Research Article

Yi Xiu, SiYi Wang, Jiaqi Yu, Lijia Jing, Na Guo, Yuzhi Jiao*, Weiwei Zhai*, Xiaomao Li*

Study on the pharmacological effects and active compounds of *Apocynum venetum* L.

https://doi.org/10.1515/chem-2025-0156
received February 14, 2025; accepted April 4, 2025

Abstract: The aim of this study was to provide a comprehensive overview of the botanical characteristics, chemical composition, pharmacological activities, toxicology, and metabolic pathways of the primary active compounds, especially flavonoids, found in *Apocynum venetum* and offer new insights and scientific evidence for further research on this plant. Information on *A. venetum* was obtained from traditional Chinese medicine books and electronic databases such as PubMed, CNKI, ScienceDirect, Scifinder, the Chinese Pharmacopoeia (2020), and the Flora of China. *A. venetum*, with a long history of use, was valuable across multiple. A total of 174 compounds were identified; flavonoids were the primary active constituents. Numerous pharmacological studies demonstrated the leaf extract's antidepressant, hepatoprotective, antihypertensive, lipid-lowering, cardiotonic, anxiolytic, and antioxidant properties, with a high safety profile. *A. venetum* leaves contain diverse chemical constituents with broad pharmacological activities. Modern pharmacological research provides reliable evidence supporting the plant's traditional uses, such as calming the liver and promoting diuresis. However, several issues remain unresolved. Further research on non-flavonoid compounds is needed. Additionally, the potential of *A. venetum* leaves in the treatment of epilepsy is discussed, highlighting future prospects for the plant's development and utilization.

Keywords: *Apocynum venetum* L., oxidative stress, inflammation, active compounds, epilepsy

*** Corresponding author: Yuzhi Jiao,** College of Food, Jiangsu Food & Pharmaceutical Science College, Huai'an, Jiangsu 223001, China, e-mail: 20041007@jsfpc.edu.cn
*** Corresponding author: Weiwei Zhai,** College of Food, Jiangsu Food & Pharmaceutical Science College, Huai'an, Jiangsu 223001, China, e-mail: zaiww6810@126.com
*** Corresponding author: Xiaomao Li,** College of Pharmacy, Jiangsu Food & Pharmaceutical Science College, Huai'an, Jiangsu 223001, China, e-mail: 20221007@jsfpc.edu.cn
Yi Xiu, Jiaqi Yu: College of Life Science, Northeast Forestry University, Harbin, 150040, China; College of Pharmacy, Jiangsu Food & Pharmaceutical Science College, Huai'an, Jiangsu 223001, China
SiYi Wang: Key Laboratory of Chinese Materia, Heilongjiang University of Chinese Medicine, Ministry of Education, Harbin, 150040, China
Lijia Jing: College of Pharmacy, Jiangsu Food & Pharmaceutical Science College, Huai'an, Jiangsu 223001, China
Na Guo: College of Pharmacy, Jiangsu Food & Pharmaceutical Science College, Huai'an, Jiangsu 223001, China; College of Food Science and Technology, East University of Heilongjiang, Harbin, 150040, China

Abbreviations

DA	dopamine
CYP	cytochrome P450 enzyme
FST	forced swimming test
TST	tail suspension test
OFT	open field test
S100A10	S100 calcium-binding protein A10
5-HT	serotonin
ALT	alanine aminotransferase
TNF-α	tumor necrosis factor-α
APAP	acetaminophen
LDH	lactate dehydrogenase
Ang-II	carbachol angiotensin II
L-NAME	an inhibitor of nitric oxide [NO] synthase
TG	triglycerides
MDA	malondialdehyde
SOD	superoxide dismutase
SREBP-1c	sterol regulatory element-binding protein
GLUT	glucose transporters
PDE3	phosphodiesterase 3
GABA	γ-aminobutyric acid
TT	thrombin time
MYD	maximum tolerated dose
TCMs	traditional Chinese medicines

1 Introduction

Apocynum venetum L., commonly known as luobuma in Chinese, is a perennial herbaceous plant belonging to the *Apocynaceae* family. It is also referred to as "tea flower,"

"wild hemp," and "zeqi hemp," and has two varieties: red hemp and white hemp [1]. In China, *A. venetum* is mainly distributed in regions such as East China and Northwest China, typically growing wild in saline-alkaline wastelands, desert fringes, and barren lands, as depicted in Figures 1 and 2.

The bast fiber of *A. venetum* is characterized by its fine, soft, corrosion-resistant, wear-resistant, and tensile-resistant properties, which make it widely applicable in the textile, paper, aviation, and maritime industries. Additionally, *A. venetum* leaves are used as a tea, offering benefits such as heat clearing, dizziness prevention, and cardiotonic effects. Various parts of the plant, including the roots, stems, leaves, and flowers, are used in traditional medicine. The plant is considered slightly cold in nature, with a bitter and sweet taste. *A. venetum* contains a wide range of important phytochemicals, including flavonoids and their glycosides, phenylpropanoids, steroids and their glycosides, terpenoids, volatile oils, organic acids, pyrrolizidine alkaloids, and polysaccharides. These compounds have demonstrated pharmacological activities such as antidepressant, hepatoprotective, antihypertensive, lipid-lowering, cardiotonic, anxiolytic, and antioxidant effects [2]. This review aimed to summarize recent advances in the chemical composition and pharmacological activities of *A. venetum*, exploring its active compounds and mechanisms of action to provide a scientific basis for future research.

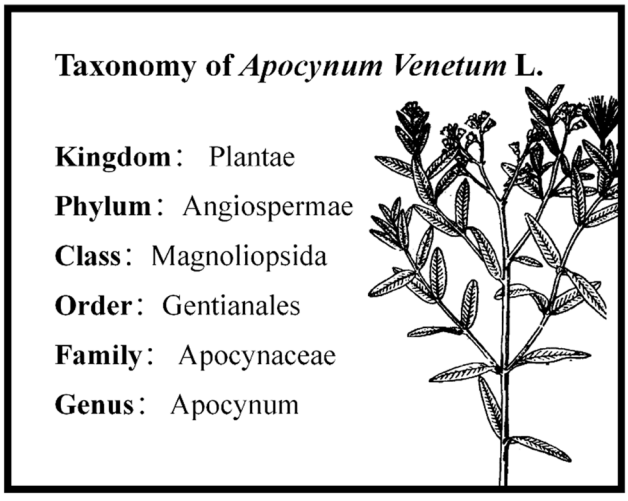

Figure 1: Taxonomy of *A. venetum* L.

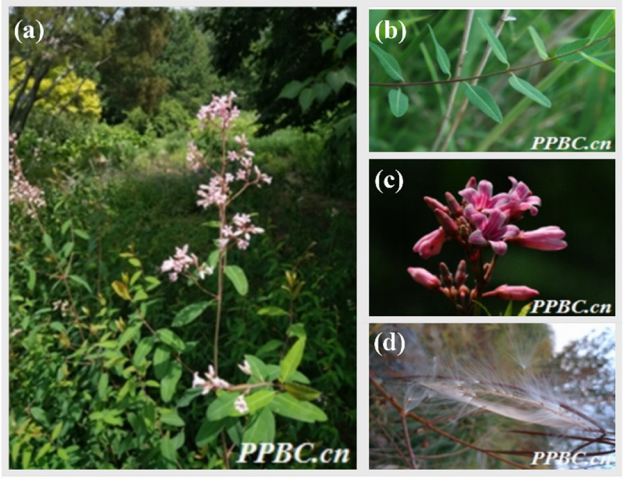

Figure 2: Different parts of *A. venetum* L. [(a) plant, (b) stem and leaf, (c) flower, and (d) fruit].

2 Materials and methods

This study utilized data from electronic databases, including PubMed, CNKI, ScienceDirect, Scifinder, and the Flora of China, focusing on information related to *A. venetum*. The search terms included "*Apocynum venetum* L.," "*Apocynum venetum* L. leaves," "*Apocynum venetum* L. flowers," and "*Apocynum venetum* L. roots." Additionally, the 2020 edition of the Chinese Pharmacopoeia and other relevant books, such as the Dictionary of Chinese Medicine, were consulted to further supplement the content of this review.

3 Results

3.1 Study on the pharmacological action and mechanism of *A. venetum*

Previous studies have reported that various parts of *A. venetum*, including the roots, stems, leaves, and flowers, possess biological activities such as antidepressant, hepatoprotective, antihypertensive, lipid-lowering, cardiotonic, and anxiolytic effects. It may play a role by inhibiting inflammation and regulating oxidative stress response (Figure 3).

3.1.1 *A. venetum* flavonoids demonstrate antidepressant effects through the regulation of calcium ion channels, which enhances neurohormone levels and inhibits neuroinflammatory responses

It has been reported that the antidepressant activity of *A. venetum* is mainly attributed to its flavonoid compounds, and the total flavonoid content is positively correlated with its antidepressant effects [3]. Studies have shown that treatment with *A. venetum* extracts at doses of 30–125 mg/kg for 14 days significantly shortened the immobility time of male SD rats in the forced swimming

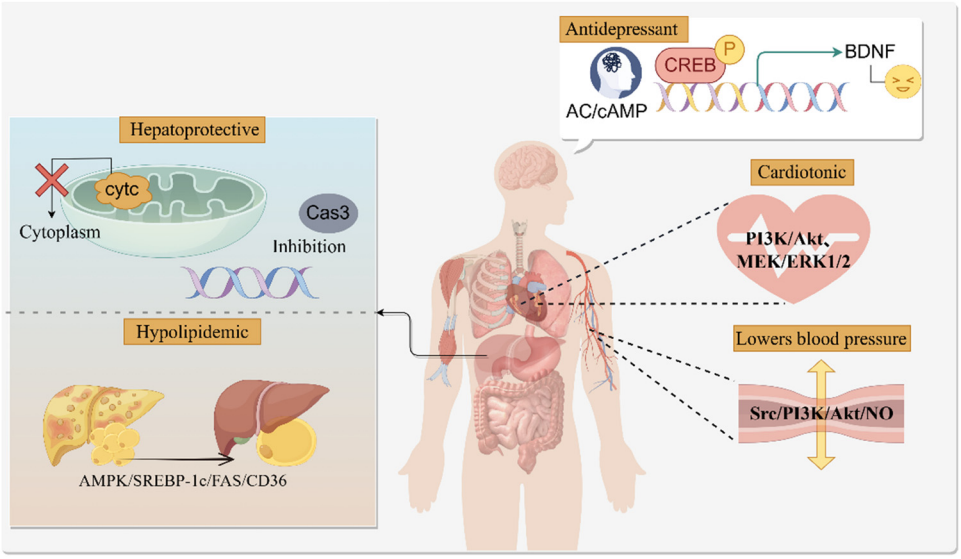

Figure 3: The graphical abstract of pharmacological action.

test (FST). Hyperoside and isoquercitrin, at doses of 0.6–1.3 mg/kg, produced similar effects. Moreover, treatment with *A. venetum* extract at doses of 15, 60, and 250 mg/kg for 8 weeks resulted in a reduction in norepinephrine and dopamine (DA) concentrations in rats. Through radioligand binding assays, it was found that treatment with *A. venetum* extract did not alter the binding of $^{[125I]}$CYP (cytochrome P450 enzyme) to β-adrenergic receptors in the frontal cortex of rats, suggesting that *A. venetum* extract may exert its antidepressant effects by modulating the presynaptic α2-receptor sensitivity through the adrenergic system [4].

