Food & Medicine Homology

ISSN 3006-6867 (print); 3006-4252 (online)
https://doi.org/10.26599/FMH.2025.9420030

Review Article

Critical Review for active iridoids in *Gardenia jasminoides* J.Ellis as a plant of food and medicine homology

Ya-Dan Zhang[1], Meng-Han Wang[1, 2], Miao Guan[1, 2], Fathy Mohamed Saber Ali Mehaya[3], Xiao-Yu Chen[1, 2] (✉), Xu-Qiang Liu[1, 2, 4] (✉)

[1] *National R & D Center for Edible Fungus Processing Technology, Henan University, Kaifeng 475004, China*
[2] *College of Agriculture, Henan University, Kaifeng 475004, China*
[3] *Food Technology Department, National Research Centre, Dokki 12622, Egypt*
[4] *Joint International Research Laboratory of Food & Medicine Resource Function, Henan Province, Kaifeng 475004, China*

Received: 25 April 2024 / **Revised:** 1 June 2024 / **Accepted:** 29 June 2024

Abstract: Iridoids compounds are one of the main active components of *Gardenia jasminoides*, which were divided into two categories: iridoid glycosides and non-glucosylated iridoids according to their chemical structures. Relevant studies have shown that components such as geniposide, deacetyl asperulosidic acid methyl ester, and geniposidic acid play an important role in anti-inflammatory, hypoglycemia, and the protection of cardiomyocytes. While the pharmacological effects of most iridoid glycosides are still not clear. This paper's systematic summary was created by searching for relevant iridoids material on websites such as Google Scholar, PubMed, SciFinder Scholar, Science Direct, and others. Up to now, a total of 94 iridoids had been identified in *G. jasminoides*, among which 40 iridoids had extensive biological activities and the mechanisms involved in MAPK, NF-κB, JNK signal pathways. This paper reviews the literature on types and pharmacological effects of iridoid compounds in *G. jasminoides*, in order to provide a reference for its development and application.

Keywords: *Gardenia jasminoides*; iridoids; biological activity

Citation: Zhang Y. D., Wang M. H., Guan M., et al. Critical Review for active iridoids in *Gardenia jasminoides* J.Ellis as a plant of food and medicine homology. *Food & Medicine Homology*, 2025, 2: 9420030. https://doi.org/10.26599/FMH.2025.9420030

1 Introduction

Iridoids are an important class of monoterpenoids comprising the cyclopentane [*c*]-pyran system. The iridoids and their glycosides can be further subdivided into carbocyclic iridoids and secoiridoids, the latter being obtained via oxidative cleavage of the 7, 8-bond of the cyclopentane moiety. If cyclopentane is cracked, the seco-iridoids are formed[1,2]. Up to now, about 800 iridoids have been isolated and identified from natural plants, most of which are iridoids glycosides, only more than 60 non-glycosidic iridoids, and more than 30 seco-iridoids[3].

Gardenia jasminoides J. Ellis as a plant of food and medicine homology belongs to the Rubiacea family[4]. on the one hand, *G. jasminoides* is a classic traditional Chinese medicine in China, which has many pharmacological functions, including liver and gallbladder protection, anti-inflammatory, immunomodulatory, antiviral and other properties[5]. It is also used as a resolutive in the treatment of sprains and bruises[6]. *G. jasminoides* iridoids glycoside extracts can be used to treat ischemic brain injury[7] and cerebral ischemia[8]. On the other hand, *G. jasminoides* has rich edible value as a food [9,10]. *G. jasminoides* is widely used as a health food for making tea and cooking porridge, the fruit oil extracted from gardenia is comparable to tea oil and olive oil, the gardenia yellow pigment in *G. jasminoides* is a natural pigment, and it is also a kind of food additive in China, which is often used in fruit juice, jelly and pasta and other foods. With the increasing application of *G. jasminoides* in health products, food and medicine, the safety of *G. jasminoides* has attracted more and more attention. In recent decades, there have been frequent reports of liver damage caused by *G. jasminoides*, which contradicts the hepatoprotective and choleretic properties of gardenia. According to existing studies, gardenia hepatotoxicity and nephrotoxicity are mainly caused by the geniposide of iridoids[11]. However, iridoids are generally considered the main bioactive and characteristic ingredients. Therefore, this review summarizes the structures of iridoids in *G. jasminoides*, biological activities and action mechanisms in order to provide a basis for further research and utilization.

2 Iridoids from *G. jasminoides*

So far, 94 iridoids compounds had been isolated and identified from *G. jasminoides*, of which 83 are iridoids terpene glycosides, which can be divided into four structural types according to

Address correspondence to Xiao-Yu Chen, chenxiaoyu@njau.edu.cn; Xu-Qiang Liu, liuxuqiang6230@163.com

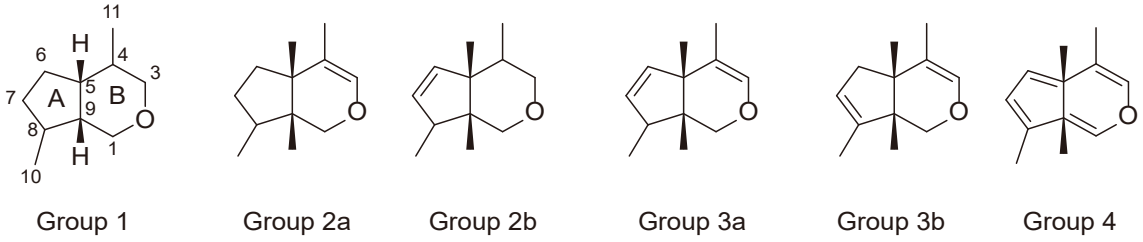


Figure 1 Basic skeleton of the iridoids terpene from the *G. jasminoides*.

whether cyclopentane and pyran ring contain double bonds, the position and number of double bonds (Fig. 1 Groups 1-4). The upper substituents of iridoids are mainly carboxyl or acetic acid groups at position 4, glucoyl glycan groups at position 1, caffeoyl glycans, *p*-coumarinyl glycans, and gentian disaccharides (Figs. 2 and 3).

2.1 Cyclopentane pyrans, cyclic iridoids ether terpenes

Such compounds generally have substituents at C-1, C-4, C-6, C-8, and C-10. According to the position and number of double bonds contained in the cyclopentane ring (A ring) and pyran ring (B ring), they are divided into non-double bond-free iridoids, mono-ene iridoids terpenes, diene iridoids terpenes and iridoids ether terpenes with four double bonds, and are divided into different isotypes according to the difference in the position of their double bonds.

2.1.1 Iridoids with no double bond in the ring

So far, there are only 2 compounds isolated from *G. jasminoides* (Fig. 4).

2.1.2 Monoene iridoids

So far, 26 monoene-type iridoids terpenes (Group 2) have been isolated from *G. jasminoides* (Fig. 5). The double bonds in the structure of these iridoids terpenes are mainly located at the C-3 and C-4 positions (Group 2a) or C-7 and C-8 (Group 2b), and when C-10 and C-1 are replaced by hydroxyl groups at the same time, dehydration can occur to form compounds with ether bonds (**28**, **29**, **30**), and C-3 to form cyclolactone compounds (**26**, **27**): the hydroxyl groups of C-7 and C-8 can be dehydrated to form ethylene oxide, as in compound (**25**).

2.1.3 Diene iridoids

To date, 63 diene iridoids terpenes and their glycosides (Group 3) (**35-92**) have been isolated from *G. jasminoides* (Fig. 6). The structure of these iridoids ether terpenes contains two double bonds, mainly in C-3, 4 and C-6, 7 (**31-34**) and C-3, 4 and C-7, 8 (**35-92**), when C-10 and C-1 are replaced by hydroxyl groups at the same time, dehydration can occur to form compounds with ether bonds (**33**), in its C-10, C-11 positions are mostly oxygen-containing substitutions, or C-11 positions have carbonyl or carboxyl substitutions, and between C-5 and C-6 cyclolactones are formed (**92**).

2.1.4 Other iridoids

Other iridoids terpenoids mainly include tetraene-type iridoids terpenes and dimeric irides formed by two iridoids ether terpenes (Fig. 7). The structure of tetraenoiric ether terpenes contained four double bonds (Group 5), which were located at C-3, 4, C-5, 6, C-7, 8 and C-1, 9, respectively, and the C-10 position was oxidized to aldehyde groups (compound **93**). The dimeric iridoids polymerization method is a dimer formed by the dehydration of

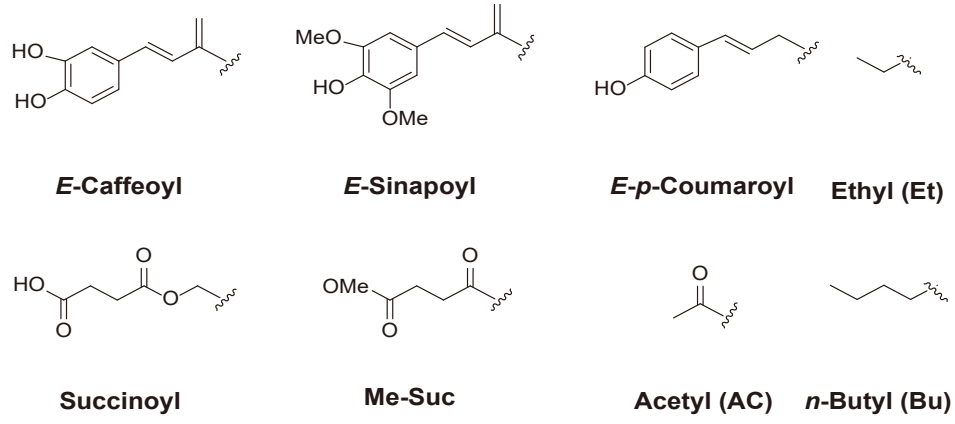


Figure 2 Structure diagram of iridoids substituents from the *G. jasminoides*.

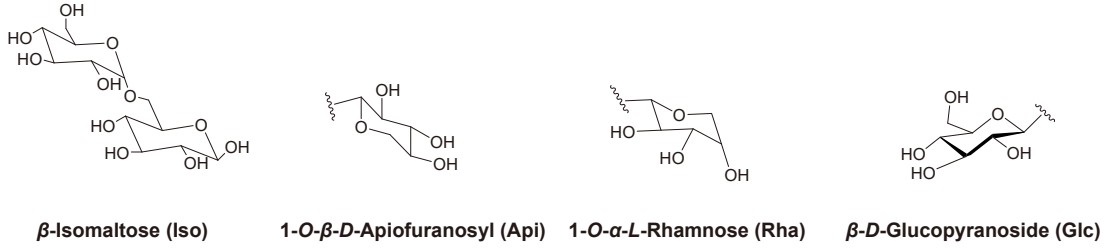


Figure 3 Carbohydrates of iridoids from the *G. jasminoides*.

