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Review Article

Chemistry and bioactivity of *Gardenia jasminoides*

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ABSTRACT

Gardenia jasminoides, grown in multiple regions in China, was commonly used as a natural yellow dye but has been one of the popular traditional Chinese medicines since the discovery of its biological property a few decades ago. It has been reported that *G. jasminoides* possess multiple biological activities, such as antioxidant properties, hypoglycemic effect, inhibition of inflammation, antidepression activity, and improved sleeping quality. In this review, our aim was to have a comprehensive summary of its phytochemistry including the extraction, isolation, and characterization of volatiles and bioactive molecules in *G. jasminoides*, focusing on the two major phytochemicals, genipin and crocin, which possess potent medicinal properties. Furthermore, this study attempted to establish a structure–activity relationship between the two major series of molecules with two pharmcophores and their biological activities, which would serve further exploration of the properties of phytocompounds in *G. jasminoides* as potential functional foods and medicines.

1. Introduction

Gardenia jasminoides, an evergreen tree that belongs to the Rubiaceae family, is cultivated in multiple areas in China, with a Chinese name of Zhi Zi. It grows in many temperate regions and has fragrant white flowers [1]. It is not only used as natural yellow dyes for many years [2,3], but also has various biological activities, such as antidiabetic [4], anti-inflammatory [5], antidepression [6], and antioxidant properties [7], and improvement of the quality of sleep [8]. It is commonly used in traditional Chinese medicine. The chemical analysis of *G. jasminoides* has been mainly focused on extraction technologies in recent years. Obtained extracts have exerted certain biological activities both *in vitro* and *in vivo*. Recent research showed that the oil extract from the *G. jasminoides* had antidepressant activity [6], and other new techniques to extract the oil and the complex biological activity have also been discussed. Herein, we reviewed the chemical components and biological activities of *G. jasminoides* as well as new techniques to extract and isolate the natural compounds from *G. jasminoides*.

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2. Chemistry

A number of chemical components of *G. jasminoides* have been isolated and characterized, including iridoids, iridoid glucosides, triterpenoids, organic acids, and volatile compounds. Geniposide, genipin, gardenoside, crocin, and iridiod are the major bioactive compounds found in *G. jasminoides*. For instance, the yield of geniposide reached 10.9% under certain extraction conditions [9].

2.1. Volatiles in G. jasminoides

The major volatile compounds in essential oil of *G. jasminoides* are aliphatic acids, ketones, aldehydes, esters, alcohols, and aromatic derivatives [6,10]. Because of the different temperature and duration of processing, the essential oil from *G. jasminoides* contains varied contents and proportions of volatile compounds. In addition, unstable components such as iridoids may be partially converted to volatile components during high temperature processing [6].

Gas chromatography–mass spectrometry (GC/MS) was the major technique used to identify volatile components from *G. jasminoides* [6]. He et al [11] reported that the oil of the fruits of *G. jasminoides* was extracted by supercritical fluid CO_2, in which 16 major components of the oil extract were revealed by GC/MS. Myristic acid (15.3%) had the highest relative content, whereas the lowest one was caproic acid (0.24%) [12]. Because of the pharmacological activities exerted by *G. jasminoides* oil and the availability of modern extraction techniques, many efforts were invested in the extraction of the *G. jasminoides*, in order to find the optimal extraction method. The extraction methods of volatile oil from *G. jasminoides* are listed in Table 1.

2.2. Iridoids and iridoid glycoside

Iridoids and iridoid glycoside are rich in *G. jasminoides*. The iridoids and iridiod glycosides include genipin, geniposide, and gardenoside. Many researchers have found multiple positive health effect of geniposide, including anti-inflammation [16], antidepression [16], antidiabetic properties [4], antithrombotic activities [18], as well as protection against lipopolysaccharide (LPS)-induced apoptotic liver damage [19]. The content of iridoid glycosides may vary from different regions at about 5–6% [20]. A study quantified the content of geniposide, gardenoside, geniposidic acid, and chlorogenic acid as 56.37 ± 26.24 μg/mg, 49.57 ± 18.78 μg/mg, 3.15 ± 3.27 μg/mg, and 0.69 ± 0.39 μg/mg, respectively, measured in 68 samples from different regions in China and Korea [21].

2.2.1. Extraction of iridoids

Because of the pharmacological effects of *G. jasminoides* and the application of modern extraction technology, many efforts have been invested in the preparation of different *G. jasminoides* extracts, in an attempt to find a potent ingredient that can have significant effects on diseases, such as high blood pressure, hyperglycemia, cancer, hyperlipidemia, and Alzheimer's disease (AD) [22]. Certain positive results have been obtained with specified extracts, but in the future, further fractionation and evaluation of the active components of this plant should be a better direction. With the emergence of several new extraction methods, several minor components with potent biological activity may be found in *G. jasminoides*. Extraction methods such as solvent extraction, as well ultrasound- and microwave-assisted extraction (MAE) have been used to extract iridoids.

2.2.2. Solvent extraction method

Most solvent extraction methods require heating. The optimal solvent extraction parameters of *G. jasminoides* were 51.3% of ethanol/water mixture with an extraction temperature of 70.4°C for 28.6 minutes. Under this condition, the yield of geniposide and total phenolic compounds 10.9% and 2.497%, respectively [9].

2.2.3. Ultrasound- and microwave-assisted extraction

Many advanced extraction techniques have been introduced in recent years including ultrasound- and microwave-assisted extraction. Ultrasonic extraction was conducted by ultrasonic-assisted solvent extraction; with this technique,

Table 1 – Extraction method of volatile oil from *Gardenia jasminoides*.

Extraction method	Parameters of extraction	Results (%)	Refs
Supercritical fluid extraction (SFE)	Extraction pressure: 36.8 MPa Temperature: 65°C CO_2 flow rate: 15 kg/h	Linoleic acid, 44; palmitic acid, 26.4; oleic acid, 24.6	[12]
	Temperature: 49.94°C Pressure: 29.89 MPa Time: 93.82 min	16 major components of the oil extract were characterized	[6]
	Pressure: 30 MPa Temperature: 55°C CO_2 flow rate: 15 kg/h	Linoleic acid, 44.38; oleic acid, 24.96; palmitic acid, 24.83; stearic acid, 2.55; linolenic acid, 1.31	[13]
	Pressure: 12 MPa or 25 MPa Temperature: 45°C	Oil yield, 12	[13]
Subcritical fluid extraction	Subcritical butane	Fatty acids, 77.6	[14]
Ultrasound-assisted extraction	28 kHz & 100 W Material/solvent ratio: 1:10 (g/mL)	Oil yield, 16.49	[15]
Steam distillation	Distilled water	Oil yield, 0.12	[14]

the sound waves can produce strong shear force and agitation to disrupt plant cells, which allows the solvent to penetrate into the cells, thereby shortening the extraction time and increasing the extraction yield. It has been found that the optimum conditions that obtain the highest yields of geniposide from *G. jasminoides* using ultrasound-assisted extraction were as follows: water with a solid/liquid ratio of 1:30 at a temperature of 70°C for 30 minutes, yielding geniposide of 4.1% [23].

