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, antidepressive 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 pharmacophores 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], antidepressive [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.
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 iridoid 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 CO₂, 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 iridoid glycosides include genipin, geniposide, and gardenoside. Many researchers have found multiple positive health effect of geniposide, including anti-inflammatory [16], antidepress [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,

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

| Extraction method                  | Parameters of extraction | Results (%)               | Refs |
|------------------------------------|--------------------------|---------------------------|------|
| Supercritical fluid extraction (SFE) | Temperature: 65°C; CO₂ flow rate: 15 kg/h; Pressure: 30 MPa; Time: 28.6 min | Linoleic acid, 44.1; palmitic acid, 26.4; oleic acid, 24.6 | [12] |
| Subcritical fluid extraction       | Subcritical butane; Pressure: 12 MPa; Temperature: 45°C | 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] |
Chapter 2. Isolation of Iridoids

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, iridoid 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 (C₈, C₆, C₄, 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, C₁₈ 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].
| No. | Name                                      | Structure | Extraction & isolation                                                                 | Refs  |
|-----|-------------------------------------------|-----------|----------------------------------------------------------------------------------------|-------|
| 1   | Geniposide                                | ![Geniposide Structure](image) | Reflux with 50% ethanol, HSCCC, MSPD                                                   | [29]  |
|     |                                           |           |                                                                                        | [30]  |
|     |                                           |           |                                                                                        | [33]  |
| 2   | 6β-Hydroxy geniposide                     | ![6β-Hydroxy Geniposide Structure](image) | Cold percolate with 40% ethanol, macroporous resin HSCCC                                | [30]  |
| 3   | Geniposidic acid                          | ![Geniposidic Acid Structure](image) | Cold percolate with 40% ethanol Macroporous resin HSCCC                                  | [30]  |
| 4   | Gardenoside                               | ![Gardenoside Structure](image) | Cold percolate with 40% ethanol, macroporous resin, HSCCC                               | [25]  |
| 5   | 6α-Hydroxy geniposide                     | ![6α-Hydroxy Geniposide Structure](image) | Reflux with 60% ethanol, Silica gel column, C<sub>18</sub> column, preparative HPLC    | [25]  |
| 6   | 6-O-Methylscandoside methyl ester         | ![6-O-Methylscandoside Structure](image) |                                                                                        |       |
| 7   | 6-O-Methyldeacetylasperulosidic acid methyl ester | ![6-O-Methyldeacetylasperulosidic Structure](image) |                                                                                       |       |
| 8   | 8-O-Methylmonotropein methyl ester        | ![8-O-Methylmonotropein Structure](image) |                                                                                        |       |
| 9   | Shanzhiside                               | ![Shanzhiside Structure](image) |                                                                                        |       |
| No. | Name                                | Structure | Extraction & isolation | Refs |
|-----|-------------------------------------|-----------|------------------------|------|
| 10  | Gardoside                           | ![Gardoside Structure](image) |                        |      |
| 11  | 10-O-trans-Sinapoylgeniposide       | ![10-O-trans-Sinapoylgeniposide Structure](image) | R=sinapoyl             |      |
| 12  | 6''-O-trans-Sinapoylgenipin gentiobioside | ![6''-O-trans-Sinapoylgenipin gentiobioside Structure](image) | R=sinapoyl             |      |
| 13  | 6''-O-trans-p-Coumaroylgenipin gentiobioside | ![6''-O-trans-p-Coumaroylgenipin gentiobioside Structure](image) | R = p-coumaroyl       |      |

(continued on next page)
| No. | Name                                      | Structure | Extraction & isolation                      | Refs |
|-----|-------------------------------------------|-----------|---------------------------------------------|------|
| 14  | 6′-O-Sinapoylgeniposide                    | ![Structure](image1.png) | Reflux with 90%, 70% EtOH  
|     |                                           |           | Silica gel & Sephadex column               | [34] |
| 15  | 6″-O-Caffeoylgenin gentiobioside           | ![Structure](image2.png) | 60% EtOH  
|     |                                           |           | Silica gel, & preparative HPLC             | [35] |
| 16  | Genipin 1-O-β-α-apiofuranosyl (1→6) β-α-Glucopyranoside | ![Structure](image3.png) |                                           |      |
| 17  | Genipin 1-O-α-xylopyranosyl (1→6) β-α-glucopyranoside | ![Structure](image4.png) |                                           |      |
| 18  | 6β-Hydroxy genipin                         | ![Structure](image5.png) |                                           |      |
| 19  | Genipin                                   | ![Structure](image6.png) |                                           |      |
| 20  | Gardenoside                               | ![Structure](image7.png) | HPLC–MS                                    | [28] |
| No. | Name                                      | Structure | Extraction & isolation                      | Refs |
|-----|-------------------------------------------|-----------|---------------------------------------------|------|
| 21  | Deacetylasperulosidic acid methyl ester   | ![Structure](image1) | 80% EtOH Silica gel column                  | [36] |
| 22  | Scandoside methyl ester                   | ![Structure](image2) |                                              |      |
| 23  | 4'-O-[(E)-p-Coumaroyl] gentiobiosylgenipin| ![Structure](image3) |                                              |      |
| 24  | 6'-O-[(E)-Sinapoyl]gardoside              | ![Structure](image4) |                                              |      |
| 25  | Bartsioside                               | ![Structure](image5) |                                              |      |
| 26  | Gardenal-I                                | ![Structure](image6) | EtOH/H$_2$O (9:1) at room temperature       | [37] |
| 27  | Gardenal-II                               | ![Structure](image7) |                                              |      |