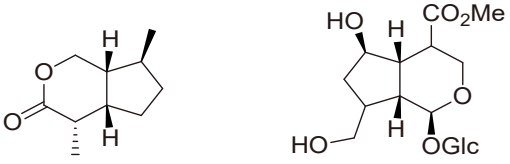


Figure 4 Iridoids compounds with no double bond inside the ring from the *G. jasminoides*.

two iridoids terpenes at the C-1 and C-10 positions (compound **94**).

3 Active iridoids terpenes in *G. jasminoides* and their mechanism of action

There are a 40 iridoids terpenoids which had antioxidant, anti-inflammatory, antitumor, and hypoglycemic effect (Fig. 8, Table 1). Due to the difference in structure or substituents, the biological activity and dose dependence of different iridoids terpenes are also different, and the active compounds and activity distribution of each active compound are listed in Figs. 8A and 8B.

3.1 Anti-inflammatory

Iridoids has a wide range of pharmacological effect, the most prominent being anti-inflammatory activity, and 12 compounds (**4**, **12**, **34**, **36**, **38**, **55**, **62**, **83**, **84**, **88**, **91** and **92**) with anti-inflammatory activity have been isolated from *G. jasminoides*. Cell models such as LPS-induced RAW264.7, Caco-2, BV2 microglia, human periodontal ligament, and acute lung injury cells were commonly used for anti-inflammatory activity, and animal models were acute kidney injury, ulcerative colitis, and dextran sulfate sodium salt-induced colitis mice, *Staphylococcus aureus* induced pneumonia, and LPS-induced breast cancer mice (Table 2).

Lipopolysaccharide (LPS), the most common inflammatory trigger in cell models, causes elevated levels of inflammatory mediators and cytokines such as nitric oxide (NO), tumor necrosis

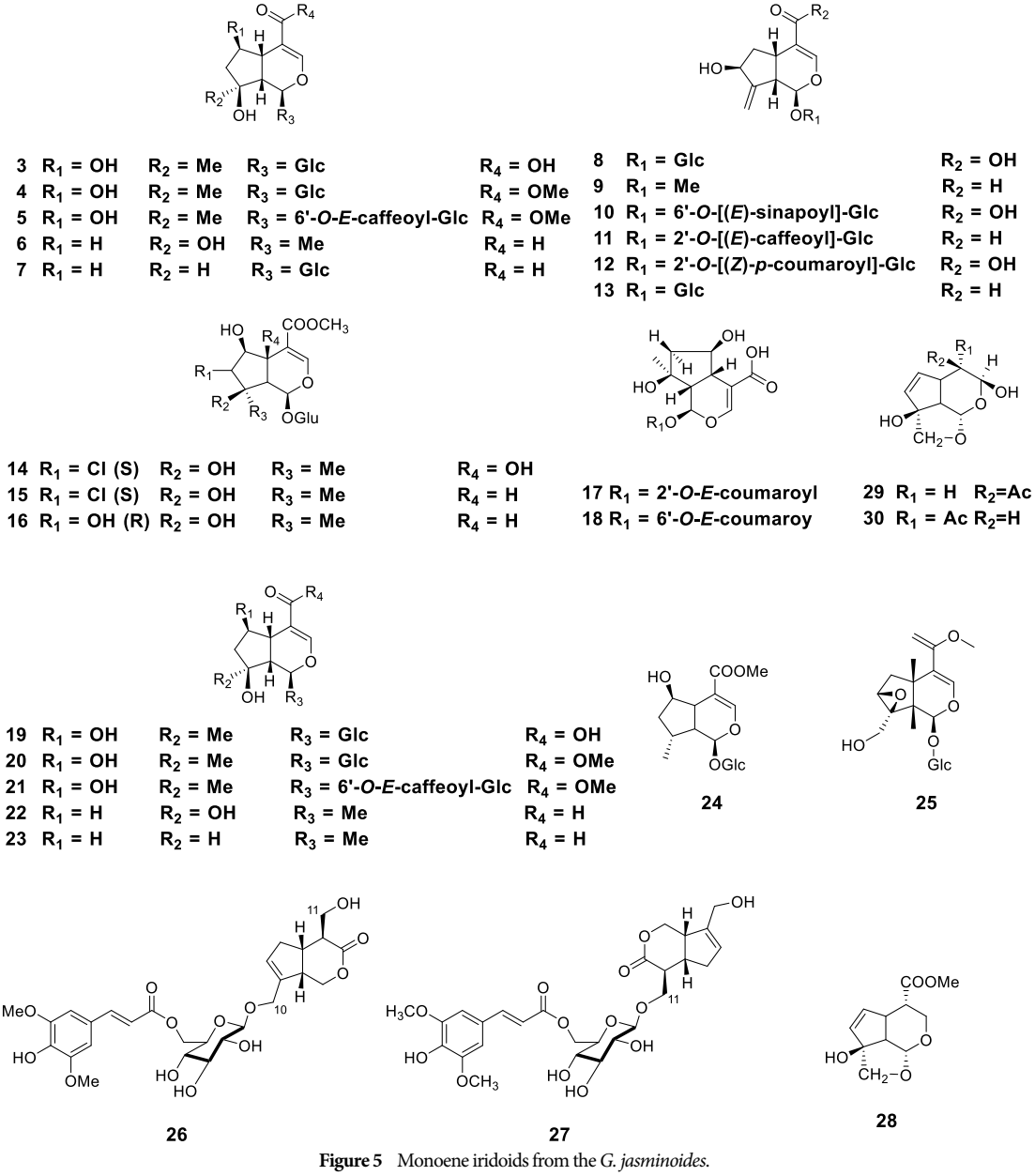
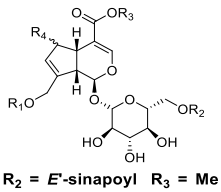
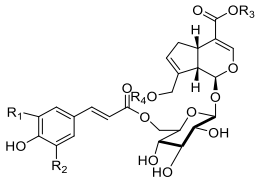


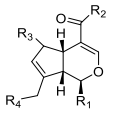
Figure 5 Monoene iridoids from the *G. jasminoides*.



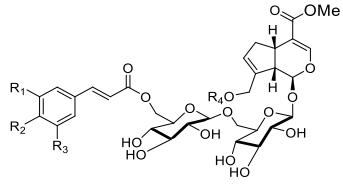
35 R_1 = H R_2 = *E*'-sinapoyl R_3 = Me R_4 = H
36 R_1 = H R_2 = H R_3 = H R_4 = H
37 R_1 = H R_2 = H R_3 = Me R_4 = OH (*R*)
38 R_1 = Me R_2 = H R_3 = H R_4 = H
39 R_1 = CH_2COMe R_2 = H R_3 = Me R_4 = H
40 R_1 = H R_2 = *E*-caffeoyl R_3 = Me R_4 = OH (*R*)
41 R_1 = Me R_2 = Glc R_3 = Me R_4 = H
42 R_1 = H R_2 = 6'-*p*-coumaroyl→Glc R_3 = Me R_4 = H
43 R_1 = Me R_2 = H R_3 = H R_4 = OH (*S*)
44 R_1 = Me R_2 = H R_3 = H R_4 = OH (*S*)
45 R_1 = H R_2 = H R_3 = Me R_4 = OH (*R*)
46 R_1 = H R_2 = H R_3 = Me R_4 = OH (*S*)
47 R_1 = Me R_2 = H R_3 = Me R_4 = OMe (*R*)
48 R_1 = Me R_2 = H R_3 = Me R_4 = OMe (*S*)
49 R_1 = OH R_2 = Api (*R*) R_3 = Me R_4 = H
50 R_1 = H R_2 = Glu R_3 = Me R_4 = H
51 R_1 = Glu R_2 = H R_3 = Me R_4 = H
52 R_1 = H R_2 = Glu R_3 = Me R_4 = H
53 R_1 = succinoyl R_2 = H R_3 = Me R_4 = H
54 R_1 = H R_2 = Ac R_3 = Me R_4 = H
55 R_1 = Suc-Me R_2 = H R_3 = Me R_4 = H
56 R_1 = H R_2 = H R_3 = Me R_4 = OBu (*R*)
57 R_1 = H R_2 = H R_3 = Me R_4 = OBu (*S*)
58 R_1 = Glc R_2 = H R_3 = Me R_4 = H

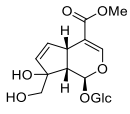


59 R_1 = H R_2 = H R_3 = Me R_4 = H
60 R_1 = OMe R_2 = OMe R_3 = Me R_4 = H

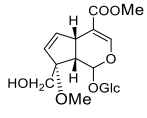


62 R_1 = OH R_2 = OH R_3 = H R_4 = H
63 R_1 = OMe R_2 = H R_3 = H R_4 = H
64 R_1 = OH R_2 = OH R_3 = H R_4 = OH
65 R_1 = Glu→Glu(6→1) R_2 = H R_3 = H R_4 = OH
66 R1 = Rha→Glu(1→6) R_2 = OMe R_3 = H R_4 = H
67 R_1 = Glu R_2 = H R_3 = OH R_4 = OH
68 R_1 = Glu R_2 = H R_3 = H R_4 = OH
69 R_1 = OH R_2 = OH R_3 = H R_4 = OMe
70 R_1 = Rha (*S*) R_2 = OMe R_3 = H R_4 = Rha (*S*)
71 R_1 = Xyl (*R*) R_2 = OMe R_3 = H R_4 = Xyl (*R*)
72 R_1 = Rha (*S*) R_2 = OMe R_3 = H R_4 = OH
73 R_1 = Xyl (*R*) R_2 = OMe R_3 = H R_4 = OH

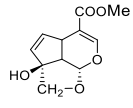




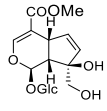
31



32

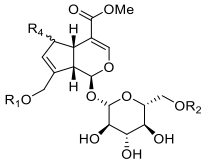


33

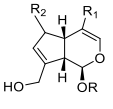


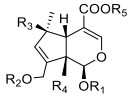
34

74 R_1 = OH R_2 = OH R_3 = H R_4 = Me
75 R_1 = H R_2 = OH R_3 = H R_4 = Me
76 R_1 = OMe R_2 = OH R_3 = OMe R_4 = H
77 R_1 = H R_2 = H R_3 = H R_4 = H
78 R_1 = H R_2 = OH R_3 = OMe R_4 = H