2.2.4. *Isolation of iridoids*

The isolation of iridoids includes solvent partition separation, classic column chromatography, preparative high-performance liquid chromatography (prep-HPLC), high-speed countercurrent chromatography (HSCCC), and other isolation methods. At least 15 iridoids were reported to be isolated and identified, including iridoids, iridiod glucosides, secoiridoids, and secoiridoid glucosides. Table 2 summarizes the reported iridoids isolated from *G. jasminoides*.

2.2.5. *Solvent partition*

As an example of solvent extraction, dried fruit (8.0 kg) of *G. jasminoides* was powdered and extracted with 60% ethanol solution (64 L) for 2 hours under reflux. The extraction process was repeated three times. The combined extract (1000 g) after concentration under vacuum was suspended in 3 L of water and partitioned with cyclohexane, ethyl acetate, and *n*-butanol, respectively [25]. The compounds in cyclohexane fraction were dominated with volatile oil and some fat-soluble pigments. The major components in ethyl acetate fraction were iridoids and iridoid glycosides. The compounds found in *n*-butanol fraction are mostly iridoid glycosides. The substances in the water fraction were glycosides and water-soluble pigments.

2.2.6. *Column chromatography*

The different extract fractions from the plant can be subjected to different kinds of column chromatography. Column chromatography has been classified as normal phase (silica gel) column chromatography, reversed-phase (C_4, C_8, C_{18}, etc.) column chromatography, macroporous resin column chromatography, polyamide column chromatography, or Sephadex column chromatography, depending on the packing material used. The separation mechanism and the solvents used to elute the column are different for different packing materials. For example, the ethyl acetate fraction of *G. jasminoides* was subjected to silica gel column chromatography eluting with a gradient mixture of chloroform and methanol and yielded nine fractions, which were respectively subjected to different kinds of column and prep-HPLC when needed. The structures of the compounds were identified by nuclear magnetic resonance [25]. In another example, dried *G. jasminoides* (6.0 kg) were extracted by 95% ethanol/water (v/v), and the filtration was concentrated under reduced pressure. Then the extract (1.2 kg) was suspended in water and extracted with petroleum ether and chloroform. The chloroform fraction (210.3 g) was subjected to silica gel column chromatography eluting with petroleum ether–ethyl acetate mixture, and six fractions were obtained. The six fractions were respectively subjected to repeated silica gel column chromatography, C_{18} column chromatography, macroporous resin (D101) column, and prep-HPLC eluting with methanol–water (v/v 25:75). The obtained compounds were iridoids and iridoid glucosides [26]. In some cases, there was no solvent extraction prior to the classical column chromatography. For example, *G. jasminoides* (8.0 kg) was refluxed with 60% of aqueous ethanol. The extract was concentrated, suspended with water, and subjected to macroporous resin (D101) column eluted with an ethanol/water gradient. The 50% ethanol elute was subjected to silica gel eluting with chloroform/methanol. The fraction was further subjected to prep-HPLC, to obtain two new compounds—a new lignan glucoside and a new iridoid glucoside [27]. In another example, six iridoid glycosides were isolated and purified from *G. jasminoides* by two-dimensional prep-HPLC [28].

2.2.7. *High-speed countercurrent chromatography*

HSCCC is a liquid–liquid separation technology. It has been reported that HSCCC successfully isolated geniposide from *G. jasminoides*. Zhou et al [29] showed that 389 mg of geniposide was recovered from 1 g of partially purified sample from macroporous resin column. In another research, after HSCCC isolation, 151.1 mg of gardenoside, 52.2 mg of 6β-hydroxy geniposide, 24.5 mg of geniposidic acid, 587.2 mg of geniposide, 246.2 mg of crocin-1, 34.2 mg of crocin-2, 24.4 mg of crocin-3, and 24.7 mg of crocin-4 were extracted and isolated from 2 kg of *G. jasminoides* after macroporous resin (HPD-100) column separation and HSCCC with purities ranging from 91.7% to 98.9% [30]. Four new water-soluble iridoid glucosides were isolated by HSCCC. They are shanzhiside methyl ester (I), phloyoside (II), chlorotuberside (III), and penstemonoside (IV) [31].

2.2.8. *Other isolation methods*

It has been reported that water-soluble residue from *G. jasminoides* was treated with sodium carbonate and extracted with *n*-butanol several times. Then, the *n*-butanol extracts are treated with activated granular charcoal. At least 70 g of geniposide with 98% purity was obtained from 10 kg of *G. jasminoides* [32]. Another isolation method is matrix solid phase dispersion (MSPD); the optimal conditions that can isolate the geniposide by MSPD is 0.5 g of fruit of *G. jasminoides*, 0.75 g of Celite (diatomaceous earth) as the dispersing sorbent, and a volume of 25 mL of 70% of methanol solution as the elution solvent [33].

2.3. *Crocin and its derivatives in* G. jasminoides

Crocin and its derivatives extracted from *G. jasminoides* have been characterized as low toxicity, low allergy, and eco-friendly compared with saffron [3]. Crocin and crocetin were initially found in saffron, which was the dried stigma of the flower of *Crocus sativus* L. Saffron has a wide range of uses especially in the dye and pharmaceutical industry. It also has medicinal effects in certain conditions such as weight loss, sexual dysfunction, and premenstrual syndrome. These medicinal properties of saffron are likely attributable to a number of compounds it contains, including crocetin, crocins, and safrana [39].

Table 2 – Iridoids and iridoid glycosides isolated from *Gardenia jasminoides*.

