting assay, which effectively reduced the ischemic stroke neurotoxicity (Shi et al., 2018). The brain injury could be prevented by 4-HBA **(12)**, the workflow is realized by causing necrosis of neuronal cells in the hippocampus and cortex and reducing the expression of TNF-α and TUNEL-positive cells, similarly. It was reported detailly by modulating protein disulfide isomerase (PDI) cytoprotective genes and several neurotrophic factor genes (BDNF, GDNF and MBP genes) to protect neurons and improve the prognosis of ischemic stroke, and exerts a neuroprotective effect on VD by modulating mitochondrial function and energy metabolism (Kam et al., 2011; Wu et al., 2023a). Other reports have shown that 4-HBAL **(22)** proliferates reactive astrocytes (RAs) through activation of the Wnt/β-catenin pathway, thereby dealing with the subacute phase of ischaemic stroke. It also ensures that the *peri*-infarct cortex (PIC) in which some RAs are converted into neurons, remains unchanged in terms of brain structure (Yuan et al., 2022). Notably 3,4-Dihydroxybenzaldehyde **(3)** the active ingredient in *G. elata*, also upregulates the UDP-GlcNAc regulatory enzyme O-GlcNAc transferase (OGT), inhibits neuronal apoptosis or ameliorates through MAPK and NF-κB p65 fiber-optic behavior the signaling pathway in ischaemic stroke disease with significant reduction in infarct size (Li et al., 2020d; Luo et al., 2023). Parishin C **(48)** also has an ameliorative effect on

cerebral tissue damage in rat cerebral ischemia by reducing oxidative stress and inflammatory responses (Wang et al., 2021). Furthermore, Wang et al., (2019a) studies have shown that *G. elata* polysaccharides inhibit neuronal apoptosis and the expression of Bax, and promote the expression of Bcl-2, which has the effect of enhancing the intelligence of pups with cerebral palsy. In a rat model of focal cerebral ischemia, Liu et al. 2016 showed that GEP was also able to promote the expression of BDNF, SCF, and vascular endothelial growth factor (VEGF) proteins in the basal nucleus of Meynert and hypothalamic paraventricular nucleus (PVN).

G.elata improved glucose metabolism, cholesterol and blood flow impairment in norchidectomised (ORX) rats to show prevention of testosterone deficiency-related cardiovascular disease, combined with Acanthopanax senticosus (Rupr. & Maxim.) Harms to reduce cerebral I/R injury through oxidative stress (Kim et al., 2017; Lin et al., 2021). New research shows that *G. elata* can also reverse the inflammatory response, intestinal flora and amino acid metabolism disorders induced by rat brain I/R injury, and effectively reduce the area of brain necrosis and the volume of cerebral infarction in I/R rats (Ding et al., 2022). Therefore, using intestinal flora as a therapeutic target could be a new idea for treating cardiovascular and cerebrovascular diseases in TCM. The above studies have shown that the phenolic compounds and polysaccharides of *G. elata* are closely related to cerebral ischemia repair. Their mechanisms for treating cerebral hypoperfusion are not only associated with the decrease of inflammation, oxidative stress, neurotoxicity and apoptosis but also mediated *in vivo* via gut flora, arachidonic acid metabolism, histidine metabolism, pyrimidine metabolism, arginine and proline metabolism, sphingolipid metabolism as well as glycerophospholipid metabolism.

6.2.3. Lipid-lowering effects

Obesity has become one of the most prevalent diseases globally, occupying a proportion of all ages, and is associated with several metabolic disorders such as hypertension, type 2 diabetes mellitus and dyslipidaemia (Lavie et al., 2009). However, aqueous extracts of *G. elata* can improve insulin resistance ameliorating metabolic disorders in these diseases by reducing fat storage (Park et al., 2011). Among gastrodin has the ability to protect β cells and alleviate insulin resistance from insulin signaling pathway, inflammation, mitochondrial and endoplasmic reticulum, and improve type 2 diabetes mellitus (T2DM) role (Li et al., 2023).

Park et al. (2011) administered *G. elata* water extract (0.3, 1 g) daily to HFD male SD rats for 8 weeks and found that *G. elata* water extract (4-hydroxybenzaldehyde **(26)** and vanillin **(2)**) reduced insulin resistance by reducing fat accumulation during fat oxidation and enhancing leptin signaling. It was also able to increase the expression of glucose transporter 4 (GLUT4) and inhibit toll-like receptor 4-nuclear factor kappa-B signaling pathway in white adipose tissue (WAT), respectively, and remodel the gut microbiota, The high-fat diet (HFD)-induced hyperglycemia can be significantly improved and is useful for anti-T2DM (Wang et al., 2022a). In the meantime, *G. elata* can exert a lipid-lowering effect by increasing fatty acid oxidation in 3 T3-L adipocytes, enhancing the leptin signaling pathway and decreasing triglyceride accumulation, as well as elevating the level of high-density lipoprotein cholesterol (HDL-C) and reducing the levels of low-density lipoprotein cholesterol (LDL-C), serum, total cholesterol (TC) and triglyceride (Ming et al., 2012a; Park et al., 2011).

6.2.4. Anti-AS activities

Atherosclerosis (AS) is an ischaemic disease that severely damages the human circulatory system and causes high mortality (Sun et al., 2023). Its pathogenesis and complexity are related to thrombosis, inflammation, epigenetics, oxidative stress and immunology (Soehnlein and Libby, 2021). Therefore, it is important to study its pathogenesis and take precise therapeutic measures.

It was demonstrated that *G. elata* helps delay the onset of AS and reduces the risk of cardiovascular disease. An ethanolic extract of *G. elata* reduced TNF-α-induced matrix metalloproteinase (MMP)-2/-9 activity and expression levels (Lee et al., 2009). Zhu et al. (2012) showed that gastrodin **(10)** attenuated platelet-derived growth factor-BB (PDGF-BB)-induced vascular smooth muscle cell (VSMC) proliferation *in vitro*, inhibited neoplastic intima after carotid artery injury *in vivo*, or blocked the G/S cell cycle transition by inhibiting ERK1/2, p38, Akt/GSK3β signaling pathways and VSMC proliferative phenotypic transition. Moreover, it may also achieve amelioration of atherosclerosis by repairing the intestinal mucosal barrier, remodeling the intestinal pore space, and reducing the inflammatory response induced by circulating LPS through these pathways (Liu et al., 2021). It is important to note that gastrodin **(10)** improves atherosclerosis by inhibiting foam cells formation and inflammation through down-regulating of the NF-κB pathway (Xue et al., 2023). Tao et al., (2021) investigated the impact of 20 μmol/L gastrodin **(10)** on a model of foam cell formation induced by treatment of mouse macrophages with oxygenated low-density lipoproteins (ox-LDL). RT-PCR, Immunofluorescence and western blotting assay results indicated that the impact of gastrodin on foam cell formation and the induction of foam cell lysosomal biogenesis and autophagy via the AMPK-FoxO1-TFEB signaling axis may become a new therapeutic target for atherosclerosis.

6.2.5. Antihypertensive activities

Hypertension is an important cause of common cardiovascular diseases (e.g., atrial fibrillation, coronary artery disease, myocardial infarction), often accompanied by mild symptoms such as dizziness and palpitations, as well as a major risk factor for dementia, chronic kidney disease and cognitive decline (Vargas Vargas et al., 2022). It can activate the renin-angiotensin-aldosterone system (RAAS) and Autonomic nervous system dysregulation, resulting in enhanced endogenous vasopressin and angiotensin II (Ang II) (Ghazi and Drawz, 2017). It was found that *G. elata* polysaccharides, gastrodin, 3,4-dihydroxybenzaldehyde, and other active ingredients in *G. elata* extracts could exert hypotensive effects through relevant mechanisms.

Miao and Shen et al. 2006 explored the effects of GEP (50, 100, 200 mg/kg) in a rat model of "two-kidney, one clip" renal hypertension (2K1C-RHR), resulting GEP significantly reduced systolic and diastolic blood pressure in RHR rats ($P < 0.05$) (in a dose-dependent manner over the dose range. In addition, by chemically analyzing the blood of spontaneously hypertensive rats (SHR), the acidic polysaccharides of *G. elata* also led to a reduction in hypertension and an improvement in lipid levels in SHR (Lee et al., 2012). Gastrodin also shows better effects on lowering blood pressure, through exhibited by attenuation of phenylephrine hydrochloride-induced aortic ring contraction in a dose-dependent manner (Xie et al., 2015). And, regardless of the presence or absence of endothelial cells, it was able to significantly diastole blood vessels that were constricted due to NE and KCl-induced constriction (Zhang et al., 2012a). Also, Chen et al. 2017 investigated the effects of gastrodin **(10)** after acting on rat vascular smooth muscle cells for 24 h. Resulting in gastrodin also activates K_{ATP} channels in vascular smooth muscle via PKA-dependent signaling pathways, thereby dilating the vasculature of small mesenteric arteries. Liu et al. 2015 injected gastrodin **(10)** at a dose of 100 mg/kg for 4 consecutive weeks in SHRs. The results showed that it could effectively interfere with RAAS and peroxisome proliferator-activated receptor (PPAR) system, reduce serum angiotensin II and aldosterone (ALD) levels, up-regulate PPAR γ messenger in myocardial tissue ribonucleic acid (mRNA), and down-regulate angiotensin type 1 receptor (AT1R) in myocardial tissue, thereby reducing blood pressure. Meanwhile, *G. elata* phenolics 4-hydroxybenzaldehyde **(26)**, 4-methoxybenzyl alcohol **(25)** and 4,4′-methylenediphenol **(113)** inhibited constriction induced by Ca^{2+} in-flux and intracellular Ca^{2+} release from rat aortic rings, thus regulated vascular tone and plays an important role in ameliorating hypertension (Dai et al., 2017). Fermented *G. elata* manifested higher antioxidant activity and relieved control of elevated blood pressure than *G. elata*,

which means the processing method has a critical role in the pharmacological activity of *G. elata* determination (Wang et al., 2019). These results suggested that *G. elata* is useful for the treatment of hypertension and the prevention of cardiovascular diseases, and its mechanism of action may be related to the promotion of NO production, interference with the RAAS and PPAR systems, and the inhibition of renin, ALD, ACE activity, Ang I and Ang II.

6.2.6. Anti-MIRI

Myocardial ischemia–reperfusion injury (MIRI): refers to a series of injury phenomena triggered when the myocardium recovers blood flow in an ischaemic state, which may lead to myocardial cell death and cardiac dysfunction (Heusch, 2020). *G. elata* modulates lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase-myocardial band (CK-MB) to exhibit anti-MIRIs (Fu et al., 2018).

Gastrodin **(10)** applied in MIRI was attributed to the inhibition of NLRP3/caspase-1 pathway that blocks sepsis in cardiac microvascular endothelial cells, simultaneously, reduced IL-1β production, suppressed extracellular Ca^{2+} in-flow and increased the SOD content were found in Wang et al. 2013 and Sun et al. (2019). These processes reduce infarct size, remove ROS, reduce serum MDA levels, inhibit cell death pathways, and have a protective effect on the heart. In addition, gastrodin strongly inhibits nuclear factor-κb (NF-κB) and MAPKs, activates phosphatidylinositol 3-kinase (PI3-K)/protein kinase B(PKB/Akt) and AMPK-mTOR signaling pathways as well as increased mitochondrial membrane potential (Fu et al., 2018; Yang et al., 2013). Of interest, Zhu et al. (2018a) effects of gastrodin **(10)** on anoxia/reoxygenation (A/R) H9c2 cells with a concentration of 20 mg/L. MTS, TUNEL and western blotting analyses showed that gastrodin protects cardiomyocytes from A/R injury. It also exerts cardioprotective effects by increasing autophagy in dysfunctional mitochondria through up-regulation of 14–3-3η protein. Alternatively, inhibition of autophagy through the miR-30a-5p/ATG5 pathway regulates and protects against ischaemic myocardial injury (Yin et al., 2023). Interestingly gastrodin **(10)** significantly ameliorated the deterioration of cardiac systolic function due to fibrosis, cardiac hypertrophy and pressure overload in mice, and glucose transporter-mediated gastrodin was protective against cardiac hypertrophy (Zhang et al., 2023). In summary, *G. elata* exerts its anti-MIRI effects through inhibition of oxidative stress, inhibition of apoptosis (optimal concentration of 20 μmol/L), modulation of autophagy, resistance to apoptosis in cardiomyocytes and reduction of focal death (Zhang et al., 2019). Therefore, *G. elata* is a promising cardioprotective drug.

6.3. Anti-osteoporosis effect

G. elata is a new anti-osteoporotic drug discovered in the last few years. As can be found *in vivo/in vitro* experiments, the function of gastrodin **(10)** was not restricted to ameliorating IL-1β-induced chondrocytes by inhibiting the NF-κB pathway or reducing the release of inflammatory mediators (IL-6, TNF-α), which also ameliorated the degenerative changes in the knee joint cartilage from the model of osteoarthritis rats. Besides, gastrodin **(10)** protects osteoblasts through activating of the Nrf2/Keapl signaling pathway, inhibition of the NF-κB pathway and reduction of the release of inflammatory mediators (IL-6, TNF-α), mitochondrial, and endoplasmic reticulum stress-related networking channels (GRP78, CHOP, and eIF2α), thereby ultimately ameliorating the rat's osteoporosis (Chen et al., 2018b; Yin et al., 2020). In addition, *G. elata* can promote M2 macrophage polarisation and modulate inflammation through the Janus kinase-signal transducer and activator of the transcription (JAK/STAT1) pathway, inhibiting of osteogenic and chondrogenic differentiation of tendon stem/progenitor cells (TSPCs) by restricting the activation of the mTOR signaling and improving macrophage paracrine secretion (Zhu et al., 2023). With the help of glucocorticoid-treated MC3T3-E1 mouse osteoblasts, gastrodin manifested the anti-osteoporotic effect by up-regulating the levels of the osteogenic genes osterix, Runx2, bone morphogenetic protein-2, and osteocalcin mRNA, and increasing calcium deposition and alkaline phosphatase activity (Liu et al., 2018a). Or osteoclastogenesis and differentiation was inhibited by down-regulating the nuclear factor of activated T cells cl (NFATc1) signaling pathway (Zhou et al., 2017).

6.4. Intestinal protection effect

Usually, intestinal protection was influenced by many factors, parishin A **(46)** through modulating the fecal microbiota composition and reduction or increase the expression of aging-related biomarkers (e.g., CASPASE3, P21, FOXO3a and SIRT), those conclusions were found in Gong et al. (2023). In addition, it can inhibit serotonin and acetylcholine-induced contraction of isolated guinea pigs' ileum, ileum and has antispasmodic effects on the small intestine (Gong et al., 2023; Hayashi et al., 2002). It is interesting that *G. elata* polysaccharides GEP-1 **(273)** ameliorates UV-induced inflammation of intestinal tissues by promoting the growth of microbiota such as Ackerman's muciniphila (*A. muciniphila*) and Lactobacillus paracasei (*L. paracasei*) strains in the gut (Huo et al., 2021). This suggests that *G. elata* enriches the intestinal tract with probiotic growth and attenuates the deterioration of intestinal morphology. It was studied that *G. elata* could significantly promote gastric acid secretion, regulate energy and purine metabolism, improve gastric gland injury and biochemical indexes in rats, and effectively treat Chronic atrophic gastritis (CAG) (Chen et al., 2018).

6.5. Antivirus and antitumor activities

Both dengue virus (DV2) and tumors cause high mortality rates, and the drugs currently associated with them have various side effects. Therefore, there is a need to develop treatments with natural products.

Tong et al (2010) investigated the mode of action of WSS45 **(271)** (0.1, 1, 10 μg/mL) on the proliferative cycle of serotype 2 dengue virus (Dv2), and detected the proliferation of the virus in BHK through by qRT-PCR and flow cytometry, etc., and WSS45 effectively inhibited the BHk cells from Dv2 infection in BHk cells, with EC_{50} values of 0.68 + 0.17 μg/mL. WSS25 **(270)** blocked bone morphogenetic protein/inhibitor of DNA binding/differentiation (BMP/Smad/Id1) signaling interfered with angiogenesis and was able to reduce the expression of Id1 and the endothelial cell marker CD31 to inhibit tumor angiogenesis (Hong et al., 2010). At the same time, its noteworthy that gastrodin could hinder the VSV and HSV-1 infection through facilitating the production of IFN-I in macrophages, and increase antiviral activity by upregulating the type I interferon (IFN-I) (Li et al., 2023; Zhou et al., 2021). Moreover, four *G. elata* polysaccharides, WTM-2 **(278)**, WTM-3 **(279)**, WTM-5 **(281)** and WTM-6 **(282)**, showed inhibitory effects on tumor cells (HepG 2, Hela and A549) (Chen, 2019). *In vivo* and *in vitro* experiments have shown that the tumor inhibition rate of GEP in H22 hormone mice was as high as 44.7%, and its mechanism of action may be correlated with the influence of cell cycle distribution and the activation of the caspase system to induce apoptosis of tumor cells (Liu et al., 2015a; Wang et al., 2014a). The extracts of *G.elata* of antitumour effects were provided by increasing GTP-Ras, an active form of a G-coupled protein family, and inhibiting tumor growth and the expression of the Ki-67 or β-catenin genes, as well as preventing cell damage through β-amyloid in neuroblastoma cells (Heo et al., 2007; Kim et al., 2017).