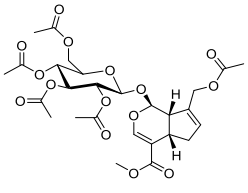
85 R_1 = OH (*S*) R_2 = H R_3 = Me R_4 = Me
86 R_1 = OH (*R*) R_2 = H R_3 = Me R_4 = Me
87 R_1 = H R_2 = H R_3 = Me R_4 = Me



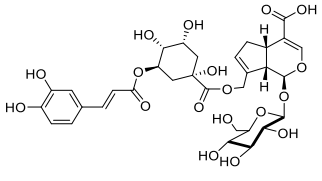


79 R = H R_1 = Ac R_2 = Et (*S*)
80 R = H R_1 = Ac R_2 = Et (*R*)
81 R = H R_1 = H R_2 = H
82 R = Glc R_1 = H R_2 = H

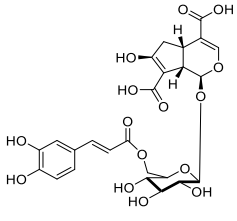
83 R_1 = Z R_2 = AC R_3 = R_4 = H R_5 = Me
84 R_1 = R_2 = X R_3 = R_4 = H R_5 = Me
Z = *β*-isomaltoside
X = *β*-glucopyranosy



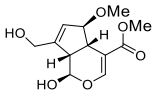
88



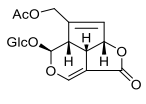
89



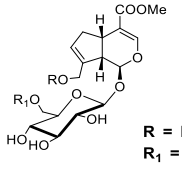
91



63

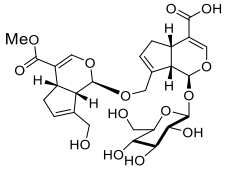


92



R = Me-Suc
R_1 = H

61



90

Figure 6 Diene iridoids from the *G. jasminoides*.

factor-β (TNF-β), and interleukin-6 (IL-6). the signaling pathways involved mainly include mitogen-activated protein kinases (MAPK), nuclear factor kappa-B (NF-κB), Janus kinase (JAK), c-Jun N-terminal kinase (JNK) and Nuclear factor erythroid

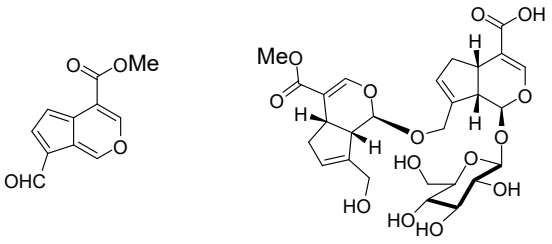


Figure 7 Other-iridoids from *G. jasminoides*.

2-related factor 2 (Nrf2). NF-κB and MAPK are two major signaling pathways, which, once activated, subsequently induce gene expression of pro-inflammatory cytokines. For example, compound **4** regulates the inflammatory response of stimulated rat neutrophils by inhibiting the release of pro-inflammatory enzymes such as myeloperoxidase (MPO), elastase, and matrix metalloproteinase-9 enzymes (MMP-9), as well as the formation of pro-inflammatory cytokines such as IL-8, TNF-α, and leukotriene B4 (LTB4), in a concentration-dependent manner without cytotoxic effects[12]. Compounds **12** and **91** reduce Prostaglandin E2 (PEG2) levels and half maximal inhibitory concentration values (IC_{50}) of 121.4 and 83.38 μmol/L in LPS-activated RAW 264.7 macrophages, respectively[13]. In IL-1β-induced osteoarthritis, compound **34** decreases gene expression of *COX-2*, *iNOS*, *IL-6*, and reduces IL-1β-induced reactive oxygen species (ROS) production in chondrocytes, inhibiting the NF-κB signaling pathway in chondrocytes to ameliorate inflammation[15]. Compound **36** blocks LPS-stimulated phosphorylation of inhibitor kappa B alpha (IκBα), p65, p38, extracellular regulated protein kinases (ERK), and JNK in mouse primary macrophages. Compounds **38** and **58** inhibit the release of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and LPS-primed NF-κB signaling in macrophages to reduce inflammatory damage[23, 24]. Compound **88** exhibits better pharmacological activity than **36**, which is an acetyl derivative of **36**, which can alleviate the progression and severity of collagen-induced arthritis in rats, is associated with reduced levels of IL-1β, IL-6, IL-8, MMP-2, and MMP-9 and inhibition of the Wnt/β-catenin pathway in synovial tissue[34]. In a mouse model of colitis, **92** inhibited oxidative stress

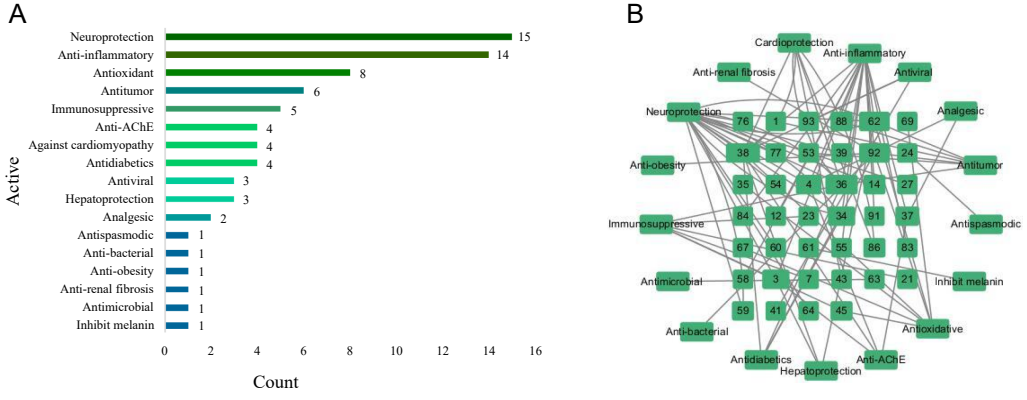


Figure 8 Biological activity of the iridoids in *G. jasminoides*. (A) The length of the column bar indicates the number of compounds with this biological activity. (B) The relationship network of the biological activity of iridoids. The blue number represents the compound number, the color area size represents the biological activity quantity of the compound, the peripheral box represents the biological activity, and each edge represents the corresponding compound and biological activity.

Table 1 Active iridoids terpenoids in *G. jasminoides*

No.	Compound	Activity	Source	Reference
1	Iridomyrmecin	Antitumor	Fruit of *G. jasminoides*	[44]
3	Shanzhiside	Neuroprotection immunosuppressive Hepatoprotection Anti-AchE	Fruit of *G. jasminoides*	[55]
			Fruit of *G. jasminoides*	[56]
			Rehmannia glutinosa	[70]
			Fruit of *G. jasminoides*	[67]
4	Shanzhiside methyl ester	Anti-inflammatory Neuroprotection anti-AchE	*Barleria prionitis*	[12]
			Vaccinium	[56]
			Fruit of *G. jasminoides*	[70]
7	Ixoroside	Immunosuppressive	Fruit of *G. jasminoides*	[71]
12	2'-*O*-*cis*-Coumaroylgardoside	Anti-inflammatory	Fruit of *G. jasminoides*	[13]
14	Phloyoside (II)	Anti-inflammatory	Fruit of *G. jasminoides*	[14]
21	6'-*O*-[(*E*-sinapoyl)gardoside]	Immunosuppressive	Fruit of *G. jasminoides*	[71]
23	Ixoroside	Immunosuppressive	Fruit of *G. jasminoides*	[71]
24	Penstemonoside (IV)	Antispasmodic	*Phillyrea latifolia*	[73]
27	10-(6-*O*-*trans*-Sinapoylglucopyranosyl) gardendiol	Neuroprotection	Fruit of *G. jasminoides*	[57]
34	Gardenoside	Anti-inflammatory Neuroprotection neuroprotection neuroprotection antidiabetics	Fruit of *G. jasminoides*	[15]
			Fruit of *G. jasminoides*	[58]
			Fruit of *G. jasminoides*	[59]
			Fruit of *G. jasminoides*	[60]
			Fruit of *G. jasminoides*	[74]
35	6'-*O*-Sinapoylgeniposide	Antioxidative	*Leptodesmia microphylla*	[38]

(Continued)

