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REVIEW

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Gentiana macrophylla Pall.: a review of the basic source, traditional use, chemical components, pharmacological activities and quality control

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Author contributions

Mu QE, A YS , Bai YQ contributed significantly to query papers and paper analysis. Mu QE organized the data and wrote the manuscript. Sa CL helpd perfom the anlysis with constructive discussions.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

AIA, adjuvant-induced arthritis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B19, human parvovirus; CCl_4, carbon tetrachloride; CIA, collagen-induced arthritis; ConA, Concanavalin A; *G. macrophylla*, *Gentiana macrophylla* Pall.; *G. straminea*, *Gentiana straminea* Maxim.; *G. crassicanlis*, *Gentiana crassicanlis* Duthie ex Burk.; *G. dahurica*, *Gentiana dahurica* Fisch.; GMI, iridoids from the flower of *Gentiana macrophylla* Pall.; HPLC, high performance liquid chromatography; IL-6, interleukin-6; IL-10, interleukin-10; IL-1β, interleukin-1β; LV, left ventricle; MDA, malondialdehyde; MIC, minimum inhibitory concentration; NS1, nonstructural protein; PBS, Phosphate buffered saline; sh-NC, miR-512-5p mimic or the controls; SLE, systematic lupus erythomatosus; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; R, Root; F, Flower; S, Stem; L, Leaf; NF-κB, nuclear factor kappa-B; QZ, N-butanol part; MMP1, matrix metalloproteinase 1; MMP3, matrix metalloproteinase 3.

Citation

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Abstract

Gentiana macrophylla Pall. (*G. macrophylla*), whose genus and family belong to the Gentianaceae and Gentiana. The main distribution centers of *G. macrophylla* resources were the Loess Plateau and the eastern Qinghai-Tibet Plateau in China. *G. macrophylla*, as a traditional medicine, has a long history and was used in different ethnic medicines. Its roots were used in traditional Chinese medicine, which had the effect of anti-inflammatory, anti-rheumatism, antiviral, promote blood circulation, eliminate swelling and pain, while its flowers were used in traditional Mongolian medicine, which had the effect of removing "Xieriwusu" ("Xieriwusu" means rheumatism), antiviral, reducing swelling. From previous studies, it could be found that there were more than forty components isolated and identified from *G. macrophylla*. The main chemical components were iridoids, flavonoids, triterpenoids, steroids, phenylpropanoids, and alkaloids. Iridoid terpenoid components represented by gentiopicroside and Loganic acid were the main components of the root of *G. macrophylla*, which had anti-inflammatory, antioxidant, hepatoprotective, analgesic, antibacterial and promote gastrointestinal tract activities. The flower mainly contains isoorientin and isovitexin as the representative of flavonoids. They have anti-tumor, liver protection, heart protection, inhibition of acetylcholinesterase and inhibition of melanin. It could be seen from previous studies that the research on *G. macrophylla* was mainly focused on the root, and the flower was rarely studied. It was reported that the experimental data of the anti-inflammatory and anti-tumor effects of *G. macrophylla* flowers show that its curative effect was very good. Therefore, the flowers of the flower of *G. macrophylla* can be used as potential medicinal parts for research. Given that flavonoids are mostly found in flowers and exhibit a range of functions, it is possible to investigate the flowers in order to learn more about *G. macrophylla*'s potential medical benefits. Based on botanical books, Chinese classic texts, medical monographs and academic search engines (Google, Google Scholar, Web of Science, SciFinder, Pubmed, CNKI, Sci-hub, Elsevier and Wanfang), the data and information on *G. macrophylla* in the past 20 years are inquired and summarized comprehensively. The basic source, traditional use, chemical composition, biological activity, pharmacodynamics and quality control of *G. macrophylla* was systematically reviewed, in order to provide reliable basis for the subsequent development and utilization of *G. macrophylla*.

Keywords: *Gentiana macrophylla* Pall.; basic source; chemical component; pharmacological activity; quality control

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Highlights

Gentiana macrophylla Pall. (*G. macrophylla*) has many effects, such as anti-inflammatory, analgesic, antioxidant, antibacterial. While these effects have been studied based on its roots, there has been little research about its flowers. In this review, the research of *G. macrophylla* was reviewed. It was discovered that the flowers of *G. macrophylla* were rich in iridoids as well as flavonoids, which might be higher than those in the roots. These results indicated that the flowers of *G. macrophylla* had many potential pharmacological effects and could be used as a new medicinal part of *G. macrophylla*.