6.6. Anti-bacterial

Zhan et al. (2007) and Chen et al. (2018a) analyzed *G. elata* polysaccharides by using methods such as the Thin-layer plate agarose pore diffusion method and found that it has broad-spectrum antimicrobial activity, with minimum inhibitory concentrations against G^+, G^- and fungi ranging from 0.9375-120 mg/ mL, 0.46875–15 mg/mL and 0.9375–30 mg/mL, respectively. In the meanwhile, the volatile constituents of *G. elata* showed significant inhibitory effects on the growth of Aspergillus oryz ae, aspergillus f lav us, Rhiz octonia cerealis,

Pestalotiopsis there (Guan et al., 2008). Gastrodinol **(223)** was the active compound in *G. elata* and can inhibit enterococcus, staphylococcus, streptococcus, and viridans, exhibiting the strongest inhibitory effect on staphylococcus and possessing, the minimum inhibitory concentration of 1 μg/mL (Yang et al., 2020). Thus, gastrodinol is the main compound that exerts antimicrobial action in *G. elata* and may result in the development of new antibiotics.

6.7. Immune regulation

The polysaccharide of *G. elata* (PGE) not only increased immunoglobulin (IgA, IgG, IgM), hemolysin, thymus, and spleen indices in mice (Li et al., 2016) but also lowered liver indices as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), NO, TNF-α, interleukin-1 (IL-1) and MDA levels (Li et al., 2015). This indicated that it can both reduce the inhibitory effect of cyclophosphamide on the humoral immune function of mice and enhance the humoral immunity of immunodeficient organisms by regulating the immune function of the organism. Moreover, Guan et al., (2022) showed by RNA-seq analysis that the immunomodulation induced by the polysaccharide of *G. elata*-1 (GEP-1) **(273)** was achieved by activating the NF-κB fiber pathway. Other studies have shown that the MAPK and TLR4 pathways are also important for immune regulation (Wang et al., 2014; Zhang et al., 2022a). Therefore, follow-up studies can be conducted to investigate whether the active ingredients of TIANMA can play a role in the immune response of the organism through MAPK and TLR4 pathways in corresponding pharmacological experiments.

6.8. Anti-cancer effects

G. elata water soluble dextran WTMA and its acidic derivative WTNA-AD-O possessed a specific inhibitory effect for cell proliferation of pancreatic cancer cells, which appeared almost no cytotoxicity for other cells but it had no inhibitory application on live LO_2 cells (Chen et al. 2011). Liu et al 2023 by MTT results suggested that GEP derivatives had better anti-breast cancer activity related to GEP, an acetylated derivative can trigger apoptosis of MCF-7 cells and hinder the proliferation of MCF-7 cells through blocking in the S phase. Meanwhile, extruded *Gastrodiae* Rhizoma (50 and 200 mg/kg/d) obviously lost the tumor weight, tumor volume, and spleen weight, and decreased the expression levels of Ki-67 and β-Catenin in CT26 carcinoma-bearing mice (Kim et al., 2017). Furthermore, Huo et al (2021a) showed after the bioactivity test that GEP-3 (272) and GEP-4 (274) were able to promote the growth of Akkemmansia muciniphila (Akk. muciniphila) and regulate intestinal flora. However, Akk. muciniphila could prevent nonalcoholic steatohepatitis by modulating Toll-like receptor 2 (TLR2)-activated γδT17 cells and further macrophage polarization (Han et al., 2023). Interestingly, Akk. muciniphila protects mice from developing colon cancer development by specifically hindering tryptophan-mediated aryl hydrocarbon receptor (AhR)/β-Catenin signaling (Zhang et al., 2023). *G. elata* therefore has the potential to prevent and treat hepatitis and cancer. However, how *G. elata* acts directly on these diseases requires further research (Huo et al., 2021).

6.9. Hepatic and renal protective effect

Gastrodin and *G. elata* polysaccharides can protect against various types of hepatic and renal injuries. Examples include vincristine-induced liver injury, alcoholic liver injury, as well as acetaminophen-induced liver and kidney injury, as well as bile duct ligation (BDL)-induced liver injury and fibrotic injury, etc. (Seok et al., 2018; Zhao et al., 2015). During the simulation of a high cholesterol diet induced zebrafish juvenile model of non-alcoholic fatty liver disease (NAFLD), the Nrf2, HO-1 pathway, and PPARa pathway were taken as the basis for the lipid regulation and antioxidant effects of gastrodin (10) or 4-HBA (12). Among it, the mechanism of the anti-NAFLD effect by gastrodin could be attributed to inhibiting the molecular levels of il6, srebp1, il1b, fans, tgfb, tnfa, and keap1. (Ahmad et al., 2019; An et al., 2021). Furthermore, gastrodin **(10)** attenuates CCl_4-induced renal inflammation and fibrosis through the inhibition of adenosine 5′-monophosphate AMPK and also attenuates CCl4-induced renal inflammation and fibrosis by enhancing the high-mobility group box-1 (HMGB1)/Nrf2 pathway (Liao et al., 2022; Ma et al., 2020). What's more, Wen et al. (2023) investigated the effects of gastrodin **(10)** on hypertensive rats (SHRs) and its mechanism by ex vivo validation and network pharmacological analysis. The results showed that SMAD2 and TGFB1 as the two main candidate targets of gastrodin against renal injury in SHRs, and inhibition of the *in vivo* and *in vivo* factor-β1/Smad2/3 signaling pathways significantly attenuated renal injury and renal fibrosis in SHRs. Notably, the hepatoprotective effect of *G. elata* can be achieved by inhibiting mitochondrial damage through inhibition of the IL6/JAK2/STAT3 pathway and up-regulation of SIRT1/PGC-1α protein expression (Gao et al., 2014; Zhou et al., 2018).

6.10. Other activities

In addition to these activities, *G. elata* has other pharmacological effects. Wen et al. (2019) conducted metabolomics and 16S rRNA gene sequencing to study the role of *G. elata* and *Uncara rhynchophyla* (Miq.) Mig. ex Havil (GU) in combination with a rat model of nitroglycerin-induced chronic migraine (CM). The resultd suggest that GU may treat CM by modulating the structure and function of the gut microbial community. *G. elata* may also promote the migration of keratinocytes and wound healing in mouse skin via the Src/mitogen-activated protein kinase pathway (Kang et al., 2017). Its water extract has also shown obvious therapeutic impacts on acute UV-induced skin damage through decreasing oxidative stress and pro-inflammatory cytokines (TNF-α, IL-13, IL-4) associated with the skin-gut flora axis (Zhang et al., 2022b). At the same time, *G. elata* has anti-asthmatic, therapeutic effects on attention deficit and hyperactivity disorder (ADHD) and bladder smooth muscle contraction (Jang et al., 2010; Teong et al., 2011). Significantly, Wang et al. (2021c) used micro-positron emission tomography (PET) and stereotypical behavior experiments to assess the therapeutic effect of gas on tourette syndrome (TS). The results indicated that gastrodin **(10)** had a therapeutic effect on TS-like behaviors in rats by indirectly decreasing the level of DA through decreasing the number of dopamine D2 receptors (D2Rs) and 5-HT transporters (SERTs) and increasing the number of dopamine DATs. Zhu et al., (2023) showed that *G. elata* active ingredient parishin A **(46)** can inhibit heterotopic ossification and inflammatory infiltrates to promote endogenous tendon repair capacity to attenuate tendinopathy. NHBA **(185)** activates the adenosine A_{2A}-r and regulates equilibrative nucleoside transporter 1 (ENT1) inhibiting ethanol drinking and seeking behavior suggesting a potential therapeutic agent for the treatment of alcohol use disorders (Hong et al., 2019). At the same time, the sulfur atoms of BIS, the active ingredient in *G. elata*, can bind to copper ions in the active site of tyrosinase, reducing the body's ability to synthesize melanin (Chen et al., 2015). Furthermore, Shim et al. (2017) suggested that *G. elata* displays dose-dependent inhibition of melanin synthesis by suppressing tyrosinase activity as well as molecular levels of MITF, tyrosinase, Trp1, and Trp2 in murine B16F10 melanoma. As a result, *G. elata* may become an efficient and natural skin-whitening agent in the cosmetic industry. Meantime, the potential of *G. elata* for cosmetic application has been evaluated by Hu et al., (2023).

7. The toxicity evaluation of *G. Elata*

(Ben cao gang mu) recorded that *G. elata* is not toxic and not only protects neurons from the toxic effects of Zn^{2+} (Luo et al., 2018), but gastrodin also inhibits the NLRP3/caspase-1 pathway blocking cardiac microvascular cellular pyemia. Lu et al., 2022 *In vitro* genotoxicity assay of five Salmonella typhimurium strains (TA98, TA100, TA102, TA1535

and TA1537) with Water extract of *Gastrodia elata* Blume (WGE). With or without metabolic activation, WGE did not cause mutagenicity, nor did it trigger teratogenicity in Chinese hamster ovary (CHO-K1) cells, did not influence the proportion of immature to total erythrocytes or the number of micronuclei in immature erythrocytes of ICR mice. *In vivo* dose-dependent repeated-dose toxicity assessment in mice over 28 days showed no adverse effects of WGE (2040, 4080, and 8065 mg/kg body weight, p.o.) on behavior, mortality, body weight, hematology, clinical biochemistry, or organ weights. However, it has been found that long-term use of fresh *G. elata* has certain toxic side effects, the toxic dose is more than 40 g, and the incubation period of toxicity is 1–6 h. There is a report of death caused by cardiac arrhythmia in a 76-year-old man who took a large amount of fresh *G. elata* (500–600 g). (Pu, 1997; Wang, 2005). There are case reports: 26 middle-aged men stewed with 80 g of *G. elata* and ate about 15 g of *G. elata* and experienced facial burning, and headache and then fainted. 50-year-old middle-aged women ate 1 tablespoon of *G. elata* powder in the morning and 1 tablespoon of *G. elata* powder in the afternoon, and then the next day developed flaky and striated edematous erythematous plaques, which gradually spread over the whole body (Pu, 1997; Zhan, 2007a). It is worth noting that improper processing of *G. elata* can also produce toxic side effects. Pan et al put 1 g/mL of flash *G.elata* and "Jiao Tianma" solution, respectively, at 2 g/kg static injection for about 30 min, then 6 g/kg intraperitoneal injection of 10 rabbits of the same age, the results of the "Jiao Tianma" group appeared to be the phenomenon of heart rate, respiratory acceleration, agitation and restlessness, which may be due to the process of concocting, caused by the temperature is too high (Pan and Zhu, 1993).

8. Discussions and prospectives

G. elata has a wide range of applications in clinical practice in China and healthcare in several Asian countries. Therefore, the present study is a comprehensive review of the literature on *Gastrodia*, systematically investigating it folklore, traditional and clinical uses, botany, phytochemistry, pharmacological studies and toxicity evaluations (Fig. 19). This review aims to provide a thorough understanding of the current status of *Gastrodia* research, highlight the limitations in its development, andoffer a theoretical foundation for future studies.

G. elata has a long history of medicinal use, with folk herbal remedies documented for 18 ethnic groups in our country. There remedies are primarily employed to treat conditions such as dizziness, headache, stroke, convulsions, rheumatism, limb numbness, and high blood pressure. Additionally, records indicate the existence of over 700 different dosage forms of *G. elata*, including decoctions, pills, tablets, capsules, and granules, with TGDs and BBTDs ranking among the top ten in term of usage. Clinically, *G. elata* is commonly used to address conditions such as spontaneous hypertension, Parkinson's, diabetes, and epilepsy. Studies of both formulas have involved effects on organismal mechanisms in cellular or mouse models.Jiang et al. (2019) demonstrated that BBT treatment significantly reversed the course of heart damage caused by SHRs. Meanwhile, BBT attenuated inflammatory signaling by significantly lowering IL-1, IL-6, TNF-α, and iNOS levels in SHR cardiac samples. Deng et al. (2020) conducted a study using TGD action in SHR, which showed that TGD provides cardiovascular protection by exerting antihypertensive mechanisms through the antiapoptotic effects of

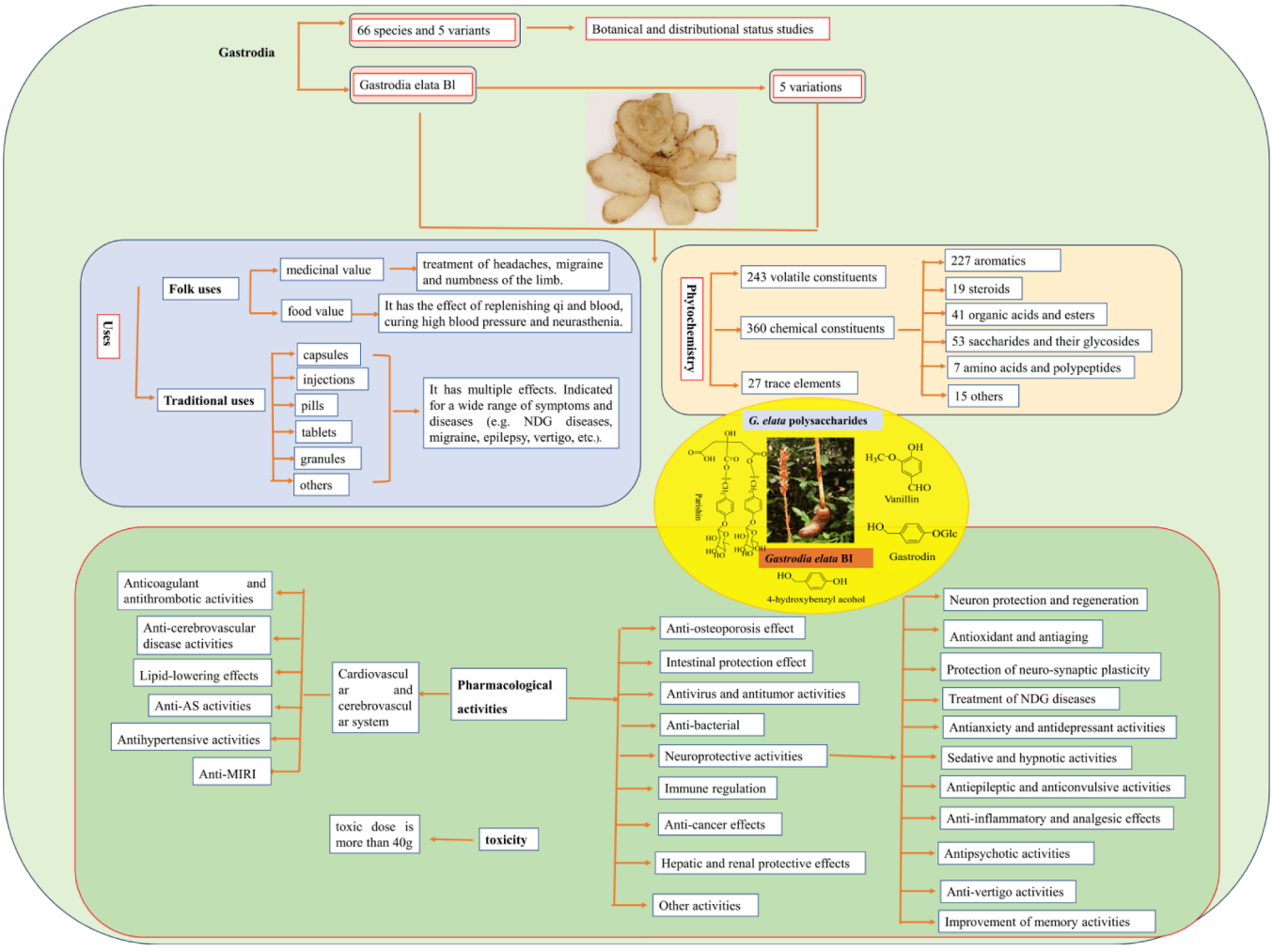


Fig. 19. The traditional and folkloric uses, phytochemistry, pharmacological studies and toxicity evaluations of *G.elata*.

osteoprotegerin and TNF-related apoptosis-inducing ligands. It is interesting to note that modifications to the formulas based on the original formulas can lead to better results.Loh et al. (2017) investigated different extraction methods for the preparation of five herbs (*Gastrodia elata*, *Uncaria rhynchophylla*, *Pueraria thomsonii*, *Panax notoginseng*, and *Alisma orientale*) and the combination ratio of the extracts to obtain a formulation with a better vasodilatory effect of the formula.