(continued on next page)
| No. | Name                                      | Structure                                                                 | Extraction & isolation                  | Refs |
|-----|-------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------|------|
| 28  | Gardenal-III                              | ![Structure](structure_28.png)                                           | Reflux with 50% aqueous ethanol         | [38] |
|     |                                           |                                                                           | Macroporous Resin column                |      |
| 29  | Ixoroside                                 | ![Structure](structure_29.png)                                           | Reflux with 60% EtOH                    | [27] |
|     |                                           |                                                                           | Prep-HPLC                               |      |
| 30  | (+)-(7S,8R,8'R)-Lyoniresinol 9-O-β-D-(6'-O-trans-sinapoyl)glucopyranoside | ![Structure](structure_30.png)                                           |                                        |      |
| 31  | 10-O-trans-Sinapoylgeniposide             | ![Structure](structure_31.png)                                           |                                        |      |
|     |                                           | R = sinapoyl                                                             |                                        |      |
| 32  | Shanzhiside methyl ester (I)              | ![Structure](structure_32.png)                                           | Reflux with 65% EtOH                    | [31] |
|     |                                           |                                                                           | HSCCC                                    |      |
| 33  | Phloyoside (II)                           | ![Structure](structure_33.png)                                           |                                        |      |
| 34  | Chlorotuberside (III)                     | ![Structure](structure_34.png)                                           |                                        |      |
| 35  | Penstemonoside (IV)                       | ![Structure](structure_35.png)                                           |                                        |      |
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 C18 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

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

| Name       | Structure |
|------------|-----------|
| Crocin     | ![Crocin Structure](image) |
| Crocin1    | ![Crocin1 Structure](image) |
| Crocin2    | ![Crocin2 Structure](image) |
| Crocin3    | ![Crocin3 Structure](image) |
| Crocin4    | ![Crocin4 Structure](image) |
| Crocetin   | ![Crocetin Structure](image) |
| cis-Crocin1| ![cis-Crocin1 Structure](image) |
| Gardecin   | ![Gardecin Structure](image) |
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)glutarylquinic acid, 3,5-di-O-caffeoylquinic acid, 4-O-sinapoyl-5-O-caffeoyl-quinic acid [27], and chlorogenic acid [46]. One new lignin glucoside, (−)-(7S,8R,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$_2$O and subjected to column chromatography eluting with increasing proportions of EtOH and H$_2$O. 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 eluted with different proportions of EtOH and H$_2$O. The 60% EtOH was refluxed with 60% of EtOH (v/v). The 60% EtOH was concentrated and produced a dark brown residue, which was suspended with H$_2$O and subjected to column chromatography eluting with increasing proportions of EtOH and H$_2$O. 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$_2$O 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 antioxidant activity, which was evaluated using the thiocyanate method and the thiobarbituric acid method. At a concentration of 20 ppm, crocin’s antioxidant 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 mitochondrial 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          | ![Structure](image1) | [25,27] |
| 2   | 6’-O-trans-Sinapoyljasminoside A          | ![Structure](image2) |        |
| 3   | Rehmapicrogenin                           | ![Structure](image3) | [25]    |
| 4   | Jasminoside C                             | ![Structure](image4) |        |
| 5   | Jasminoside B                             | ![Structure](image5) |        |
| 6   | Jasminoside G                             | ![Structure](image6) |        |
| 7   | Jasminoside K                             | ![Structure](image7) | [25,44] |

(continued on next page)
| No. | Name                                | Structures                                      | Refs |
|-----|-------------------------------------|-------------------------------------------------|------|
| 8   | Jasminoside I                       | ![Structure](image_url)                         |      |
| 9   | Jasminoside H                       | ![Structure](image_url)                         |      |
| 10  | Epi-jasminoside H                   | ![Structure](image_url)                         |      |
| 11  | 6'-O-trans-Sinapoyljasminoside L    | ![Structure](image_url)                         |      |
| 12  | Jasminoside S                       | ![Structure](image_url)                         | [35] |
| 13  | Jasminoside J                       | ![Structure](image_url)                         | [44] |
| 14  | 6'-O-trans-Sinapoyljasminoside B    | ![Structure](image_url)                         |      |
| No. | Name                      | Structures                                      | Refs |
|-----|---------------------------|-------------------------------------------------|------|
| 15  | 6’-O-trans-Sinapoyljasminoside L | ![Structure](image1)                              |      |
| 16  | Jasminoside M             | ![Structure](image2)                              |      |
| 17  | Jasminoside N             | ![Structure](image3)                              |      |
| 18  | 6-O-β-D-Xylopyranosyl-β-D-glucopyranosyl (2E)-3, 7-dimethylocta-2,6-dienoate | ![Structure](image4) |      |
| 19  | 6-O-β-D-Glucopyranosyl-β-D-glucopyranosyl (2E)-3, 7-Dimethylocta-2,6-dienoate | ![Structure](image5) |      |
| 20  | Jasminoside C             | ![Structure](image6)                              |      |
| 21  | Jasminoside E             | ![Structure](image7)                              |      |
| 22  | Sacranoside B             | ![Structure](image8)                              |      |