Medical history of objective

G. macrophylla, as a traditional medicine, has a long history and was used in different ethnic medicines. For a long time, it has been chosen to use its dried roots as medicinal parts in traditional Chinese medicine, *Shen Nong's Herbal Classic* (Han Dynasty, *Shen Nong Ben Cao Jing*) was the first to document this method of therapy. Its effects included anti-inflammatory, anti-rheumatism, antiviral, promoting blood circulation, eliminating swelling, and pain. As a Mongolian medicine, its dried flowers were used as medicinal parts, which were first recorded in the *Classic Canon of Mongolian Materia Medica* (19th century, Robusan, *Meng Yao Zheng Dian*). The effects of the medicinal materials included antiviral, decreasing swelling, and eliminating "Xieriwusu" ("Xieriwusu" means rheumatism).

Background

G. macrophylla (Figure 1), whose genus and family belong to the Gentianaceae and *Gentiana*. According to the *2020 edition of the Pharmacopoeia of the People's Republic of China*, *G. macrophylla* was a genus of Gentiaceae; the four species were the dry roots of *G. macrophylla*, *Gentiana straminea* Maxim. (*G. straminea*), *Gentiana crassicanlis* Duthie ex Burk. (*G. crassicanlis*), and *Gentiana dahurica* Fisch. (*G. dahurica*) [1]. *G. macrophylla* has been widely considered by people for its wide distribution and long history of medicinal use, and it is now the main source of *Gentianae Macrophyllae Radix*. From the perspective of resource distribution, the main distribution centers of *G. macrophylla* resources were the Loess Plateau and the eastern Qinghai-Tibet Plateau in China. Shanxi, Gansu, Sichuan, and other provinces in this region are the main producing areas of *G. macrophylla*, and Shanxi was the genuine producing area of *G. macrophylla* [2]. *G. macrophylla* was used in different ethnic medicines, such as its root in traditional Chinese medicine, anti-inflammatory, anti-rheumatism, antiviral, promote blood circulation, eliminate swelling and pain. It can be used clinically for rheumatoid arthritis (e.g. rheumatic arthritis), spasms of the meridians and joints, tuberculosis, erythema, edema, etc. [3]. As a Mongolian medicine, it was used for its flowers, with the effect of removing "Xieriwusu", antiviral, reducing swelling [4]. According to modern research reports, the flowers and roots of *G. macrophylla* contain different chemical components and their respective pharmacological activities. In its roots, it mainly contains schizocyclic iridoid glycosides, which are represented by gentiopicroside, and swertiamarin. Among them, gentiopicroside has the functions of protecting the liver, strengthening the stomach, anti-inflammation, and raising blood sugar; and swertiamarin has an analgesic effect. In addition to the schizoiridoid glycosides represented by gentiopicroside and swertiamarin, the flower also contains flavonoids represented by isoorientin. Isoorientin has a therapeutic effect on cardiovascular disease. According to the above description, *G. macrophylla* has many plant sources and was used in different ethnic medicines in China, and its medicinal parts were also different. Based on this, this paper reviewed the basic source, traditional uses, chemical composition, pharmacological action and mechanism of different drug parts, and quality control, of *G. macrophylla*, to provide a theoretical basis for the development of *G. macrophylla* and lay a foundation for its later development.