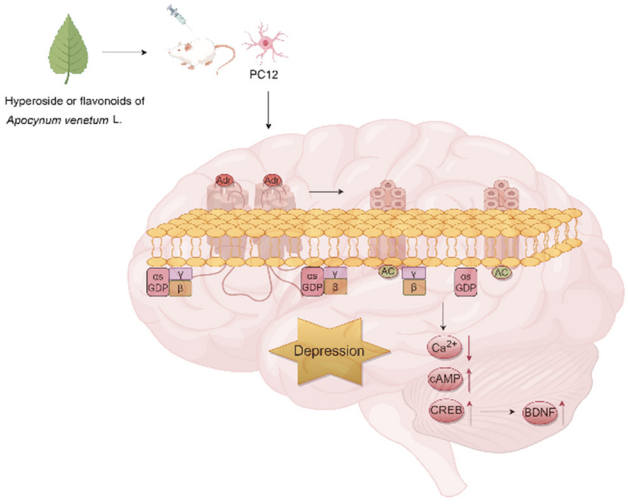

Figure 4: Antidepressant effects of *A. venetum* flavonoids and hyperoside.

Further research revealed that *A. venetum* flavonoid extract (25, 50, and 100 μg/mL) or hyperoside (2.5, 5, and 10 g/mL) could protect PC12 cells from cortisol-induced neurotoxicity by upregulating BDNF through reducing intracellular Ca^{2+} levels and activating the AC-cAMP-CREB signaling pathway, thereby exerting antidepressant effects [5,6] (Figure 4). Additionally, male ICR mice were pretreated with 50 mg/kg sulpiride (DA D2 receptor antagonist), 0.05 mg/kg SCH23390 (DA D1 receptor antagonist), and 50 mg/kg *A. venetum* extract for 10 days before being subjected to the FST, tail suspension test (TST), and open field test (OFT). The DA receptor antagonists blocked the anti-depressant effects of *A. venetum* extract in the TST, indicating that DA D1 receptors are involved in the antidepressant mechanism of *A. venetum* extract [6]. Furthermore, studies found that treatment with *A. venetum* water extract at doses of 0.58, 1.17, and 2.34 g/kg for 4 weeks increased the sleep occurrence rate, sleep duration, and brain coefficient in male ICR mice. Treatment with 1.62 g/kg *A. venetum* water extract for 4 weeks elevated the brain coefficient in male SD rats, decreased DA levels, and increased 5-hydroxyindoleacetic acid levels. These results suggest that *A. venetum* water extract improves sleep, potentially through mechanisms involving the upregulation of hypothalamic 5-HT (serotonin) levels and downregulation of DA levels [7–9].

Ion channels play a crucial role in the antidepressant effects of *A. venetum* leaves. Through whole-cell patch-clamp recording on N2A cells, researchers have found that *A. venetum* water extract exerts neuropharmacological effects by regulating voltage-gated Na^+ and K^+ channels [10]. To further explore the antidepressant mechanism of *A. venetum* leaves, the chronic unpredictable mild stress

model was used, wherein female SD rats were subjected to mild stress for 4 weeks, followed by an OFT. It was observed that pretreatment with 40 or 80 mg/kg of total flavonoid extract from *A. venetum* significantly increased the total horizontal movement distance and vertical activity counts of the rats. Reverse transcription polymerase chain reaction analysis revealed a reduction in the expression level of the S100A10 gene. S100A10, a member of the calcium-binding protein S100 family, is a widely distributed protein involved in various intracellular and extracellular processes. The total flavonoid components of *A. venetum* may exert antidepressant effects by regulating the expression of the S100A10 (S100 calcium-binding protein A10) gene.

3.1.2 The extract of *A. venetum* leaves has the potential to protect the liver by modulating oxidative stress and inhibiting cellular apoptosis

The use of *A. venetum* leaves as a hepatoprotective agent has a history of over 1,000 years. Modern pharmacological studies have shown that pretreatment with *A. venetum* extracts at doses of 50 and 500 mg/kg for 1 week inhibits the elevation of alanine aminotransferase (ALT) levels induced by CCL_4 or D-galactosamine/lipopolysaccharide (LPS) in male ddY mice, and reduced tumor necrosis factor-α (TNF-α) levels. The flavonoid compounds in *A. venetum* were found to inhibit TNF-α-induced cell death, suggesting that flavonoids might be the hepatoprotective components in *A. venetum* leaves [11]. Furthermore, pretreatment with 50 or 100 mg/kg *A. venetum* leaf extract for 3 days alleviated acetaminophen (APAP)-induced liver damage in male Kunming mice. Histopathological examination, DNA ladder assay, and Western blot analysis showed that *A. venetum* leaf extract inhibited APAP-induced hepatocyte apoptosis by suppressing the release of cytochrome c, activation of caspase-3, and DNA fragmentation, thereby exerting its hepatoprotective effects [12] (Figure 5). To further investigate the hepatoprotective mechanism of *A. venetum* leaves, *in vitro* studies using 25, 50, and 100 μg/mL of total flavonoid extract from *A. venetum* showed significant protection against CCL_4-induced damage in HepG2 cells. Cell viability was increased, the number of apoptotic cells decreased, and lactate dehydrogenase (LDH) release was reduced in a dose-dependent manner. Subsequent *in vivo* experiments revealed that pretreatment with 100, 200, and 400 mg/kg of total flavonoid extract from *A. venetum* for 14 days significantly reduced the elevation of ALT and aspartate aminotransferase levels in male Kunming mice, and provided dose-dependent protection against the reduction in peroxidase activity induced by CCL_4 [13]. These findings suggest that the total flavonoid components of *A. venetum* may exert hepatoprotective effects by scavenging free radicals, inhibiting apoptosis, and enhancing the antioxidant defense system.

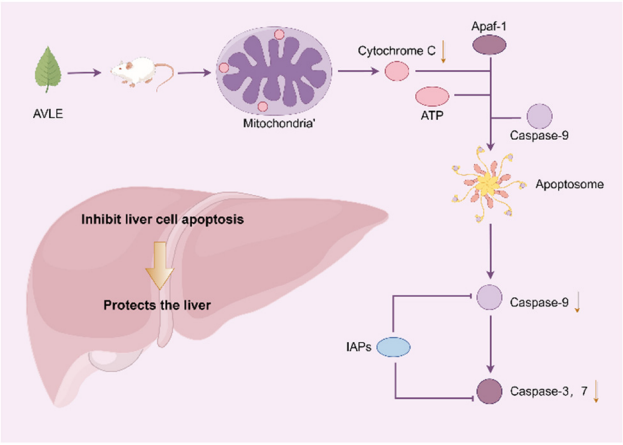

Figure 5: Hepatoprotective effects of *A. venetum* leaf extract.

3.1.3 The leaf extract of *A. venetum* has been shown to lower blood pressure through the inhibition of inflammation and the enhancement of vascular endothelial function

It has been reported that the aqueous extract of *A. venetum* leaves exhibits significant antihypertensive effects. Pretreatment with 10 mg/mL of *A. venetum* extract for 15 min effectively inhibited the contraction of aortic rings in male SD rats induced by KCl, carbachol, angiotensin II (Ang-II), and phenylephrine [14,15]. Further studies revealed that this inhibitory effect could be reversed by L-NAME (an inhibitor of nitric oxide [NO] synthase), suggesting that the antihypertensive effect of *A. venetum* extract may be mediated through the scavenging of superoxide anions and the release of NO [15]. An in-depth investigation into the antihypertensive mechanism of *A. venetum* leaves showed that treatment with 10 μg/mL of *A. venetum* extract increased NO levels in the aorta of male SD rats, and this effect was abolished by inhibitors of Src kinase and PI3K. Moreover, in the presence of Src kinase inhibitors, PI3K inhibitors, and NO synthase inhibitors, the same concentration of *A. venetum* extract led to the upregulation of Akt and eNOS expression in human umbilical vein endothelial cells. The expression of these two proteins was inhibited by Src kinase and PI3K inhibitors, which subsequently reduced NO levels [16]. Therefore, *A. venetum* extract induces NO-mediated vasodilation through the Src/PI3K/Akt signaling pathway, as illustrated in Figure 6. Network pharmacology studies on the anti-hypertensive mechanisms of *A. venetum*

suggest that its active components primarily exert therapeutic effects on hypertension by inhibiting inflammatory responses, improving vascular endothelial function, and influencing hemorheology [17].

3.1.4 The leaf extract of *A. venetum* contributes to the reduction of blood lipid levels by enhancing oxidative stress management and suppressing inflammation

A. venetum leaves exhibit significant lipid-lowering effects. After 1 month of treatment with total flavonoid extracts of *A. venetum* at doses of 5, 50, and 100 mg/kg, or with isoquercitrin at doses of 0.1, 0.5, and 5 mg/kg, male Wistar rats, male SD rats, or male ICR mice fed a high-fat diet showed reduced lipid deposition, aortic thickening, and a decrease in subendothelial foam cells and lipid vacuoles in the aorta. In addition, the levels of total cholesterol, triglycerides (TG), low-density lipoprotein cholesterol, vascular cell adhesion molecule-1, malondialdehyde (MDA), and Ang-II in serum decreased, while high-density lipoprotein cholesterol levels and superoxide dismutase (SOD) activity increased. The atherosclerosis index and NO levels were also elevated [18–20]. In summary, the total flavonoids in *A. venetum* may exert lipid-lowering effects by improving endothelial damage and oxidative stress caused by hyperlipidemia.

Moreover, genetic studies on male ICR mice using SREBP-1c (sterol regulatory element-binding protein) and AMPK inhibitors, along with glucose uptake experiments, revealed that inhibition of SREBP-1c and AMPK for 2 weeks attenuated the anti-obesity effects of isoquercitrin. Administration of isoquercitrin reduced blood glucose levels and increased the gene expression of glucose transporters (GLUT1, GLUT2, and GLUT4) in obese mice. Additionally, the levels of SREBP-1c, fatty acid synthase (FAS), stearoyl-CoA de-saturase-1, and CD36 were significantly elevated in obese mice. These findings suggest that *A. venetum* water extract and its main component isoquercitrin may improve obesity symptoms by inhibiting the AMPK/SREBP-1c/FAS/CD36 signaling pathway and promoting glucose uptake [20] (Figure 7). Network pharmacology studies investigating the anti-atherosclerosis and lipid-lowering mechanisms of *A. venetum* leaves suggest that the plant primarily exerts its therapeutic effects through inhibiting inflammatory responses, improving vascular endothelial function, and influencing hemorheology in the treatment of atherosclerosis. It treats hyperlipidemia through processes such as lipid biosynthesis, regulation of inflammatory responses, and oxidative stress [18,21].