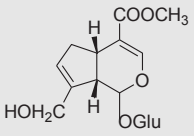
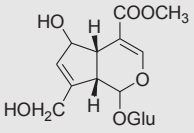
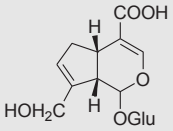
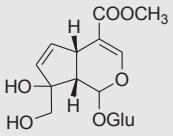
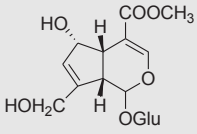
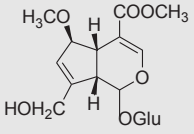
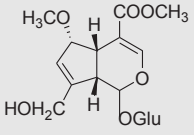
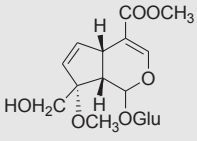
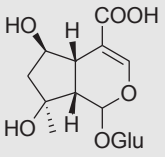
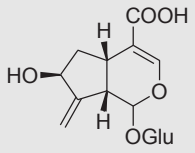
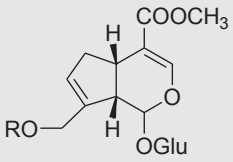
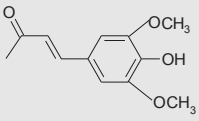
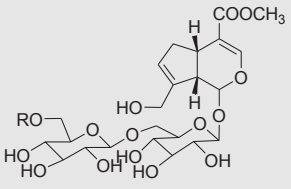
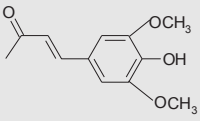
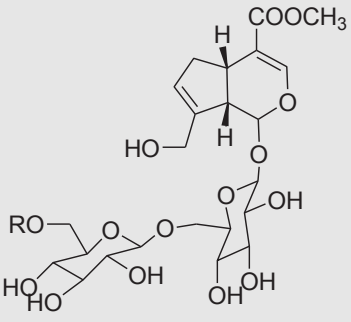
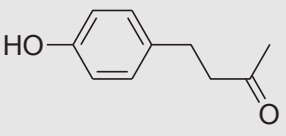
No.	Name	Structure	Extraction & isolation	Refs
1	Geniposide		Reflux with 50% ethanol, HSCCC, MSPD	[29] [30] [33]
2	6β-Hydroxy geniposide		Cold percolate with 40% ethanol, macroporous resin HSCCC	[30]
3	Geniposidic acid		Cold percolate with 40% ethanol Macroporous resin HSCCC	[30]
4	Gardenoside		Cold percolate with 40% ethanol, macroporous resin, HSCCC	[30] [25]
5	6α-Hydroxy geniposide		Reflux with 60% ethanol, Silica gel column, C_{18} column, preparative HPLC	[25]
6	6-O-Methylscandoside methyl ester			
7	6-O-Methyldeacetylasperulosidic acid methyl ester			
8	8-O-Methylmonotropein methyl ester			
9	Shanzhiside			

Table 2 – (*continued*)

No.	Name	Structure	Extraction & isolation	Refs
10	Gardoside			
11	10-*O*-*trans*-Sinapoylgeniposide	 R=sinapoyl 		
12	6″-*O*-*trans*-Sinapoylgenipin gentiobioside	 R=sinapoyl 		
13	6″-*O*-*trans*-*p*-Coumaroylgenipin gentiobioside	 R = *p*-coumaroyl 		

(*continued on next page*)

Table 2 – (*continued*)

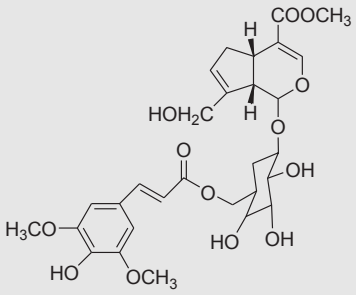
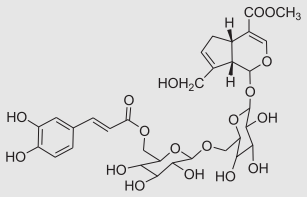
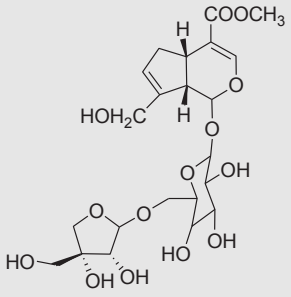
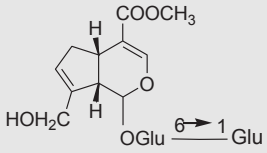
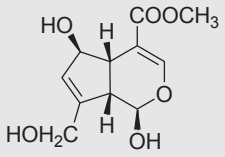
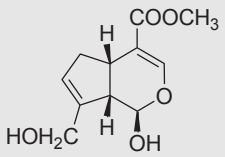
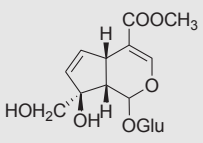
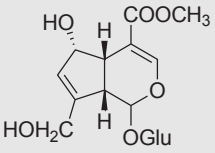
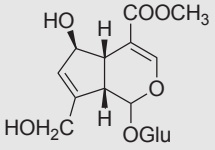
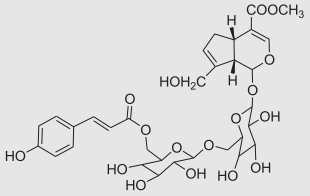
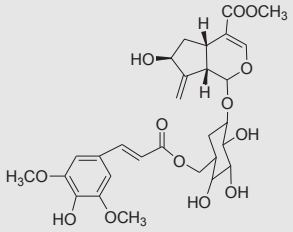
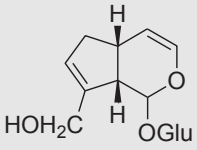
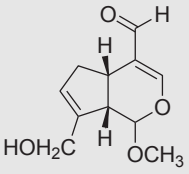
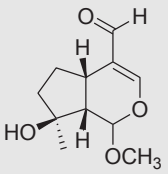
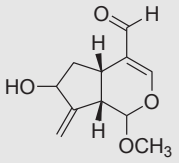
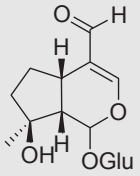
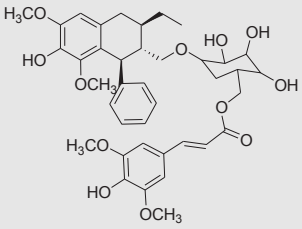
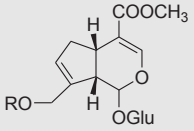
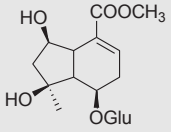
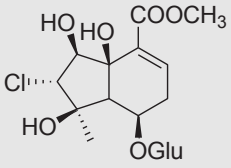
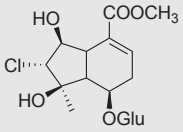
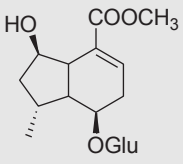
No.	Name	Structure	Extraction & isolation	Refs
14	6′-O-Sinapoylgeniposide		Reflux with 90%, 70% EtOH Silica gel & Sephadex column	[34]
15	6″-O-Caffeoylgenipin gentiobioside		60% EtOH Silica gel, & preparative HPLC	[35]
16	Genipin 1-O-β-D-apiofuranosyl (1→6)-β-D-Glucopyranoside			
17	Genipin 1-O-α-D-xylopyranosyl (1→6)-β-D-glucopyranoside			
18	6β-Hydroxy genipin			
19	Genipin			
20	Gardenoside		HPLC–MS	[28]