No.	Compound	Activity	Source	Reference
			Fruit of *G. jasminoides*	[39]
		Anti-Inflammatory	Fruit of *G. jasminoides*	[45]
		Antitumor	*Eucommia ulmoides*	[60, 62]
36	Geniposide	Neuroprotection neuroprotection immunosuppressive	*E. ulmoides*	[63]
		Anti-Cardiomyopathy	Fruit of *G. jasminoides*	[71]
		Antidiabetics	Fruit of *G. jasminoides*	[75]
			Fruit of *G. jasminoides*	[76, 77]
		Anti-Inflammatory	*Lasianthus Acuminatissimus*	[22]
37	Deacetyl asperulosidic acid	Anti-AchE	Fruit of *G. jasminoides*	[78]
		Analgesic	Fruit of *G. jasminoides*	[14]
			Fruit of *G. jasminoides*	[23]
			E. ulmoides (ESF) tea	[40]
		Anti-Inflammatory	Fruit of *G. jasminoides*	[64]
		Antioxidative	Fruit of *G. jasminoides*	[78]
		Neuroprotection anti-AchE	Fruit of *G. jasminoides*	[79]
38	Geniposidic acid	Antiviral activity	Fruit of *G. jasminoides*	[79]
		Hepatoprotection	Fruit of *G. jasminoides*	[80]
		Anti-Cardiomyopathy	Fruit of *G. jasminoides*	[80]
		Anti-Cardiomyopathy	Fruit of *G. jasminoides*	[81]
		Antidiabetics	Fruit of *G. jasminoides*	[82]
			Fruit of *G. jasminoides*	[32]
39	10-*O*-Acetyl geniposide	Neuroprotection	Fruit of *G. jasminoides*	[57]
41	Genipin-1-gentiobioside	Anti-antiviral	Fruit of *G. jasminoides*	[83]
43	Deacetyl asperulosidic acid	Anti-Cardiomyopathy	*Oldenlandia diffusa*	[37]
45	6*α*-Hydroxy-geniposide	Immunosuppressive	Fruit of G. jasminoides	[72]
53	10-*O*-Succinoylgeniposide	Antitumor	Fruit of *G. jasminoides*	[46]
54	6'-*O*-Acetylgeniposide	Neuroprotection	Fruit of *G. jasminoides*	[57]
58	Bartsioside	Anti-inflammatory	*Ipomoea grandifolia*	[24]
59	6'-*O*-*trans*-*p*-Coumaroylgeniposide	Neuroprotection	Fruit of *G. jasminoides*	[57]
60	6'-*O*-*trans*-Sinapoylgeniposide	Neuroprotection	Fruit of *G. jasminoides*	[57]
61	10-*O*-(4″-*O*-Methylsuccinoyl)-geniposide	Anti-Cardiomyopathy	Fruit of *G. jasminoides*	[84]
			Fruit of *G. jasminoides*	[25, 31]
		Anti-inflammatory	Fruit of *G. jasminoides*	[41]
62	Genipin	Antioxidant	Fruit of *G. jasminoides*	[47, 52]
		Antitumor	Fruit of *G. jasminoides*	[65, 66]
		Neuroprotection hepatoprotection	Fruit of *G. jasminoides*	[85]
64	6*β*-Hydroxygenipin	Neuroprotection	Fruit of G. *jasminoides*	[57]
67	Scandoside methyl ester	Antioxidant	*Wendlandia formosana*	[42]
69	6*α*-Methoxygeniposide	Antioxidant	Fruit of *G. jasminoides*	[37]
76	6''-*O*-*trans*-Sinapoylgenipin gentiobioside	Neuroprotection	Fruit of *G. jasminoides*	[57]
77	6''-*O*-*trans*-Cinnamoylgenipin gentiobioside	Neuroprotection	Fruit of *G. jasminoides*	[57]
86	Scandoside methyl ester	Neuroprotection	Fruit of *G. jasminoides*	[67]
88	Penta-acetylgeniposide (Ac)5GP	Anti-inflammatory	Fruit of *G. jasminoides*	[34]
		Antitumor		[53]
91	6'-*O*-Caffeoylioxide	Anti-inflammatory	Fruit of *G. jasminoides*	[13]
		Anti-inflammatory	*Hedyotis diffusa*	[35, 36]
		Antioxidant		[43]
		Antitumor	*E. ulmoides*	[54]
92	Asperulosidic	Anti-pilocarpine	*E. ulmoides*	[60]
		Anti-obesity	*Morinda citrifolia*	[86]
		Anti-bacterial	*Morinda citrifolia*	[82]
		Antidiabetics	*E. ulmoides*	[86]
93	Cerbinal	Anti-antiviral	Fruit of *G. jasminoides*	[88]

by increasing Nrf2, heme oxygenase 1 (HO-1), and quinone oxidoreductase 1 (NQO-1) protein expression, and down-regulated nuclear p65 protein expression, thereby inhibiting DSS-induced oxidative stress and inflammation in the colon[35]. At the same time, compounds **36** and **62** have also been validated for their anti-inflammatory effects in a variety of cell and animal models. For example, in cecal ligation and puncture (CLP) surgery, compound **36** can significantly reduce pro-inflammatory cytokines such as TNF-α and IL-1β, and significantly increase anti-inflammatory cytokine IL-10 to reduce inflammation in a mouse

Table 2 Iridoid terpenes with anti-inflammatory activity in *G. jasminoides*

No.	Compound	Model	IC_{50}	Source	Reference
4	Shanzhiside methyl ester	Neutrophils		*Barleria prionitis*	[12]
12	2'-*O*-*cis*-Coumaroylgardoside	RAW 264.7 (LPS induced)	121.40 μmol/L	Fruit of *G. jasminoides*	[13]
14	Phloyoside (II)			Fruit of *G. jasminoides*	[14]
34	Gardenoside	Rat chondrocytes (IL-1β-induced)		Fruit of *G. jasminoides*	[15]
					[16]
				Fruit of *G. jasminoides*	[17]
		acute kidney injury (CLP-induced)		Fruit of *G. jasminoides*	
		HK-2 cells (LPS-induced)		Fruit of *G. jasminoides*	[18]
		UC mice (TNBS-induced)		Fruit of *G. jasminoides*	
36	Geniposide	Caco cells (LPS-induced)		Fruit of *G. jasminoides*	[19]
		Pneumonia mice (aureus-induced)			
		Mastitis mice (LPS-induced)		Fruit of *G. jasminoides*	
				Fruit of *G. jasminoides*	[18]
					[21]
37	Deacetyl asperulosidic acid	Vacancy cells (LPS-induced)	1.00 μg/mL	*Lasianthus acuminatissimus*	[22]
38	Geniposidic acid	RAW 264.7cells (LPS induced)		Fruit of *G. jasminoides*	[23]
58	Bartsioside	BV-2 microglial cells	7.09 μmol	*E. ulmoides*	[24]
					[25]
		AGS cells (*H. pylori*-induced)		Fruit of *G. jasminoides*	[26]
		Colitis in mice (DSS-induced)		Fruit of *G. jasminoides*	[27]
62	Genipin	Corneal infectious keratitis (*S. aureus* and *P. aeruginosa* induced)		Fruit of *G. jasminoides*	
		BV2 microglia cells (LPS-induced)		Fruit of *G. jasminoides*	[28]
		RAW 264.7 cells		Fruit of *G. jasminoides*	[29, 30]
		A rat model of ALI (LPS-induced)			[31]
83	Genipin1-*O*-*β*-*D*-isomaltoside	Treatment ankle sprain		Fruit of *G. jasminoides*	[32]
84	Genipin1,10-di-*O*-*β*-*D*-glucopyranoside	Treatment ankle sprain		Fruit of *G. jasminoides*	[33]
88	penta-Acetylgeniposide (Ac)5GP	MH7A cells (TNF-α-induced)		Fruit of *G. jasminoides*	[34]
91	6'-*O*-Caffeoylioxide	RAW 264.7 (LPS induced)	83.38 μmol/L	Fruit of *G. jasminoides*	[13]
92	Asperulosidic	RAW 264.7 (LPS induced)			[35]
		RAW 264.7 (DSS induced))		Fruit of *G. jasminoides*	[36]

model of acute kidney injury induced by sepsis and in rat colonic inflammatory injury induced by TNBS[16, 17]. In a mouse model of *S. aureus*-induced pneumonia, the activation of NF-κB signaling pathway was inhibited by inhibition of the Toll-like receptor 2 (TLR2) signaling pathway, thereby reducing the production of inflammatory cytokines TNF-α and IL-1β[19]. In LPS-induced mastitis model mice, **36** inhibits the phosphorylation of IL-1β, NF-κB, p38, ERK, and JNK, as well as the expression of TLR4 to inhibit inflammation[20]. In a mouse model of *Helicobacter pylori* infection, compounds **36** and **62** down-regulated serum interferon-α (IFN-α), IL-1α, immunoglobulin A, and M levels, and reduced the inflammatory marker cyclooxygenase-2 (COX-2) levels[21]. In a model of keratitis induced by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, compound **62** inhibits keratitis infection by significantly reducing the expression of the inflammatory factors IL-1β, IL-6, IL-8, IL-15, TNF-α, and MMP2 and MMP9 in the cornea[27]. **62** inhibits LPS-induced NF-κB activation and upregulates the expression of Nrf2 and HO-1. LPS-induced inflammatory response is inhibited by activating the Nrf2 signaling pathway in BV-2 microglia[28]. In a mouse model of periodontitis, **62** prevents TNF-α-mediated production of MMP-1 and MMP-3 in human periodontal ligament cells (HPDLCs). Not only can it inhibit phosphorylation of ERKs and JNKs, but it also inhibits phosphorylation of AMPK. ERK and AMPK inhibitors inhibit both MMP-1 and MMP-3 production. In addition, ERK inhibitors could inhibit AMPK phosphorylation in TNF-α-stimulated HPDLCs[29]. In the LPS-induced inflammation model, **62** enhances the anti-inflammatory effect of RAW264.7 macrophages through the regulation of heme oxygenase-1 via the PI264.2-Nrf2 signaling pathway[30]. In a model of acute lung injury, **62** blockade nuclear factor NF-κB signaling activation and decrease tumor necrosis factor α (TNF-α), IL-1β, and IL-6 levels in lung and bronchoalveolar lavage fluids, significantly activating PI3K/AKT signaling to ameliorate mitochondria-dependent apoptosis, ERS, and inflammation in LPS-induced acute lung injury[31].

In conclusion, the Iridoids in *G. jasminoides* not only significantly down-regulated the level of ROS, but also reduced the production of NF-κB-related inflammatory factors. Notably, Nrf2 has a very close relationship with NF-κB, and it has been reported that the important role of Nrf2 in attenuating the inflammatory response is closely related to its ability to antagonize NF-κB. In

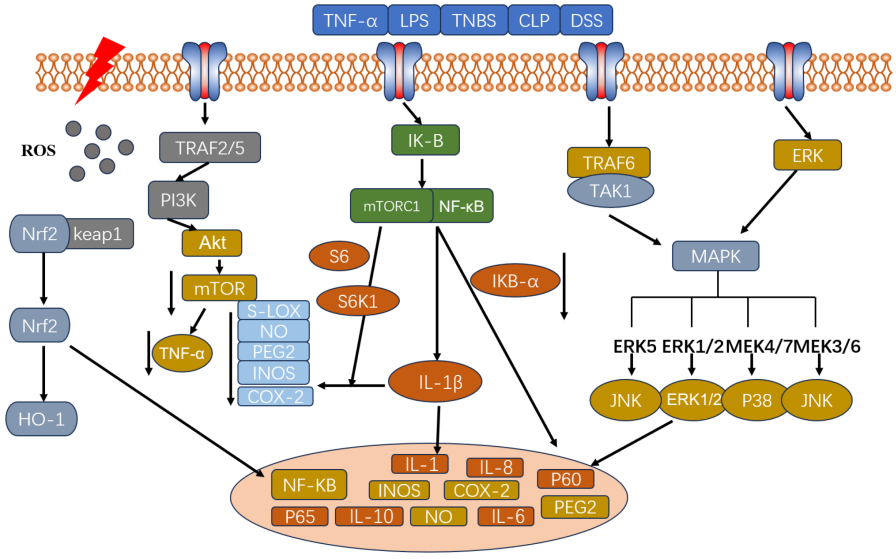


Figure 9 Anti-inflammatory mechanism of active iridoid in *G. jasminoides*. AP-1, activator protein 1; 5-LOX, 5-lipoxygenase; IRF3, interferon regulatory factor 3; Sirt 1, polyclonal antibody to sirtuin 1.

addition, activation of Nrf2 increases antioxidant defense and HO-1 expression, effectively neutralizes ROS and detoxifies toxic chemicals, thereby inhibiting ROS-mediated NF-κB activation. The mechanism diagram of the relevant is shown in Fig. 9.