3.1.5 The leaf extract of *A. venetum* may exert a cardiotonic effect by interacting with proteins and pathways associated with inflammation and the immune system

A. venetum leaves contain various cardiac glycosides, which exhibit significant cardiotonic effects. Studies have shown that treatment with 1 mg/mL of *A. venetum* extract significantly increased the contractile force and pulse rate of the right atrium in male Hartley guinea pigs. *In vitro* assays on human platelet phosphodiesterase 3 (PDE3) revealed that *A. venetum* extract at this concentration inhibited PDE3 activity, suggesting that the cardiotonic effects of *A. venetum* extract may be mediated through PDE3 inhibition [22]. Further research demonstrated that pretreatment with 500 mg/kg of *A. venetum* leaf extract for 7 days reduced myocardial infarction size and the number of apoptotic cardiomyocytes in male SD rats subjected to myocardial ischemia/reperfusion injury. The treatment also decreased the AI and reduced the levels of creatine kinase, LDH, SOD, caspase-3, and

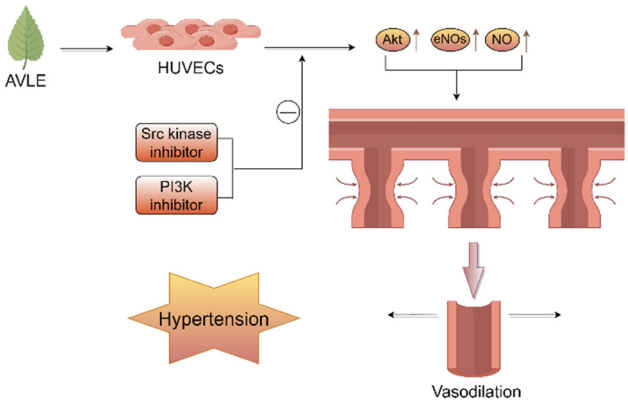

Figure 6: Vasodilatory effects of *A. venetum* leaf extract.

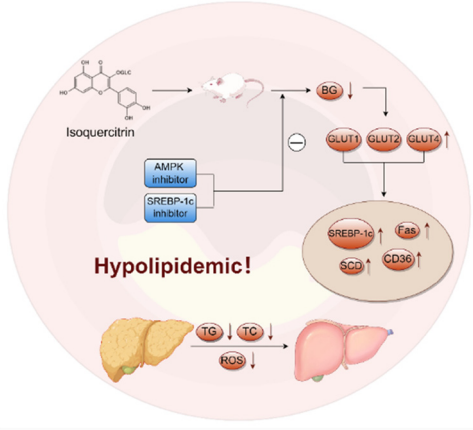

Figure 7: Lipid-lowering effects of isoquercitrin.

gp91phox. Additionally, *A. venetum* leaf extract inhibited the production of superoxide and MDA while increasing the phosphorylation levels of Akt and ERK1/2. These protective effects were blocked by the PI3K inhibitor wortmannin or the ERK1/2 inhibitor PD98059, indicating that *A. venetum* leaf extract exerts its cardioprotective effects through the PI3K/Akt and MEK/ERK1/2 signaling pathways [23,24] (Figure 8).

Moreover, network pharmacology studies on the cardioprotective mechanisms of *A. venetum* leaves suggest that the plant may treat cardiovascular diseases by targeting proteins and pathways related to inflammation, the immune system, endocrine system, signal transduction, hormone regulation, smooth muscle relaxation, and angiogenesis [21]. Experimental validation has shown that pretreatment with *A. venetum* leaf extract for 30 min alleviated doxorubicin-induced apoptosis in rat cardiomyocyte H9C2 cells and human cardiomyocyte HCM cells. The survival rate of cardiomyocytes increased in a dose-dependent manner from 0 to 70 μg/mL, with the highest survival rate observed at 70 μg/mL. However, this effect was reversed by the Akt inhibitor, suggesting that *A. venetum* leaf extract may protect cardiomyocytes by inhibiting apoptosis through the Akt/Bcl-2 signaling pathway [25].

3.1.6 *A. venetum* extract exerts anti-anxiety effects by mediating GABA system

Traditionally, *A. venetum* has been known for its calming effects, and modern pharmacological studies have shown that ethanol extracts of *A. venetum* at doses of 22.5–30 and 100–125 mg/kg, as well as kaempferol at 0.02–1.0 mg/kg, increased the time spent and the number of entries into the open arms of male C57BL/6 mice in the elevated plus maze test. However, this anxiolytic effect was blocked by the GABA (γ-aminobutyric acid) receptor antagonists flumazenil and WAY-100635, which effectively inhibited the effects of *A. venetum* extracts at doses of 125 and 30 mg/kg, respectively [26,27]. These findings suggest that kaempferol contributes to the anxiolytic activity of *A. venetum* and that the anxiolytic effect of its ethanol extract is mediated through the GABAergic system.

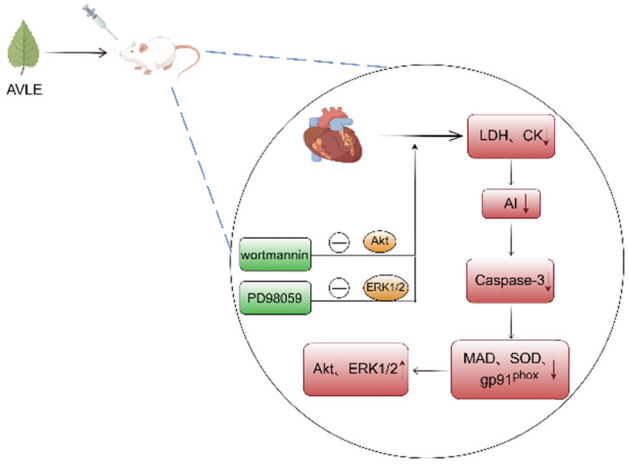

Figure 8: Cardioprotective effects of *A. venetum* leaf extract.

3.1.7 Other effects

In addition to the aforementioned activities, *A. venetum* exhibits inhibiting oxidative stress, anti-inflammatory, and anticoagulant effects.

A. venetum extract is abundant in polyphenolic compounds and may function as an *in vitro* aldose reductase inhibitor. It has the potential to restore the polyol pathway, inhibit oxidative stress, and maintain intracellular autophagy through the AMPK/mTOR/ULK1 signaling pathway. These mechanisms may underlie the therapeutic effects of *A. venetum* in the treatment of diabetic retinopathy [22]. *A. venetum* polysaccharide, which mainly consists of arabinose, galactose, rhamnose, glucose, xylose, caramel, and mannose, can inhibit the expression of cyclooxygenase-2, tumor necrosis factor-α, and interleukin-6 mRNA in RAW 264.7 macrophages induced by LPS. It also significantly reduced paw edema in mice after carrageenan injection. It can be developed as a potential antioxidant and anti-inflammatory agent [28].

In terms of anticoagulant activity, *A. venetum* has unique effects. Studies have shown that *A. venetum* extracts at concentrations of 200–500 μg/mL can significantly inhibit ADP-induced platelet aggregation in venous blood samples from male rabbits in a dose-dependent manner. The ethyl acetate fraction of *A. venetum* extract exhibited the strongest anti-platelet aggregation activity, suggesting that the flavonoid glycosides in *A. venetum* possess potent anti-platelet properties [29]. Additionally, polysaccharides such as Vp3, at a concentration of 1 mg/200 μL, were found to prolong prothrombin time and thrombin time (TT), while Vp2a-II at the same concentration prolonged activated partial thromboplastin time and TT. Vp3 exerts anticoagulant effects through the extrinsic pathway, whereas Vp2a-II inhibits coagulation via both intrinsic and extrinsic pathways [30].

Network pharmacology studies on the antiseptic effects of *A. venetum* leaves revealed that compounds such as kaempferol, luteolin, proanthocyanidin B1, and stigmasterol may target predictive biological markers such as AKT1, VEGFA, MAPK3, EGFR, SRC, and PTGS2 to regulate signal transduction, hormone levels, and anti-infection processes. These compounds

Table 1: Flavonoid compounds identified in *A. venetum*

Classification	Name	Source	References
Flavonoids	(1) Luteolin	Leaf	[35]
	(2) Apigenin	Leaf	[35]
	(3) Isoorientin	Leaf	[35]
	(4) Acacetin	Leaf	[35]
	(5) Chrysoeriol	Leaf	[36]
Flavonols	(6) Kaempferol	Leaves, flowers	[37]
	(7) Quercetin	Leaves, flowers	[38]
	(8) Rutin	Leaf	[39]
	(9) Tamarixetin	Leaf	[40]
	(10) Isorhamnetin	Leaf	[39,41]
	(11) Myricetin	Leaf	[42]
	(12) Baicalein	Leaf	[43–45]
	(13) Avicularin	Leaf	[44]
	(14) Hyperoside	Leaf	[38]
	(15) Isoquercitrin	Leaf	[38]
	(16) Quercetin-3-glucuronide	Leaf	[43]
	(17) Trifolin	Leaf	[43,44]
	(18) Quercetin 7-*O*-rutinoside	Leaf	[35]
	(19) Acetylated hyperoside	Leaf	[43,44]
	(20) Acetylated isoquercetin	Leaf	[38]
	(21) Malonated hyperoside	Leaf	[45]
	(22) Malonated isoquercetin	Leaf	[45]
	(23) Kaempferol-6′-*O*-acetate	Leaf	[11]
	(24) Isoquercetin-6′-*O*-acetate	Leaf	[11]
	(25) Kaempferol-3-*O*-*α*-D-galactopyranoside	Leaf	[46]
	(26) Quercetin-3-*O*-*α*-D-glucosy-*α*-D-glucopyranoside	Toast leaves	[43,44]
	(27) Astragalin	Leaf	[47]
Dihydroflavones	(28) Hesperetin	Leaf	[36]
	(29) Bavachin	Leaf	[37]
Double flavonoids	(30) Amentoflavone	Leaf	[11,12]
	(31) Biapigenin	Leaf	[11,12]
Isoflavones	(32) 8-*O*-methylretusin	Leaf	[48]
Chalcones	(33) Carthamin	Leaf	[36]
Anthocyanins	(34) Delphinidin	Leaf	[36]
	(35) Pelargonidin	Leaf	[36]
	(36) Malvidin chloride	Leaf	[36]
	(37) Peonidin chloride	Leaf	[36]
	(38) Cyanidin	Leaf	[36]
Flavanols	(39) Epicatechin	Leaf	[49]
	(40) Catechin	Leaf	[49]
	(41) Gallic catechin	Leaf	[49]
	(42) Epigallocatechin	Leaf	[49]
Proanthocyanidins	(43) Procyanidin C1	Leaf	[3]
	(44) Procyanidin B2	Leaf	[50,51]
	(45) Procyanidin B1	Leaf	[52]
	(46) Procyanidin	Leaf	[53]

may treat sepsis through pathways such as VEGF, EGFR, ErbB, HIF-1, and Ras, playing an important role in controlling inflammation and infection [24].

3.2 Toxicological analysis of *A. venetum*

A. venetum tea, made from the dried leaves of the plant, has a long history of use for lowering blood pressure, reducing blood lipids, and delaying aging. It remains widely consumed today, with a recommended daily dosage of 0.3 g/kg. Modern studies have shown that *A. venetum* tea contains flavonoids, sterols, glycosides, amino acids, and other chemical constituents, with the total flavonoid content ranging from 0.20 to 2.5%. Flavonoids are the primary active compounds in *A. venetum*, providing antihypertensive, cardiotonic, diuretic, and lipid-lowering effects. Acute toxicity experiments with total flavonoid extracts of *A. venetum* in mice revealed that the maximum tolerated dose (MTD) was 10.24 g/(kg d), which is 161 times the recommended human daily dose, indicating a high level of safety [31].

Although there are few safety evaluations of *A. venetum* both domestically and internationally, a safety assessment was conducted following the national standard “Procedures and Methods for Toxicological Evaluation of Food Safety (GB15193.1-1994).” This assessment indicated that when consumed as a natural health tea, *A. venetum* tea did not produce toxic effects on any toxicological parameters in experimental animals at doses up to 10 times the human intake [32]. Additionally, acute toxicity tests in mice showed that the oral MTD of *A. venetum* tea was greater than 30.0 g/kg bw, classifying it as a non-toxic substance [33]. However, *A. venetum* water extract administered at a maximum dose of 24 g/(kg day), equivalent to 800 times the intended human dose, exhibited some acute toxic effects. Subacute toxicity tests indicated that the safe dose of *A. venetum* water extract was 40–80 times the clinical dose [34]. Overall, the safety margin of *A. venetum* extract is relatively high.