Basic source

G. macrophylla, whose genus and family belong to the Gentianaceae and *Gentiana*. *G. macrophylla*, as a traditional medicine, has a long history and was used in different ethnic medicines. For a long time, it has been chosen to use its dried roots as medicinal parts in traditional Chinese medicine, *Shen Nong's Herbal Classic* (Han Dynasty, *Shen Nong Ben Cao Jing*) was the first to document this method of therapy. As a Mongolian medicine, its dried flowers were used as medicinal parts, which were first recorded in the *Classic Canon of Mongolian Materia Medica* (19th century, *Meng Yao Zheng Dian*). According to the *2020 edition of the Pharmacopoeia of the People's Republic of China*, *G. macrophylla* was a genus of Gentiaceae; the four species were the dry roots of *G. macrophylla*, *G. straminea*, *G. crassicanlis* and *G. dahurica* [1]. *Gentiana* group plants were mainly distributed in mountains, plateau meadows, forest margins, and shrubland at altitudes of 1,500–4,500 m, preferring moist, humus-rich soil and sunny places. So because of their different growth habits, the distribution of resources will be different. From the perspective of resource distribution, the main distribution centers of *G. macrophylla* resources were the Loess Plateau and the eastern Qinghai-Tibet Plateau in China. Gansu, Shanxi, Sichuan, and other provinces in this region were the main producing areas of *G. macrophylla*, and Shanxi was the genuine producing area of *G. macrophylla*. In addition, among the other three species of original plants specified in the pharmacopeia, *G. straminea* was mainly distributed in Qinghai, Tibet, Sichuan, Gansu, and other alpine meadow areas with an altitude of 2,000–4,500 m [2]. *G. crassicanlis* was mainly distributed in hillside forest margins and alpine meadow areas at an altitude of 2,700–3,700 m; the main producing

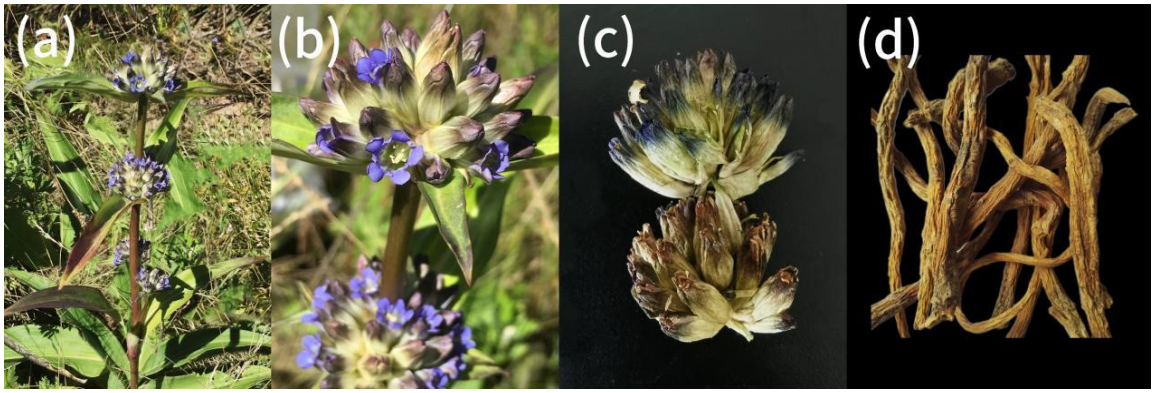

Figure 1 The overground and underground parts of *G. macrophylla*. (a) Whole plants; (b) Flowers; (c) Dried flowers; (d) Dried roots.

areas were in Yunnan, Guizhou, Sichuan, Qinghai, Tibet, and other provinces [5]. *G. dahurica* was mainly distributed in grasslands, meadows, fields, and roadsides at an altitude of 870–4,500 m; it was by people for its wide distribution and long history of medicinal use, and it is now the main source of *Gentianae Macrophyllae Radix*. The specific distributions and general lifestyles of *G. macrophylla*, *G. straminea*, *G. crasicaulis*, and *G. daurica* in China were showed in Table 1 [2, 5, 6].

Traditional use

With a high medicinal value, the flowers and roots of *G. macrophylla* were extensively used in traditional Chinese and Mongolian medicine to treat a wide range of illnesses. For example, in traditional Chinese medicine, the dried root of the plant was used to be anti-inflammatory, anti-rheumatism, antiviral, promote blood circulation, eliminate swelling and pain. It can be used clinically for rheumatoid arthritis (e.g., rheumatic arthritis), spasms of the meridians and joints, tuberculosis, erythema, edema, etc. [3]. As a Mongolian medicine, it was used for its flowers, with the effect of removing "Xieriwusu", antiviral, reducing swelling [4]. In addition to having a lot of effects, it can also be used to treat diseases with other herbs. The traditional clinical prescriptions was showed in Table 2 [7–17].