It is worth noting that a total of 67 species and 9 varieties of *Gastrodia* plants have been identified, but only one species, *G. elata*, is included in the Chinese Pharmacopoeia, and its medicinal part is the tuber. Therefore, the current study primarily focuse on the tuber of *G. elata*. Nevertheless, the Materia Medica states that both the leaves and stems of *G. elata* are also considered medicinal parts of the liver meridian and are utilized to treat diseases caused by wind. Jia et al. (2018) and Wang et al. 2020. demonstrated that gastrodin extracted from *G. elata* stalks possessed bacteriostatic and anticonvulsant effects. In addition, there are notable chemical and pharmacological similarities among species within the same genus. Therefore, investigating the chemical composition and pharmacological activity of other *Gastrodia* species is meaningful and may lead to the discovery of new compounds with beneficial properties.

To present, 630 different chemical constituents have been identified or isolated from *G. elata*, including volatile constituents, trace elements aromatics, steroids, organic acids and esters, saccharides and their glycosides, amino acids and polypeptides, and others. Among them, phenolic compounds, and polysaccharides are the main active compounds that promote its pharmacological activity. Specifically gastrodin, 4-HBA, and parishins canserve as characterization index to evaluate *G. elata* (Ji et al., 2024). This has led to a great deal of attention being paid to the pharmacological effects of gastrodin, 4-HBA and parshins, which has resulted in the effects of the other chemical components being overlooked. Modern pharmacological studies have shown that *G. elata* possesses a variety of beneficial pharmacological properties for organisms, such as anti-anxiety and antidepressant activities, treatment of neurodegenerative diseases, anticonvulsive activities, and improvement of memory activities. Although *G.elata* has a wealth of pharmacological activities and has been studied mainly in mice, rats, Drosophila and cells, its clinical applications have rarely been described, leading to a lack of clarity as to the exact mechanism. It is important to note that while phytochemical and pharmaceutical studies performed in the past have demonstrated many ethnopharmacological benefits of *G. elata* in the treatment of different diseases. However, following a long period of clinical application and research found that *G. elata* has a certain degree of toxicity, poisoning dose of more than 40 g (fresh *G. elata*), an incubation period of 1–6 h. Therefore, adults should intake no more than 12 g of *Gastrodiae* Rhizoma daily to exert a modest effect on their health and a high level of safety (Shangguan et al., 2022).

Thus, although the study of *G. elata* in terms of clinical, chemical composition, and modern pharmacological activity is widely involved, there are some obvious drawbacks. (1) Most classical formulas have fewer studies on animal or cellular modelling mechanisms, leaving a gap in the constitutive relationship between formulas and pharmacological activity, which leads to the failure of classical formulas to achieve higher therapeutic efficacy and fewer side effects. (2) Except for *G. elata* tubers, which are used as a raw material for traditional Chinese medicine and food, there is almost no research on other *Gastrodia* species and other parts. In order to fully exploit the medicinal and food potential of *Gastrodia*, it is necessary to expand the study of its constituents to include other *Gastrodia* species and non-medicinal parts, to fully utilise the resources of *Gastrodia*. (3) Most pharmacological studies have focused on extracts, gastrodin, 4-HBA and parishin, neglecting the study of other single chemical and volatile components. (4) *G. elata* is rich in polysaccharides, accounting for 21.6 %. Unfortunately, the structure of most of the polysaccharides in *G. elata* was not determined, making it difficult to analyse the conformational relationships of the polysaccharides in *G. elata*. (5) Modern pharmacological research has focused on models such as rats, mice and cells, with less clinical research, making it difficult to provide sufficient evidence to ensure drug efficacy and patient safety. (6) The evaluation system of *G. elata* toxicology is not perfect.

In summary, *G. elata* is a plant containing a variety of chemical and volatile constituents with well-defined biological functions that have been widely used in traditional Chinese medicine. Currently, research on *G. elata* focuses on important classical formulas, chemical composition and pharmacological activity. We have found that the pharmacology of *G. elata* and the expanding range of clinical applications of classical formulas are the most recent and important results in this field. Researchers have been most extensively involved in the study of the cardioprotective and neuroprotective potential of *G. elata*. In recent years, more and more pharmacological effects of *G. elata* have been explored. For instance, the anti-osteoporosis effect, anti-cancer effects, hepatoprotective and renoprotective abilities have been studied and have potential for development in the cosmetic industry. Preparations or prescriptions related to *G. elata* are used in traditional and clinical practice to treat a variety of conditions such as hypertension, Parkinson's and diabetes. The present studies on pharmacological activities and chemical constituents are mainly focused on the species *G. elata*. The studies on its pharmacological activities have focused on the extracts of *G. elata* tubers, gastrodin, 4-HBA and parshin. Therefore, future research can focus on other species of *Gastrodia*. There is also a need for more in-depth and detailed studies on the pharmacological activities of *G. elata*, such as enhancing the characterization of the polysaccharide structure, refining the constitutive relationship of the formulae, mining of the active ingredients, utilizing the non-medicinal parts and toxicological studies.

CRediT authorship contribution statement

Yingfeng Zhong: Writing – review & editing, Writing – original draft, Conceptualization. **Jieqing Li:** Validation, Investigation. **Honggao Liu:** Visualization, Resources. **Yuanzhong Wang:** Project administration, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by National Natural ScienceFoundation of China [GrantNumber: 82460746]; Special Program for the Major Science and Technology Projects of Yunnan Province [Grant Number: 202202AE090001]; National Natural ScienceFoundation of China [GrantNumber: 82460746]; Yunnan Provincial Department of Education Scientific and Technological Innovation Team for Development and Utilization of Gastrodia Resources(Grant Number: 2024); Zhaotong "Xingzhao Talent Support Program" Team Project(Grant Number: 2023-3).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2024.106086.

References

Abdel Salam, O., Youness, E., Mohammed, N., Morsy, S., Omara, E., Sleem, A., 2014. Citric acid effects on brain and liver oxidative stress in lipopolysaccharide-treated mice. J MedFood 17 (5), 588–598. https://doi.org/10.1089/jmf.2013.0065.

Ahmad, O., Wang, B., Ma, K.J., Deng, Y., Li, M.R., Yang, L.P., Yang, Y.Q., Zhao, J.Y., Cheng, L.J., Zhou, Q.Y., Shang, J., 2019. Lipid modulating anti-oxidant stress

activity of gastrodin on nonalcoholic fatty liver disease larval zebrafish model. Int Mol Sci20 (8), 1984. 10.3390/ijms20081984.
Ahn, E.K., Jeon, H.J., Lim, E.J., Jung, H.J., Park, E.H., 2007. Anti-inflammatory and anti-angiogenic activities of *Gastrodia elata* Blume. J Ethnopharmacol 110 (3), 476–482. https://doi.org/10.1016/j.jep.2006.10.006.
An, J., Cheng, L., Yang, L., Song, N., Zhang, J., Ma, K., Ma, J., 2021. P- hydroxybenzyl alcohol alleviates oxidative stress in a nonalcoholic fatty liver disease larval zebrafish model and a BRL-3A hepatocyte via the Nrf2 pathway. Frot Pharmacol12. 10.3389/fphar.2021.646239.
Bates, G.P., Dorsey, R., Gusella, J.F., Hayden, M.R., Kay, C., Leavitt, B.R., 2015. Huntington's disease.
Chen, S.P., 2019b. Purification structure characterization and antitumoractivity study of polysaccharides from *Gastrodiae elata*. Shandong University of Chinese Medicine, in.
Chen, X., Cao, D.X., Zhou, L., Jin, H.Y., Dong, Q., Yao, J., Ding, K., 2011. Structure of a polysaccharide from *Gastrodia elata* Bl. And oligosaccharides prepared thereof with anti-pancreatic cancer cell growth activities. Carbohydr Polym. 86 (3), 1300–1305. https://doi.org/10.1016/j.carbpol.2011.06.029.
Chen, C., Fu, Y.H., Li, M.H., Ruan, L.Y., Xu, H., Chen, J.F., Zhao, W.L., Meng, H.H., Xing, Y.X., Hong, W., 2018a. Nuclear magnetic resonance-based metabolomics approach to evaluate preventive and therapeutic effects of *Gastrodia elata* Blume on chronic atrophic gastritis. J Pharm Biomed 164, 231–240. https://doi.org/10.1016/j.jpba.2018.10.035.
Chen, S.Y., Geng, C.A., Ma, Y.B., Chen, J.J., 2019a. Melatonin receptors agonistic activities of phenols from *Gastrodia elata*. Nat Prod Bioprospect. 9 (4), 297–302. https://doi.org/10.1007/s13659-019-0213-2.
Chen, S.Y., Geng, C.A., Ma, Y.B., Huang, X.Y., Yang, X.T., Su, L.H., He, X.F., Li, T.Z., Deng, Z.T., Gao, Z., Zhang, X.M., Chen, J.J., 2019b. Polybenzyls from *Gastrodia elata*, their agonistic effects on melatonin receptors and structure-activity relationships. Bioorg Med Chem. 27 (15), 3299–3306. https://doi.org/10.1016/j.bmc.2019.06.008.
Chen, J., Gu, Y.T., Xie, J.J., Wu, C.C., Xuan, J., Guo, W.J., Yan, Y.Z., Chen, L., Wu, Y.S., Zhang, X.L., Xiao, J., Wang, X.Y., 2018c. Gastrodin reduces iL-1β-induced apoptosis, inflammation, and matrix catabolism in osteoarthritis chondrocytes and attenuates rat cartilage degeneration *in vivo*. Biomed Pharmacother. 97, 642–651. https://doi.org/10.1016/j.biopha.2017.10.067.
Chen, S., Hao, X., Yu, L., Zhang, P., Cao, W., Chen, H., Zhu, D., 2017b. Gastrodin causes vasodilation by activating k(ATP) channels in vascular smooth muscles via PKA-dependent signaling pathway. Transduct Res. 37 (6), 543–549. https://doi.org/10.1080/10799893.2017.1369118.
Chen Hong, S., Bo, Z., Chen, C., 2022. Research progress on safety evaluation of edible and medicinal *Gastrodia elata*. *J. Food Saf. Qual.* 13 (18), 5946–5954.
Chen, F., Jiang, N., Zhang, Y.W., Xie, M.Z., Liu, X.M., 2023. Protective effect of *Gastrodia elata* Blume ameliorates simulated weightlessness-induced cognitive impairment in mice. Life Sci Space Res 36, 1–7. https://doi.org/10.1016/j.lssr.2022.10.001.
Chen, W.C., Lai, Y.S., Lin, S.H., Panyod, S., Ho, C.T., Sheen, L.Y., 2016. Anti-depressant effects of *Gastrodia elata* Blume and its compounds gastrodin and 4-hydroxybenzyl alcohol, via the monoaminergic system and neuronal cytoskeletal remodeling. J Ethnopharmacol. 182, 190–199. https://doi.org/10.1016/j.jep.2016.02.001.
Chen, C., Li, X.X., Fu, Y.D., Liu, X., Zheng, H.X., Wu, S.Q., Li, X.D., 2018b. Study on the antibacterial activity of GE polysaccharides from Hanzhong. China. *Jiangsu Agricultural Sciences* 46 (11), 156–159. https://doi.org/10.15889/j.issn.1002-1302.2018.11.041.
Chen, L.M., Liu, X.N., Wang, H., Qu, M., 2017a. Gastrodin attenuates pentylenetetrazole-induced seizures by modulating the mitogen-activated protein kinase-associated inflammatory responses in mice. Neurosci Bull 33 (3), 264–272. https://doi.org/10.1007/s12264-016-0084-z.
Chen, W.C., Tseng, T.S., Hsiao, N.W., Lin, Y.L., Wen, Z.H., Tsai, C.C., Lee, Y.C., Lin, H.H., Tsai, K.C., 2015. Discovery of highly potent tyrosinase inhibitor, T1, with significant anti-melanogenesis ability by zebrafish in vivo assay and computational molecular modeling. Sci Rep. 5 (1). https://doi.org/10.1038/srep07995.
Chen, S.P, 2019. Purification, structure characterization and antitumor activity study of polysaccharides from *Gastrodia elata*. in: Shandong University of Chinese Medicine. 10.27282/d.cnki.gsdzu.2019.000051.
Cheng, P., 2019. Systematic Chinese medicine. China Press of Traditional Chinese Medicine.
Chik, S.C.C., Or, T.C.T., Luo, D., Yang, C.L.H., Lau, A.S.Y., 2013. Pharmacological effects of active compounds on neurodegenerative disease with Gastrodia and Uncaria decoction, a commonly used poststroke decoction. *Scientific World Journal* 2013, 1–22. https://doi.org/10.1155/2013/896873.
Choi, J.H., Lee, D.U., Department, O.B., Dongguk, U., 2006. A new citryl glycoside from *Gastrodia elata* and its inhibitory activity on GABA transaminase. Chem Pharm Bull. 54 (12), 1720-1721. 10.1248/cpb.54.1720.
Lori A. Coburn, M., Sara N. Horst, M., Margaret M. Allaman, B., Caroline T. Brown, M., Christopher S. Williams, M.P., Mallary E. Hodges, M., Jennifer P. Druce, B., 2016. L-arginine availability and metabolism is altered in ulcerative colitis. Inflamm Bowe Dis 22 (8), 1847-1858. 10.1097/MIB.0000000000000790.
Committee, N.P., 2015. Pharmacopoeia of the people's republic of China. China Medical Science and Technology Press, Beijing.
Committee, N.P., 2020. Pharmacopoeia of the people's republic of China. China Medical Publishing House, Beijing.
Dai, R., Wang, T., Si, X.Q., Jia, Y.Y., Wang, L.L., Yuan, Y., Lin, Q., Yang, C., 2017. Vasodilatory effects and underlying mechanisms of the ethyl acetate extracts from *Gastrodia elata*. Can J Physiol Pharmacol. 95 (5), 564–571. https://doi.org/10.1139/cjpp-2016-0407.
Dang, X.J., Wang, Y.X., Jiao, H.S., 2017. Effects of Gastrodia capsule and gastrodin combined with carbamazepine on the hippocampal neurons and the expression level of mrp1 gene of PTZ-kindled mice. *Chinese Journal of New Drugs* 26 (13), 1556–1561.
Deng, L.H., Li, L., Zhai, Y., Michael, S., Yang, C.Y., Guo, R., Chen, S.F., Fan, G.W., Zhao, Y.Q., Liu, W., 2020. Tianma gouteng decoction exerts cardiovascular protection by upregulating opg and trail in spontaneously hypertensive rats. Evid Based Complement Alternat Med. 2020 (1). https://doi.org/10.1155/2020/3439191.
Deng, L., Liu, W., Xu, Q., Guo, R., Zhang, D., Ni, J., Li, L., Cai, X., Fan, G., Zhao, Y., 2022. Tianma Gauteng decoction regulates oxidative stress and inflammation in angina-induced hypertensive mice via transcription factor EB to exert anti-hypertension effect. Biomed Pharmacother. 145, 112383. https://doi.org/10.1016/j.biopha.2021.112383.
Dian, J.X., Chen, S.L., Zhou, T.H., Zhu, C.G., 2017. Research progress on germplasm resources of *Gastrodia elata* Bl. Front Cell Infect Microbiol. 6), 100–101, 107. https://doi.org/10.3969/j.issn.1007-5739.2017.06.066.
Ding, Y.F., Bao, X.M., Lao, L.F., Ling, Y.X., Wang, Q.W., Xu, S.J., 2019. P-hydroxybenzyl alcohol prevents memory deficits by increasing neurotrophic factors and decreasing inflammatory factors in a mice model of Alzheimer's disease. *J. Alzheimers Dis.* 67 (3), 1007–1019. https://doi.org/10.3233/JAD-180910.
Ding, X.M., Liu, Z.L., Liu, Y., Xu, B.Y., Chen, J., Pu, J.Z., Wu, D.L., Yu, H., Jin, C.S., Wang, X.L., 2022. Comprehensive evaluation of the mechanism of *Gastrodia elata* Blume in ameliorating cerebral ischemia-reperfusion injury based on integrating fecal metabonomics and 16s rDNA sequencing. *Front. Cell. Infect. Microbiol.* 12. https://doi.org/10.3389/fcimb.2022.1026627.
Dong, H., Zhang, S., Du, W., Cong, H., Zhang, L., 2020. Pharmacodynamics and metabonomics study of Tianma Gauteng decoction for treatment of spontaneously hypertensive rats with liver-yang hyperactivity syndrome. J Ethnopharmacol. 253, 112661. https://doi.org/10.1016/j.jep.2020.112661.
Du, F.T., Wang, X.N., Shang, B., Fang, J.F., Xi, Y.T., Li, A.J., Diao, Y.Z., 2016. Gastrodin ameliorates spinal cord injury via antioxidant and anti-inflammatory effects. Acta Biochim Pol. 63 (3), 10.18388/abp.2016_1272.
Du, Q.Q., Yang, Y.H., Xu, T.R., Wang, Z.Q., Xiang, C., 2022. An analysis of the formation causes of *Gastrodia elata* Bl authenticity based on bibliometric. Journal of Kunming University of Science and Technology (natural Science Edition) 47 (6), 93–107. https://doi.org/10.16112/j.cnki.53-1223/n.2022.06.253.
Duan, H., Zhou, Y.X., Zhou, S.Q., Yan, W.J., 2023. Application of *Gastrodia elata* in functional food in China. Scienceand Technology of Food Industry. 44 (9), 403–412. https://doi.org/10.13386/j.issn1002-0306.2022050051.
Farooq, U., Pan, Y.J., Lin, Y.F., Wang, Y., Osada, H., Xiang, L., Qi, J.H., 2019. Structure characterization and action mechanism of an antiaging new compound from *Gastrodia elata* Blume. Oxid Med Cell Longev. 2019, 1–10. https://doi.org/10.1155/2019/5459862.
Fasina, O.B., Wang, J.Y., Mo, J.X., Osada, H., Ohno, H., Pan, W.S., Xiang, L., Qi, J.H., 2022. Gastrodin from *Gastrodia elata* enhances cognitive function and neuroprotection of ad mice via the regulation of gut microbiota composition and inhibition of neuron inflammation. Front Pharmacol. 13. https://doi.org/10.3389/fphar.2022.814271.
Fiest, K.M., Sauro, K.M., Wiebe, S., Patten, M.S.B., Kwon, C., 2017. Prevalence and incidence of epilepsy a systematic review and meta-analysis of international studies. *Neurology* 88 (3), 296. https://doi.org/10.1212/WNL.0000000000003509.
Fu, S.S., Chen, L.L., Wu, Y.Z., Tang, Y., Tang, L., Zhong, Y.K., Wang, S.Y., Liu, H.Q., Wang, X.B., Chen, A.H., 2018. Gastrodin pretreatment alleviates myocardial ischemia/reperfusion injury through promoting autophagic flux. Biochem Biophys Res Commun. 503 (4), 2421–2428. https://doi.org/10.1016/j.bbrc.2018.06.171.
Gao, J.M., Lu, G.H., Li, Y.R., Zhou, X.M., 2014. Effects of gastrodin against tert-butyl hydroperoxide-induced injury in HL7702 cells via SIRT1/PGC-1α pathway. *Pharmacology and Clinics of Chinese Medicines* 30 (4), 32-35. 10.13412.cnki.zyy1.2014.04.011.
Gao, M., Wu, Y., Yang, L., Chen, F., Li, L.Q., Li, Q.J., Wang, Y., Li, L., Peng, M., Yan, Y.F., Yang, J., Yang, X.S., 2023. Anti-depressant-like effect of fermented *Gastrodia elata* Bl. By regulating monoamine levels and BDNF/NMDAR pathways in mice. J Ethnopharmacol. 301, 115832. https://doi.org/10.1016/j.jep.2022.115832.
Ghazi, L., Drawz, P., 2017. Advances in understanding the renin-angiotensin-aldosterone system (RAAS) in blood pressure control and recent pivotal trials of RAAS blockade in heart failure and diabetic nephropathy. *F1000 Research* 6, 297. 10.12688/f1000research.9692.1.
Gong, X., Ivanov, V.N., Hei, T.K., 2016. 2,3,5,6-tetramethylpyrazine (TMP) down-regulated arsenic-induced heme oxygenase-1 and ARS2 expression by inhibiting Nrf2, Nf-kB, AP-1 and MAPK pathways in human proximal tubular cells. Arch Toxicol. 90 (9), 2187–2200. https://doi.org/10.1007/s00204-015-1600-z.
Gong, C.X., Ma, C., Irge, D.D., Li, S.M., Chen, S.M., Zhou, S.X., Zhao, X.X., Li, H.Y., Li, J. Y., Yang, Y.M., 2023. *Gastrodia elata* and parishin ameliorate aging induced 'leaky gut' in mice: correlation with gut microbiota. Biomed J. 46 (4), 100547. https://doi.org/10.1016/j.bj.2022.07.001.
Guan, H., Ling, X., Xu, J., Zhu, Y.Q., Zhang, J.Y., Liu, X.Y., 2022. Structural characterization of polysaccharide derived from *Gastrodia elata* and its immunostimulatory effect on raw264.7 cells. *Molecules* 27 (22), 8059. https://doi.org/10.3390/molecules27228059.
Guan, P., Shi, J.M., Gao, Y.Q., 2008. Study on the volatile components from *Gastrodia elata* Bl. F. Glauca s. Chow and the antibiotic activities. *Journal of Southwest China Normal University (naturel Science Edition)* 33 (1), 101–105.
Guo, Q., Wang, Y., Lin, S., Zhu, C.G., Chen, M.H., Jiang, Z.B., Xu, C.B., Zhang, D., Wei, H. L., Shi, J.G., 2015a. 4-hydroxybenzyl-substituted amino acid derivatives from *Gastrodia elata*. Acta Pharm Sin *B* 5 (4), 350–357. https://doi.org/10.1016/j.apsb.2015.02.002.