3.2 Antioxidant

DPPH, ABTS and FRAP methods, hydrogen peroxide radical scavenging and reducing capacity determination, reactive oxygen species (OH, NO, H_2O_2, ONOO−, HOCl), hydroxyl group, superoxide anion and reducing force are common methods for antioxidant activity research *in vitro*. Eight compounds with significant antioxidant activity were isolated and identified from *G. jasminoides* fruit (Table 3). Studies on the antioxidant structure-activity relationship of compounds showed that the absolute configuration of hydroxyl group 6 (OH) was essential for the biological activity of iridoid glycosides. The compounds of the *S* and *α* configurations of the hydroxyl group at position 6 had better antioxidant activity.

3.3 Anti-tumor

At present, 6 compounds (**1**, **36**, **53**, **62**, **88**, **92**) with tumor cytotoxic activity have been isolated from *G. jasminoides*. Methylthiazolyldiphenyl-tetrazolium bromide (MTT) was mainly used to detect cytotoxicity, and its activity was mainly evaluated by IC_{50} values (Table 4). Compounds **1, 36, 53, 62** has anticancer effects on human cervical cancer cells (HeLa), cell proliferation, invasion, angiogenesis, lung cancer[44-46]. Compound **62** inhibits the growth of liver cancer, oral squamous cell carcinoma, human

Table 3 Iridoid compounds with antioxidant activity in *G. jasminoides*

No.	Compound	Method	Dose or IC_{50}	Source	Reference
45	6*α*-Hydroxygeniposide	DPPH assays	200 μg/mL	Fruit of *G. jasminoides*	[37]
35	6'-*O*-Sinapoylgeniposide	DPPH assays	(0.607 ± 0.100) μmol/L	*D. microphylla*	[38]
36	Genipin	Peroxyl radical-scavenging	100 μmol/L	Fruit of *G. jasminoides*	[39]
38	Geniposidic acid	DPPH ABTS	(24.45 ± 0.74) μg/mL (17.25 ± 0.04) μg/mL	*E. ulmoides* *O. staminate* (ESF) tea	[40]
62	Geniposide	ROS and GSH-Px assay	12.5, 25, 50 μg/mL	Fruit of *G. jasminoides*	[41]
67	Scandoside methyl ester	Hydroxyl radicals	0.303 μmol/L	*W. formosana*	[42]
69	6*α*-Methoxygeniposide	DPPH assays	200 μg/mL	Fruit of *G. jasminoides*	[37]
92	Asperuloside	RAW 264.7 (LPS-induced)			[43]

Table 4 Iridoid terpenoids with antitumor activity in *G. jasminoides*

No.	Compound	Method	IC_{50} (μmol/L)	Source	Reference
1	Iridomyrmecin	HeLa, a human-cervical cell	17.2 μmol/L (24 h)	Fruit of *G. jasminoides*	[44]
36	Geniposide	PLC/PRF/5 cells and HUVECs		Fruit of *G. jasminoides*	[45]
53	10-*O*-Succinoylgeniposide			Fruit of *G. jasminoides*	[46]
62	Genipin	MDA-MB-231 breast cancer cell non-small-cell lung cancer H1299 cells human leukemia K562 cells	327 μmol/L 90 μg/mL 351.5 μmol/L 250 μmol/L	Fruit of *G. jasminoides*	[47, 52]
88	Penta-Acetylgeniposide $(Ac)_5GP$	Hepatocytes (AFB1- induced)		Fruit of *G. jasminoides*	[53]
92	Asperuloside	Human cervical cancer cell lines Hela NSCLC cells	683.0 μg/mL	Fruit of *G. jasminoides*	[54]

bladder cancer cells, gastric cancer cells, cervical cancer cells, and lung cancer cells[47-52]. Its mode of action includes induction of tumor cell apoptosis, tumor cell cycle blockade, inhibition of tumor cell invasion, and specific inhibition of uncoupling protein 2 (UCP2). Compounds **88** and **92** are predominantly anti-hepatocellular carcinoma cells and cervical cancer cells[53,54]. The current animal and cellular experimental studies mainly start from the direct effect of anti-tumor, but have not carried out in-depth research on the mechanism of tumor treatment from the perspective of the overall tumor microenvironment, which is the main problem to be solved in future experimental studies.

3.4 Anti-central nervous system disease activity

Central nervous system diseases mainly include dementia, stroke and depression, epilepsy and Alzheimer's disease, etc. From the beginning of the study to the present, 14 iridoid terpene compounds (**3**, **4**, **27**, **34**, **36**, **38**, **41**, **54**, **59**, **60**, **62**, **76**, **77**, **92**) with central nervous system protective effect have been isolated from *G. jasminoides*. (Table 5) Neuroprotective mechanisms include regulation of MAPK, JAK, PI3K/Akt, and Nrf2 signaling pathways. Compound **3** was treated with oxidopamine hydrochloride (6-OHDA) (100 μmol/L) to establish a Parkinson's disease (PD) cell model with neuroblastoma SH-SY5Y cells, with increased cell viability, decreased ROS levels, increased levels of Nrf2 and HO-1 proteins, and increased levels of *HO-1* mRNA[55]. The combination of compounds **4** and **34** has synergistic rapid-onset antidepressant effects by triggering hippocampal pituitary adenylate cyclase activiting polypeptide (PACAP) activity and associated CaMKII-BDNF signaling[71]. Compounds **27**, **54**, **59**, **60**, **76**, and **77** can improve the short-term learning and memory ability of transgenic Alzheimer's flies to varying degrees, suggesting that these compounds may have potential anti-dementia effects[57]. Compound **34** can improve sleep disturbance in PD model rats, and its mechanism may be related to increasing dopamine levels in the striatum[58]. Compound **34** can ameliorate spatial learning, memory impairment and fear memory extinction disorders in tail vein injected STZ mice, and the mechanism may be related to the enhanced activity of glycogen synthase kinase 3 beta (P-GSK3β) and the inhibition of GSK-3β activation to protect nerve cells[59]. Compound **34** exerts antidepressant effects in a variety of depression models, such as the chronic unpredictable mild stress model (CMS), the LPS-induced acute inflammatory depression model, and the diabetes mellitus complicated depression model[60]. Compounds **36** and **92** significantly inhibited the protein expression of activator protein 1 in epileptic mice, increased the activation of Akt, and increased the protein expression of GSK-3β and PI3K (these results suggest that attenuate epilepsy in mice through the PI3K/Akt/GSK-3β signaling pathway)[61]. Compound **36** Antidepressant effects may be associated with activated PI3K/Akt/GSK3β signaling, decreased ceramide levels, and hippocampal neuronal apoptosis in mice with chronic unpredictable mild stress (CUMS)-induced depression[63]. Compound **38** increased growth associated protein-43 (GAP43) expression through PI3K/AKT pathway activation and ultimately ameliorated nerve damage in AD mice[64]. The effects of compound **62** on PRS (prenatal stress maternal) mice occur by inhibiting DNA demethylation of DNA methyltransferase 1 (DNMT1), normalizing the expression of reduced brain-derived neurotrophic factor (BDNF) in the hippocampus[65]. In a rat model of GUMS-induced depression, this may be caused by the underlying dysregulation of the monoaminergic neurotransmitter system and post-receptor signaling pathways, which specifically affects 5-HT1A receptor (5-HT1AR), 5-HT2AR, and BDNF levels in the hippocampus[66].

3.5 Other activities

In addition, 21 other active compounds were obtained from *G. jasminoides* (Table 6), including, immunosuppressive activity (**3**, **7**, **21**, **36**, **45**), hepatoprotective (**3**, **38**, **62**), antiacetylcholine (**3**, **4**, **37**, **38**), induced endorphins (**4**), antinociception (**14**), antispasmodic (**24**), antidiabetic (**34**, **36**, **38**, **92**), cardiovascular protection (**36**, **38**), antihypertensive (**36**, **38**), antiviral (**38**, **41**, **93**), Induces muscle atrophy (**38**), anti-TMV (**41**, **93**), anti-LDL oxidative stress (**43**, **86**), reduces melanin (**61**), hepatotoxicity (**36**, **62**), anti-insect (**63**), antibacterial (**63**, **92**), analgesia (**37**), treatment of ankle sprain (**83**, **84**), anti-renal fibrosis (**92**), anti-

Table 5 Iridoid terpenoids in *G. jasminoides* against central nervous system diseases

No.	Compound	Activity	Source	Reference
3	Shanzhiside	Anti-PD	Fruit of *G. jasminoides*	[55]
4	Shanzhiside methyl ester	Anti-depression	Yueju	[56]
27	10-(6-*O*-*trans*-Sinapoylglucopyranosyl) gardendiol	Anti-AD	Fruit of *G. jasminoides*	[57]
34	Gardenoside	Anti-AD Anti-PD Anti-depression	Fruit of *G. jasminoides* Fruit of *G. jasminoides* Fruit of *G. jasminoides*	[58] [59] [60]
36	Geniposide	Anti-epilepsy Anti-depression	*E. ulmoides* Fruit of *g. Jasminoides*	[60, 62] [63]
38	Geniposide acid	Anti-AD	Fruit of *G. Jasminoides*	[64]
39	10-*O*-Acetyl geniposide	Anti-AD	Fruit of *G. Jasminoides*	[57]
54	6'-*O*-Acetylgeniposide	Anti-AD	Fruit of *G. Jasminoides*	[57]
59	6'-*O*-*trans*-*p*-Coumaroylgeniposide	Anti-PD Anti-AD	Fruit of *G. Jasminoides*	[57]
60	6'-*O*-*trans*-Sinapoylgeniposide	Anti-AD	Fruit of *G. Jasminoides*	[57]
62	Genipin	Anti-depression Anti-AD Anti-PD	Fruit of *G. Jasminoides*	[65, 66] [67]
64	6*β*-Hydroxygenipin	Neuroprotection	Fruit of *G. Jasminoides*	[57]
76	6''-*O*-*trans*-Sinapoylgenipin gentiobioside	Anti-AD	Fruit of *G. Jasminoides*	[57]
77	6''-*O*-*trans*-Cinnamoylgenipin gentiobioside	Anti-AD	Fruit of *G. Jasminoides*	[57]
86	Scandoside methyl ester	Neuroprotection	Fruit of *G. Jasminoides*	[67]