Therefore, *A. venetum* is considered a safe natural plant for consumption and has potential for further development and utilization. However, due to the relatively high

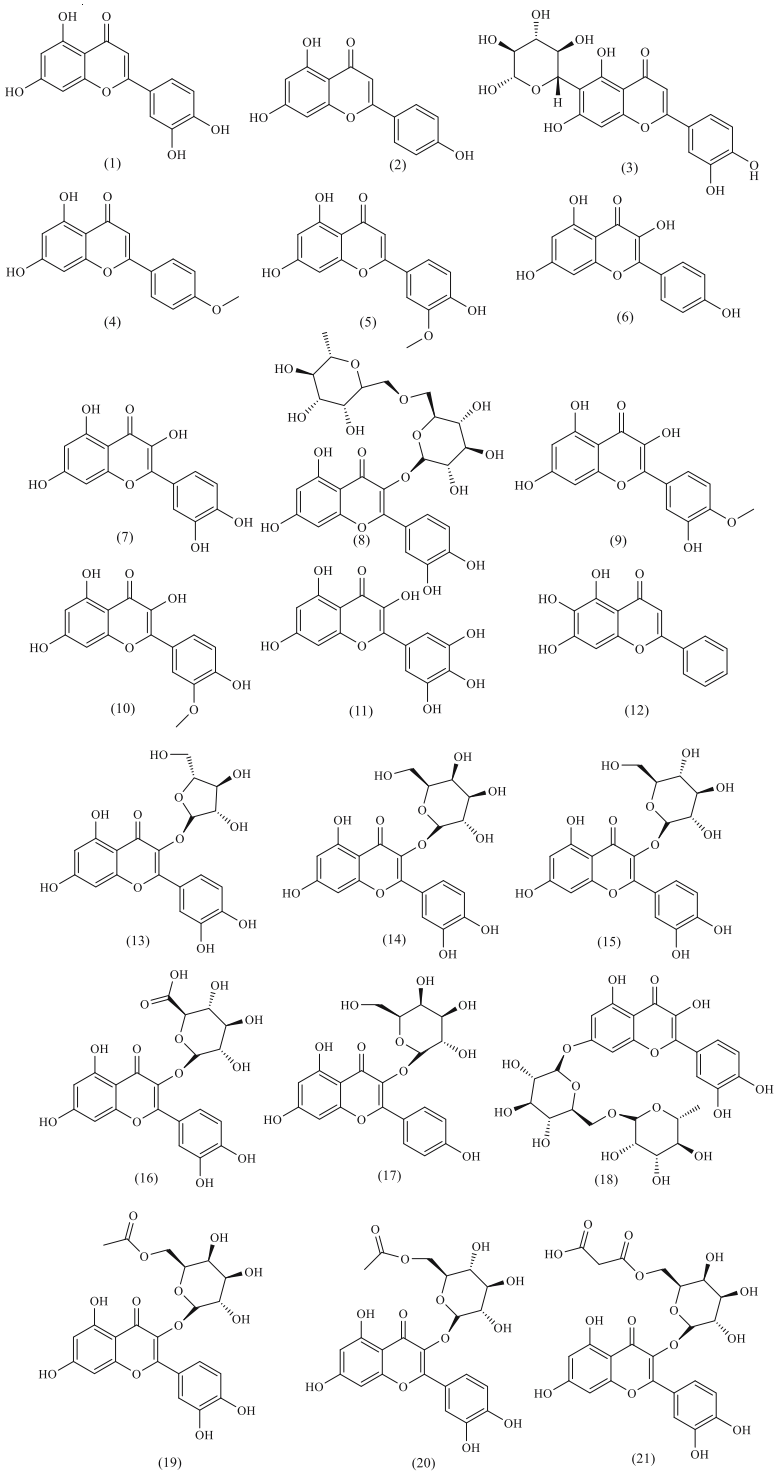

Figure 9: Chemical structures of flavonoids and their glycosides.

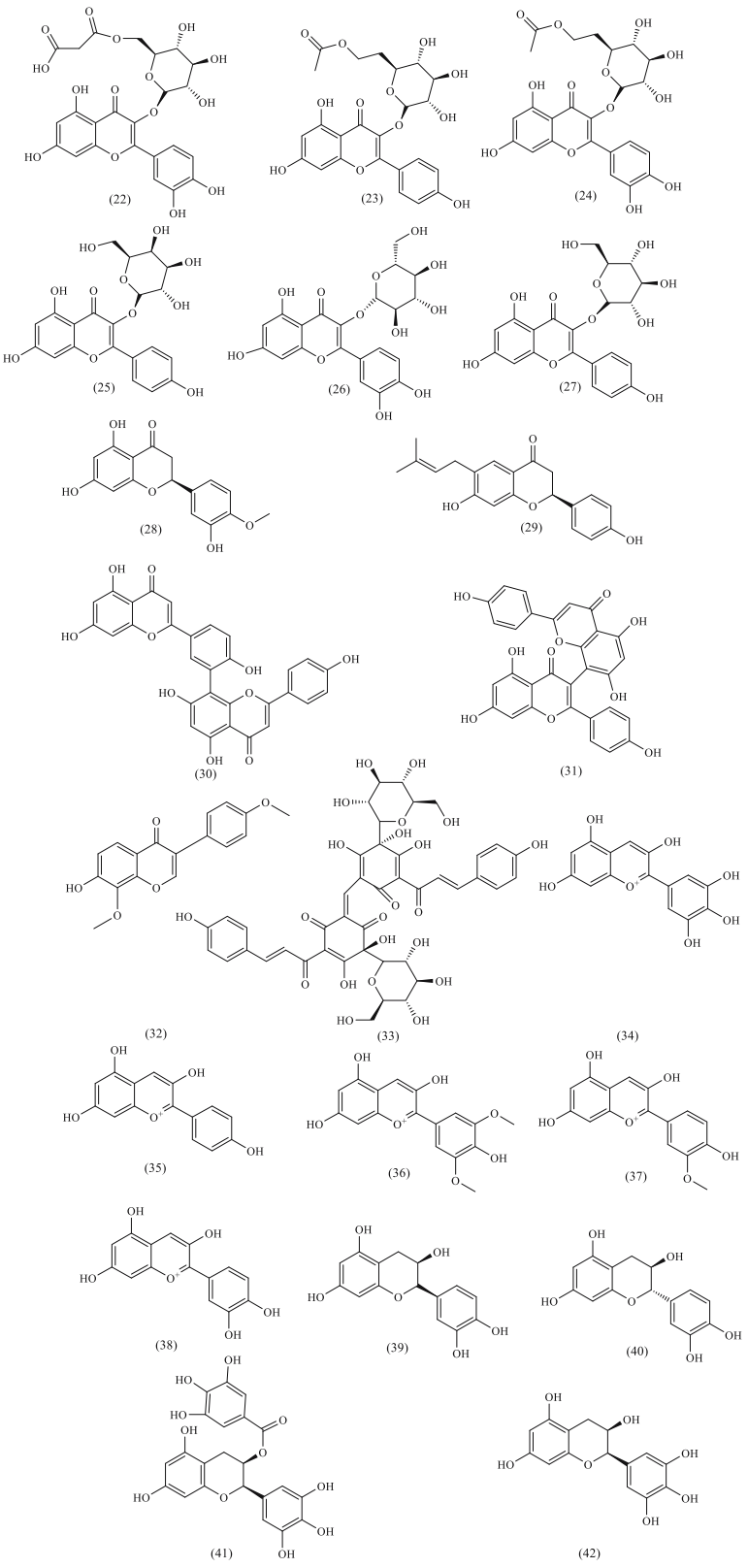

Figure 9: (*Continued*)

Table 2: Phenylpropanoid compounds identified in *A. venetum*

Serial number	Name	Source	References
(1)	Scopoletin	Leaf	[54]
(2)	Esculetin	Leaf	[55]
(3)	Esculin	Leaf	[54]
(4)	Isofraxidin	Leaf	[54]
(5)	2-Methyl-5-acetonyl-7-hydroxychromone	Leaf	[56]
(6)	Neochlorogenic acid	Leaf	[57]
(7)	Chlorogenic acid	Leaf	[55]
(8)	Cryptochlorogenic acid	Leaf	[57]
(9)	3-*O*-Caffeoylquinic acid methyl ester	Leaf	[55]
(10)	Isochlorogenic acid C	Leaf	[53]
(11)	1-CQA	Leaf	[53]

content of alkaloids, which have certain toxic effects, *A. venetum* tea should not be consumed in large quantities over prolonged periods to avoid toxicity. It is also not recommended for individuals with weak digestive systems or those with heart conditions.

4 Active components

To date, various chemical constituents have been identified and isolated from *A. venetum*, including flavonoids, phenylpropanoids, steroids, terpenoids, volatile oils, organic acids, alkaloids, and polysaccharides. Each of these compounds plays distinct pharmacological roles.

4.1 Flavonoids and their glycosides

Over the past two decades, several flavonoid compounds have been isolated from *A. venetum*, including flavones, flavonols, flavanols, dihydroflavonoids, biflavonoids, isoflavones, chalcones, anthocyanins, and proanthocyanidins. Increasing research has reported the biological activities of

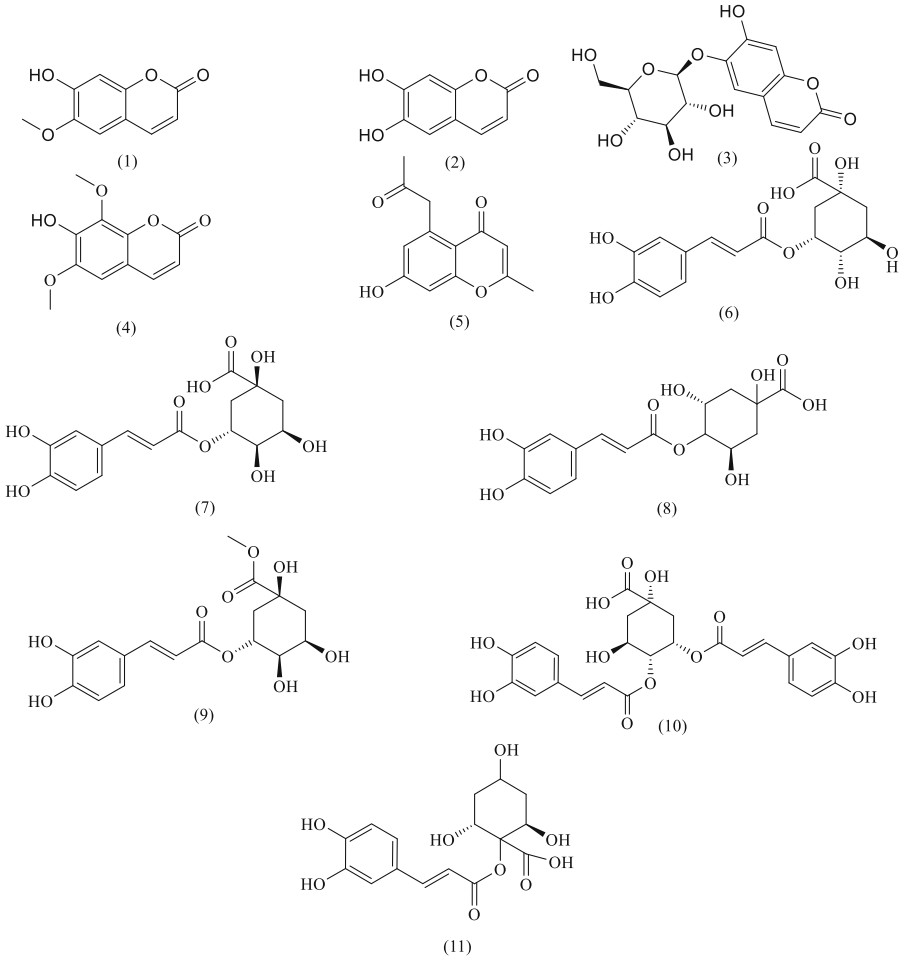

Figure 10: Chemical structures of phenylpropanoids.