Table 2 – (*continued*)

No.	Name	Structure	Extraction & isolation	Refs
21	Deacetylasperulosidic acid methyl ester			
22	Scandoside methyl ester			
23	4″-*O*-[(*E*)-*p*-Coumaroyl] gentiobiosylgenipin		80% EtOH Silica gel column	[36]
24	6′-*O*-[(*E*)-Sinapoyl]gardoside			
25	Bartsioside			
26	Gardenal-I		EtOH/H_2O (9:1) at room temperature C_{18} column	[37]
27	Gardenal-II			

(*continued on next page*)

Table 2 – (*continued*)

No.	Name	Structure	Extraction & isolation	Refs
28	Gardenal-III			
29	Ixoroside		Reflux with 50% aqueous ethanol Macroporous Resin column	[38]
30	(+)-(7S,8R,8′R)-Lyoniresinol 9-*O*-β-D-(6″-*O*-*trans*-sinapoyl) glucopyranoside		Reflux with 60% EtOH Prep-HPLC	[27]
31	10-*O*-*trans*-Sinpoylgeniposide	 R = sinapoyl		
32	Shanzhiside methyl ester (I)		Reflux with 65% EtOH HSCCC	[31]
33	Phloyoside (II)			
34	Chlorotuberside (III)			
35	Penstemonoside (IV)			

2.3.1. *Extraction and isolation of crocin and its derivatives*

G. jasminoides was extracted using a homogenate extraction technology under the condition of 50% ethanol/water solution, with a liquid/material ratio of 15:1 (v/w), and particle size of material 1.7 mm with an extraction time of 41 seconds [40]. In another report, the extraction condition of *G. jasminoides* used the following conditions: ethanol/water (40:60, v/v) and cold percolation without damaging percolation [41]. By using the MAE system, the extraction yield of the edible yellow pigment from *G. jasminoides* was 50% higher than that obtained with the conventional extraction method [24].

The isolation of crocin and its chain derivatives is similar to that of iridoids (Table 3). However, the polarity of solvents in the isolation of crocin is slightly higher than that in iridoids (Table 4). The extracts can be suspended in water, then partitioned with ethyl acetate. The ethyl acetate extract was successively subjected to silica gel column, Sephadex (LH-20) column, and medium pressure preparative liquid chromatography, and yielded gardecin. The water extract was successively subjected to macroporous resin (HPD-100), silica gel, and C_{18} column, and crocin was obtained [41].

2.4. *Terpenoids in G. jasminoides*

Terpenoids in *G. jasminoides* include secoiridoids and monoterpenoid. Iridoids mentioned above belong to secoiridoids. Here, we summarize monoterpenoids and their glycosides. Some terpenoids, especially the small number of carbon atoms, exist in volatile oil. The extraction and isolation methods of terpenoids are mostly the same as in iridoids. In

Table 3 – Crocin and its chain derivatives in *Gardenia jasminoides*.

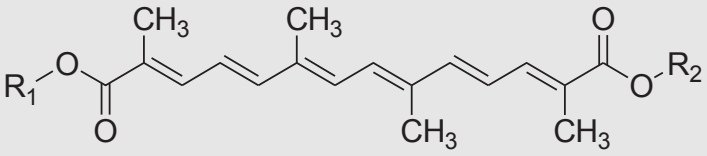
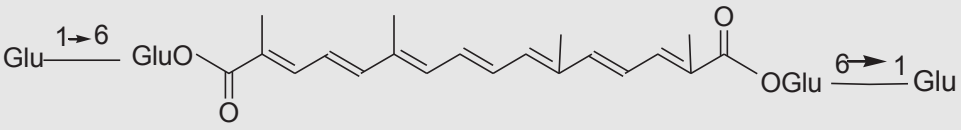
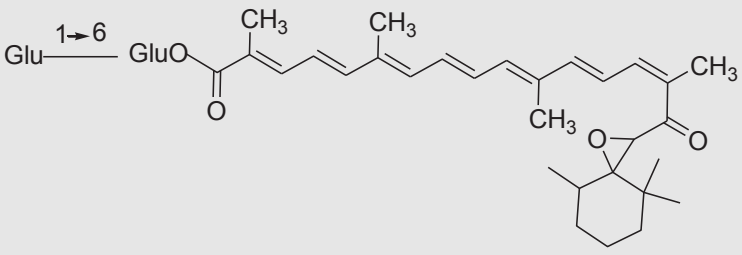
Name	Structure
Crocin	
Crocin1	R_1: Glu 6→1 Glu; R_2: Glu 6→1 Glu
Crocin2	R_1: Glu 6→1 Glu; R_2: Glu
Crocin3	R_1: Glu 6→1 Glu; R_2: H
Crocin4	R_1: Glu; R_2: H
Crocetin	R_1: H; R_2: H
cis-Crocin1	
Gardecin	

Table 4 – Isolation methods of crocin and its chain derivatives.