(continued on next page)
by suppressing MeCP2 (methyl cytosine binding protein-2) in mice with CCl₄-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 E₂, 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].

| No. | Name               | Structures                  | Refs |
|-----|--------------------|-----------------------------|------|
| 23  | Jasminodiol        | ![Structure](image1.png)    | [45] |
| 24  | Jasminoside H      | ![Structure](image2.png)    |      |
| 25  | 6′-O-Sinapoyljasminoside A | ![Structure](image3.png) |      |
| 26  | 6′-O-Sinapoyljasminoside C | ![Structure](image4.png) |      |
| 27  | Jasminoside I      | ![Structure](image5.png)    |      |
| Water extracts                          | Antioxidant activity | In vitro | Exert a peroxisome proliferator activated receptor | [7] |
|----------------------------------------|----------------------|----------|----------------------------------------------------|-----|
|                                        | Improvement of insulin sensitivity | In vivo mouse |                                             | [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 | Associated with the elevated expression of brain-derived neurotrophic factor in the hippocampus | [54] |
| Ethanol extract                        | Antidepressant activity | In vivo |                                             | [57] |
| n-Butanol fraction                     | Antigastric activity | In vivo | A close relationship with the improvement of hepatic oxidative stress, mitochondrial dysfunction & insulin signal impairment | [65] |
| Genipin                                | Antiangiogenic activity | In vivo |                                             | [49] |
| Geniposide                             | Reduce insulin resistance | In vivo |                                             | [49] |
| Geniposide                             | Antidiabetes         | In vivo | Inhibited the adhesion of monocytes to HUVECs & the expression of CAMs induced by high glucose | [78] |
| Geniposide                             | Antithrombotic effect | In vivo | Inhibition of PLA2 activity                   | [18] |
| Geniposide                             | Genotoxicity         | In vivo | Damage of DNA in rec assay using V79 cells    | [51] |
| Geniposide                             | Antidepressant activity | In vivo |                                             | [49] |
| Geniposide                             | Protection of liver damage | In vivo | Antioxidative, antiapoptotic activities, & inhibition of NF-κB nuclear translocation & nuclear p-c-Jun expression | [19] |
| Geniposide                             | Inhibit gastric damage | In vivo | Was relevant with the antioxidant activities, acid-neutralizing capacities, & anti-Helicobacter pylori action | [65] |
| Geniposide                             | Antithrombotic & antiangiogenic | In vivo | Inhibited collagen-induced, but did not inhibit arachidonate-induced, mouse platelet aggregation | [62] |
| Crocin                                 | Anti-inflammatory     | In vivo | Reducing the expression of TLR4 by LPS         | [16,55] |
| Crocetin                               | Antiarthritis        | In vivo | Downregulated the expression of p-JNK.         | [68] |
| Crocetin                               | Protecting the injured liver | 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] |
| Crocetin                               | Antithrombotic & antiangiogenic | In vivo | Increased the levels of serotonin in striatum & hippocampus in mice | [17] |
| Crocetin                               | Antidepressant activity | In vivo | Monooamine oxidase-B                           | [59] |
| Crocetin                               | Effects on AD & PD   | In vivo | Increased growth factor signaling & decreases apoptosis | [71] |
| Crocetin                               | Antioxidant          | In vivo | Selectively inhibited the activity of pancreatic lipase | [47] |
| Crocetin                               | Anti-inflammatory    | In vivo | Inhibited COX-1 & COX-2 enzymes                | [56] |
| Crocetin                               | Protective of the injured liver | In vivo |                                             | [56] |
| Crocetin                               | Antihyperlipidemic   | In vivo | Selectively inhibited the activity of pancreatic lipase | [67] |
| Crocetin                               | Antihypertensive & antithrombotic effects | In vivo | Related to the increase in bioavailable NO | [73] |
| Crocetin                               | Prevent insulin resistance | In vivo | Inhibited increase in caspase-3 & -9 activities | [63] |
| Crocetin                               | Inhibit retinal damage | In vivo |                                             | [64] |
| Crocetin                               | Alleviate renal dysfunction | In vivo |                                             | [52] |
| Crocetin                               | Improve the quality of sleep | In vivo |                                             | [76] |
| Crocetin                               | 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. |
Both genipin and geniposide had antithrombotic effect in vivo via the suppression of platelet aggregation by inhibiting of PLA₂ 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 anti-inflammatory 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 unsaturated 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 antiapoptotic 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
extractions, 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 anti-diabetes, anti-inflammatory, antiarthritis, anti-thrombotic, 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 antiinflammatory 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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