Guo, Q.L., Wang, Y.N., Zhu, C.G., Chen, M.H., Jiang, Z.B., Chen, N.H., Song, X.Y., Zhang, M.J., Shi, J.G., 2015b. 4-hydroxybenzyl-substituted glutathione derivatives from *Gastrodia elata*. J Asian Nat Prod Res. 17 (5), 439–454. https://doi.org/10.1080/10286020.2015.1040000.

Han, Y.J., Je, J.H., Kim, S.H., Ahn, S.M., Kim, H.N., Kim, Y.R., Choi, Y.W., Shin, H.K., Choi, B.T., 2014. *Gastrodia elata* shows neuroprotective effects via activation of PI3k signaling against oxidative glutamate toxicity in HT22 cells. *Am. J. Chin. Med.* 42 (04), 1007–1019. https://doi.org/10.1142/S0192415X14500633.

Han, Y., Ling, Q., Wu, L., Wang, X., Wang, Z., Chen, J., Zheng, Z., Zhou, Z., Jia, L., Li, L., Wang, B., 2023. Akkermansia muciniphila inhibits nonalcoholic steatohepatitis by orchestrating tlr2-activated γδt17 cell and macrophage polarization. Gut Microbes 15 (1). https://doi.org/10.1080/19490976.2023.2221485.

Hayashi, J., Sekine, T., Deguchi, S., Lin, Q., Horie, S., Tsuchiya, S., Yano, S., Watanabe, K., Ikegami, F., 2002. Phenolic compounds from Gastrodia rhizome and relaxant effects of related compounds on isolated smooth muscle preparation. Phytochemistry 59 (5), 513–519. https://doi.org/10.1016/s0031-9422(02)00008-0.

He, J., Li, X., Yang, S., Li, Y., Lin, X., Xiu, M., Li, X., Liu, Y., 2021. Gastrodin extends the lifespan and protects against neurodegeneration in the drosophila PINK1 model of Parkinson's disease. *Food Funct.* 12 (17), 7816–7824. https://doi.org/10.1039/d1fo00847a.

He, S.C., Niu, Q., Niu, P.Y., He, M.W., Sun, X.S., Shao, F.G., Ge, S., Opler, M., 2008. Protective effects of *Gastrodia elata* on aluminum-chloride-induced learning impairments and alterations of amino acid neurotransmitter release in adult rats. Restor Neurol Neurosci. 26 (6), 467–473.

He, F., Wu, C.L., Li, P., Li, N.Z., Zhang, D., Zhu, Q.Q., Ren, W.K., Peng, Y.Y., Lidong, Z., Zhai, L.D., 2018. Functions and signaling pathways of amino acids in intestinal inflammation. Biomed Res Int 1–13. https://doi.org/10.1155/2018/9171905.

Heo, J.C., Woo, S.U., Son, M., Park, J.Y., Choi, W.S., Chang, K.T., Kim, S.U., Yoon, E.K., Kim, Y.H., Shin, H.M., Lee, S.H., 2007. Anti-tumor activity of *Gastrodia elata* Blume is closely associated with a GTP-ras-dependent pathway. Oncol Rep. 18 (4), 849–853.

Heusch, G., 2020. Myocardial ischaemia–reperfusion injury and cardioprotection in perspective. *Nat. Rev. Cardiol.* 1–17. https://doi.org/10.1038/s41569-020-0403-y.

Himoto, T., Masaki, T., 2020. Current trends of essential trace elements in patients with chronic liver diseases. Nutrients 12 (7), 2084. https://doi.org/10.3390/nu12072084.

Hong, Q., Bo, Y., Chao, P.Z., Zhang, Z., Kan, D., 2010. WSS25 inhibits growth of xenografted hepatocellular cancer cells in nude mice by disrupting angiogenesis via blocking bone morphogenetic protein (BMP)/Smad/Id1 signaling. J Biol Chem. 285 (42), 32638–32646. https://doi.org/10.1074/jbc.M110.105544.

Hong, S.I., Peyton, L., Chern, Y.J., Choi, D.S., 2019. Novel adenosine analog,N^6-(4-hydroxybenzyl)-adenosine, dampens alcohol drinking and seeking behaviors. J Pharmacol Exp Ther. 371 (2), 260–267. https://doi.org/10.1124/jpet.119.261529.

Hou, J.Y., Fang, T.H., 2012. Pharmacology of Chinese materia medica. China Tradi_x0002_tional Chinese. Medicine Press, Beijing.

Hou, M.N., Hou, S.P., 2018. Experimental study on the antioxidant activity of polysaccharides of *Gastrodia elata* from Shaanxi province. *Shaanxi. Journal of Agricultural Sciences* 64 (6), 31–32, 71. https://doi.org/10.3969/j.issn.0488-5368.2018.06.010.

Hsu, W.H., Huang, N.K., Shiao, Y.J., Lu, C.K., Chao, Y.M., Huang, Y.J., Yeh, C.H., Lin, Y. L., 2021. *Gastrodiae* rhizoma attenuates brain aging via promoting neuritogenesis and neurodifferentiation. Phytomedicine. 87, 153576. https://doi.org/10.1016/j.phymed.2021.153576.

Hu, F., Chen, H., Huang, B., Fang, S., Liu, Y., Shen, K., 2023. Application potential of *Gastrodia elata* in cosmetics. Academic Periodical of Farm Products Processing (4), 96-100. 10.16693/j.cnki.1671-9646(X).2023.02.050.

Huang, N.K., Chern, Y., Fang, J.M., Lin, C.I., Chen, W.P., Lin, Y.L., 2007. Neuroprotective principles from *Gastrodia elata*. J Nat Prod. 70 (4), 571–574. https://doi.org/10.1021/np0605182.

Huang, Y.J., Choong, L.X.C., Panyod, S., Lin, Y.E., Huang, H.S., Lu, K.H., Wu, W.K., Sheen, L.Y., 2021. *Gastrodia elata* Blume water extract modulates neurotransmitters and alters the gut microbiota in a mild social defeat stress-induced depression mouse model. Phytother Res. 35 (9), 5133–5142. https://doi.org/10.1002/ptr.7091.

Huang, L.Q., Li, Z.F., Wang, Q., Cui, Y.R., Ou, Y.H., Xiong, S.S., Huang, W.P., Feng, Y.L., Yang, S.L., 2015. Two new furaldehyde compounds from the rhizomes of *Gastrodia elata*. Nat Prod Res. 17 (4), 352–356. https://doi.org/10.1080/10286020.2014.984698.

Huang, H., Zhang, Y.W., Yao, C.H., He, Q.H., Chen, F., Yu, H., Lu, G.H., Jiang, N., Liu, X. M., 2022. The effects of fresh *Gastrodia elata* Blume on the cognitive deficits induced by chronic restraint stress. Front Pharmacol. 13. https://doi.org/10.3389/fphar.2022.890330.

Huo, J.Y., Lei, M., Li, F.F., Hou, J.J., Zhang, Z.J., Long, H.L., Zhong, X.C., Liu, Y.M., Xie, C., 2021a. Structural characterization of a polysaccharide from *Gastrodia elata* and its bioactivity on gut microbiota. *Molecules* 26 (15), 4443. https://doi.org/10.3390/molecules26154443.

Huo, J.Y., Lei, M., Zhou, Y., Zhong, X.C., Liu, Y.M., Hou, J.J., Long, H.L., Zhang, Z.J., Tian, M.H., Xie, C., Wu, W.Y., 2021b. Structural characterization of two novel polysaccharides from *Gastrodia elata* and their effects on Akkermansia muciniphila. Int J Biol Macromol. 186, 501–509. https://doi.org/10.1016/j.ijbiomac.2021.06.157.

Hwang, S.M., Lee, Y.J., Kang, D.G., Lee, H.S., 2009. Anti-inflammatory effect of *Gastrodia elata* rhizome in human umbilical vein endothelial cells. *Am. J. Chin. Med.* 37 (02), 395–406. https://doi.org/10.1142/S0192415X09006916.

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

Jeon, Y.D., Lee, J.H., Park, M.R., Lim, J.Y., Kang, S.H., Kim, D.K., Lee, Y.M., 2021. *Gastrodia elata* Blume and zanthoxylum schinifolium siebold & zucc mixed extract suppress platelet aggregation and thrombosis. Medicina 57 (10), 1128. https://doi.org/10.3390/medicina57101128.

Ji, Z.Y., Gao, L.H., Qing, L.J., Zhong, W.Y., 2024. Research progress on chemical constituents and pharmacological and activity of *Gastrodia elata* Blume quality marker. Journal of Speciality Research 1–12, 10.16720/j.cnki.tcyj.2024.143.

Ji, N., Liu, P., Zhang, N., Yang, S., Zhang, M., 2022. Comparison on bioactivities and characteristics of polysaccharides from four varieties of *Gastrodia elata* Blume. Front Chem. 10, 956724. https://doi.org/10.3389/fchem.2022.956724.

Jia, M.R., Li, X.W., 2005. Dictionary of Chinese ethnomedicine. China Science and Medicine Press, Beijing.

Jia, C.Q., Ma, R., Lei, R.L., Gui, Q.B., Yu, J.S., 2018. Preliminary study on antimicrobial activity of chemical composition of *Gastrodia* stems. *Yunnan Chemical Technology* 45 (7), 68–69. https://doi.org/10.3969/j.issn.1004-275X.2018.07.029.

Jia Xin, G., Jia, X., Li Shi, J., Ji Hai, G., Chao Long, R., Lei Lei, Z., 2022. Analysis on development status of *Gastrodiae* rhizoma health food. *Chin. Tradit. Herb. Drug* 53 (7), 2247–2254. https://doi.org/10.7501/j.issn.0253-2670.2022.07.034.

Jiang, T., Cheng, H., Su, J.J., Wang, X.C., Wang, Q.X., Chu, J., Li, Q.L., 2020. Gastrodin protects against glutamate-induced ferroptosis in HT-22 cells through Nrf2/HO-1 signaling pathway. *Toxicol. in Vitro* 62, 104715. https://doi.org/10.1016/j.tiv.2019.104715.

Jiang, G.L., Hu, Y.Q., Liu, L.L., Cai, J.L., Peng, C., Li, Q.L., 2014. Gastrodin protects against mpp+-induced oxidative stress by up regulates heme oxygenase-1 expression through p38 MAPK/Nrf2 pathway in human dopaminergic cells. Neurochem Int 75, 75–88.

Jiang, J., Huang, D., Li, Y., Gan, Z., Li, H., Li, X., Bian, K., Ke, Y., Jae, Y.C., Cho, J.Y., 2019. Heart protection by herb formula Banxia Baizhu Tianma decoction in spontaneously hypertensive rats. Evid Based Complement Alternat Med. 2019, 5612910–5612929. https://doi.org/10.1155/2019/5612929.

Jiang, H.M., Yang, X.Q., Liu, H.L., 2012. Contents of gastrodin from different growth periods and different tissues of Hong *Gastrodia* in Zhejiang county of Guizhou province. *Guizhou Agricultural Sciences* 40 (5), 43–44. https://doi.org/10.3969/j.issn.1001-3601.2012.05.014.

Jiang, N., Yao, C., Zhang, Y., Chen, Y.Z., Chen, F., Luo, Y., Choudhary, M.I., Pan, R., Liu, X., 2024. Antidepressant effects of parishin C in chronic social defeat stress-induced depressive mice. J Ethnopharmacol. 325, 117891. https://doi.org/10.1016/j.jep.2024.117891.