Table 6 Iridoid compounds in *G. jasminoides* against other diseases

No.	Compound	Activity	Source	Reference
3	Shanzhiside	Immunosuppressive Hepatoprotection Anti-AchE	Fruit of *G. jasminoides Rehmannia* Fruit of *G. jasminoides*	[69] [70] [67]
4	Shanzhiside methylester	Analgesic	*L. rotata, Duyiwei* Fruit of *G. jasminoides*	[71]
7	Ixoroside	Immunosuppressive Anti-cardiomyopathy	Fruit of *G. jasminoides*	[69] [72]
21	6α-Hydroxygeniposide	Immunosuppressive	Fruit of *G. jasminoides*	[73]
23	Ixoroside	Immunosuppressive	Fruit of *G. jasminoides*	[74]
24	Penstemonoside (IV)	Antispasmodic	*P. latifolia*	[75]
34	Gardenoside	Antidiabetics	Fruit of *G. jasminoides*	[74]
36	geniposide	Immunosuppressive Anti-cardiomyopathy. Antidiabetics	Fruit of *G. jasminoides*	[71] [75, 76] [77]
37	Deacetyl asperulosidicacid methyl ester	Anti-AchE Analgesic	Fruit of *G. jasminoides* Ji shi teng	[78] [14]
38	Geniposidic acid	Anti-AchE Antiviral Hepatoprotection Anti-cardiomyopathy; antidiabetics	Fruit of *G. jasminoides*	[78] [79] [64] [80, 82] [32]
41	Genipin-1-gentiobioside	Antiviral; anti-cardiomyopathy	Fruit of *G. jasminoides*	[83] [84]
43	Deacetyl asperulosidic acid	Anti-cardiomyopathy	*O. diffusa* Roxb	[37]
45	6α-Hydroxy-geniposide	Immunosuppressive	Fruit of *G. jasminoides*	[71]
61	10-*O*-(4″-*O*-methylsuccinoyl)-geniposide	Anti-Cardiomyopathy	Fruit of *G. jasminoides*	[86]
62	Genipin	Hepatoprotection	Fruit of *G. jasminoides*	[85]
92	Asperuloside	Anti-obesity Anti-bacterial Antidiabetics	*M.citrifolia* *M. citrifolia* *E. ulmoide*	[86] [82] [87]
93	Cerbinal	Antiviral	Fruit of *G. jasminoides*	[88]

obesity (**92**). Among them, compounds **36**, **62** and **92** contain a variety of pharmacological activities[68].

It is worth mentioning that compounds **36** and **62** are the main active ingredients of *G. jasmine* and have a therapeutic effect on liver damage, however, it can also cause hepatotoxicity. They have dual pharmacological activity in liver injury. When administered at a dose of 20–150 mg/kg for 5–28 days, it exerts an effective hepatoprotective effect. Mechanistically, *G. jasminoides* exert protective or toxic effects by regulating the TNF-α/NF-κB pathway to control oxidative stress and inflammatory responses.

4 Conclusion and prospects

G. jasminoides is a major medicinal material in China, with a long history of medicinal use, iridoids are one of its main active ingredients. This article is mainly about the chemical composition, pharmacological effects and mechanism of iridoids in *G. jasminoides* were reviewed. Many scholars at domestic and international have been interested in the iridoids of *G. jasminoides*. There are more than 94 iridoids isolated from *G. jasminoides*, and their structures are diversified. The substitution position is changeable and modifiable. By comparing the four types of iridoids glycosides in *G. jasminoides*, Monoene Iridods were the most diverse of the four types. Iridods compounds have various pharmacological activities and structures, and there are few studies on the pharmacological activities of Iridods with different structures. We can further study the structure-effect relationship of Iridods in *G. jasminoides* to provide reference for the future research and development of new drugs and foods.

Conflicts of interest

All authors declare that there are no conflicts of interest regarding this study. Xuqiang Liu is the managing editor of Food & Medicine Homology.

Acknowledgments

This work was funded by National Key R&D Program of China (No. 2022YFF1100300), Key Project in Science and Technology Agency of Henan Province (No. 242102310561), and key research projects of higher education institutions in Henan Province (No. 24B350002).

References

[1] Sampaio-Santos, M. I., Kaplan, M. A. C. Biosynthesis significance of iridoids in chemosystematics. *Journal of the Brazilian Chemical Society*, **2010**, 12: 144–153. https://doi.org/10.1590/S0103-50532001000200004

[2] Franzyk, H. Synthetic aspects of iridoid chemistry. *Organic Chemistry Frontiers*, **2000**, 79: 1–114. https://doi.org/10.1007/978-3-7091-6341-21

[3] Kong, Y. F. Research progress on structures and structure-activity relationships of iridoids. *Natural Product Research*, **2021**, 33: 1236–1250. https://doi.org/10.7501/j.issn.0253-2670.2013.19.025

[4] Çelikel, F. G., Reid, M. S., Jiang, C. Z. Postharvest physiology of cut *Gardenia jasminoides* flowers. *Scientia Horticulturae*, **2020**, 261: 108983. https://doi.org/10.1016/j.scienta.2019.108983

[5] Chen, L. P., Tian, X. Y., Li, X. L., et al. *Gardenia jasminoides* Ellis: ethnopharmacology, phytochemistry, and pharmacological and

industrial applications of an important traditional Chinese medicine. *Journal of Ethnopharmacology*, **2020**, 257: 112829. https://doi.org/10.1016/j.jep.2020.112829

[6] Feng, J., He X., Zhou, S., et al. Preparative separation of crocins and geniposide simultaneously from gardenia fruits using macroporous resin and reversed-phase chromatography. *Journal of Separation Science*, **2014**, 37: 314–322. https://doi.org/10.1002/jssc.201300601

[7] Li, N., Wu, H. M., Zhou. H. Antioxidative property and molecular mechanisms underlying geniposide-mediated therapeutic effects in diabetes mellitus and cardiovascular disease. *Oxidative Medicine and Cellular Longevity*, **2019**, 2019: 20. https://doi.org/10.1155/2019/7480512

[8] Hobbs, C. A., Koyanagi. M., Swartz, C., et al. Genotoxicity evaluation of the naturally-derived food colorant, gardenia blue, and its precursor, genipin. *Food and Chemical Toxicology*, **2018**, 118: 695–708. https://doi.org/10.1016/j.fct.2018.06.001

[9] Zhang, Q. H. Homology of medicine and food and Chinese herb taken as food. *Journal of Liaoning University of Traditional Chinese Medicine*, **2009**, 11: 54–55. https://doi.org/10.13194/j.jlunivtcm.2009.07.56.zhangqh.096

[10] Jina, C. Y., Zongoa, A. W., Dub, H. J., et al. Gardenia (*Gardenia jasminoides* Ellis) fruit: a critical review of its functionalnutrients, processing methods, health-promoting effects, comprehensiveapplication and future tendencies. *Critical Reviews in Food Science and Nutrition*, **2023**: 1–28. https://doi.org/10.1080/10408398.2023.2270530

[11] Wang, C., Gong, X., Bo, A., et al. Iridoids: research advances in their phytochemistry. *Biological Activities and Pharmacokinetics Molecules*, **2020**, 25: 287. https://doi.org/10.3390/molecules25020287

[12] Ghule, B. V., Kotagale, N. R., Patil, K. S., Inhibition of the pro-inflammatory mediators in rat neutrophils by shanzhiside methyl ester and its acetyl derivative isolated from Barleria prionitis. *Journal of Ethnopharmacology*, **2020**: 112374. https://doi.org/10.1016/j.jep.2019.112374

[13] Li, H. B., Ma, J. F., Mei, Y. D., et al. Two new iridoid glycosides from the fruit of *Gardenia jasminoides*. *Natural Product Research*, **2022**, 36: 186–192. https://doi.org/10.1080/14786419.2020.1775227

[14] Chen, Y. F., Zhang, J. Y., Zhao, M., et al. The analgesic activity and possible mechanisms of deacetyl asperulosidic acid methyl ester from Ji Shi Teng in mice. *Pharmacology Biochemistry and Behavior*, **2012**, 102: 585–592. https://doi.org/10.1016/j.pbb.2012.07.005

[15] Xia, T., Zhao, R., He, S., et al. Gardenoside ameliorates inflammation and inhibits ECM degradation in IL-1β-treated rat chondrocytes via suppressing NF-κB signaling pathways. *Biochemical and Biophysical Research Communications*, **2023**, 640: 164–172. https://doi.org/10.1016/j.bbrc.2022.12.016

[16] Liu, J., Zhao, N., Shi, G., et al. Geniposide ameliorated sepsis-induced acute kidney injury by activating PPARγ. *Neurobiology of Aging*, **2020**, 12: 22744–22758. https://doi.org/10.18632/aging.103902

[17] Yu, Y., Bian, Y., Shi, J. X., et al. Geniposide promotes splenic Treg differentiation to alleviate colonic inflammation and intestinal barrier injury in ulcerative colitis mice. *Bioengineered*, **2022**, 13: 14616–14631. https://doi.org/10.1080/21655979.2022.2092678

[18] Chen, J. Y., Li, H. H., Hu, S. L., et al. Anti-inflammatory effects and pharmacokinetics study of geniposide on rats with adjuvant arthritis. *International Immunopharmacology*, **2015**, 24: 102–109. https://doi.org/10.1016/j.intimp.2014. 11.017

[19] Yu, B., Shen, Y., Qiao, J., et al. Geniposide attenuates *Staphylococcus aureus*-induced pneumonia in mice by inhibiting NF-κB activation. *Microbial Pathogenesis*, **2017**, 112: 117–121. https://doi.org/10.1016/j.micpath.2017.09.050

[20] Song, X., Zhang, W., Wang, T., et al. Geniposide plays an anti-inflammatory role via regulating TLR4 and downstream signaling pathways in lipopolysaccharide-induced mastitis in mice. *Inflammopharmacology*, **2014**, 37: 1588–1598. https://doi.org/10.1007/s10753-014-9885-2

[21] Chang, C. H., Wu, J. B., Yang, J. S., et al. The suppressive effects of geniposide and genipin on *Helicobacter pylori* infections *in vitro* and *in vivo*. *Journal of Food Science*, **2017**, 82: 3021–3028. https://doi.org/10.1111/1750-3841.13955