Table 3: Steroid compounds identified in *A. venetum*

Serial number	Name	Source	References
(1)	*β*-Sitosterol	Stems	[58]
(2)	Daucosterol	Flowers	[43]
(3)	Stigmasterol	Leaf	[58]
(4)	Campesterol	Leaf	[58]
(5)	Cholesterol	Leaf	[58]
(6)	Uvaol	Leaf	[58]
(7)	Cardenolide B-1	Leaves, stems, roots	[59]

these flavonoids. For instance, hyperoside and isoquercitrin have been shown to exhibit antihypertensive effects. Moreover, many traditional Chinese medicines (TCMs) used to treat coronary heart disease or promote blood circulation, such as rutin and quercetin, contain flavonoid compounds, which have demonstrated significant coronary dilation effects. Some flavonoids have also been shown to reduce blood lipid levels and prevent atherosclerosis. The names and structures of these flavonoid compounds are listed in Table 1 and Figure 9.

4.2 Phenylpropanoids

The phenylpropanoids isolated from *A. venetum* to date primarily include simple phenylpropanoids and coumarins. Coumarins, which are widely found in nature, have become a research hotspot in recent years for the development of new drugs due to their strong biological activities, such as antiviral, antitumor, anti-osteoporotic, and anticoagulant effects. The names and structures of these phenylpropanoid compounds are listed in Table 2 and Figure 10.

4.3 Steroids and their glycosides

Among the steroid compounds isolated from *A. venetum*, *β*-sitosterol and lupeol are the most prominent active components, known for their antibacterial and antiviral activities. Cardiac glycosides, which are essential for the treatment of heart failure, have their biological activity and toxicity influenced by the type and number of sugar moieties attached. Certain cardiac glycosides also exhibit antitumor effects in animals, such as hyrcanoside, which has demonstrated significant inhibitory effects on human nasopharyngeal carcinoma.

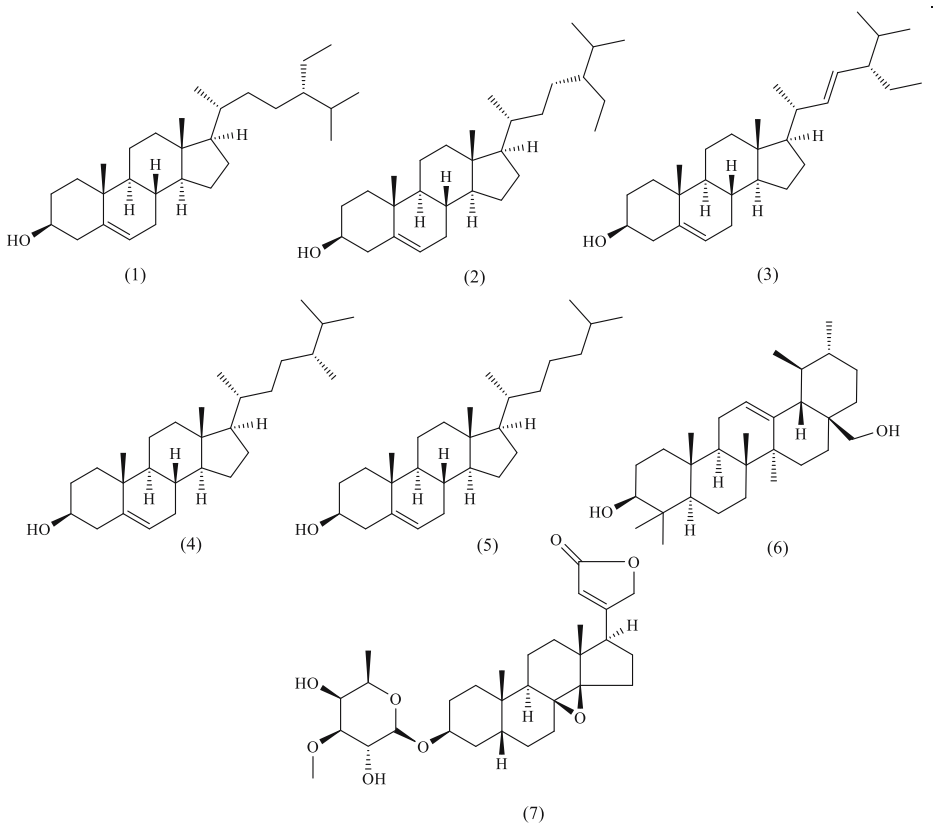

Figure 11: Steroids and their glycosides.

Table 4: Terpenoids and volatile oils identified in *A. venetum*

Classification	Serial number	Name	References
Terpenoids	(1)	Lupeol	[60]
	(2)	Phytol	[60]
Aromatic compounds	(3)	*P*-xylene	[61]
	(4)	4-Ethylphenol	[61]
	(5)	3,5-diMethylphenol	[61]
	(6)	3-Methylphenol	[61]
	(7)	1,2-Benzenedimethanol	[61]
	(8)	5,6,7,7*a*-Tetrahidro-4,4,7a-trimetil-(4*H*)-benzofuranosa	[61]
	(9)	Dibutyl phthalate	[62]
	(10)	Phenethyl alcohol	[62]
	(11)	Benzyl alcohol	[62]
	(12)	1,1-Dimetoxi-etanoacetofenona	[62]
	(13)	2-Feniletil acetato	[62]
	(14)	Benzoin acid 2 phenyl ethyl ester	[62]
	(15)	Ethyl formate	[62]
	(16)	Diisobutyl phthalate	[62]
	(17)	Alcohol *cis*-oxoaromatico	[61]
	(18)	Alcoholes aromaticos transoxidados	[61]
	(19)	Benzaldehyde	[61]
	(20)	Anethol	[61]
	(21)	1,2-Dihidro-1,5,8-trimetil-naftaleno	[61]
	(22)	2-Penten-1-ol	[61]
	(23)	4,4-Dimetil-2-ciclopenten-1-ona	[61]
	(24)	Metilciclohexano	[61]
	(25)	2-Metildihidro-3(2*H*)-furanona	[61]
	(26)	1,2,5,5-Tetrametil-1,3-ciclopentadieno	[61]
	(27)	*N*-Hexen-3-ol	[61]
	(28)	1,3,5-Octatrieno	[61]
	(29)	2-Furanmetanol	[61]
	(30)	1,3,5,7-Cicloocteno	[61]
	(31)	2-Acetilfuran	[61]
	(32)	6-Methyl-5-hepten-2-one	[61]
	(33)	2-Pentilfurano	[61]
	(34)	Limoneno	[61]
	(35)	2,2,6-Trimetilciclohexanona	[61]
	(36)	1-Octanol	[61]
	(37)	*α*-Terpinene	[61]
	(38)	2,6-Dimetilciclohexanol	[61]
	(39)	6-Methyl-3,5-pentadien-2-one	[61]
	(40)	Camphene	[61]
	(41)	Menthone	[61]
	(42)	Menthol	[61]
	(43)	*α*-Terpineol	[61]
	(44)	Safranal	[61]
	(45)	Decyl aldehyde	[61]
	(46)	*β*-Cyclocitraldehyde	[61]
	(47)	*α*-Purineno	[61]
	(48)	Damascenone	[61]
	(49)	Tetradecane	[61]
	(50)	*δ*-Eudesmene	[61]
	(51)	1,2,4-Triethylcyclohexane	[61]
	(52)	*β*-Caryophyllene	[61]
	(53)	Damascenone	[61]
	(54)	Pristane	[61]
Aromatic compounds	(55)	*N*-Eicosane	[61]

(*Continued*)

Table 4: *Continued*

Classification	Serial number	Name	References
	(56)	2,6,11,15-Tetrametilhexadecano	[61]
	(57)	10-Methylnonadecane	[61]
	(58)	Ácido *E*-15-heptadecenoico	[61]
	(59)	6,10,14-Trimetil-2-pentadecanona	[62]
	(60)	Methyl palmitate	[62]
	(61)	Palmitic acid	[62]
	(62)	1-Octadeceno	[62]
	(63)	*N*-eicosane	[62]
	(64)	Oleic acid	[62]
	(65)	10,13-Octadecadienoato de metilo	[62]
	(66)	*N*-heneicosane	[62]
	(67)	Linoleic acid	[62]
	(68)	1-(1,5-Dimetilhexil)-4-(4-metilpentil) ciclohexano	[62]
	(69)	2-Octilciclopropanocarboxaldehído	[62]
	(70)	(*Z*)-9,17-Octadecadienal	[62]
	(71)	Olealdehyde	[62]
	(72)	Linolenic alcohol	[62]
	(73)	Tetracosene	[62]
	(74)	*N*-tetracosane	[62]
	(75)	Ethyl acetate	[62]
	(76)	Leaf alcohol	[62]
	(77)	15-Nonacosanone	[62]
	(78)	2-Methoxy-1,3-dioxolane	[62]
	(79)	Squalene	[62]
	(80)	Octadecanaldehyde	[62]
	(81)	Pentadecane	[62]
	(82)	Hexadecane	[62]
	(83)	*N*-heptadecane	[62]
	(84)	Nineteenth carbon dioxide	[62]
	(85)	Methyl oleate	[62]
	(86)	*N*-hentriacontane	[62]
	(87)	Palmitic acid	[58]
	(88)	Linolenic acid	[55]

The names and structures of these steroid compounds are listed in Table 3 and Figure 11.

4.4 Terpenoids and volatile oils

To date, two terpenoid compounds, lupeol and phytol, have been isolated from the leaves of *A. venetum*. Additionally, 19 volatile compounds have been identified from the leaves of *A. venetum*. Furthermore, 88 aliphatic and aromatic compounds have been isolated from the flowers and leaves. According to ancient medical texts, volatile oils possess various medicinal properties, including expectorant, antitussive, antiasthmatic, antipyretic, analgesic, antibacterial, and anti-inflammatory effects. The names and structures of these terpenoid compounds and volatile oils are listed in Table 4 and Figure 12.

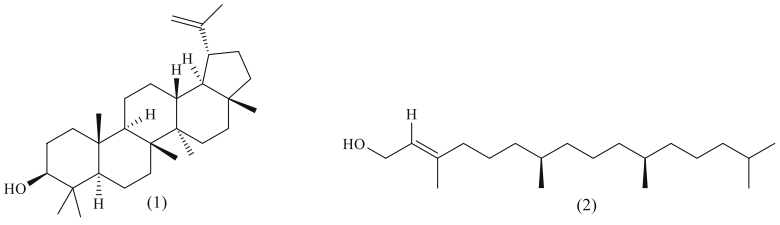

Figure 12: Chemical structures of terpenoids.