Jin, M., He, Q.X., Zhang, S.S., Cui, Y.X., Han, L.W., Liu, K.C., 2018. Gastrodin suppresses pentylenetetrazole-induced seizures progression by modulating oxidative stress in zebrafish. Neurochem Res. 43 (4), 904–917. https://doi.org/10.1007/s11064-018-2496-9.

Jin, J., Li, Z., Yang, X., Yin, A.H., Yang, L.Y., Liu, J., 2021. Bioinformatics analysis of main volatile components of *Gastrodia elata* Bl. From Guizhou province. *Information On Traditional. Chin. Med.* 38 (1), 17–23. https://doi.org/10.19656/j.cnki.1002-2406.210105.

Jing, C., Liu, S.X., Hu, G.H., Zhang, X.Y., Yen, X., 2004. Gastrodin injection in the treatment of vertigo: a multi-center single-blind randomized controlled trial. *Chinese J Evidence-Based Medicine* 4 (12), 864–870.

Jou, S.B., Tsai, C.J., Fang, C.Y., Yi, P.L., Chang, F.C., 2021. Effects of n6-(4-hydroxybenzyl) adenine riboside in stress-induced insomnia in rodents. J Sleep Res. 30 (1). https://doi.org/10.1111/jsr.13156.

Jung, T.Y., Suh, S., Lee, H., Kim, I.S., Kim, H.J., Yoo, H.S., Lee, S.R., 2007. Protective effects of several components of *Gastrodia elata* on lipid peroxidation in gerbil brain homogenates. *Phytother. Res.* 21, 960–964. https://doi.org/10.1002/ptr.2193.

Jung, J.W., Yoon, B.H., Oh, H.R., Ahn, J.H., Kim, S.Y., Park, S.Y., Ryu, J.H., 2006. Anxiolytic-like effects of *Gastrodia elata* and its phenolic constituents in mice. *Biol. Pharm. Bull.* 29 (2), 261–265. https://doi.org/10.1248/bpb.29.261.

Kam, K.Y., Yu, S.J., Jeong, N., Hong, J.H., Jalin, A.M.A.A., Lee, S., Choi, Y.W., Lee, C.K., Kang, S.G., 2011. P-hydroxybenzyl alcohol prevents brain injury and behavioral impairment by activating Nrf2, PDI, and neurotrophic factor genes in a rat model of brain ischemia. Mol Cells. 31 (3), 209–215. https://doi.org/10.1007/s10059-011-0028-4.

Kang, C.W., Han, Y.E., Kim, J., Oh, J.H., Cho, Y.H., Lee, E.J., 2017. 4-hydroxybenzaldehyde accelerates acute wound healing through activation of focal adhesion signalling in keratinocytes. Sci Rep. 7 (1). https://doi.org/10.1038/s41598-017-14368-y.

Kenji, S., 2022. A new variety of the mycoheterotrophic plant Gastrodia takeshimensis (Orchidaceae) from Yakushima island, japan. *Acta Phytotax Geobot* 73 (3), 211–217. https://doi.org/10.18942/apg.202209.

Kim, N.H., Xin, M.J., Cha, J.Y., Ji, S.J., Kwon, S.U., Jee, H.K., Park, M.R., Park, Y.S., Kim, C.T., 2017b. Antitumor and immunomodulatory effect of *Gastrodia elata* on colon cancer *in vitro* and *in vivo*. *Am. J. Chin. Med.* 45 (02), 319–335. https://doi.org/10.1142/S0192415X17500203.

Kim, M.J., Yang, H.J., Moon, B.R., Kim, J.E., Kim, K.S., Park, S., Deyhim, F., 2017a. *Gastrodia elata* Blume rhizome aqueous extract improves arterial thrombosis, dyslipidemia, and insulin response in testosterone-deficient rats. Evid Based Complement Alternat Med. 2017, 1–11. https://doi.org/10.1155/2017/2848570.

Kryger, M.H., Roth, T., Dement, W.C., 2006. The principles and practice of sleep medicine, fourth edition. Edited by Michael J. Aminof.

Kuijpers, M.J., van der Meijden, P.E., Feijge, M.A., Mattheij, N.J., May, F., Govers-Riemslag, J., Meijers, J.C., Heemskerk, J.W., Renne, T., Cosemans, J.M., 2014. Factor xii regulates the pathological process of thrombus formation on ruptured plaques. Arterioscler Thromb Vasc Biol. 34 (8), 1674–1680. https://doi.org/10.1161/ATVBAHA.114.303315.

Lai, Y., Wang, R., Li, W., Zhu, H., Fei, S., Shi, H., Lu, N., Ung, C.O.L., Hu, H., Han, S., 2022. Clinical and economic analysis of gastrodin injection for dizziness or vertigo: a retrospective cohort study based on electronic health records in China. *Chin Med-Uk* 17 (1) (6). https://doi.org/10.1186/s13020-021-00561-9.

Lambros, M., Tran, T.H., Fei, Q., Nicolaou, M., 2022. Citric acid: a multifunctional pharmaceutical excipient. *Pharmaceutics* 14 (5), 972. https://doi.org/10.3390/pharmaceutics14050972.

Lavie, C.J., Milani, R.V., Ventura, H.O., 2009. Obesity and cardiovascular disease. J Am Coll Cardiol. 53 (21), 1925–1932. https://doi.org/10.1016/j.jacc.2008.12.068.

Lee, Y.J., Hwang, S.M., Kang, D.G., Kim, J.S., Lee, H.S., 2009. Effect of *Gastrodia elata* on tumor necrosis factor-alpha-induced matrix metalloproteinase activity in endothelial cells. J Nat Med. 63 (4), 463–467. https://doi.org/10.1007/s11418-009-0352-6.

Lee, J.Y., Jang, Y.W., Kang, H.S., Moon, H., Sim, S.S., Kim, C.J., 2006. Anti-inflammatory action of phenolic compounds from *Gastrodia elata* root. Arch Pharm Res. 29 (10).

Lee, O.H., Kim, K.L., Han, C.K., Kim, Y.C., Hong, H.D., 2012. Effects of acidic polysaccharides from *Gastrodia* rhizome on systolic blood pressure and serum lipid concentrations in spontaneously hypertensive rats fed a high-fat diet. *International Journal of Molecular Sciences* 13 (1), 698–709. https://doi.org/10.3390/ijms13010698.

Lee, D.S., Ko, W., Song, B.K., Son, I., Kim, D.W., Kang, D.G., Lee, H.S., Oh, H., Jang, J.H., Kim, Y.C., Kim, S., 2016. The herbal extract KCHO-1 exerts a neuroprotective effect by ameliorating oxidative stress via heme oxygenase-1 upregulation. Mol Med Rep. 13 (6), 4911–4919. https://doi.org/10.3892/mmr.2016.5129.

Lee, D.K., Lim, D.K., Um, J.A., Lim, C.J., Hong, J.Y., Yoon, Y.A., Ryu, Y., Kim, H.J., Cho, H.J., Park, J.H., Seo, Y.B., Kim, K., Lim, J., Kwon, S.W., Lee, J., 2014. Evaluation of four different analytical tools to determine the regional origin of *Gastrodia elata* and Rehmannia glutinosa on the basis of metabolomics study. *Molecules* 19 (5), 6294–6308. https://doi.org/10.3390/molecules19056294.

Lee, Y.K., Woo, M.H., Kim, C.H., Kim, Y., Lee, S.H., Jeong, B.S., Chang, H.W., Son, J.K., 2007. Two new benzofurans from *Gastrodia elata* and their DNA topoisomerases I and ii inhibitory activities. Planta Med 73 (12), 1287–1291. https://doi.org/10.1055/s-2007-981619.

Lertnitikul, N., Pattamadilok, C., Chansriniyom, C., Suttisri, R., 2020. A new dihydrophenanthrene from *cymbidium finlaysonianum* and structure revision of cymbinodin-a. J Asian Nat Prod Res. 22 (1), 83–90. https://doi.org/10.1080/10286020.2018.1540605.

Li, Z.Z., 2013. Lei gong pao zhi yao xing jie. People's Military Medical Press, Beijing.

Li, D.G., 2019. Precious drugs in rhyme. China Press of Traditional Chinese Medicine, Beijing, Classified according to nature to drug.

Li, H.T., Duan, R.T., Liu, T., Yang, R.N., Wang, J.P., Liu, S.X., Yang, Y.B., Zhou, H., Ding, Z.T., 2020b. Penctrimertone, a bioactive citrinin dimer from the endophytic fungus penicillium sp. T2-11. *Fitoterapia* 146, 104711. https://doi.org/10.1016/j.fitote.2020.104711.

Li, Z.B., Deng, W., Xu, D.D., Zhou, L., Yang, Z.F., Zhang, C.H., 2016. Comparative study on the morphological histology of different varieties of *Gastrodia elata*. *West China Journal of Pharmaceutical Sciences* 31 (1), 51-53. 10.13375/j.cnki.wcjps.2016.01.016.

Li, Y., Ji, Y.Y., Li, F.L., 2023. A review: mechanism and prospect of gastrodin in prevention and treatment of t2dm and covid-19. Heliyon. 9 (11), e21218. https://doi.org/10.1016/j.heliyon.2023.e21218.

Li, M., Kang, R.X., Jia, S.B., Shi, J.G., Liu, G.T., Zhang, J.J., 2014. Sedative and hypnotic activity of N^6-(3-methoxyl-4-hydroxybenzyl) adenine riboside (B2), an adenosine analog. Pharmacol Biochem Behav. 117, 151–156. https://doi.org/10.1016/j.pbb.2013.12.016.

Li, F., Ping, Z.J., Wang, Y.M., Zhou, E.H., Shen, Y.S., 2015. Protection effect of polysaccharides from *Gastrodia elata* Bl. on the immunological liver injury in mice. *Pharmacology and Clinics of Chinese Materia. Medica* 31 (1), 111–113.

Li, H., Su, Q., Bai, L., Li, M., Liu, J., Liu, X., Zhang, C., Jiang, Z., He, J., Shi, J., Li, G., 2020a. Recent research progress on natural small molecule bibenzyls and its derivatives in dendrobium species. Eur J Med Chem. 204, 112530. https://doi.org/10.1016/j.ejmech.2020.112530.

Li, H.T., Tang, L.H., Liu, T., Yang, R.N., Yang, Y.B., Zhou, H., Ding, Z.T., 2019. Polyoxygenated meroterpenoids and a bioactive illudalane derivative from a co-culture of armillaria sp. And Epicoccum Sp. Org Chem Front. 6 (23), 3847–3853. https://doi.org/10.1039/C9QO01087D.

Li, H.T., Tang, L.H., Liu, T., Yang, R.N., Yang, Y.B., Zhou, H., Ding, Z.T., 2020c. Protoilludane-type sesquiterpenoids from Armillaria sp. By co-culture with the endophytic fungus epicoccumsp. Associated with *Gastrodia elata*. Bioorg Chem. 95, 103503. https://doi.org/10.1016/j.bioorg.2019.103503.

Li, Z.F., Wang, Q., Ouyang, H., Huang, L.Q., Feng, Y.L., Wang, R.K., Yang, S.L., 2016c. New compounds with neuroprotective activities from *Gastrodia elata*. Phytochem Lett. 15, 94–97. https://doi.org/10.1016/j.phytol.2015.11.015.

Li, Y., Wang, L.M., Xu, J.Z., Tian, K., Gu, C.X., Li, Z.F., 2017. *Gastrodia elata* attenuates inflammatory response by inhibiting the NF-κB pathway in rheumatoid arthritis fibroblast-like synoviocytes. Biomed Pharmacother.y 85, 177–181. https://doi.org/10.1016/j.biopha.2016.11.136.

Li, Y.G., Wang, X.W., Yan, H.C., Xiang, Z.Y., 2022. Gastrodin promotes the regeneration of peripheral nerves by regulating miR-497/BDNF axis. Bmc Complement Med Ther. 22 (1), 45. https://doi.org/10.1186/s12906-021-03483-z.

Li, X.F., Xiang, B., Shen, T., Xiao, C., Dai, R., He, F.Y., Lin, Q., 2020d. Anti-neuroinflammatory effect of 3,4-dihydroxybenzaldehyde in ischemic stroke. Int Immunopharmacol. 82, 106353. https://doi.org/10.1016/j.intimp.2020.106353.

Li, X.B., Zhan, J.P., Zhang, Y.T., Xie, Z.L., Zhu, Y.Q., 2016a. Effect of polysaccharide from *Gastrodia elata* B1 on humoral immune function in immunosuppressed mice induced by cyclophosphamide. *Chin. J. Gerontol.* 36 (5), 1027–1028. https://doi.org/10.3969/j.issn.1005-9202.2016.05.002.

Liang, Q., Yang, J., He, J.J., Chen, X.L., Zhang, H., Jia, M.L., Liu, K., Jia, C.C., Pan, Y.H., Wei, J.W., 2020. Stigmasterol alleviates cerebral ischemia/reperfusion injury by attenuating inflammation and improving antioxidant defenses in rats. Biosci Rep. 40 (4). https://doi.org/10.1042/BSR20192133.

Liao, C.C., Yu, H.P., Chou, A.H., Lee, H.C., Hu, L.M., Liu, F.C., 2022. Correction to: gastrodin alleviates acetaminophen–induced liver injury in a mouse model through inhibiting MAPK and enhancing Nrf2 pathways. *Inflammation* 45 (4), 1463. https://doi.org/10.1007/s10753-022-01679-0.

Lin, Y.E., Lin, C.H., En Peng, H., Ke, Y.C., Petridi, S., Elliott, C.J.H., Lee Yan, S., Cheng Ting, C., 2021. Glial Nrf2 signaling mediates the neuroprotection exerted by *Gastrodia elata* Blume in Lrrk2-G2019S Parkinson's disease. *Biorxiv*. https://doi.org/10.1101/2021.08.25.457612.

Lin, Y.F., Sun, Y.J., Weng, Y.F., Matsuura, A., Xiang, L., Qi, J.H., 2016. Parishin from *Gastrodia elata* extends the lifespan of yeast via regulation of Sir2/Uth1/TOR signaling pathway. Oxid Med Cell Longev. 2016, 1–11. https://doi.org/10.1155/2016/4074690.

Liu, X.Y., Dou, Y.W., Hao, T.T., Wang, M., Yang, L., Zheng, H.L., Liu, H.M., Dou, H.Y., 2023b. Assessment of the effects of structural modification of Gastrodia elata polysaccharide on anti-breast cancer activity using asymmetrical flow field-flow fractionation. Molecules 28 (12), 4669. https://doi.org/10.3390/molecules28124669.

Liu, S., Fang, T., Yang, L., Chen, Z., Mu, S., Fu, Q., 2018c. Gastrodin protects MC3T3-E1 osteoblasts from dexamethasone-induced cellular dysfunction and promotes bone formation via induction of the NRF2 signaling pathway. Int J Mol Med. 41 (4), 2059–2069. https://doi.org/10.3892/ijmm.2018.3414.

Liu, H.Y., Feng, B., Wang, J., Wang, X.J., 2018b. Effect of gastrodin on the depression-like behaviors and the expression of inflammatory factors in mice. Central South Pharmacy. 16 (2), 166–170. https://doi.org/10.7539/j.issn.1672-2981.2018.02.006.

Liu, B., Gao, J.M., Li, F., Gong, Q.H., Shi, J.S., 2018a. Gastrodin attenuates bilateral common carotid artery occlusion-induced cognitive deficits via regulating aβ-related proteins and reducing autophagy and apoptosis in rats. Front Pharmacol. 9, 405. https://doi.org/10.3389/fphar.2018.00405.

Liu, Y., Tang, X.L., Pei, J.F., Li, Z., Liu, F., 2006. Gastrodin interaction with human fibrinogen: anticoagulant effects and binding studies. *Chem-Eur J* 12, 7807–7815. https://doi.org/10.1002/chem.200600549.

Liu, Y., Gao, J., Peng, M., Meng, H., Ma, H., Cai, P., Xu, Y., Zhao, Q., Si, G., 2018d. A review on central nervous system effects of gastrodin. Front Pharmacol. 9, 24. https://doi.org/10.3389/fphar.2018.00024.

Liu, Y., Ge, L.Q., Waang, Y.X., 2018e. Principal component analysis of volatile compounds in different grades of Lu mountain clouds-mist tea from three regions. *Food Sci.* 39 (10), 206–214. https://doi.org/10.7506/spkx1002-6630-201810032.

Liu, X.H., Guo, X.N., Zhan, J.P., Xie, Z.L., Wang, J.M., 2015c. The effects of polysaccharide from *Gastrodia elata* B1 on cell cycle and caspase proteins activity in H22 tumor bearing mice. *Chin. J. Gerontol.* 35, 5681–5682.