Name	Extraction & isolation methods	Refs
Crocin1	Temperature 25°C; Time: 1 h; solvent: methanol, ethanol, 1-propanol, 2-propanol	[3]
	Temperature: 60°C; Time: 2 h; Solvent: water	[42]
	Temperature: 70.4°C; Time: 28.6 min; Solvent: 51.3% ethanol	[9]
Crocin1, crocin 2, crocin 3, crocin 4	Ethanol–water (40%) by cold percolation macroporous resin (HPD-100); HSCCC	[30]
Crocin1, crocin 2, crocin 3, crocin 4	Ethanol–water (40%) cold percolation; silica gel & C_{18} column; macroporous resin (HPD-100)	[43]
Crocin1, crocin 2, crocin 3, crocin 4; *cis*-crocin1, gardecin	Ethanol/water (40:60); cold percolation; silica gel column; macroporous resin (HPD-100)	[41]
Crocetin	Ethanol–water (40%) cold percolation; silica gel; macroporous resin (HPD-100)	[43]
Crocin1, crocin 2, crocin 3, crocetin	Macroporous resin; C_{18}	[40]
Crocin 1, crocin 3, crocetin	70% ethanol	[44]

recent years, many terpenoids in *G. jasminoides* have been found. Their structures are listed in Table 5.

2.5. *Phenolic compounds*

Several phenolic acids have been identified in *G. jasminoides*, such as 3,5-di-*O*-caffeoyl-4-*O*-(3-hydroxy-3-methyl)glutaroylquinic acid, 3,5-di-*O*-caffeoylquinic acid, 4-*O*-sinapoyl-5-*O*-caffeoyl-quinic acid [27], and chlorogenic acid [46]. One new lignin glucoside, (+)-(7*S*,8*R*,8′*R*)-lyoniresinol 9-*O*-β-D-(6″-*O*-*trans*-sinapoyl)glucopyranoside, has been found in *G. jasminoides*. The extraction and isolation of the new lignin glucoside were as follows: *G. jasminoides* (8 kg) was cut into small pieces and refluxed with 60% of EtOH (v/v). The 60% EtOH was concentrated and produced a dark brown residue, which was suspended with H_2O and subjected to column chromatography eluted with different proportions of EtOH and H_2O. The 50% EtOH elute (105 g) was subjected to column chromatography (silica gel), eluting with increasing MeOH in $CHCl_3$. Fraction G was further separated by column chromatography over octadecylsilyl (ODS), eluting with increasing MeOH in H_2O to give G1–G7. G5 was purified by Toyopearl HW-40 and prep RP-HPLC to obtain the new lignin glucoside [27]. Its structure is shown in Figure 1.

3. Biological activities

G. jasminoides has been reported to possess various biological activities and positive effects on human health, which are summarized in Table 6.

3.1. *Antioxidant activity*

Both water and ethanol extracts from the fruit of *G. jasminoides* had been found to exert antioxidant activity. The IC_{50} (half-maximal inhibitory concentration) values of the water extracts from *G. jasminoides* for DPPH (1,1-diphenyl-2-picrylhydrazyl), ABTS [2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt], hydroxyl, and superoxide radical-scavenging activities were 0.14 mg/mL, 0.21 mg/mL, 1.08 mg/mL, and 1.43 mg/mL, respectively, and those of ethanol extracts were 0.36 mg/mL, 0.39 mg/mL, 1.56 mg/mL, and 1.99 mg/mL, respectively. Hence, water extract had a higher antioxidant activity than the ethanol extract. Purified crocin at concentrations of up to 40 ppm showed potent antioxidative activity, which was evaluated using the thiocyanate method and the thiobarbituric acid method. At a concentration of 20 ppm, crocin's antioxidative activity was comparable to that of butylated hydroxyanisole (BHA) [47].

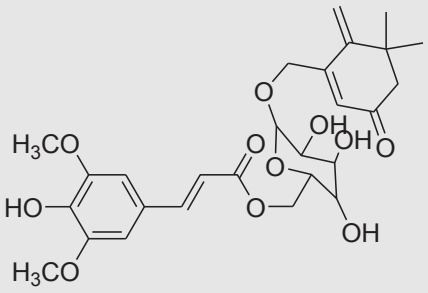
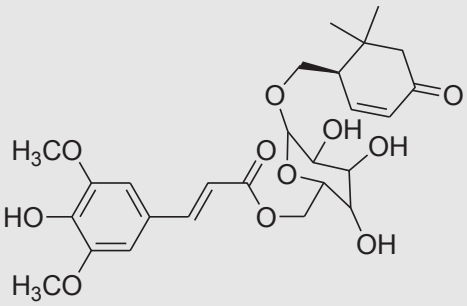
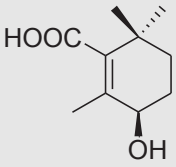
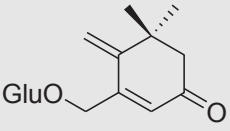
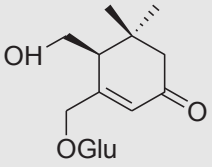
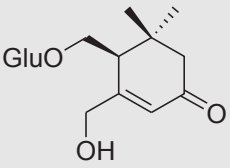
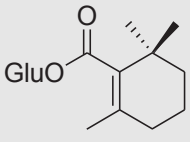
3.2. *Improving insulin sensitivity and antidiabetes*

Insulin resistance leads to type 2 diabetes. Water extracts from *G. Jasminoides* improve insulin sensitivity in steroid-induced insulin-resistant rats with an optimal dose of *G. jasminoides* water extract of 200 mg/kg [48]. Genipin ameliorated age-related insulin resistance, which had a close relationship with the improvement of hepatic oxidative stress and mitochondria dysfunction and insulin signal impairment [49]. Geniposide alleviated abnormal glucose tolerance and hyperinsulinemia, which are recognized in genetic type 2 diabetes patients caused by visceral fat accumulation [50] Geniposide (200 mg/kg and 400 mg/kg) was shown to be an effective hypoglycemic agent in diabetic mice that significantly decreased blood glucose, insulin, and triglyceride levels in diabetic mice in a dose-dependent manner [4]. Geniposide also demonstrated beneficial effects on diabetic vascular injury by inhibiting the adhesion of monocytes to human umbilical vein endothelial cells and the expression of cell adhesion molecules induced by high glucose [51]. It was suggested that crocetin might prevent dexamethasone-induced insulin resistance by lowering serum insulin, free fatty acids, and blood triglyceride [52].

3.3. *Anti-inflammatory activity*

Water extracts of *G. jasminoides* exhibited anti-inflammatory properties by significantly reducing JNK2/1 (c-Jun N-terminal protein kinase) and p38 MAPKs (mitogen-activated protein kinase) phosphorylation, and decreasing COX-2 (cyclooxygenase-2) expression in LPS-induced BV-2 cells. When the water extracts of *G. jasminoides* was used on LPS-induced hepatic injury of rats, the liver pathology was substantially reduced [53]. Geniposide was shown to alleviate inflammation

Table 5 – Structures of monoterpenoids in *Gardenia jasminoides*.