Table 5: Organic acids identified in *A. venetum*

Serial number	Name	Source	References
(1)	Vanillic acid	flowers	[58]
(2)	Caffeic acid	Leaf	[63]
(3)	Succinic acid	Leaf	[64]
(4)	Fumaric acid	Leaf	[65]
(5)	3-Hydroxy-4-methoxybenzoic acid	Leaf	[58]
(6)	Protocatechuic acid	Leaf	[58]

Table 6: Alkaloid compounds identified in *A. venetum*

Serial number	Name	Source	References
(1)	Intermedine	Leaf	[66]
(2)	Lycopsamine	Leaf	[66]
(3)	Intermedine *N*-oxide	Leaf	[66]
(4)	Lycopsamine *N*-oxide	Leaf	[66]
(5)	Scopolamine	Root	[52]

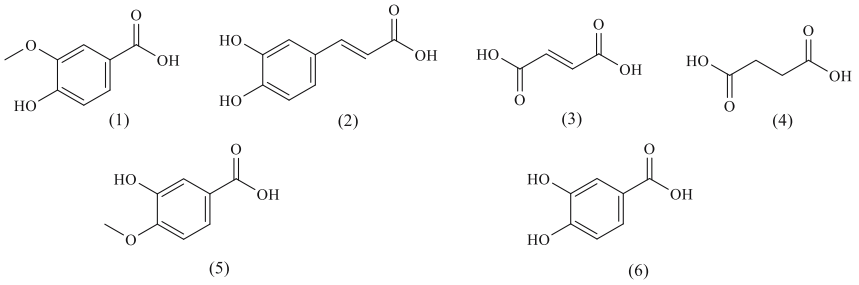

Figure 13: Chemical structures of organic acids.

4.5 Organic acids

Six organic acid compounds have been isolated from *A. venetum*, exhibiting biological activities, such as antioxidant, anticancer, hepatoprotective, and immunomodulatory effects. The names and structures of these organic acids are listed in Table 5 and Figure 13.

4.6 Alkaloids

Alkaloids are often the active ingredients in many medicinal plants, capable of regulating the activities of various metabolic enzymes and transporters, making them an important class of natural organic compounds. The alkaloids isolated from *A. venetum* are primarily pyrrolizidine alkaloids and tropane alkaloids. Pyrrolizidine alkaloids are naturally occurring compounds widely distributed across plant species worldwide. However, most pyrrolizidine alkaloid *N*-oxides and their metabolically activated products, dehydropyrrolizidine alkaloids, exhibit various toxic effects, including multi-organ damage, carcinogenicity, and developmental toxicity [67]. The pyrrolizidine alkaloid content in *A. venetum* leaves has been measured, showing that the concentrations of indicine, lycopsamine, indicine *N*-oxide, and

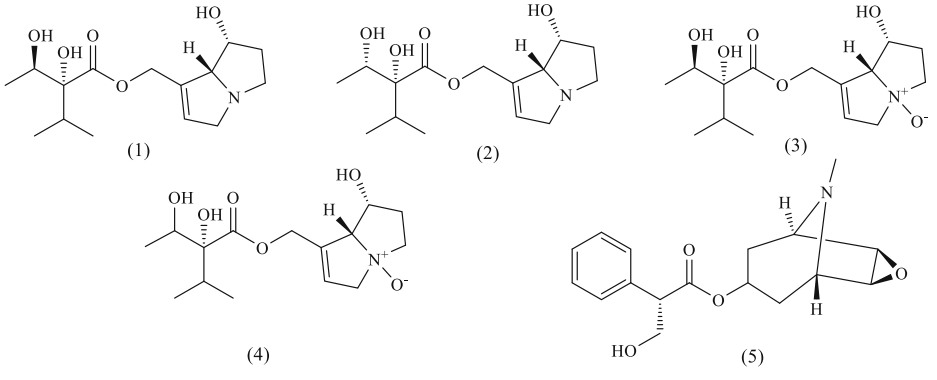

Figure 14: Chemical structures of alkaloids.

Table 7: Polysaccharide and other compounds identified in *A. venetum*

Classification	Serial number	Name	Source	References
Polysaccharide	(1)	AVRP-N	Root	[65]
	(2)	Vp2a-II	Flowers	[68]
	(3)	Vp3	Flowers	[68]
	(4)	ATPC-A mixture	Leaf	[69]
	(5)	ALP	Leaf	[67]
Other ingredients	(6)	Grasshopper ketone	Leaf	[36]
	(7)	Inositol	Leaf	[58]
	(8)	Phytol	Leaf	[58]
	(9)	Methoxytocopherol	Leaf	[58]
	(10)	Caryophyllene oxide	Leaf	[56]
	(11)	Anthraquinone	Leaf	[56]

lycopsamine *N*-oxide range from 10.51 to 27.56, 20.66 to 42.54, 40.54 to 76.89, and 61.45 to 164.23 μg/kg, respectively. These alkaloid levels exceed the limits set by some countries or organizations, indicating a potential safety risk with long-term use. Further research on the hepatotoxicity of these alkaloids is necessary to ensure the safe use of this medicinal plant. The names and structures of these alkaloid compounds are listed in Table 6 and Figure 14.

4.7 Polysaccharides and other components

In addition to alkaloids, several polysaccharides have also been isolated from *A. venetum*. One such polysaccharide, AVRP-N [67], is composed of mannose, arabinose, glucose, and galactose in a molar ratio of 35.10:34.18:23.67:7.04, with a molecular weight of 6.43 kDa [67]. Vp2a-II, another polysaccharide, consists of rhamnose, arabinose, xylose, mannose, glucose, and galactose in a molar ratio of 1.94:16.7:0.38:1.76:0.17:15.4, with a molecular weight of 7 kDa [68]. Vp3 comprises rhamnose, arabinose, xylose, mannose, glucose, and galactose in a molar ratio of 8.09:7.87:2.12:2.46:0.41:8.43, with a molecular weight of 9 kDa. Another notable compound, ATPC-A, is a polysaccharide conjugate extracted from *A. venetum* tea residue under alkaline conditions, with strong emulsification properties [69]. Alkaline phosphatase is a water-soluble crude polysaccharide extracted from dried *A. venetum* leaves through hot water extraction, ethanol precipitation, and the Sevag method for protein removal. It is composed of mannose, rhamnose, glucuronic acid, glucose, galactose, and arabinose in a molar ratio of 0.29:1.0:0.55:3.88:1.12:2.20:1.29. Many reports have highlighted the biological activities of plant polysaccharides, including hypoglycemic, lipid-lowering, anti-thrombosis, antibacterial, anti-inflammatory, immunomodulatory, and anti-fatigue effects. Polysaccharides in natural medicines often possess strong bioactivities and are considered the active ingredients of these medicines. Their biological activities are influenced by associated proteins, pigments, metal ions, and stereochemical structures. This article also explored the potential role of polysaccharides from *A. venetum* in treating central nervous system (CNS) diseases,

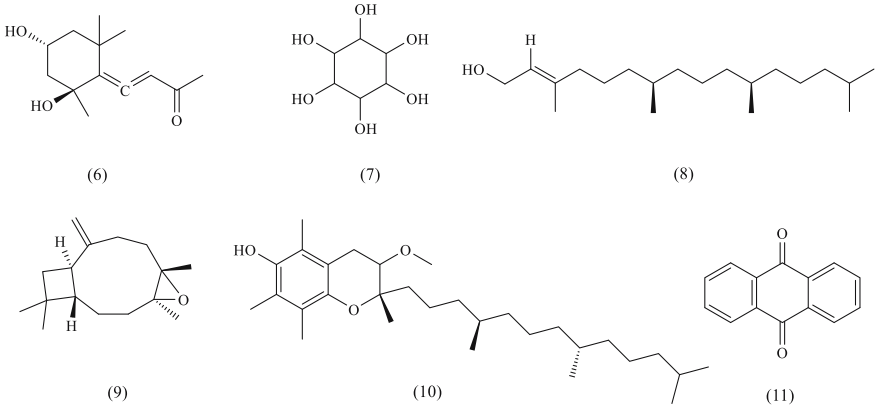

Figure 15: Chemical structures of other components.

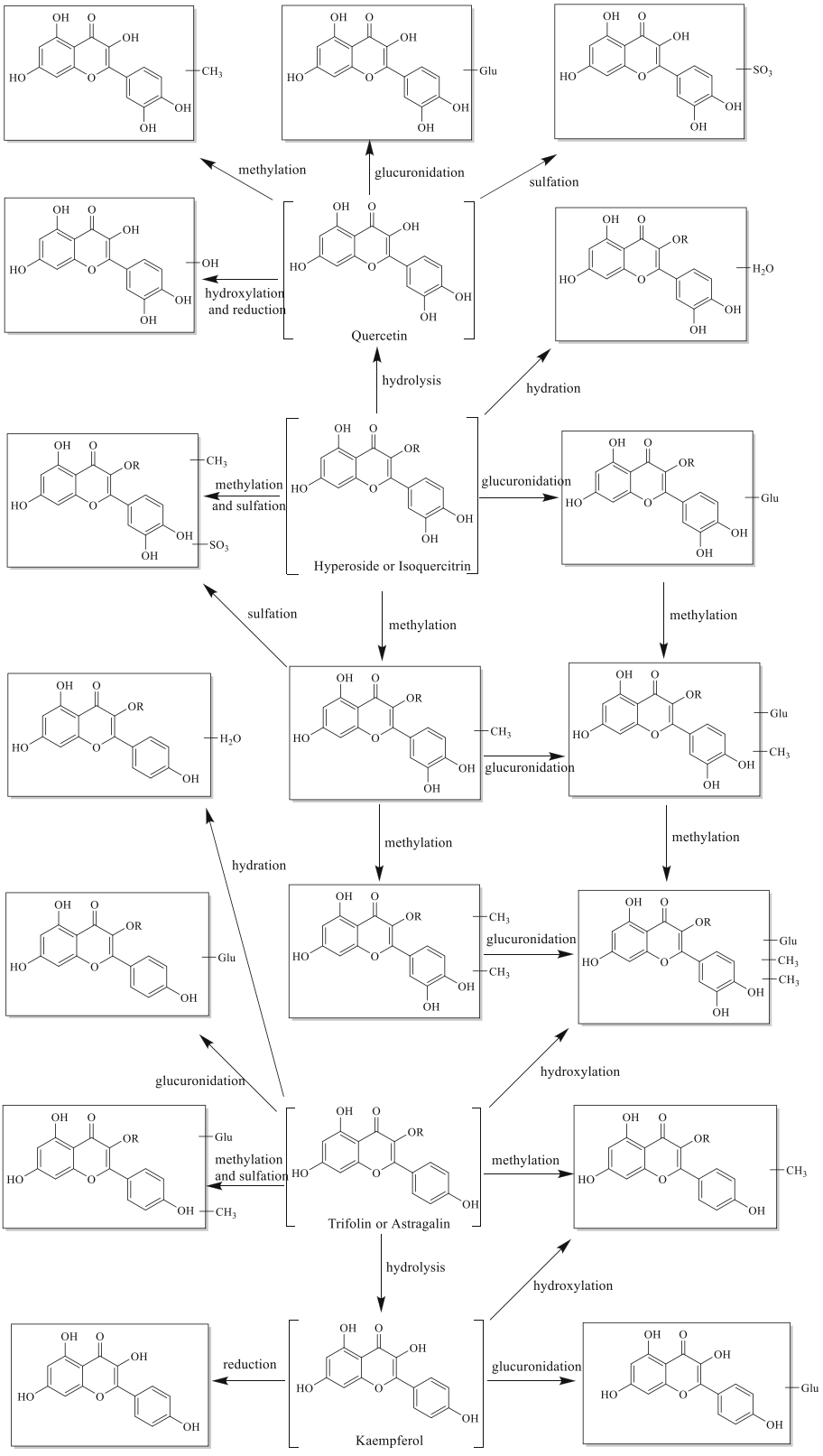

Figure 16: Chemical structures of flavonoid metabolites and their major metabolic pathways.

such as epilepsy. Additionally, *A. venetum* contains essential amino acids, inorganic elements, and trace elements, whose names and structures are presented in Table 7 and Figure 15.