Chemical component

More than 40 chemical components have been isolated and identified from *G. macrophylla*, according to literature reports (Figure 2, Table 3) [2, 18–28]. These chemical components primarily consist of iridoids, flavonoids, triterpenoid, steroids, phenylpropanoid, alkaloids, and other compounds, with varying distributions of each component. Nowadays, a lot of approaches are used by researchers to investigate the chemical components of their studies, including thin-layer chromatography, crystallization, preparative liquid chromatography, semi-preparative high-performance liquid chromatography, and column chromatography. In addition to using analytical techniques including circular dichroism, high-resolution mass spectrometry, nuclear magnetic resonance spectroscopy, spectrum analysis, and comparison analysis to identify the chemical components [29].

Iridoid components were mostly combined with sugars to form glycosides, and the carbon frame of aglycone was mostly composed of 10 carbons. C-1 hemiacetal structure was mostly glycoside with β-D-glucose. C-4, C-8 polylinked methyl group (-CH_3), hydroxymethyl group (-CH_2OH), hydroxymethyl ester (-CH_2OR), carboxyl group (-COOH), methyl carboxylate (-COOR), etc. [30]. Iridoid terpenoids were the characteristic components of the whole Gentiaceae plant, as well as the main active and bitter components. Two types of iridoid glycosides and cleaved iridoid glycosides were isolated from *G. macrophylla*. These iridoid glycosides were represented by harpagoside and loganic acid, and cleaved iridoid glycosides were represented by gentiopicroside, sweroside and swertiamarin, and the active ingredients mainly include gentiopicroside, sweroside and loganic acid [31]. Iridoid terpenoids have many activities, such as anti-inflammation, anti-oxidation, and liver protection [18]. These components are mainly found in roots and flowers, and their structural characteristics were that the chemical bonds at positions 7 and 8 of the cyclopentane ring in the terpenoid mother nucleus were broken, and sometimes C_7 can also form a six-membered lactone structure with C_{11}. Flavonoids often occur as glycosides in plants and consist of two aromatic rings linked by a carbon bridge that often forms a heterocyclic ring. Natural flavonoids were usually linked to substituents such as -OH, -OCH_3, and isopentenyl on the parent nucleus and were yellowish to yellow. According to the characteristics

Table 1 The specific distributions and general growth habits of *G. macrophylla*, *G. straminea*, *G. crasicaulis*, and *G. daurica* in China

Species	Distribution area	Growth habit	Reference(s)
G. macrophylla	Shanxi, Gansu, Ningxia, Qinghai, Xinjiang, Heilongjiang, Inner Mongolia, Hebei, Northwest Sichuan	Mountain meadows, on the sides of streams, on roadside slopes and shrubland in altitude of 400–2,400 m	[2]
G. straminea	Qinghai, Gansu, Sichuan, Tibet	Alpine meadow areas in altitude of 2,000–4,500 m	[2]
G. crasicaulis	Yunnan, Sichuan, Tibet	Hillside forest margins and alpine meadow areas in altitude of 2,700–3,700 m	[5]
G. daurica	Inner Mongolia, Shanxi, Gansu, Ningxia, Qinghai, Sichuan, Hebei	Rasslands, meadows, fields, and roadsides in altitude of 870–4,500 m	[6]

G. macrophylla, *Gentiana macrophylla* Pall.; *G. straminea*, *Gentiana straminea* Maxim.; *G. crassicanlis*, *Gentiana crassicanlis* Duthie ex Burk.; *G. dahurica*, *Gentiana dahurica* Fisch.