No.	Name	Structures	Refs
1	6′-*O*-*trans*-Sinapoyljasminoside C		[25,27]
2	6′-*O*-*trans*-Sinapoyljasminoside A		
3	Rehmapicrogenin		[25]
4	Jasminoside C		
5	Jasminoside B		
6	Jasminoside G		
7	Jasminoside K		[25,44]

(*continued on next page*)

Table 5 – (*continued*)

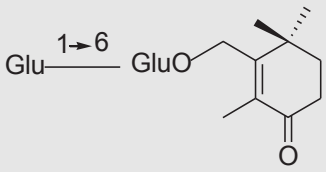
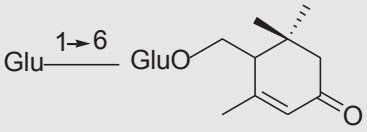
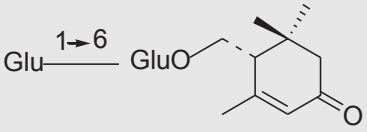
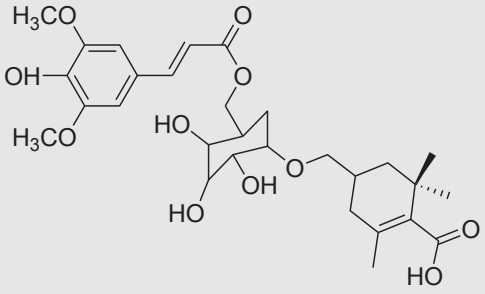
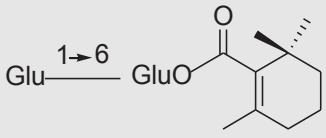
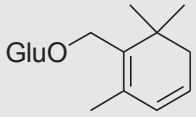
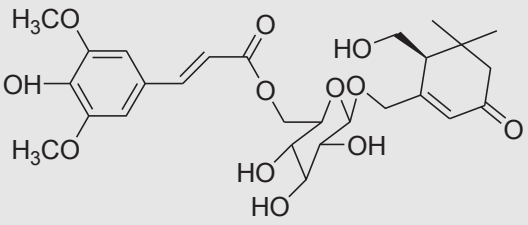
No.	Name	Structures	Refs
8	Jasminoside I		
9	Jasminoside H		
10	Epi-jasminoside H		
11	6′-*O*-*trans*-Sinapoyljasminoside L		
12	Jasminoside S		[35]
13	Jasminoside J		[44]
14	6′-*O*-*trans*-Sinapoyljasminoside B		

Table 5 – (*continued*)

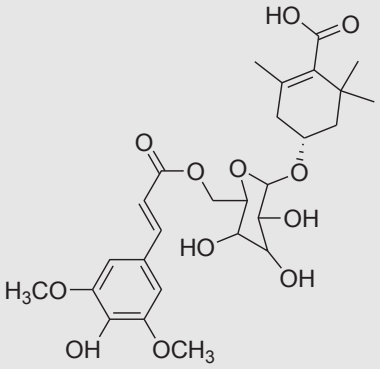
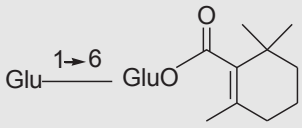
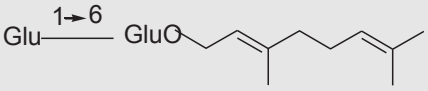
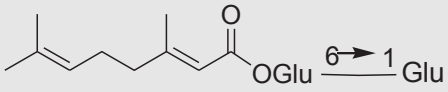
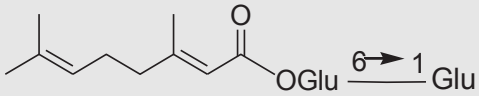
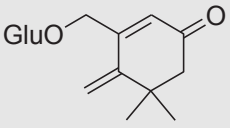
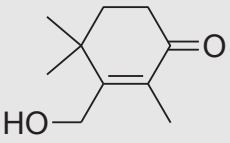
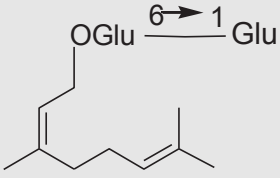
No.	Name	Structures	Refs
15	6′-*O*-*trans*-Sinapoyljasminoside L		
16	Jasminoside M		
17	Jasminoside N		
18	6-*O*-β-D-Xylopyranosyl-β-D-glucopyranosyl (2*E*)-3, 7-dimethylocta-2,6-dienoate		
19	6-*O*-β-D-Glucopyranosyl-β-D-glucopyranosyl (2*E*)-3, 7-Dimethylocta-2,6-dienoate		
20	Jasminoside C		
21	Jasminoside E		
22	Sacranoside B		

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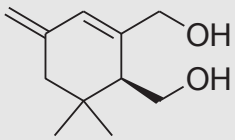
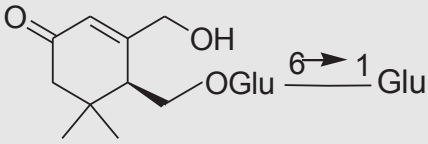
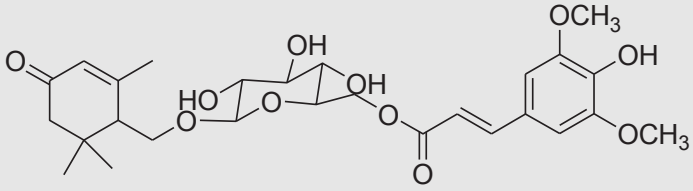
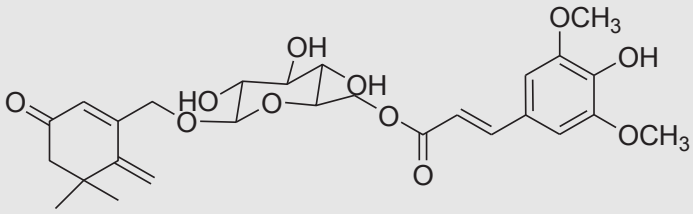
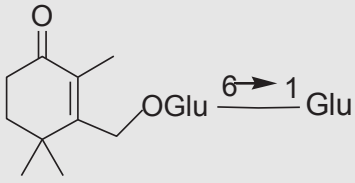
Table 5 – (*continued*)