5 Metabolic study of flavonoids in *A. venetum* leaves

The metabolism of TCM in the body involves both prototype compounds and metabolites. The former are referred to as the "chemical constituents of TCM," while the latter are known as the "metabolome of TCM." In a study [52], *A. venetum* leaf extract (2 mL) was administered orally to rats, and urine was collected 12 h after administration. Eight prototype compounds were identified, including chlorogenic acid, scopoletin, hyperoside, isoquercitrin, trifolirhizin, formononetin, quercetin, and kaempferol. Among these, hyperoside, isoquercitrin, trifolirhizin, formononetin, quercetin, and kaempferol are flavonoid compounds. Additionally, 34 metabolites were detected, 30 of which were related to flavonoid metabolism. The urinary metabolite profile indicated that *A. venetum* leaf extract underwent the following metabolic reactions to form these 34 metabolites: (1) Phase I reactions, including methylation, hydroxylation, hydration, reduction, and hydrolysis, and (2) Phase II reactions, primarily sulfate conjugation and glucuronidation. Methylation, sulfate conjugation, and glucuronidation were the major metabolic pathways. The metabolic process of the key active compounds is illustrated in Figure 16. Both *A. venetum* leaf extract and urine containing the extract showed flavonoid compounds as the primary constituents. Hyperoside is the most abundant compound in *A. venetum*, while isoquercitrin, an isomer of hyperoside, is also present in significant amounts. Hyperoside lacks hydrolytic enzymes in the intestine, so upon ingestion, it is rapidly absorbed into the bloodstream and metabolized into other forms in the plasma, resulting in low bioavailability. Isoquercitrin, on the other hand, may undergo enterohepatic circulation, but its absorption in the small intestine is poor, and the unabsorbed portion is metabolized by intestinal microbiota, also resulting in low bioavailability. Isoquercitrin is readily metabolized into glucuronidated quercetin in the body, although the presence of other components in *A. venetum* extract may enhance its bioavailability.

It is known that the flavonoid compounds hyperoside, quercetin, isoquercitrin, trifolirhizin, and kaempferol are the primary active ingredients responsible for the pharmacological effects of *A. venetum*. Additionally, *A. venetum* leaves have been found to improve TG metabolism, regulate blood lipids, reduce lipid peroxidation levels in rats, and enhance the immune system and amino acid metabolism in Tan sheep, promoting carbohydrate absorption. Furthermore, *A. venetum* leaves also influence serum metabolite levels in Tan sheep. Through UPLC-Q-TOF/MS, differential metabolites such as chlorophenol, β-hydroxybutyrate, catechol, fumarate, ethylmalonate, 2-hydroxyphenylacetic acid, gentisic acid, and protocatechuic acid were identified [48].

6 Potential of *A. venetum* L. leaves in the treatment of epilepsy

Existing studies have demonstrated that *A. venetum* leaves exhibit anxiolytic, antidepressant, and sedative effects, but further research is required to explore their potential in treating CNS disorders such as epilepsy. In the development of antiepileptic drugs, traditional Chinese medicines have garnered widespread attention for their natural, safe, and low-toxicity profiles. Research has shown that LPS exacerbates hippocampal neuronal damage and induces hippocampal neuroinflammation in epileptic mice, with an increased expression of interleukin-1 receptor type 1 (IL-1R1) signaling during this process. Blocking central IL-1R1 can reduce seizure susceptibility and severity in epilepsy [66]. This indicates that IL-1R1 mediates LPS-induced central inflammatory responses, increasing seizure susceptibility.

Polysaccharides from *A. venetum* leaves, such as ALRPN-1 (composed of glucose, ga-lactose, and arabinose) and ALRPN-2 (composed of glucose, galactose, and mannose), have demonstrated significant anti-inflammatory activity in LPS-induced macrophages by regulating the levels of pro-inflammatory mediators (NO) and cytokines (TNF-α, IL-6, and IL-1β) and activating the ERK/MAPK signaling pathway. It is hypothesized that *A. venetum* polysaccharides may reduce LPS-induced seizure susceptibility. Furthermore, *A. venetum* leaf extract has been shown to exert neuroprotective effects by inhibiting neuronal apoptosis in rat cortical neurons via the downregulation of caspase-3 expression and modulation of the Bcl-2/Bax ratio [68]. Additionally, the extract directly inhibits superoxide production by significantly reducing the expression of gp91phox, a key component of NADPH oxidase, enhancing SOD activity, and reducing the formation of MDA, thereby inhibiting neuronal apoptosis [69]. Based on this, it can be concluded that *A. venetum* leaves may exert neuroprotective effects through oxidative stress modulation, providing a foundation for further research into the pharmacodynamics and mechanisms of *A. venetum* in epilepsy treatment.

7 Conclusions

This article systematically reviews the chemical constituents isolated from *A. venetum* leaves, their pharmacological mechanisms of action, and the metabolism of the major active compounds. *A. venetum* leaves are rich in essential nutrients and represent a safe, healthy, and eco-friendly herbal medicine with medicinal uses, offering great potential for development in the medical and textile industries. Numerous studies have reported on the pharmacological effects of the primary active compounds in *A. venetum* leaves, particularly flavonoids. However, there has been relatively little research on other constituents, such as steroids, phenylpropanoids, and organic acids. Further studies could explore the medicinal and economic potential of *A. venetum* leaves, as well as the possibility of developing new drug formulations by combining *A. venetum* with other herbal or Western medicines to enhance therapeutic efficacy.

Funding information: This research was funded by a grant from Natural Science Research of Jiangsu Higher Education Institutions of China (No. 23KJD360002), Science and Technology Program of Huai'an City, China (Nos. HABZ202226, HAB202368), Engineering Research Center for the Development and Processing Technology of Precision Health Pharmaceutical Food Products of Jiangsu Province, "Huai Shang Elite" project [Grant number (2023) 8], Heilongjiang Provincial Science Foundation Project (No. LH2021C076), and Jiangsu Food & Pharmaceutical Science College college-level Fund (No. JSFPC2024003).

Author contributions: Writing – original draft preparation, Yi Xiu and Xiaomao Li; validation, Siyi Wang and Jiaqi Yu; resources, Lijia Jing and Na Guo; and project administration, Yuzhi Jiao and Weiwei Zhai. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: The authors state no conflict of interest.

Ethical approval: The conducted research is not related to either human or animal use.

Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

[1] Editorial board of Flora of China of Chinese Academy of Sciences. Flora of China. Beijing: Science Press; 1977.
[2] Xiang T, Wu L, Isah MB, Chen C, Zhang X. *Apocynum venetum*, a medicinal, economical and ecological plant: a review update. PeerJ 2023;11:e14966.
[3] Guo HL, Guo SB, Zhao XJ, Hu LJ, Hu ZF, Xiao XM, et al. Experimental comparison of antidepressant pharmacological effects of *Apocynum venetum* L. Jiangxi J Tradit Chin Med. 2014;45:55–7.
[4] Butterweck V, Nishibe S, Sasaki T, Uchida M. Antidepressant effects of *Apocynum venetum* leaves in a forced swimming test. Biol Pharm Bull. 2001;24:848–51.
[5] Zheng M, Liu C, Pan F, Shi D, Ma F, Zhang Y, et al. Protective effects of flavonoid extract from *Apocynum venetum* leaves against corticosterone-induced neurotoxicity in PC12 cells. Cell Mol Neurobiol. 2011;31:421–8.
[6] Zheng M, Liu C, Pan F, Shi D, Zhang Y. Antidepressant-like effect of hyperoside isolated from *Aapocynum venetum* leaves: possible cellular mechanisms. Phytomedicine. 2012;19:145–9.
[7] Wang J, Xie J, Chen YM. Antidepressant effect of flavonoids extracted from *Apocynum venetum* leaves and expression of S100A10 in rat model of depression. Zhejiang Prev Med 2016;28:574–7.
[8] Wang J, Xie J, Chen YM, Gao LS, Zhang HS. Antidepressant effect of flavonoids extracted from *Apocynum venetum* leaves in rat model of depression. Zhejiang Med 2016;38:14–6.
[9] He W, Wang L, Huang JF, Liu L, Liu XY, Du TF, et al. Sedative and hypnotic effects of water extract of *Apocynum venetum* leaves. Drug Eval Respir. 2022;45:274–80.
[10] Kuo CS, Kwan CY, Gong CL, Tsai MF, Nishibe S, Tatsuzaki J, et al. *Apocynum venetum* leaf aqueous extract inhibits voltage-gated sodium channels of mouse neuroblastoma N2A cells. J Ethnopharmacol. 2011;136:149–55.
[11] Xiong Q, Fan W, Tezuka Y, Adnyana IK, Stampoulis P, Hattori M, et al. Hepatoprotective effect of *Apocynum venetum* and its active constituents. Planta Med. 2000;66:127–33.
[12] Xie W, Chen C, Jiang Z, Wang J, Melzig MF, Zhang X. *Apocynum venetum* attenuates acetaminophen-induced liver injury in mice. Am J Chin Med. 2015;43:457–76.
[13] Zhang W, Dong Z, Chang X, Zhang C, Rong G, Gao X, et al. Protective effect of the total flavonoids from *Apocynum venetum* L. On carbon tetrachloride-induced hepatotoxicity in vitro and in vivo. J Physiol Biochem. 2018;74:301–12.
[14] Kwan CY, Zhang WB, Nishibe S, Seo S. A novel in vitro endothelium-dependent vascular relaxant effect of *apocynum venetum* leaf extract. Clin Exp Pharmacol Physiol. 2005;32:789–95.
[15] Lau YS, Kwan CY, Ku TC, Hsieh WT, Wang HD, Nishibe S, et al. *Apocynum venetum* leaf extract, an antihypertensive herb, inhibits rat aortic contraction induced by angiotensin ii: a nitric oxide and superoxide connection. J Ethnopharmacol. 2012;143:565–71.
[16] Lau YS, Ling WC, Murugan D, Kwan CY, Mustafa MR. Endothelium-dependent relaxation effect of *Apocynum venetum* leaf extract via SRC/PI3K/AKT signalling pathway. Nutrients. 2015;7:5239–53.
[17] Pei Y, Wang R, Zhou HW. Network pharmacology mechanism in treating hypertension with *Apocynum venetum*. Cent South Pharm. 2019;17:1997–2001.