Liu, B., Li, F., Shi, J.S., Yang, D.L., Deng, Y.Y., Gong, Q.H., 2016a. Gastrodin ameliorates subacute phase cerebral ischemia-reperfusion injury by inhibiting inflammation and apoptosis in rats. Mol Med Rep. 14 (5), 4144–4152. https://doi.org/10.3892/mmr.2016.5785.

Liu, B., Li, F., Xu, Y.Y., Wu, Q., Shi, J.S., 2023a. Gastrodin improves cognitive dysfunction in rem sleep-deprived rats by regulating TLR4/NF-κB and Wnt/β-catenin signaling pathways. Brain Sci. 13 (2), 179. https://doi.org/10.3390/brainsci13020179.

Liu, Y., Lu, Y.Y., Huang, L., Shi, L., Zheng, Z.Y., Chen, J.N., Qu, Y., Xiao, H.T., Luo, H.R., Wu, G.S., 2022. Para-hydroxybenzyl alcohol delays the progression of neurodegenerative diseases in models of caenorhabditis elegans through activating multiple cellular protective pathways. Oxid Med Cell Longev. 2022, 1–18. https://doi.org/10.1155/2022/8986287.

Liu, C., Ma, M., Jin, G., Geng, F., Wang, Q., Sun, S., 2015a. Research process on squalene and bioactivities. *Journal of Chinese Institute of. Food Sci. Technol. (* 15 (5), 147–156. https://doi.org/10.16429/j.1009-7848.2015.05.020.

Liu, M., Miao, H.C., Li, H.B., Zhao, J., Xiong, K.R., 2016b. Effect of electroacupuncture combined with polysaccharide of *Gastrodia elata* Blume on expression of brain derived neurotrophic factor and vascular endothelial growth factor in the paraventricular nucleus of hypothalamus in cerebral ischemia rat. *Acupuncture Research* 41 (2), 119–123. https://doi.org/10.13702/j.1000-0607.2016.02.005.

Liu, J., Mori, A., 1993. Antioxidant and pro-oxidant activities of p-hydroxybenzyl alcohol and vanillin: effects on free radicals, brain peroxidation and degradation of benzoate, deoxyribose, amino acids and DNA. *Neuropharmacology* 32 (7), 659–669. https://doi.org/10.1016/0028-3908(93)90079-i.

Liu, C.M., Tian, Z.K., Zhang, Y.J., Ming, Q.L., Ma, J.Q., Ji, L.P., 2020. Effects of gastrodin against lead-induced brain injury in mice associated with the Wnt/Nrf2 pathway. *Nutrients* 12 (6), 1805. https://doi.org/10.3390/nu12061805.

Liu, W., Wang, L.Y., Yu, J.H., Asare, P.F., Zhao, Y.Q., 2015b. Gastrodin reduces blood pressure by intervening with RAAS and PPARγ in shrs. Evi Based Complement Alternat Med. 2015, 1–8. https://doi.org/10.1155/2015/828427.

Liu, Z.H., Wang, W.P., Feng, N., Wang, L., Shi, J.G., Wang, X.L., 2016c. ParishinC's prevention of aβ1–42-induced inhibition of long-term potentiation is related to NMDA receptors. Acta Pharm Sin b. 6 (3), 189–197. https://doi.org/10.1016/j.apsb.2016.03.009.

Liu, F.Y., Wen, J., Hou, J., Zhang, S.Q., Sun, C.B., Zhou, L.C., Yin, W., Pang, W.L., Wang, C., Ying, Y., 2021. *Gastrodia* remodels intestinal microflora to suppress inflammation in mice with early atherosclerosis. Int Immunopharmacol. 96, 107758. https://doi.org/10.1016/j.intimp.2021.107758.

Loh, Y.C., Tan, C.S., Ch'Ng, Y.S., Ahmad, M., Asmawi, M.Z., Yam, M.F., 2017. Vasodilatory effects of combined traditional Chinese medicinal herbs in optimized ratio. J Med Food. 20 (3), 265–278. https://doi.org/10.1089/jmf.2016.3836.

Lu, K.H., Ou, G.L., Chang, H.P., Chen, W.C., Liu, S.H., Sheen, L.Y., 2020. Safety evaluation of water extract of Gastrodia elata Blume: genotoxicity and 28-day oral toxicity studies. Regulatory Toxicology and Pharmacology: Rtp. 114, 104657. https://doi.org/10.1016/j.yrtph.2020.104657.

Luo, Y., Chen, P., Yang, L., Duan, X., 2023. Metabolomic analysis and pharmacological validation of the cerebral protective effect of 3,4-dihydroxybenzaldehyde on cerebral ischemia-reperfusion injury. Mol Med Rep. 27 (1). https://doi.org/10.3892/mmr.2022.12896.

Luo, L., Kim, S.W., Lee, H.K., Kim, I.D., Lee, H., Lee, J.K., 2018. Anti-Zn^{2+}-toxicity of 4-hydroxybenzyl alcohol in astrocytes and neurons contribute to a robust neuroprotective effects in the postischemic brain. Cell Mol Neurobiol. 38 (3), 615–626. https://doi.org/10.1007/s10571-017-0508-y.

Luo, K.X., Wang, Y.H., Chen, W.S., Feng, X.J., Liao, Y.H., Cheng, S.C.C., 2022. Treatment combining focused ultrasound with gastrodin alleviates memory deficit and neuropathology in an Alzheimer's disease-like experimental mouse model. J Funct Foods. 77. https://doi.org/10.1155/2022/5241449.

Ma, J.Q., Sun, Y.Z., Ming, Q.L., Tian, Z.K., Zhang, Y.J., Liu, C.M., 2020. Effects of gastrodin against carbon tetrachloride-induced kidney inflammation and fibrosis in mice associated with the AMPK/Nrf2/HMGB1 pathway. Food Funct 11 (5), 4615–4624. https://doi.org/10.1039/D0FO00711K.

Manavalan, A., Feng, L., Sze, S.K., Hu, J., Heese, K., 2012a. New insights into the brain protein metabolism of *Gastrodia elata*-treated rats by quantitative proteomics. J Proteomics. 75 (8), 2468–2479. https://doi.org/10.1016/j.jprot.2012.02.029.

Manavalan, A., Ramachandran, U., Sundaramurthi, H., Mishra, M., Sze, S.K., J.h.z.w.,, 2012b. *Gastrodia elata* Blume (Tianma) mobilizes neuro-protective capacities. Int J Biochem Cell Biol.

Miao, H.C., Shen, Y.S., 2006. Anti hypertensive effect of polysaccharides substracted from *Gastrodia elata* Blume. *Chin J Hypert Ension* 14 (7).

Ming, J., Zeng, K.F., Wu, S.R., Fu, A.L., Zhao, G.H., Gui, M.Y., Chen, Z.D., 2010. Effect of soluble polysaccharide PGEB-3-H from *Gastrodia elata* Blume on scopolamine-induced learning and memory disorders in mice. *Food Sci.* 31 (3), 246–249.

Ming, J., Liu, J., Wu, S., Guo, X., Chen, Z., Zhao, G., 2012. Structural characterization and hypolipidemic activity of a polysaccharide PGEB-3H from the fruiting bodies of *Gastrodia elata* Blume. *Procedia Eng.* 37, 169–173. https://doi.org/10.1016/j.proeng.2012.04.221.

Mishra, M., Huang, J., Lee, Y.Y., Chua, D.S.K., 2011. *Gastrodia elata* modulates amyloid precursor protein cleavage and cognitive functions in mice. Biosci Trends. 5 (3), 129–138. https://doi.org/10.5582/bst.2011.v5.3.129.

Ng, C.F., Ko, C.H., Koon, C.M., Chin, W.C., Kwong, H.C., Lo, A.W., Wong, H.L., Fung, K. P., Lau, C.B., Lam, P.K., Poon, W.S., Leung, P.C., 2016. The aqueous extract of rhizome of *Gastrodia elata* Blume attenuates locomotor defect and inflammation after traumatic brain injury in rats. J Ethnopharmacol. 185, 87–95. https://doi.org/10.1016/j.jep.2016.03.018.

Pan, S.Q., Zhu, H.R., 1993. Vigilance against the toxic side effects of *G. elata* jiao. *Chinese. J. Tradit. Chin. Med.* 18 (10).

Park, S., Kim, D.S., Kang, S., 2011. *Gastrodia elata* Blume water extracts improve insulin resistance by decreasing body fat in diet-induced obese rats: vanillin and 4-hydroxybenzaldehyde are the bioactive candidates. Eur J Nutr. 50 (2), 107–118. https://doi.org/10.1007/s00394-010-0120-0.

Peng, Y., Ye, J.R., Wang, S.S., He, W.B., Feng, Z.P., Sun, H.S., Chu, S.F., Zhang, Z., Chen, N.H., 2023. A small molecule 20c from Gastrodia elata inhibits alpha-synuclein aggregation and prevents progression of Parkinson's disease. Cell Death Dis. 14 (9), 594. https://doi.org/10.1038/s41419-023-06116-0.

Percario, S., Da, S.B.A., Varela, E., Gomes, A., Ferreira, M., de Nazare, A.M.T., Dolabela, M.F., 2020. Oxidative stress in Parkinson's disease: potential benefits of antioxidant supplementation. Oxid Med Cell Longev. 2020, 2360872. https://doi.org/10.1155/2020/2360872.

Pittenger, C., Duman, R.S., 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology* 33 (1), 88–109. https://doi.org/10.1038/sj.npp.1301574.

Pu, Z.H., 1997. Clinical reports and awareness of toxic side effects of *Gastrodia elata*. *China Journal of Information on Tcm* 4 (3), 12–13.

Pyo, M.K., Jin, J.L., Koo, Y.K., Choi, H.S.Y., 2004. Phenolic and furan type compounds isolated from *Gastrodia elata* and their anti-platelet effects. Arch Pharm Res. 27 (4), 381–385. https://doi.org/10.1007/BF02980077.

Qin, C., 2018. Clinical study on the treatment of patients with chronic cerebral insufficiency of blood supply in combination with nourishing blood and clearing brain granules by Quan Tianma capsule. *Chinese Primary Health Care* 32 (6), 72–73. https://doi.org/10.3969/j.issn.1001-568X.2018.06.0027.

Qin, Z., Dong Fang, Z., Ming Li, W.U., Jie, G., Cheng Zhong, S., Cai Xiang, X., 2017. Predicting the global areas for potential distribution of *Gastrodia elata* based on ecological niche models. *Chinese Journal of Plant Ecology* 41 (7), 770-778. 10.17521/cjpe.2016.0380.

Quan, M., Yanqun, X., Hang, X., Mariga, A.M., Yanpei, C., Zhang, L.W.D.L., 2022. Rethinking of botanical volatile organic compounds applied in food preservation: challenges in acquisition, application, microbial inhibition and stimulation. Trends Food Sci Technol. 125, 166-184. org/10.1016/j.tifs.2022.05.007.

Ramachandran, U., Manavalan, A., Sundaramurthi, H., Sze, S.K., Feng, Z.W., Hu, J.M., Heese, K., 2012. Tianma modulates proteins with various neuro-regenerative modalities in differentiated human neuronal SH-SY5Y cells. Neurochem Int. 60 (8), 827–836. https://doi.org/10.1016/j.neuint.2012.03.012.

Ruwizhi, N., Aderibigbe, B.A., 2020. Cinnamic acid derivatives and their biological efficacy. *Int. J. Mol. Sci.* 21 (16). https://doi.org/10.3390/ijms21165712.

Seok, P.R., Kim, J.H., Kwon, H.R., Heo, J.S., Choi, J.R., Shin, J.H., 2018. Protective effects of *Gastrodia elata* Blume on acetaminophen-induced liver and kidney toxicity in rats. *Food Sci. Biotechnol.* 27 (5), 1445–1454. https://doi.org/10.1007/s10068-018-0374-5.

Shan, T., Yin, M., Wu, J., Yu, H., Liu, M., Xu, R., Wang, J., Peng, H., Zha, L., Gui, S., 2021b. Comparative transcriptome analysis of tubers stems, and flowers of *Gastrodia elata* Blume reveals potential genes involved in the biosynthesis of phenolics. *Fitoterapia* 153, 104988. https://doi.org/10.1016/j.fitote.2021.104988.

Shan, F., Zhou, L., Jiang, C., Liu, L., 2021a. History of consumption of *Gastrodia elata* Bl and proposals for its development. *China Food Drug Administration* 13 (3), 110–115. https://doi.org/10.3969/j.issn.1673-5390.2021.03.013.

Shangguan, C.H., Quan, Y.H., Chen, C., 2022. Situation analysis of *Gastrodia elata* drug research and development based on patent metrology. Chinese Traditional and Herbal Drugs. 53 (15), 4915–4924. https://doi.org/10.7501/j.issn.0253-2670.2022.15.035.

Shao, M.G., Wang, X.W., Fang, B., Yang, K.X., Chen, S.H., 1994. Research on chemical constituents in trace elements and amino acids of wild and growing rhizoma *Gastrodiae* in Zhaotong. Journal of Yunnancollege of Traditional. Chin. Med. 04, 1–5. https://doi.org/10.19288/j.cnki.issn.1000-2723.1994.04.001.

Shao, S., Xu, C.B., Chen, C.J., Shi, G.N., Guo, Q.L., Zhou, Y., Wei, Y.Z., Wu, L., Shi, J.G., Zhang, T.T., 2021. Divanillyl sulfone suppresses NLRP3 inflammasome activation via inducing mitophagy to ameliorate chronic neuropathic pain in mice. J Neuroinflammation. 18 (1). https://doi.org/10.1186/s12974-021-02178-z.

Shao, H., Yang, Y., Qi, A.P., Hong, P., Zhu, G.X., Cao, X.Y., 2017. Gastrodin reduces the severity of status epilepticus in the rat pilocarpine model of temporal lobe epilepsy by inhibiting nav1.6 sodium currents. Neurochem Res. 42 (2), 360–374. https://doi.org/10.1007/s11064-016-2079-6.

Shao, Q.H., Zhang, X.L., Chen, Y., Zhu, C.G., Shi, J.G., Yuan, Y.H., Chen, N.H., 2018. Corrigendum to "anti-neuroinflammatory effects of 20C from *Gastrodia elata* via regulating autophagy in Lps-activated BV-2 cells through MAPKs and Tlr4/AKT/mTTOR signaling pathways" [molecular immunology 99 (2018) 115–123]. Mol Immunol. 101, 640. https://doi.org/10.1016/j.molimm.2018.06.272.

Shi, Y., Dong, J.W., Tang, L.N., Kang, R.X., Shi, J.G., Zhang, J.J., 2014. N^6-(3-methoxyl-4-hydroxybenzyl) adenine riboside induces sedative and hypnotic effects via gad enzyme activation in mice. Pharmacol Biochem Behav. 126, 146–151. https://doi.org/10.1016/j.pbb.2014.09.004.

Shi, S., Yang, H.J., Wei, X.F., Liang, Q.Y., Yang, X.D., Xian, X., Xie, C.L., 2021. Gastrodia qingyunshanensis (Orchidaceae: Epidendroideae)—a new holomycotrophic orchid from Guangdong, China. *Phytotaxa* 483 (2), 177-182. org/10.11646/phytotaxa.483.2.10.

Shi, H., He, Q., Lou, Y.J., Shao, S.J., 2017. Effect of *Gastrodiae* rhizoma polysaccharide on brain neutral transmitter in immature rats with cerebral palsy. *Chin. J. Exp. Tradit. Med. Formulae* 23 (23), 140–145. https://doi.org/10.13422/j.cnki.syfjx.2017230140.

Shi, D.C., Shou, S.Y., Li, G., Zi, W., Feng, H., 2007. Expression of pten in athymic mice with HCC treated by complex prescription of Chinese crude drug. China Journal of Chinese Materia Medica 32 (11).

Shi, A.H., Xiang, J.M., He, F.Y., Zhu, Y.P., Zhu, G.B., Lin, Y.H., Zhou, N.N., 2018. The phenolic components of *Gastrodia elata* improve prognosis in rats after cerebral ischemia/reperfusion by enhancing the endogenous antioxidant mechanisms. Oxid Med Cell Longev. 2018, 1–16. https://doi.org/10.1155/2018/7642158.

Shim, E., Song, E., Choi, K.S., Choi, H.J., Hwang, J., 2017. Inhibitory effect of Gastrodia elata Blume extract on alpha-melanocyte stimulating hormone-induced melanogenesis in murine b16f10 melanoma. Nutr Res Pract. 11 (3), 173–179. https://doi.org/10.4162/nrp.2017.11.3.173.