[22] Li, C., Mu, Y. R. Penta-acetyl geniposide suppresses migration, invasion, and inflammation of TNF-α-stimulated rheumatoid arthritis fibroblast-like synoviocytes involving Wnt/β-catenin signaling pathway. *Inflammopharmacology*, **2021**, 44: 2232–2245. https://doi.org/10.1007/s10753-021-01495-y

[23] Song, M., Chen, Z., Qiu, R., et al. Inhibition of NLRP3-mediated crosstalk between hepatocytes and liver macrophages by geniposidic acid alleviates cholestatic liver inflammatory injury. *Redox Biology*, 2022, 55: 102404. https://doi.org/10.1016/j.redox.2022.102404

[24] Tang, J. J., Zhao, N., Gao, Y. Q., et al. Phytosterol profiles and iridoids of the edible Eucommia ulmoides Oliver seeds and their anti-inflammatory potential. *Food Bioscience*, **2021**, 43: 2212–4292. https://doi.org/10.1016/j.fbio.2021.101295

[25] Sohn, Y. A., Hwang, I. Y., Lee, S. Y., Cho, et al. Protective Effects of Genipin on Gastrointestinal Disorders. *Biological and Pharmaceutical Bulletin*, **2017**, 40: 151–154. https://doi.org/10.1248/bpb.b16-00545

[26] Kim, T. H., Yoon, S. J., Lee, S. M. Genipin attenuates sepsis by inhibiting Toll-like receptor signaling. *Molecular Medicine*, **2012**, 18: 455–465. https://doi.org/10.2119/molmed.2011.00308

[27] Li, Z., Ma, T., Zhang, W., et al. Genipin attenuates dextran sulfate sodium-induced colitis via suppressing inflammatory and oxidative responses. *Inflammopharmacology*, **2020**, 28: 333–339. https://doi.org/10.1007/s10787-019-00639-9

[28] Huertas-Bell, M., Cuéllar-Sáenz, J. A., Rodriguez, C. N., et al. A pilot study to evaluate genipin in *Staphylococcus aureus* and *Pseudomonas aeruginosa* keratitis models: modulation of pro-inflammatory cytokines and matrix metalloproteinases. *International Journal of Molecular Sciences*, **2023**, 24: 6904. https://doi.org/10.3390/ijms24086904

[29] Wang, J., Chen, L. Genipin inhibits LPS-induced inflammatory response in BV2 microglial cells. *Neurochemical Research*, **2017**, 42: 2769–2776. https://doi.org/10.1007/s11064-017-2289-6

[30] Shindo, S., Hosokawa, Y., Hosokawa, I., et al. Genipin inhibits MMP-1 and MMP-3 release from TNF-a-stimulated human periodontal ligament cells. *Biochimie*, **2014**, 107: 391–395. https://doi.org/10.1016/j.biochi.2014.10.008

[31] Jeon, W. K., Hong, H. Y., Kim, B. C. Genipin up-regulates heme oxygenase-1 via PI3-kinase-JNK1/2-Nrf2 signaling pathway to enhance the anti-inflammatory capacity in RAW264.7 macrophages. *Archives of Biochemistry and Biophysics*, **2011**, 512: 119–125. https://doi.org/10.1016/j.abb.2011.05.016

[32] Luo, X., Lin, B., Gao, Y., et al. Genipin attenuates mitochondrial-dependent apoptosis, endoplasmic reticulum stress, and inflammation via the PI3K/AKT pathway in acute lung injury. *International Immunopharmacology*, **2019**, 76: 105842. https://doi.org/10.1016/j.intimp

[33] Zhang, X., Wang, L., Zheng, Z., et al. Online microdialysis-ultra performance liquid chromatography–mass spectrometry method for comparative pharmacokinetic investigation on iridoids from *Gardenia jasminoides* Ellis in rats with different progressions of type 2 diabetic complications. *Journal of Pharmaceutical and Biomedical Analysis*, **2017**, 140: 146–154. https://doi.org/10.1016/j.jpba.2017.03.040

[34] Zeng, X., Jiang, J., Liu, S., et al. Bidirectional effects of geniposide in liver injury: preclinical evidence construction based on meta-analysis. *Journal of ethnopharmacology*, **2023**, 319: 117061. https://doi.org/10.1016/j.jep.2023.117061

[35] He, J., Lu, X., Wei, T., et al. Asperuloside and asperulosidic acid exert an anti-inflammatory effect via suppression of the NF-κB and MAPK signaling pathways in LPS-Induced RAW 264.7 macrophages. *International Journal of Molecular Sciences*, **2018**, 19: 2027. https://doi.org/10.3390/ijms19072027

[36] Chen, Y. E., Xu, S. J., Lu, Y. Y., et al. Asperuloside suppressing oxidative stress and inflammation in DSS-induced chronic colitis and RAW 264.7 macrophages via Nrf2/HO-1 and NF-κB pathways. *Chemico-Biological Interactions*, **2021**, 344: 109512. https://doi.org/10.1016/j.cbi.2021.109512

[37] Zhang, H., Feng, N., Xu, Y. T., et al. Chemical constituents from the flowers of wild *Gardenia jasminoides* J. Ellis. *Chemistry & Biodiversity*, **2017**, 14: 1600437. https://doi.org/10.1002/cbdv.201600437

[38] Ijaz, F., Haq, A. U., Ahmad, I., et al. Antioxidative iridoid glycosides from the sky flower (*Duranta repens* Linn). *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2011**, 26: 88–92. https://doi.org/10.3109/14756361003724778

[39] Wei, D., Liu, B. L., Shi, Y., et al. Genipin inhibited on oxidative stress injury of ARPE-19 cells by regulating Nrf2/HO-1 pathway. *International Journal of Molecular Medicine*, **2022**, 51: 83–86. https://doi.org/10.3892/ijmm.2018.4027

[40] Cheng, S., Jia, H., Zhang, Y., et al. Geniposidic acid from *Eucommia ulmoides* oliver staminate flower tea mitigates cellular oxidative stress via activating AKT/NRF2 signaling. *Molecules*, **2022**, 27: 8568. https://doi.org/10.3390/molecules27238568

[41] Li, J., Ge, H., Xu, Y., et al. Geniposide alleviates oxidative damage in hepatocytes through regulating miR-27b-3p/Nrf2 axis. *Journal of Agricultural and Food Chemistry*, **2022**, 70: 11544–11553. https://doi.org/10.1021/acs.jafc.2c03856

[42] Lakshmana Raju, B., Lin, S. J., Hou, W. C., et al. Antioxidant iridoid glucosides from wendlandia formosana. *Natural Product Research*, **2004**, 18: 357–364. https://doi.org/10.1080/14786410310001622013

[43] Wu, Q., Gai, S., Zhang, H. J. Asperulosidic acid, a bioactive iridoid, alleviates placental oxidative stress and inflammatory responses in gestational diabetes mellitus by suppressing NF-κB and MAPK signaling pathways. *Pharmacology*, **2022**, 107: 197–205. https://doi.org/10.1159/000521080

[44] Lin, L., Cheng, X. L., Li, M. Z., et al. Antitumor effects of iridomyrmecin in HeLa cervical cancer cells are mediated via apoptosis induction, loss of mitochondrial membrane potential, cell cycle arrest and down-regulation of PI3K/Akt and up-regulation of lncRNA CCAT2 expression. *Bangladesh Journal of Pharmacology*, **2016**, 11: 856. https://doi.org/10.3329/bjp.v11i4.27539

[45] Zhang, C., Wang, N., Tan, H. Y., et al. Direct inhibition of the TLR4/MyD88 pathway by geniposide suppresses HIF-1α-independent VEGF expression and angiogenesis in hepatocellular carcinoma. *British Journal of Pharmacology*, **2020**, 14: 3240–3257. https://doi.org/10.1111/bph.15046

[46] Alamri, M. A., Alawam, A. S., Alshahrani, M. M., et al. Establishing the role of iridoids as potential Kirsten rat sarcoma viral oncogene homolog G12C inhibitors using molecular docking; molecular docking simulation; molecular mechanics poisson–boltzmann surface area; frontier molecular orbital theory; molecular electrostatic potential; and absorption, distribution, metabolism, excretion, and toxicity analysis. *Molecules*, **2023**, 28: 5050. https://doi.org/10.3390/molecules28135050

[47] Moon, A. Genipin, a constituent of *Gardenia jasminoides* Ellis, induces apoptosis and inhibits invasion in MDA-MB-231 breast cancer cells. *Oncology Reports*, **2011**, 27: 567–572. https://doi.org/10.3892/or.2011.1508

[48] Li, Z., Zhang, T. B., Jia, D. H., et al. Genipin inhibits the growth of human bladder cancer cells via inactivation of PI3K/Akt signaling. *Oncology Letters*, **2018**, 15: 2619–2624. https://doi.org/10.3892/ol.2017.7588

[49] Jo, M. J., Jeong, S., Yun, H. K., et al. Genipin induces mitochondrial dysfunction and apoptosis via downregulation of Stat3/mcl-1 pathway in gastric cancer. *BMC Cancer*, **2019**, 19: 739. https://doi.org/10.1186/s12885-019-5957-x

[50] Cao, H., Feng, Q., Xu, W., et al. Genipin induced apoptosis associated with activation of the c-Jun NH_2-terminal kinase and p53 protein in HeLa cells. *Biological & pharmaceutical bulletin*, **2010**, 33: 1343–1348. https://doi.org/10.1248/bpb

[51] Yang, X., Yao, J., Luo, Y., et al. P38 MAP kinase mediates apoptosis after genipin treatment in non-small-cell lung cancer H1299 cells via a mitochondrial apoptotic cascade. *Journal of Pharmacological Sciences*, **2013**, 121: 272–281. https://doi.org/10.1254/jphs.12234fp

[52] Feng, Q., Cao, H., Xu, W., et al. Apoptosis induced by genipin in human leukemia K562 cells: involvement of c-Jun N-terminal kinase in G2/M arrest. Acta Pharmacologica Sinica, 2011, 32: 519–527. https://doi.org/10.1038/aps.2010.158. Epub 2011 Mar 14.