[18] Xu ZG, Bai RY, Yan XM, Li Y, Zhou Y, Zhang J, et al. Effect of total flavonoids from *Apocynum venetum* L. leaves on blood lipid metabolism in hyperlipidemic rats. 2021;32:208–13.
[19] Zhang Y, Leng XW, Li YJ, Liu K, Yan MT, Ren LQ. Anti-atherosclerotic effect of flavonoids in *Folium Apocyni* Veneti. Chin J Public Health. 2016;32:1696–9.
[20] Manzoor M, Muroi M, Ogawa N, Kobayashi H, Nishimura H, Chen D, et al. Isoquercitrin from *apocynum venetum* L. Produces an anti-obesity effect on obese mice by targeting c-1-tetrahydrofolate synthase, carbonyl reductase, and glutathione s-transferase p and modification of the AMPK/SREBP-1c/FAS/CD36 signaling pathway in mice in vivo. Food Funct. 2022;13:10923–36.
[21] Qin MS, Yu H, Zhang XL, Liu HZ. Network pharmacologic analysis of the mechanism of *Apocyni Veneti* Folium in the treatment of cardiovascular disease. Tradit Chin Drug Res Clin Pharmacol. 2020;31:576–82.
[22] Li Q, Zhang YC, Liu XH, Song JP, Wang LJ. Analysis of essential components of folium *Apocyni Veneti* from different habitats by HSGC-MS. Res Pract Chin Med. 2009;23:34–7.
[23] Song R, Zhou J. Microemulsion liquid chromatographic method for simultaneous separation and determination of six flavonoids of *Apocynum venetum* leaf extract. J Chromatogr B. 2015;995–996:8–14.
[24] Qu XL, Wang WQ, Liang XY, Tie R, Liu FE, Li R, et al. Effects of *Apocynum Venetum* leaf extract on myocardial ischemia reperfusion injury rat. Chin J Microc. 2015;25:15–8.
[25] Zhang Y, Liu S, Ma JL, Chen C, Huang P, Ji JH, et al. *Apocynum venetum* leaf extract alleviated doxorubicin-induced cardiotoxicity through the akt/bcl-2 signaling pathway. Phytomedicine. 2022;94:153815.
[26] Grundmann O, Nakajima J, Seo S, Butterweck V. Anti-anxiety effects of *apocynum venetum* L. In the elevated plus maze test. J Ethnopharmacol. 2007;110:406–11.
[27] Grundmann O, Nakajima J, Kamata K, Seo S, Butterweck V. Kaempferol from the leaves of *apocynum venetum* possesses anxiolytic activities in the elevated plus maze test in mice. Phytomedicine. 2009;16:295–302.
[28] Abubakar AS, Ahmad B, Ahmad N, Liu L, Liu B, Qu Y, et al. Physicochemical evaluation, structural characterization, *in vitro* and *in vivo* bioactivities of water-soluble polysaccharides from Luobuma (*Apocynum* L.) tea. Food Chem. 2024;460(Pt 2):140453.
[29] Kasimu R, Fan Z, Wang X, Hu J, Wang P, Wang J. Anti-platelet aggregation activities of different fractions in leaves of *apocynum venetum* L. J Ethnopharmacol. 2015;168:116–21.
[30] Wang L, Zhang X, Niu Y, Ahmed AF, Wang J, Kang W. Anticoagulant activity of two novel polysaccharides from flowers of *Apocynum venetum* L. Int J Biol Macromol. 2019;124:1230–7.
[31] Hu MN, Liang TG. Experimental study on acute toxicity of total flavonoids in *Apocynum venetum*. Guide China Med. 2016;14:37–8.
[32] Yu YY. Biological effects of *Apocynum Venetum* tea on cardiovascular system and it's safety assessment. Hangzhou, China: Zhejiang University; 2006.
[33] Li L, Wang QS, Chen DF, Zhang M, Wang WY. Toxicological assessment on safety of tea of *Apoeynum venetum* leaf. Pract Prev Med. 2010;17:2081–4.
[34] Guo Y, He W, Luo FX, Abudukeremu Ma FC, Wang L, Huang JF, et al. Study the acute? Toxicity and sub-acute toxicity of *Apocynum* extract in mice by intragastric administration. Xinjiang Med J. 2019;49:770–3.
[35] Gao G, Chen P, Chen J, Chen K, Wang X, Abubakar AS, et al. Genomic survey, transcriptome, and metabolome analysis of *Apocynum venetum* and *Apocynum hendersonii* to reveal major flavonoid biosynthesis pathways. Metabolites. 2019;9(12):296. doi: 10.3390/metabo9120296.
[36] Fu HM, Yin CL, Shen ZY, Yang MH. Flavonoids from the leaves of *Apocynum venetum* and their anti-inflammatory activity. J Chem Res. 2022;46. doi: 10.1177/17475198211073871.
[37] Cheng XL, Zhang SQ, Li QS. Chemical constituents of flavonoids from *Apocynum venetum*. J Chin Med Mater 2007;30(9):1086–8.
[38] Li LH, Yuan Z. Study on flavonoids in leaves of *Apocynum ventum*. J Chin Med Mater. 2006;31(16):1337–40.
[39] Zeng HS. Study on the chemical composition of *Apocynum venetum* leaves. Xian, China: Northwest University; 2009.
[40] Hou JJ, Han LW, Yang GE, Li QS. Research progress on chemical components and pharmacological activities of *Apocynum venetum* leaves. Chin Tradit Herb Drugs. 2006;1603–5. doi: 10.3321/j.issn:0253-2670.2006.10.056.
[41] Zhang Y, Liu S, Ma JL, Chen C, Huang P, Ji JH, et al. *Apocynum venetum* leaf extract alleviated doxorubicin-induced cardiotoxicity through the akt/bcl-2 signaling pathway. Phytomedicine 2022;94:153815.
[42] Chen L, Du LJ, Ding Y, Xing DM, Wang W. Studies on chemical constituents from flowers of *Apocynum venetum*. Zhongguo Zhong Yao Za Zhi. 2005;30:1340–2.
[43] Zhang Y, Liu C, Zhang Z, Qi Y, Wu G, Li S. Solvent gradient elution for comprehensive separation of constituents with wide range of polarity in *Apocynum venetum* leaves by high-speed counter-current chromatography. J Sep Sci. 2010;33:2743–8.
[44] Zhang Y, Liu C, Zhang Z, Wang J, Wu G, Li S. Comprehensive separation and identification of chemical constituents from *Apocynum venetum* leaves by high-performance counter-current chromatography and high-performance liquid chromatography coupled with mass spectrometry. J Chromatogr B. 2010;878:3149–55.
[45] Kamata K, Seo S, Nakajima J. Constituents from leaves of *Apocynum venetum* L. J Nat Med. 2008;62:160–3.
[46] Murakami T, Kishi A, Matsuda H, Hattori M, Yoshikawa M. Medicinal foodstuffs. Xxiv. Chemical constituents of the processed leaves of *Apocynum venetum* L.: Absolute stereostructures of Apocynosides i and ii. Chem Pharm Bull. 2001;49:845–8.
[47] Kong NN, Fang ST, Liu Y, Xia CH. Nonflavonoid constituents from leaves of *Apocynum venetum*. Chin Tradit Herb Drugs. 2013;44:3114–8.
[48] Fan WZ, Tezuka Y, Xiong QB, Hattori M, Namba T, Kadota S, et al. New Phenylpropanoid-substituted flavan-3-ols isolated from leaves of *Apocynum venetum* (Luobuma-Ye). Chem Pharm Bull. 1999;47:1049–50.
[49] Yokozawa T, Nakagawa T. Inhibitory effects of luobuma tea and its components against glucose-mediated protein damage. Food Chem Toxicol. 2004;42:975–81.
[50] Xiong Q, Fan W, Tezuka Y, Adnyana IK, Stampoulis P, Hattori M, et al. Hepatoprotective effect of Apocynum venetum and its active constituents. Planta Med. 2000;66:127–33.
[51] Xu ZG, Bai RY, Yan XM, Li Y, Zhou Y, Zhang J, et al. Effect of total flavonoids from *Apocynum venetum* L. leaves on blood lipid metabolism in hyperlipidemic rats. Tradit Chin Drug Res Clin Pharmacol. 2021;32:208–13.
[52] Wei NN. Isolation, purification and structure analysis of the polysaccharides from *Apocynum venetum* leaves and its interaction with Galectin-3. Changchun: Northeast Normal University; 2010.
[53] Cai YX, MaLiKe A, Xiao ZH. Chemical constituents from flower of *Apocynum venetum*. Chin Tradit Herb Drugs. 2007;1306–7.
[54] Kong NN, Fang ST, Liu Y, Wang JH, Yang CY, Xia CH. Flavonoids from the halophyte *Apocynum venetum* and their antifouling activities

against marine biofilm-derived bacteria. Nat Prod Res. 2014;28:928–31.
[55] Pei Y, Wang R, Zhou HW. Network pharmacology mechanism in treating hypertension with *Apocynum venetum*. Cent South Pharm. 2019;17:1997–2001.
[56] Wu SZ, He MY, Li GW, Wu WP, Qiu YJ, Zeng H, et al. UPLC characteristic maps and determination of flavonoids in *Apocyni Veneti* Folium from different producing areas. Mod Chin Med. 2021;23:619–26.
[57] Du S. Studies on chemical components and anti-inflammatory activity of *Apocynum venetum* L. Shenzhen, China: Shenzhen University; 2020.
[58] Lv JR. Analysis of chemical constituents and activity studies on essential oil in flower and leaf of *Apocynum venetum* L. Xianyang, China: Northwest A&F University; 2007.
[59] Wang LL, Zhao C, He N, Liu YN, Li WQ, Wang YH, et al. Analysis of Fat-soluble constituents from flowers of Apocynum venetum L. J Henan Univ. 2017;36:260–2.
[60] Zhao L, Liang S, Lv L, Zhang H, Guo-Tan G, Chai Y, et al. Screening and analysis of metabolites in rat urine after oral administration of *Apocynum venetum* L. Extracts using HPLC-TOF-MS. J Sep Sci. 2014;37(5):515–26.
[61] Liang SS. Study on quality control and metabolism of pharmacodynamic constituents in vivo for *ApocynumVetenum* L. Shanghai, China: Naval Medical University; 2012.
[62] Zhang YF, Wei D, Guo SY, Chen F, Du NS. Research on the chemical components of *Apocynum dahuricum*. Nat Prod Res Dev. 2006;18:954.
[63] Qu XL, Wang WQ, Liang XY, Tie R, Liu FE, Li R, et al. Effects of *Apocynum Venetum* leaf extract on myocardial ischemia reperfusion injury rat. Chin J Microcirc. 2015;25:15–8.
[64] Sun XX, Xiang E, Qiu SK, Wang H, Guo Y. Research progress on toxicity of pyrrolizidine alkaloids. Chin J Pharmacovigilance. 2019;16:76–80.
[65] Chen XQ, Wang CP, Wang CY, Liu CX, Yuan Y, Wang BJ, et al. The emulsification properties of alkaline-extracted polysaccharide conjugates from *Apocynum venetum* L. tea residues. Food Hydrocoll. 2022;124:107315. doi: 10.1016/j.foodhyd.2021.107315.
[66] Jin CQ. Effects of *Apocynum venetum* feeding for Tan-sheep based on metabolomics and transcriptomics. Ningxia, China: Ningxia University; 2019.
[67] Liu D, Wang SY, Wang GN, Zheng LH, Sun Y, Liu L, et al. Structural characterization and immunoregulatory activity of a neutral polysaccharide from the roots of *Apocynum venetum* L. Int J Biol Macromol. 2022;222:90–100.
[68] Hu A, Yuan H, Qin Y, Zhu Y, Zhang L, Chen Q, et al. Lipopolysaccharide (LPS) increases susceptibility to epilepsy via interleukin-1 type 1 receptor signaling. Brain Res. 2022;1793:148052.
[69] Xiang J, Tang YP, Zhou ZY, Wu P, Wang Z, Mori M, et al. Apocynum venetum leaf extract protects rat cortical neurons from injury induced by oxygen and glucose deprivation in vitro. Can J Physiol Pharmacol. 2010;88:907–17.