Shin, E.J., Whang, W.K., Kim, S., Jae Hyung Bach, J.M.K., N, X.K.T., Guyen, Nguyen, T.T. L., 2010. Parishin C attenuates phencyclidine-induced schizophrenia-like psychosis in mice: involvements of 5-HT1A receptor. J Pharmacol Sci. 113, 404-408. 10.1254/jphs.10040SC.

Shin, E.J., Kim, J.M., Nguyen, X.K., Nguyen, T.T., Lee, S.Y., Jung, J.H., Kim, M.J., Whang, W.K., Yamada, K., Nabeshima, T., Kim, H.C., 2011. Effects of *Gastrodia elata* Blume phencyclidine-induced schizophrenia-like psychosis in mice. Curr Neuropharmacol. 9 (1), 247–250. https://doi.org/10.2174/157015911795017263.

Shiu-Min Cheng, Y.H.S.Y., Huang, C.Y., Ou, H.C., Huang, H.L., Lee, S., 2020. Anti-apoptotic effects of diosgenin in D-Galactose-induced aging brain. Am J Chin Med. 48 (2), 391–406. https://doi.org/10.1142/S0192415X20500202.

Soehnlein, O., Libby, P., 2021. Targeting inflammation in atherosclerosis - from experimental insights to the clinic. Nat Rev Drug Discov 20 (8), 589–610. https://doi.org/10.1038/s41573-021-00198-1.

Song, H.X., Chen, X.H., Zhang, G.Y., Shi, Y.Z., 2019. Effect of gastrodin injection on the expression levels of TH17 related inflammatory factors in peripheral blood of patients with schizophrenia and immune dysfunction. *Shaanxi Traditional. Chin. Med.* 40 (2). https://doi.org/10.3969/j.issn.1000-7369.2019.02.010.

Su, Z., Yang, Y., Chen, S., Tang, Z., Xu, H., 2023. The processing methods, phytochemistry and pharmacology of *Gastrodia elata* Bl.: A comprehensive review. J Ethnopharmacol. 314, 116467. https://doi.org/10.1016/j.jep.2023.116467.

Suetsugu, K., 2022. A new color variant of the mycoheterotrophic plant Gastrodia pubilabiata (Orchidaceae) from japan. Apg. 10.18942/apg.202119.

Suetsugu, K., Suleiman, M., Tsukaya, H., 2018. A new species of Gastrodia (Gastrodieae, Epidendroideae, Orchidaceae) from the Maliau basin conservation area, Sabah, Borneo. *Phytotaxa* 367 (1). org/10.11646/phytotaxa.367.1.9.

Suetsugu, K., 2017. Two new species of Gastrodia (Gastrodieae, epidendroideae, Orchidaceae) from Okinawa island, Ryukyu islands, japan. Phytotaxa 302 (3), 218-251. org/10.11646/phytotaxa.302.3.4.

Sun, X.N., Jia, B., Sun, J.R., Lin, J.G., Lu, B.J., Duan, J.L., Li, C., Wang, Q.Q., Zhang, X., Tan, M., Zhong, D.S., Zhang, X.X., Sun, Z.Y., Zhang, Y., Yao, K.W., 2023. *Gastrodia*

elata Blume: a review of its mechanisms and functions on cardiovascular systems. Fitoterapia 167, 105511. https://doi.org/10.1016/j.fitote.2023.105511.
Sun, H., Li, M., Li, Y., Zheng, N., Li, J., Li, X., Liu, Y., Ji, Q., Zhou, L., Su, J., Huang, W., Liu, Z., Liu, P., Zou, L., 2024. Gastrodin improves the activity of the ubiquitin-proteasome system and the autophagy-lysosome pathway to degrade mutant huntingtin. Int. J. Mol. Sci. 25 (14), 7709. https://doi.org/10.3390/ijms25147709.
Sun, W.J., Lu, H.Q., Lyu, L.C., Yang, P., Lin, Z., Li, L., 2019. Gastrodin ameliorates microvascular reperfusion injury–induced apoptosis by regulating the NLRP3/caspase-1 pathway. J Physiol Biochem. https://doi.org/10.1007/s13105-019-00702-7.
Sun, W., Miao, B., Wang, X.C., Duan, J.H., Ye, X., Han, W.J., Wang, W.T., Luo, C., Hu, S. J., 2012. Gastrodin inhibits allodynia and hyperalgesia in painful diabetic neuropathy rats by decreasing excitability of nociceptive primary sensory neurons. PLoS One 7 (6), e39647. https://doi.org/10.1371/journal.pone.0039647.
Taguchi, H., Yosioka, I., Yamasaki, K., Kim, I., 1981. Studies on the constituents of *Gastrodia elata* Blume. *Chem Pharm Bull* 29 (1), 55–62. https://doi.org/10.1248/cpb.29.55.
Tao, J., Yang, P., Xie, L.Q., Pu, Y.W., Guo, J.Z., Jiao, J.L., Sun, L., Lu, D., 2021. Gastrodin induces lysosomal biogenesis and autophagy to prevent the formation of foam cells via AMPK-foxO1-TFEB signalling axis. J Cell Mol Med. 25 (12), 5769–5781. https://doi.org/10.1111/jcmm.16600.
Teong, I.W.J., Ko, A.A.R., Li, M.H., Heese, K., Liang, W., 2011. *Gastrodia elata* decreases isoprenaline potency and enhances spontaneous phasic activity in the rat detrusor. *International Journal of Physiology Pathophysiology & Pharmacology* 3 (1), 29–37.
Tong, X.K., Qiu, H., Zhang, X., Shi, L.P., Wang, G.F., Ji, F.H., Ding, H.Y., Tang, W., Ding, K., Zuo, J.P., 2010. WSS45, a sulfated alpha-d-glucan, strongly interferes with dengue 2 virus infection *in vitro*. *Acta* Pharmacol Sin. 31 (5), 585–592. https://doi.org/10.1038/aps.2010.29.
Vargas Vargas, R.A., Varela Millán, J.M., Fajardo Bonilla, E., 2022. Renin–angiotensin system: basic and clinical aspects—a general perspective. *Endocrinología, Diabetes Y Nutrición (english Ed.)* 69 (1), 52–62. https://doi.org/10.1016/j.endien.2022.01.005.
Wan, H., Xu, X., Yang, X., Li, A., Ma, X., Xu, A., Yuan, X., Wang, W., Guo, T., Luo, G., He, X., Li, W., Wang, Z., Sun, Q., Pei, J., Guo, Y., Zhu, Y., 2021. Metabolomics analysis reveals interaction of base-line chemotherapy and shiyiwei shenqi tablets in breast cancer treatment. Front Pharmacol. 12, 720886. https://doi.org/10.3389/fphar.2021.720886.
Wang, Z.H., 2005. Self-administered *Gastrodia elata* Bl overdose: a case of fatal overdose. Journal of Taishan Medical College 26 (6), 538. https://doi.org/10.3969/j.issn.1004-7115.2005.06.046.
Wang, F., 2013. Protective effects of gastrodin on myocardial ischemiareperfusion injury in rats by preconditioning. Anhui Medical University, in.
Wang, T., Chen, H., Xia, S., Chen, X., Sun, H., Xu, Z., 2021a. 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, 1811–1823. https://doi.org/10.2147/NDT.S309065.
Wang, X.L., Chen, L.H., Xu, Y.J., Wang, W.L., Wang, Y.R., Zhang, Z.Y., Zheng, J., Bao, H. G., 2021b. Gastrodin alleviates perioperative neurocognitive dysfunction of aged mice by suppressing neuroinflammation. Eur J Pharmacol. 892, 173734. https://doi.org/10.1016/j.ejphar.2020.173734.
Wang, M., Dong, W.R., Wang, R.Y., Xu, X.D., Wu, Y., Sun, G.B., Sun, X.B., 2020a. Gastrodiae rhizoma water extract ameliorates hypothalamic–pituitary–adrenal axis hyperactivity and inflammation induced by chronic unpredictable mild stress in rats. Biomed Res Int. 2020, 1–7. https://doi.org/10.1155/2020/8374614.
Wang, X.L., Dong, L.P., Zhang, L., Xie, Y., Yang, C., Yu, Q., 2019a. Effect of *Gastrodiae* rhizoma polysaccharide on neuronal apoptosis gene expression in brain tissue of cerebral palsy newborn rats. Chin J Clin Pharmacol 35 (18), 2062-2064. 10. 13699/j. cnki. 1001–6821. 2019. 18. 027.
Wang, Y.Y., Liu, Y., Wang, H.F., Bao, H.Y., 2020. Anticonvulsant effect of water extract from *Gastrodia elata* stalk. Journal of Northwest a&F University(Natural Science Edition) 48 (11), 87-96, 103. 10.13207/j.cnki.jnwafu.2020.11.010.
Wang, Z.W., Li, Y., Liu, D.H., Mu, Y., Dong, H.J., Zhou, H.L., Guo, L.P., Wang, X., 2018. Four new phenolic constituents from the rhizomes of *Gastrodia elata* Blume. Nat Prod Res. 33 (8), 1140–1146. https://doi.org/10.1080/14786419.2018.1460836.
Wang, L.N., Liu, W.B., Lu, K.L., Xu, W.N., Cai, D.S., Zhang, C.N., Qian, Y., 2014a. Effects of dietary carbohydrate/lipid ratios on non-specific immune responses, oxidative status and liver histology of juvenile yellow catfish pelteobagrus fulvidraco. *Aquaculture* 426–427, 41–48. https://doi.org/10.1016/j.aquaculture.2014.01.022.
Wang, X.M., Liu, K.X., 2019. Experimental study of the effects of *Gastrodia elata* polysaccharide on delay in skeletal muscle aging. Journal of Zunyi Medical University 42 (2), 135–140. https://doi.org/10.3969/j.issn.1000-2715.2019.02.003.
Wang, R.C., Ren, Q.Y., Gao, D.L., Paudel, Y.N., Li, X., Wang, L.Z., Zhang, P.Y., Wang, B. K., Shang, X.L., Jin, M., 2022c. Ameliorative effect of *Gastrodia elata* Blume extracts on depression in zebrafish and cellular models through modulating reticulon 4 receptors and apoptosis. J Ethnopharmacol. 289, 2949–2956. https://doi.org/10.1016/j.jep.2022.115018.
Wang, R.C., Ren, Q.Y., Gao, D.L., Paudel, Y.N., Li, X., Wang, L.Z., Zhang, P.Y., Wang, B. K., Shang, X.L., Jin, M., 2022d. Ameliorative effect of Gastrodia elata Blume extracts on depression in zebrafish and cellular models through modulating reticulon 4 receptors and apoptosis. J Ethnopharmacol. 289, 115018. https://doi.org/10.1016/j.jep.2022.115018.
Wang, C.Y., Tang, L., He, J.W., Li, J., Wang, Y.Z., 2019. Ethnobotany, phytochemistry and pharmacological properties ofeucommia ulmoides: a review. Am. J. Chin. Med. 47 (02), 259–300. https://doi.org/10.1142/S0192415X19500137.
Wang, D.Q., Wang, J.X., Yan, C.R., Liu, Y.Z., Liu, H.Y., Li, D.X., Zhu, J., Luo, Z.B., Han, S. Z., Jin, Z.Y., 2022b. *Gastrodia elata* Blume extract improves high-fat diet-induced type 2 diabetes by regulating gut microbiota and bile acid profile. Front Microbiol. 13. https://doi.org/10.3389/fmicb.2022.1091712.
Wang, C., Yan, Y., Tang, C., He, X., 2022a. Research progress on extraction, separation and pharmacological activities of rhizoma *Gastrodiae* polysaccharide. *Chinese Pharmaceutical Affairs* 36 (4), 417–428. https://doi.org/10.16153/j.1002-7777.2022.04.007.
Wang, Q., Zhang, Y., Li, J., Ren, T.L., 2014b. The inhibition effect of polysaccharides from *Gastrodia elata* Blume tumor growth through immune system. *Immunological Journal* 30 (6), 566–568. https://doi.org/10.13431/j.cnki.immunol.j.20140124.
Wang, X.Y., Zhang, B.X., Li, X.D., Liu, X.G., Wang, S.S., Xie, Y., Pi, J.L., Yang, Z.Y., Li, J. C., Jia, Q.Z., Zhang, Y., 2021c. Mechanisms underlying gastrodin alleviating vincristine-induced peripheral neuropathic pain. Front Pharmacol. 12. https://doi.org/10.3389/fphar.2021.744663.
Wang, Y., Zhao, L., Li, A.Y., 2021d. Gastrodin - a potential drug used for the treatment of Tourette syndrome. J Pharmacol Sci. 145 (3), 289–295. https://doi.org/10.1016/j.jphs.2021.01.005.
Wen, Z.Q., He, M.Z., Peng, C.Y., Rao, Y.F., Li, J.M., Li, Z.F., Du, L.J., Li, Y., Zhou, M.F., 2019. Metabolomics and 16s rRNA gene sequencing analyses of changes in the intestinal flora and biomarkers induced by *Gastrodia-Uncaria* treatment in a rat model of chronic migraine. Front Pharmacol. 10. https://doi.org/10.3389/fphar.2019.01425.
Wen, Y., Zhang, X., Wei, L., Wu, M., Cheng, Y., Zheng, H.F., Shen, A., Fu, C.G., Ali, F., Long, L.Z., Lu, Y., Li, J.P., Peng, J., 2023. Gastrodin attenuates renal injury and collagen deposition via suppression of the TGF-β1/Smad2/3 signaling pathway based on network pharmacology analysis. Front Pharmacol. 14. https://doi.org/10.3389/fphar.2023.1082281.
Wong, K.S., Mok, V., Lam, W.W., Kay, R., Tang, A., Chan, Y.L., Woo, J., 2000. Aspirin-associated intracerebral hemorrhage: clinical and radiologic features. Neurology 54 (12), 2298–2301. https://doi.org/10.1212/wnl.54.12.2298.
Wu, L.Y., Chen, W.C., Tsai, F.S., Tsai, C.C., Wu, C.R., Lin, L.W., 2016. P-hydroxybenzyl alcohol, an active phenolic ingredient of *Gastrodia elata*, reverses the cycloheximide-induced memory deficit by activating the adrenal gland in rats. Am. J. Chin. Med. 43 (08), 1593–1604. https://doi.org/10.1142/S0192415X15500901.
Wu, S., Huang, R., Zhang, R.Q., Xiao, C., Wang, L.L., Luo, M., Song, N., Zhang, J., Yang, F., Liu, X., Yang, W.M., 2023b. Gastrodin and gastrodigenin improve energy metabolism disorders and mitochondrial dysfunction to antagonize vascular dementia. Molecules 28 (6), 2598. https://doi.org/10.3390/molecules28062598.
Wu, M., Zhang, S., Zhang, W., Zhou, Y., Guo, Z., Fang, Y., Yang, Y., Shen, Z., Lian, D., Shen, A., Peng, J., 2023a. Qingda granule ameliorates vascular remodeling and phenotypic transformation of adventitial fibroblasts via suppressing the TGF-β1/Smad2/3 pathway. J Ethnopharmacol. 313, 116535. https://doi.org/10.1016/j.jep.2023.116535.
Xiang, B., Xiao, C., Shen, T., Li, X., 2018. Anti-inflammatory effects of anise alcohol on lipopolysaccharide-stimulated BV2 microglia via selective modulation of microglia polarization and down-regulation of NF-κB p65 and JNK activation. Mol Immunol. 95, 39–46. https://doi.org/10.1016/j.molimm.2018.01.011.
Xiao, H., Jiang, Q.S., Qiu, H.M., Wu, K., Ma, X.J., Yang, J.X., 2021. Gastrodin promotes hippocampal neurogenesis via PDE9-cGMP-PKG pathway in mice following cerebral ischemia. Neurochem Int. 150, 105171. https://doi.org/10.1016/j.neuint.2021.105171.
Xiao, F., Qiu, H., Zhou, L., Shen, X.K., Yang, L.P., Ding, K., 2013. WSS25 inhibits dicer, downregulating microRNA-210, which targets Ephrin-A3, to suppress human microvascular endothelial cell (HMEC-1) tube formation. *Glycobiology* 23 (5), 524–535. https://doi.org/10.1093/glycob/cwt004.
Xiao, M., Zhang, Y., Wang, W., Han, W., Lin, Z., Xie, R.G., Cao, Z., Lu, N., Hu, S.J., Wu, S. X., Dong, H., Luo, C., 2016. Gastrodin protects against chronic inflammatory pain by inhibiting spinal synaptic potentiation. Sci Rep. 6 (1). https://doi.org/10.1038/srep37251.
Xie, H.T., Chen, Y.Y., Wu, W., Feng, X.B., Du, K.R., 2021. *Gastrodia elata* Blume polysaccharides attenuate vincristine-evoked neuropathic pain through the inhibition of neuroinflammation. Mediators Inflamm. 2021, 1–10. https://doi.org/10.1155/2021/9965081.
Xie, Y.L., Zhou, M., Ma, H.H., Wang, X., Liu, J.J., 2015. Vasorelaxation effect of gastrodin on isolated thoracic aorta rings of rats. Chin J Integr Med. 21 (12), 944–948. https://doi.org/10.1007/s11655-015-2082-9.
Xu, C.B., Guo, Q.L., Wang, Y.N., Lin, S., Zhu, C.G., Shi, J.G., 2019. Gastrodin derivatives from *Gastrodia elata*. Nat Prod Bioprospect. 9 (6), 393–404. https://doi.org/10.1007/s13659-019-00224-1.
Yan, J.Y., Yang, Z.S., Zhao, N.H., Li, Z.W., Cao, X., 2019. Gastrodin protects dopaminergic neurons via insulin-like pathway in a Parkinson's disease model. Bmc Neurosci. 20 (1). https://doi.org/10.1186/s12868-019-0512-x.
Yang, P., Han, Y., Gui, L., Sun, J., Chen, Y.L., Song, R., Guo, J.Z., Xie, Y.N., Lu, D., Sun, L., 2013a. Gastrodin attenuation of the inflammatory response in H9C2 cardiomyocytes involves inhibition of NF-kB and mapks activation via the phosphatidylinositol 3-kinase signaling. Biochem Pharmacol. 85 (8), 1124–1133. https://doi.org/10.1016/j.bcp.2013.01.020.
Yang, L., Tsai, T.H., 2022. Neuroprotective effect and herbal-drug pharmacokinetic interaction of Gastrodia elata extract on valproic acid. Biomed Pharmacother. 156, 113938. https://doi.org/10.1016/j.biopha.2022.113938.
Yang, L., Jiang, R., Li, H.H., Pan, Y.P., Lu, J.J., Zhang, H., Liu, S.J., Shen, J.L., Hu, J.M., 2020. Three new compounds from the flower branch of *Gastrodia elata* Blume and anti-microbial activity. Rsc Adv. 10 (25), 14644–14649. https://doi.org/10.1039/D0RA00965B.
Yang, L., Lin, I.H., Ting, C.T., Tsai, T.H., 2021. Modulation of the transport of valproic acid through the blood-brain barrier in rats by the *Gastrodia elata* extracts. J Ethnopharmacol. 278, 114276. https://doi.org/10.1016/j.jep.2021.114276.