No.	Name	Structures	Refs
23	Jasminodiol		[45]
24	Jasminoside H		
25	6′-*O*-Sinapoyljasminoside A		
26	6′-*O*-Sinapoyljasminoside C		
27	Jasminoside I		

by suppressing MeCP2 (methyl cytosine binding protein-2) in mice with CCl_4-induced acute liver injury and LPS-treated THP-1 cells [54]. Geniposide had an anti-inflammatory effect by reducing the expression of Toll-like receptor 4 upregulated by LPS, which inactivated the downstream NF-κB (nuclear factor-κB) and MAPK signaling pathways. Geniposide may be a potential anti-inflammatory drug to treat acute liver injury, acute lung injury, and mastitis [55]. Crocin could inhibit COX-1 and COX-2 activities, and production of prostaglandin E_2, and inhibited xylene-induced ear edema in mice and carrageenan-induced paw edema in rats [56].

3.4. *Antidepressant activity*

The oil extracted from *G. jasminoides* by supercritical fluid extraction and geniposide showed antidepressant activity, which was evaluated by tail suspension test and forced swim test [6]. *G. jasminoides* showed an antidepressant effect in the tail suspension test at 24 hours [57]. Genipin play an antidepressant role through regulating the glycolysis/gluconeogenesis TCA cycle and lipid metabolism of liver [58]. The mechanism of antidepressive in geniposide may be linked to the increase of serotonin level in the striatum and hippocampus of mice and monoamine oxidase B [17,59].

3.5. *Effects of blood circulation*

The hot water extracts of *G. jasminoides* did not stimulate the proliferation of cultured vascular smooth muscle cells, but selectively stimulated the endothelial cell proliferation, which might prevent arteriosclerosis and thrombosis [60].The *n*-butanol fraction of 70% ethanol extract of *G. jasminoides* showed effective antiangiogenic activity by using CAM (chick chorioallantoic membrane) assay [61]. Geniposide was also an active antiangiogenic agent that inhibited the growth of the transformed N1H3T3 cell line in the range of 25–100 μM [62].

Table 6 – Different extracts from *Gardenia jasminoides* and their bioactivities.

G. jasminoides	Bioactivities	Model	Proposed mechanism	Refs
Water extracts	Antioxidant activity	*In vitro*		[7]
	Improvement of insulin sensitivity	*In vivo* mouse	Exert a peroxisome proliferator activated receptor	[48]
	Anti-inflammation	*In vitro*	Reduce JNK1/2, & p38 MAPKs phosphorylation, & slightly reduce cyclooxygenase (COX)-2 expression in BV-2 cells	[53]
	Prevention of arteriosclerosis & thrombosis	*In vivo*	The hot water extracts of *G. jasminoides* did not stimulate the proliferation of cultured vascular smooth muscle cells	[60]
Oil	Antidepressant activity	*In vivo*		[54]
Ethanol extract	Antidepressant activity	*In vivo*	Associated with the elevated expression of brain-derived neurotrophic factor in the hippocampus	[57]
	Antigastritic activity	*In vivo*		[65]
n-Butanol fraction	Antiangiogenic activity	*In vivo*		[61]
Genipin	Reduce insulin resistance	*In vivo*	A close relationship with the improvement of hepatic oxidative stress, mitochondrial dysfunction & insulin signal impairment	[49]
	Antidepressant activity	*In vivo*	Regulating the glycolysis/gluconeogenesis, TCA cycle & lipid metabolism of liver	[58]
	Protection of liver damage	*In vivo*	Antioxidative, antiapoptotic activities, & inhibition of NF-κB nuclear translocation & nuclear p-c-Jun expression	[19]
	Inhibit gastric lesions	*In vivo*	Was relevant with the antioxidant activities, acid-neutralizing capacities, & anti-*Helicobacter pylori* action	[65]
	Antithrombotic effect	*In vivo*	Inhibition of PLA_2 activity	[18]
	Genotoxicity	*In vitro*	Damage of DNA in rec assay using V79 cells	[78]
Geniposide	Antidiabetes	*In vivo*	Inhibited the adhesion of monocytes to HUVECs & the expression of CAMs induced by high glucose	[51]
	Anti-inflammatory	*In vivo*	Reducing the expression of TLR4 by LPS	[16,55]
	Antiarthritis	*In vivo*	Downregulated the expression of p-JNK.	[68]
		In vivo	Decreased the expression level of TNF-α, IL-1, & IL-6, increasing the production of IL-10 & inhibiting the expression of phospho-p38 (p-p38) related proteins in FLS	[69]
	Antithrombotic & antiangiogenic	*In vivo*	Inhibited collagen-induced, but did not inhibit arachidonate-induced, mouse platelet aggregation	[62]
	Antidepressant activity	*In vivo*	Increased the levels of serotonin in striatum & hippocampus in mice	[17]
	Antidepressant activity	*In vivo*	Monoamine oxidase-B	[59]
	Effects on AD & PD	*In vivo*	Increased growth factor signaling & decreases apoptosis	[71]
Crocin	Antioxidant	*In vitro*		[47]
	Anti-inflammatory	*In vivo*	Inhibited COX-1 & COX-2 enzymes	[56]
	Protective of the injured liver	*In vivo*		[66]
				[67]
	Antihyperlipidemic	*In vivo*	Selectively inhibited the activity of pancreatic lipase	[73]
Crocetin	Antihypertensive & antithrombotic effects	*In vivo*	Related to the increase in bioavailable NO	[63]
				[64]
	Prevent insulin resistance	*In vivo*		[52]
	Inhibit retinal damage	*In vivo*	Inhibited increase in caspase-3 & -9 activities	[76]
	Alleviate renal dysfunction	*In vivo*		[76]
	Improve the quality of sleep	*In vivo* adult men		[8]

AD = Alzheimer's disease; CAMs = cell adhesion molecules; FLS = Fixed lag; HUVECs = human umbilical vein endothelial cells; IL = interleukin; JNK1/2 = c-Jun N-terminal protein kinase 1 and 2; LPS = lipopolysaccharide; MAPK = mitogen-activated protein kinase; NF-κB = nuclear factor-kappa B; NO = nitric oxide; PD = Parkinson's disease; PLA2 = phospholipase A2; TCA = tricarboxylic acid; TLR4 = Toll-like receptor 4; TNF-α = tumor necrosis factor alpha.