[53] Peng, C., Huang, C., Wang, C. The anti-tumor effect and mechanisms of action of penta-acetyl geniposide. *Current Cancer Drug Targets*, **2005**, 5: 299–305. https://doi.org/10.2174/1568009054064633

[54] Qi, Z. M., Wang, X., Liu, X., et al. Asperuloside promotes apoptosis of cervical cancer cells through endoplasmic reticulum stress-mitochondrial pathway. *Chinese Journal of Integrative Medicine*, **2024**, 30: 34–41. https://doi.org/10.1007/s11655-023-3695-z

[55] Zhang, H., Sun, Y., Yau, S., et al. Synergistic effects of two natural compounds of iridoids on rapid antidepressant action by up-regulating hippocampal PACAP signaling. *British Journal of Pharmacology*, **2022**, 179: 4078–4091. https://doi.org/10.1111/bph.15847

[56] Sun, Z. W., Zhan, H. G.,Wang, C., et al. Shanzhiside methylester protects against depression by inhibiting inflammation via the miRNA-155-5p/SOCS1 axis. *psychopharmacology*, **2022**, 239: 2201–2213. https://doi.org/10.1007/s00213-022-06107-7

[57] Luo, X. F., Li, Y., Hu, J. Regulatory effect of gardenoside on sleep disorder in rats with Parkinson's disease and itsmechanism. *Journal of Jilin University Medicine Edition*, **2020**, 46: 1177–1181. https://doi.org/10.13481/j.1671-587x.20200611

[58] Ma, W. W., Tao, Y., Wang, Y. Y., et al. Effects of *Gardenia jasminoides* extracts on cognition and innate immune response in an adult Drosophila model of Alzheimer's disease. *Chinese Journal of Natural Medicines*, **2017**, 15: 899–904. https://doi.org/10.1016/S1875-5364 (18)30005-0

[59] Chen, G. H., Chen, Q. Role of gardenoside and its aglycone genipine in treatment of depression. *Chinese Journal of Chemical Physics*, **2022**, 38: 1877–1882. https://doi.org/10.3969/j.issn.1000-4718.2022.10.018

[60] Uczay, M., Pflüger, P., Picada, J. N., et al. Geniposide and asperuloside alter the COX-2 and GluN2B receptor expression after pilocarpine-induced seizures in mice. *Naunyn-schmiedebergs Archives of Pharmacology*, **2023**, 396: 951–962. https://doi.org/10.1007/s00210-022-02367-4

[61] Wei, H., Duan, G., He, J., et al. Geniposide attenuates epilepsy symptoms in a mouse model through the PI3K/Akt/GSK-3β signaling pathway. *Experimental and Therapeutic Medicine*, **2017**, 1: 1136–1142. https://doi.org/10.3892/etm.2017.5512

[62] Wang, M., Yang, L., Chen, Z., et al. Geniposide ameliorates chronic unpredictable mild stress induced depression-like behavior through inhibition of ceramide-PP2A signaling via the PI3K/Akt/GSK3β axis. *Psychopharmacology*, **2021**, 238: 2789–2800. https://doi.org/10.1007/s00213-021-05895-8

[63] Chen, Q. Y., Yin, Y., Li, L., et al. Geniposidic acid confers neuroprotective effects in a mouse model of Alzheimer's disease through activation of a PI3K/AKT/GAP43 regulatory axis. *Journal of Prevention of Alzheimers Disease*, **2022**, 9: 158–171. https://doi.org/10.14283/jpad.2021.60

[64] Gao, F. Y., Chen, X. F., Cui, L. X., et al. Gut microbiota mediates the pharmacokinetics of Zhi-Zi-Chi decoction for the personalized treatment of depression. *Journal of Ethnopharmacology*, **2023**, 302: 115934. https://doi.org/10.1016/j.jep

[65] Wang, Q. S., Tian, J. S., Cui, Y. L., et al. Genipin is active via modulating monoaminergic transmission and levels of brain-derived neurotrophic factor (BDNF) in rat model of depression. *Neuroscience*, **2014**, 275: 365–373. https://doi.org/10.1016/j.neuroscience.2014.06.032

[66] Li, Y., Li, L., Hölscher, C. Therapeutic potential of genipin in central

neurodegenerative diseases. *CNS Drugs*, **2016**, 30: 889–897. https://doi.org/10.1007/s40263-016-0369-9

[67] Ramos, R. R., Gonçalo, M. P., Daniela, M. Genipin prevents alpha-synuclein aggrega tion and toxicity by affecting endocytosis, metabolism and lipid storage. *Nature Communictions*, **2023**, 14: 1918. https://doi.org/10.1038/s41467-023-37561-2

[68] Liu, X. Q., Wang, S. Y., Cui, L. L., et al. Flowers: precious food and medicine resources. *Food Science and Human Wellness*, **2023**, 12: 1020–1052. https://doi.org/10.1016/j.fshw.2022.10.022

[69] Chang, W. L., Wang, H. Y., Shi, L. S., et al. Immunosuppressive iridoids from the fruits of gardeniajasminoides. *Journal of Natural Products*, **2005**, 68: 1683–1685. https://doi.org/10.1021/np0580816

[70] Zhong, A. J., Li, G. Screening of active ingredients in *Rehmannia glutinosa* and its mechanism of action in the treatment of liver diseases. *Indian Journal of Pharmaceutical Sciences*, **2023**, 85: 445–455. https://doi.org/10.36468/pharmaceutical-sciences.1110

[71] Fan, H., Li, T. F., Gong, N., et al. Shanzhiside methylester, the principle effective iridoid glycoside from the analgesic herb *Lamiophlomis rotata*, reduces neuropathic pain by stimulating spinal microglial *β*-endorphin expression. *Neuropharmacology*, **2016**, 101: 98–109. https://doi.org/10.1016/j.neuropharm.2015.09.010

[72] Yenigun, S., Basar, Y., Ipek, Y., et al. Comprehensive evaluation of Ixoroside: An iridoid glycoside from *Nepeta aristata* and *N. baytopii*, assessing antioxidant, antimicrobial, enzyme inhibitory, DNA protective properties, with computational and pharmacokinetic analyses. *Journal of Biologically Active Products from Nature*, **2024**, 14: 286–315. https://doi.org/10.1080/22311866.2024.2358785

[73] Ortiz de Urbina, A., Martín, M., Fernández, B., et al. *In vitro* antispasmodic activity of peracetylated penstemonoside, aucubin and catalpol. *Planta Medica*, **1994**, 60: 512–515. https://doi.org/10.1055/s-2006-959561

[74] Zhou, J., Li, S. P., Feng, K. X., et al. Impact of gardenoside on insulin receptor and nuclear factor kappa B of insulin resistant in HepG2 cells. *The Chinese Journal of Clinical Pharmacology*, **2015**, 31: 362–365. https://doi.org/10.13699/j.cnki.1001-6821.2015.05.013

[75] Song, P., Shen, D. F., Meng, Y. Y., et al. Geniposide protects against sepsis-induced myocardial dysfunction through AMPK*α*-dependent pathway. *Free Radical Biology and Medicine*, **2020**, 152: 186–196. https://doi.org/10.1016/j.freeradbiomed.2020.02.011

[76] Fu, Y., Yuan, P., Cao, Y., et al. Geniposide in *Gardenia jasminoides* var. *radicans* Makino modulates blood pressure via inhibiting WNK pathway mediated by the estrogen receptors. *Journal of Pharmacy and Pharmacology*, **2020**, 72: 1956–1969. https://doi.org/10.1111/jphp.13361

[77] Zhang, Y., Ding, Y., Zhong, X., et al. Geniposide acutely stimulates insulin secretion in pancreatic β-cells by regulating GLP-1 receptor/cAMP signaling and ion channels. *Molecular and Cellular Endocrinology*, **2016**, 430: 89–96. https://doi.org/10.1016/j.mce.2016.04.020

[78] Kwak, J. H., Lee, D. U. Structure–antiamnesic activity relationship of iridoid glycosides from gardenia fruits. *Chemistry Letters*, **2015**, 44: 837–839. https://doi.org/10.1246/cl.150172

[79] Huang, A. G., Chen, C., Liu, T. Q., et al. scFv antibody-mediated targeted drug delivery system improves the antiviral activity of geniposidic acid against WSSV. *Aquaculture*, **2022**, 560: 738496. https://doi.org/10.1016/j.aquaculture

[80] Nakamura, K., Hosoo, S., Yamaguchi, S., et al. Geniposidic acid upregulates atrial natriuretic peptide secretion and lowers blood pressure in spontaneously hypertensive rats. *Journal of Functional Foods*, **2018**, 40: 634–638. https://doi.org/10.1016/j.jff.2017.10.037

[81] Huang, S. M., Lin, S. Y., Chen, M. K., et al. Effects of geniposide and geniposidic acid on fluoxetine-induced muscle atrophy in C2C12 cells. *Processes*, **2021**, 9: 1649. https://doi.org/10.3390/pr9091649

[82] Sekandi, P., Namukobe, J., Byamukama, R., et al., Antimicrobial, antioxidant, and sun protection potential of the isolated compounds from *Spermacoce princeae* (K. Schum). *BMC Complementary Medicine and Therapies*, **2023**, 23. https://doi.org/10.1186/s12906-023-04026-4

[83] L. Li, J. Zou, Q. Xia, et al. Anti-TMV and insecticidal potential of four iridoid glycosides from *Gardenia jasminoides* fruit. *Chemical Research in Chinese Universities*, **2018**, 34: 697–699. https://doi.org/10.1007/s40242-018-8197-8

[84] Kim, D. H., Lee, H. J., Kim, Y. J., et al. Iridoid glycosides isolated from *Oldenlandia diffusa* inhibit LDL-oxidation. *Archives of Pharmacal Research*, **2005**, 28: 1156–1160. https://doi.org/10.1007/BF02972979

[85] Akihisa, T., Watanabe, K., Yamamoto, A., et al. Melanogenesis inhibitory activity of monoterpene glycosides from Gardeniae Fructus. *Chemistry & Biodiversity*, **2012**, 9: 1490–1499. https://doi.org/10.1002/cbdv.201200030

[86] Hirata, T., Kobayashi, T., Wada, A., et al. Anti-obesity compounds in green leaves of *Eucommia ulmoides*. *Bioorganic & Medicinal Chemistry Letters*, **2011**, 21: 1786–1791. https://doi.org/10.1016/j.bmcl.2011.01.060

[87] Nakamura, A., Yokoyama, Y., Tanaka, K., et al. Asperuloside improves obesity and type 2 diabetes through modulation of gut microbiota and metabolic signaling. *Science*, **2020**, 23: 101522. https://doi.org/10.1016/j.isci.2020.101522

[88] Li, L., Zou, J., You, S., et al. Natural product cerbinal and its analogues *Cyclopenta pyridines*: synthesis and discovery as novel pest control agents. *Journal of Agricultural and Food Chemistry*, **2019**, 18: 10498–10504. https://doi.org/10.1021/acs.jafc.9b03699