Yang, Q., Yu, D., Zhang, Y., 2019b. B-sitosterol attenuates the intracranial aneurysm growth by suppressing TNF-alpha-mediated mechanism. *Pharmacology* 104 (5–6), 303–311. https://doi.org/10.1159/000502221.

Yang, G.M., Zeng, X.F., Li, J., Leung, C.K., Zhang, D.X., Hong, S.J., He, Y.W., Huang, J., Li, L.H., Li, Z., 2019a. Protective effect of gastrodin against methamphetamine-induced autophagy in human dopaminergic neuroblastoma sh-sy5y cells via the akt/mtor signaling pathway. Neurosci Lett. 707, 134287. https://doi.org/10.1016/j.neulet.2019.134287.

Yang, Z., Zhi Jiao, K., Xin, Z., Shi Lin, Y., 2013b. An edible medicinal plant-*Gastrodia elata* Bl. *Journal of Guizhou Normal University (natural Sciences)* 31 (4), 9–12. https://doi.org/10.3969/j.issn.1004-5570.2013.04.003.

Yin, X.P., Xu, Y.Y., Liu, X.L., 2020. Roles of gastrodin on promoting osteoblast differentiation and inhibiting osteoporosis by Nrf2/keapl signaling pathway. *Chin J Clin Pharmacol* 36 (16), 2468–2471.

Yin, Q., Yan, R., Wang, Y., Yu, J., 2023. Gastrodin from *Gastrodia elata* attenuates acute myocardial infarction by suppressing autophagy: key role of the miR-30a-5p/ATG5 pathway. J Funct Foods. 102, 105429. https://doi.org/10.1016/j.jff.2023.105429.

Yong, W., Xing, T.R., Wang, S., Chen, L., Hu, P., Li, C.C., Wang, H.L., Wang, M., Chen, J. T., Ruan, D.Y., 2009. Protective effects of gastrodin on lead-induced synaptic plasticity deficits in rat hippocampus. Planta Med 75 (10), 1112–1117. https://doi.org/10.1055/s-0029-1185452.

Yu, L., Shen, Y.S., Miao, H.C., 2006. Study on the anti-vertigo function of polysaccharides of *Gastrodia elata* and polysaccharides of *Armillaria mellea*. China Journal of Information on Traditional Chinese Medicine. 13 (8), 29, 36. https://doi.org/10.3969/j.issn.1005-5304.2006.08.015.

Yu, H., Zhang, J., Chen, B.Q., Huang, H., Li, H.H., Huang, S.W., Li, X.X., Liu, X.M., 2022. Research progress on classification of chemical constituents from *Gastrodia elata* and their pharmacological effects. Chin. Tradit. Herb. Drug 53 (17), 5553–5564. https://doi.org/10.7501/j.issn.0253-2670.2022.17.033.

Yuan, Y.J., Liu, L.J., Du, Y., Fan, R.X., Zhang, R.P., Zhou, N.N., 2022. P-hydroxy benzaldehyde revitalizes the microenvironment of peri-infarct cortex in rats after cerebral ischemia-reperfusion. Phytomedicine 105, 154379. https://doi.org/10.1016/j.phymed.2022.154379.

Yun, L., Wang, Z.W., Liu, D.H., Wang, X., Zhou, H.L., 2016. Research advances in chemical constituents of *Gastrodia elata* Blume. Shandong Science. 29 (4), 24–29. https://doi.org/10.3976/j.issn.1002-4026.2016.04.006.

Zeng, X., Li, J.X., Chen, T.Y., Li, Y.Y., Guo, S.X., 2023a. Global metabolic profile and multiple phytometabolites in the different varieties of *Gastrodia elata* Blume. Front Plant Sci. 14, 1249456. https://doi.org/10.3389/fpls.2023.1249456.

Zeng, X., Li, J.X., Chen, T.Y., Lian, Y.Y., Guo, S.X., 2023b. Global metabolic profile and multiple phytometabolites in the different varieties of *Gastrodia elata* Blume. Front Plant Sci. 14 (1), 1249456. https://doi.org/10.3389/fpls.2023.1249456.

Zeng, X.H., Zhang, S.M., Zhang, L., Zhang, K.P., Zheng, X.X., 2006. A study of the neuroprotective effect of the phenolic glucoside gastrodin during cerebral ischemia in vivo and in vitro. Planta Med. 72 (15), 1359–1365. https://doi.org/10.1055/s-2006-951709.

Zhan, M.J., 2007a. Study on extraction, purification and activity of polysaccharide in *Gastrodia elata* Blume. North West Agriculture and Forestry University, in.

Zhan, Q.H., 2007b. Gastrodin overdose causes fever in patient. *Journal of Practical Medical Techniques* 14 (21), 2846–2847.

Zhan, H.D., Zhou, H.Y., Sui, Y.P., Du, X.L., Wang, W.H., Dai, L., Sui, F., Huo, H.R., Jiang, T.L., 2016. The rhizome of *Gastrodia elata* Blume - an ethnopharmacological review. J Ethnopharmacol. https://doi.org/10.1016/j.jep.2016.06.057.

Zhang, S.P., Xu, Y.X., 2023. Clinical evaluation of gastrodin injection in the treatment of acute vertigo. China Medical Abstracts (Otolaryngology). 38 (05), 109-111. 10.19617.issn1001-1307.2023.05.109.

Zhang, T.H., Huang, C.M., Gao, X., Wang, J.W., Hao, L.L., Ji, Q., 2018. Gastrodin inhibits high glucose–induced human retinal endothelial cell apoptosis by regulating the Sirt1/Tlr4/Nf–κBP65 signaling pathway. Mol Med Rep. 17 (6), 7774–7780. https://doi.org/10.3892/mmr.2018.8841.

Zhang, T., Huang, S.K., Qiu, J.Y., Wu, X.G., Yuan, H., Park, S.M., 2022c. Beneficial effect of *Gastrodia elata* Blume and poria cocos wolf administration on acute UVB irradiation by alleviating inflammation through promoting the gut-skin axis. Int. J. Mol. Sci. 23 (18), 10833. https://doi.org/10.3390/ijms231810833.

Zhang, L., Ji, Q., Chen, Q., Wei, Z., Liu, S., Zhang, L., Zhang, Y., Li, Z., Liu, H., Sui, H., 2023a. Akkermansia muciniphila inhibits tryptophan metabolism via the ahr/beta-catenin signaling pathway to counter the progression of colorectal cancer. Int J Biol Sci. 19 (14), 4393–4410. https://doi.org/10.7150/ijbs.85712.

Zhang, Y., Li, M., Kang, R.X., Shi, J.G., Liu, G.T., Zhang, J.J., 2012a. Nhba isolated from *Gastrodia elata* exerts sedative and hypnotic effects in sodium pentobarbital-treated mice. Pharmacol Biochem Behav. 102 (3), 450–457. https://doi.org/10.1016/j.pbb.2012.06.002.

Zhang, Z.C., Su, G., Li, J., Wu, H., Xie, X.D., 2013. Two new neuroprotective phenolic compounds from *Gastrodia elata*. J. Asian Nat. Prod. Res. 15 (6), 619–623. https://doi.org/10.1080/10286020.2013.791286.

Zhang, M., Tan, Y.Z., Song, Y., Zhu, M., Zhang, B., Chen, C., Liu, Y.Y., Shi, L., Cui, J., Shan, W.J., Jia, Z.P., Feng, L.L., Cao, G.J., Yi, W., 2023b. Glut4 mediates the protective function of gastrodin against pressure overload-induced cardiac hypertrophy. Biomed Pharmacother. 161, 114324. https://doi.org/10.1016/j.biopha.2023.114324.

Zhang, B., Wu, J., Niu, J., Miao, Y., 2022a. Role of amino acids in treatment of inflammatory bowel disease. Chinese Journal of Gastroenterology. 27 (10), 632–636. https://doi.org/10.3969/j.issn.1008-7125.2022.10.010.

Zhang, M.T., Yan, M.X., Yang, J.Q., Li, F.F., Wang, Y.R., Feng, K.Y., Wang, S.Y., Lin, N. M., 2022b. Structural characterization of a polysaccharide from trametes sanguinea lloyd with immune-enhancing activity via activation of TLR4. Int J Biol Macromol. 206, 1026–1038. https://doi.org/10.1016/j.ijbiomac.2022.03.072.

Zhang, L., Yang, P., Jiang, Y.L., Pu, Y.W., Xie, L.Q., Sun, L., 2019. Gastrodin inhibits apoptosis of H9C2 cardiomyocytes through protein kinase B /p38mitogen actived protein kinase signaling pathway. Acta Anatomica Sinica 50 (01), 40–48.

Zhang, Y.Q., Yu, T., Xu, G.Y., Bian, X.H., Xu, J.L., Liu, Y.M., 2012b. Effect and mechanism of gastrodin in relaxing isolated thoracic aorta rings in rats. China Journal of Chinese Materia Medica. 37 (14), 2135–2138. https://doi.org/10.4268/cjcmm20121422.

Zhao, S.S., Li, N., Zhen, Y.Z., Ge, M.X., Li, Y., Yu, B., He, H.W., Shao, R.G., 2015. Protective effect of gastrodin on bile duct ligation-induced hepatic fibrosis in rats. Food Chem Toxicol. 86, 202–207. https://doi.org/10.1016/j.fct.2015.10.010.

Zhong, X.L., Jing, J.X., Fang, Z.M., Kuken, B., Miao, H.J., Song, H.Y., Zhong, H., 2016. Efficacy and safety analysis of gastrodin injection combined with anti-anxiety drug for treatment of climacteric hypertension. Int. J. Clin. Exp. Med.

Zhou, B.H., Tan, J., Zhang, C., Wu, Y., Liu, G., 2017. Preparation of sulfated polysaccharides from *Gastrodia elata* Blume and its antioxidant activity. *Chinese Journal of Hospital Pharmacy* 37 (17), 1685-1691. 10.13286/j.cnki.chinhosppharmacyj.2017.17.07.

Zhou, Y., Li, M.Y., Lv, T.Y., Huang, M.X., Cheng, B.L., Zhang, Y.Y., Zhu, J., 2021. Gastrodin inhibits virus infection by promoting the production of type i interferon. Front Pharmacol. 11, 103389/fphar.2020.608707.

Zhou, Z., Lin, Y.Z., Zheng, H.Y., He, Y.Z., Xu, H.H., Zhang, S.H., Weng, W., Li, W., Zhu, L. Y., Yang, H.F., 2015. Anticonvulsive and neuroprotective effects of synergetic combination of phenytoin and gastrodin on the convulsion induced by penicillin in mice. Fundam Clin Pharmacol. 29 (4), 371–381. https://doi.org/10.1111/fcp.12127.

Zhou, H.B., Lu, S.Z., Yu, Z.S., Zhang, J.L., Mei, Z.N., 2024. Mechanisms for the biological activity of *Gastrodia elata* Blume and its constituents: a comprehensive review on sedative-hypnotic, and antidepressant properties. Phytomedicine 123, 155251. https://doi.org/10.1016/j.phymed.2023.155251.

Zhou, F., Shen, Y., Liu, B., Chen, X., Wan, L., Peng, D., 2017b. Gastrodin inhibits osteoclastogenesis via down-regulating the nfatc1 signaling pathway and stimulates osseointegration in vitro. Biochem Biophys Res Commun. 484 (4), 820–826. https://doi.org/10.1016/j.bbrc.2017.01.179.

Zhou, B.H., Tan, J., Zhang, C., Wu, Y., 2018. Neuroprotective effect of polysaccharides from *Gastrodia elata* Blume against corticosterone-induced apoptosis in PC12 cells via inhibition of the endoplasmic reticulum stress-mediated pathway. Mol Med Rep. 17 (1), 1182–1190. https://doi.org/10.3892/mmr.2017.7948.

Zhou, L.J., Yang, L.Q., Xie, L.D., 2023. Clinical effects of Banxia Baizhu Tianma decoction combined with Rwandan decoction in the treatment of hypertension with hyperlipidemia:a meta-analysis and trial sequential analysis. Journal of Zhejiang Chinese Medical University 47 (7), 793–803. https://doi.org/10.16466/j.issn1005-5509.2023.07.016.

Zhu, M.F., Deng, W., Di, S.H., Qin, M.M., Liu, D., Yi, B., 2018b. Gastrodin protects cardiomyocytes from anoxia/reoxygenation injury by 14-3-3η. Oxid Med Cell Longev. 2018, 1–11. https://doi.org/10.1155/2018/368539.

Zhu, L., Guan, H., Cui, C., Tian, S., Yang, D., Wang, X., Zhang, S., Wang, L., Jiang, H., 2012. Gastrodin inhibits cell proliferation in vascular smooth muscle cells and attenuates neointima formation in vivo. International Journal of Molecular Medicineint30 (5), 1034–1040. https://doi.org/10.3892/ijmm.2012.1100.

Zhu, L., Wang, Y., Jin, S., Niu, Y., Yu, M., Li, Z., Chen, L., Wu, X., Ding, C., Wu, T., Shi, X., Zhang, Y., Luo, D., Liu, Y., 2023. Parishin A-loaded mesoporous silica nanoparticles modulate macrophage polarization to attenuate tendinopathy. Npj Regen Med. 8 (1), 14. https://doi.org/10.1038/s41536-023-00289-0.

Zhu, H., Wu, X., Huo, J., Hou, J., Long, H.L., Zhang, Z.J., Wang, B., Tian, M.H., Chen, K. X., Guo, D., Lei, M., Wu, W.Y., 2021. A five-dimensional data collection strategy for multicomponent discovery and characterization in traditional Chinese medicine: *Gastrodia* rhizoma as a case study. J. Chromatogr. A 1653, 462405. https://doi.org/10.1016/j.chroma.2021.462405.

Zhu, H.Y., Zhang, D., Zhang, Q., Zhao, Y., He, Z.M., Gao, Y.G., Zhang, L.X., 2018a. 4-hydroxybenzyl alcohol derivatives and their sedative-hypnotic activities. Rsc Adv. 8 (35), 19539–19550. https://doi.org/10.1039/c8ra01972j.

Zuo, W., Xu, F., Zhang, K., Zheng, L., Zhao, J., 2016. Proliferation-enhancing effects of gastrodin on rsc96 schwann cells by regulating erk1/2 and pi3k signaling pathways. Biomed Pharmacother. 84, 747–753. https://doi.org/10.1016/j.biopha.2016.09.106.