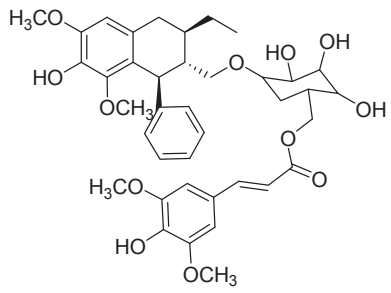


Figure 1 – Chemical structure of (+)-(7S,8R,8′R)-lyoniresinol 9-O-β-D-(6″-O-*trans*-sinapoyl) glucopyranoside.

Both genipin and geniposide had antithrombotic effect *in vivo* via the suppression of platelet aggregation by inhibiting of PLA_2 activity, which is different from that of aspirin (which exerts its effect by inhibiting arachidonate-induced platelet aggregation) [18].

Crocetin (25 mg/kg/d and 50 mg/kg/d, 3 weeks) significantly moderated the systolic blood pressure, decreasing thrombogenesis and increasing antioxidant activity and urinary nitric oxide (NO) metabolite levels. It was concluded that crocetin had antihypertensive and antithrombotic effects, which might be related to the increase in bioavailable NO [63]. Because crocetin can increase endothelial NO synthase activity, it was believed to have an antihypercholesterolemic effect [64].

3.6. Other biological activities

3.6.1. Antigastritic activity

G. jasminoides-ethanolic extracts had a protective effect against potential gastric diseases. This action may attributable to the ursolic acid and genipin in *G. jasminoides*-ethanolic extracts, which inhibit AGS and SUN638 gastric cancer cells [65].

3.6.2. Effects on liver

Genipin (25 mg/kg, 50 mg/kg, 100 mg/kg, and 200 mg/kg) was injected on mice 1 hour prior to D-galactosamine N (GalN) (700 mg/kg)/LPS (10 μg/kg) administration. The death rate in the genipin ingestion group was significantly reduced. Therefore, genipin offered remarkable hepatoprotection against damage induced by GalN/LPS because of its antioxidative and anti-apoptotic activities, and inhibition of NF-κB nuclear translocation and nuclear p-c-Jun expression [19]. The level of malondialdehyde decreased remarkably when diazinon and 25 mg crocin were used in male Wistar rats ($n = 6$) for 4 weeks, which led to the conclusion that crocin might reduce diazinon-induced hepatotoxicity [66]. In another study, male Wistar rats were given a control diet, high fat diet, or high fat diet plus crocin (25 mg/kg/d, 50 mg/kg/d, and 100 mg/kg/d) for 4 weeks. In the crocin treatment group, it was shown to reduce liver injury caused by hepatic steatosis in rats fed with high fat diet [67].

3.6.3. Antiarthritis

Geniposide had positive effects on rats with adjuvant arthritis by downregulating the expression of p-JNK (phosphorylated c-Jun N-terminal kinases) [68]. Geniposide also suppressed arthritis in adjuvant-induced arthritis rats by decreasing the expression levels of tumor necrosis factor-α, interleukin (IL)-1β, and IL-6, increasing the production of IL-10, and inhibiting the expression of phospho-p38 (p-p38) related proteins in FLS (Fixed lag) [69].

3.6.4. AD and PD

Geniposide and its derivatives, which improved the short-term memory capacity at varying extent, might be a potential drug for AD [70]. Geniposide exhibits neuroprotective property by inhibiting alpha-synuclein expression, a common pathological symptom in Parkinson's disease (PD) [79]. Geniposide has a neuroprotective effect in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model of PD [71].

3.6.5. Antihyperlipidemia

Crocin obtained from the water extracts of *G. jasminoides* was found to exhibit antihyperlipidemic effect. When crocin and crocetin were given to the tested mice, the triglyceride and total cholesterol were significantly decreased, and the high-density lipoprotein-cholesterol levels were significantly increased. Thus, it can be concluded that crocin has antihyperlipidemic effect [72]. The mechanism of crocin's hypolipidemic effect in rats was that crocin could selectively inhibit the activity of pancreatic lipase [73]. The hypolipidemic effect of crocin fermented with lactic acid bacteria can be improved [74].

3.6.6. Inhibition of retinal damage

Crocetin (100 mg/kg, p.o.) alleviated retinal damage though their antioxidant properties and by downregulating caspase-3 and -9 activities after retinal damage [75,76].

3.6.7. Improvement of the quality of sleep

Crocetin was used on healthy adult men with mild sleep complaints by reducing the number of wakening episodes compared to that of the placebo ($p = 0.025$), which potentially improved the quality of sleep [8].

3.6.8. Renal dysfunction

Crocetin (50 mg/kg) at 2 hours after resuscitation significantly alleviated renal dysfunction caused by hemorrhage shock and resuscitation [77].

3.6.9. Genotoxicity

"Gardenia yellow," containing crocetin, crocin geniposide, and genipin, was a natural colorant extracted by ethanol from *G. jasminoides*. It was reported that genipin possesses genotoxicity. Genipin caused damage of DNA in rec assay [78].

4. Conclusion

G. jasminoides is commonly used as herbal medicine in Asia. This review summarized the extraction and isolation methods of four major constituents in *G. jasminoides*—genipin, geniposide, crocin, and crocetin—and discussed their bioactivities. The main extraction methods of *G. jasminoides* are solvent

extraction method, and ultrasound- and microwave-assisted extraction. The isolation methods of *G. Jasminoides* are solvent partition, column chromatography, and HSCCC. Genipin reduces insulin resistance, demonstrates antidepressive and antithrombotic effects, provides protection against liver damage, and inhibits gastric lesions. Geniposide possesses antidiabetes, anti-inflammatory, antiarthritis, antithrombotic, and antiangiogenic properties, demonstrates antidepressant activity, and has beneficial effects on AD and PD. Crocin has many medicinal effects such as antioxidant and anti-inflammatory activities, is antihyperlipidemic, and is protective of the injured liver. Crocetin has antihypertensive and antithrombotic effects, prevents insulin resistance, inhibits retinal damage, alleviates renal dysfunction, and improves sleep quality. Most importantly, oil extract from *G. jasminoides* demonstrates antidepressant activity. It is hoped that, in the near future, oil from *G. jasminoides* could be developed as a kind of therapeutic agent in fighting depression.

Conflicts of interest

We declare that there is no conflict of interest with any parties involved in this article.

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