Table 2 The traditional clinical prescriptions contained *G. macrophylla*

Name of prescription	Therapeutic use	Composition	Reference(s)
Major *Gentian* decoction	Rheumatism, sequelae of cerebral hemorrhage	*G. macrophylla*, *Glycyrrhiza uralensis* Fisch., *Ligusticum chuanxiong* Hort., et al.	[7, 8]
Zhitong Rushen soup	Rheumatism, anorectal disease	*G. macrophylla*, *Phellodendron chinense* Schneid., *Atractylodes lancea* (Thunb.) DC., et al.	[9, 10]
Wind Stomach *Gentiana* soup	Anorectal disease	*G. macrophylla*, *Angelica sinensis* (Oliv.) Diels, *Saposhnikovia divaricata* (Trucz.) Schischk., et al.	[11]
Gentiana codonopsis soup	Anorectal disease	*G. macrophylla*, *Codonopsis pilosula* (Franch.) Nannf, *Paeonia lactiflora* Pall., et al.	[12]
Qinjiao Chunpi soup	Anorectal disease	*G. macrophylla*, *Ailanthus altissima* (Mill.) Swingle, *Gleditsia sinensis* Lam., et al.	[13]
Qinjiao pill	Skin disease	*G. macrophylla*, *Coptis chinensis* Franch., *Sophora flavescens* Aiton, et al.	[14]
Qinjiaobiejia powder	Gynecological disease	*G. macrophylla, Bupleurum chinense* DC., *Trionyx sinensis*, et al.	[15]
Qinjiaobiejia soup	Epigenetic subsepsis	*G. macrophylla*, *Trionycis Carapax*, *Angelica sinensis* (Oliv.) Diels, et al.	[16]
Qinjiaohua 27 flavor powder	Nettle-rash, "Xieriwusu" disease	*G. macrophylla*, *Abutilon theophrasti* Medicus, *Liquidambar Formosana* Hance, et al.	[17]

G. macrophylla, *Gentiana macrophylla* Pall.

Table 3 The main chemical components isolated from *G. macrophylla*

No.	Phytochemical type	Chemical component	PubChem CID/SID	Molecular weight	Molecular formula	Species from plant parts	Reference(s)
1	Iridoid	Gentiopicroside	88708	356.32 g/mol	$C_{16}H_{20}O_9$	R, F, S, L	[19]
2		Sweroside	161036	358.34 g/mol	$C_{16}H_{22}O_9$	R, F, S, L	[19]
3		Swertiamarin	442435	374.34 g/mol	$C_{16}H_{22}O_{10}$	R, F, S, L	[19]
4		Swertiapunimarin	192515	520.5 g/mol	$C_{22}H_{32}O_{14}$	R, F, S	[19]
5		Macrophylloside A	10605676	876.8 g/mol	$C_{40}H_{44}O_{22}$	R	[2]
6		Macrophylloside B	10629539	892.8 g/mol	$C_{40}H_{44}O_{23}$	R	[2]
7		Qinjiaoside A	163184202	404.4 g/mol	$C_{17}H_{24}O_{11}$	R	[24]
8		Trifloroside	101688128	782.7 g/mol	$C_{35}H_{42}O_{20}$	R	[22]
9		Rindoside	46174003	798.7 g/mol	$C_{35}H_{42}O_{21}$	R	[22]
10		Loganic acid	89640	376.36 g/mol	$C_{16}H_{24}O_{10}$	R, F, S, L	[20]
11		Secologanoside	14136854	390.34 g/mol	$C_{16}H_{22}O_{11}$	R, F, S, L	[19]
12		Harpagoside	5281542	494.5 g/mol	$C_{24}H_{30}O_{11}$	R	[23]
13		Morroniside	11228693	406.4 g/mol	$C_{17}H_{26}O_{11}$	R, F, S	[19]
14		Shanzhiside methyl ester	13892722	406.4 g/mol	$C_{17}H_{26}O_{11}$	R	[18]
15	Triterpenoids	Oleanolic acid	10494	456.7 g/mol	$C_{30}H_{48}O_3$	R, F, S, L	[25]
16		Ursolic acid	64945	456.7 g/mol	$C_{30}H_{48}O_3$	R	[21]
17		α-amyrin	73170	426.7 g/mol	$C_{30}H_{50}O$	R	[25]
18		Roburic acid	12315005	440.7 g/mol	$C_{30}H_{48}O_2$	R	[21]
19		Corosolic acid	6918774	472.7 g/mol	$C_{30}H_{48}O_4$	R, F, S, L	[19]
20	Steroids	β-sitosterol	222284	414.7 g/mol	$C_{29}H_{50}O$	R, F	[18]
21		Daucosterol	5742590	576.8 g/mol	$C_{35}H_{60}O_6$	R, F	[18]
22		Stigmasterol	5280794	412.7 g/mol	$C_{29}H_{48}O$	R	[24]
23	Flavonoids	Isoorientin	114776	448.4 g/mol	$C_{21}H_{20}O_{11}$	R, F	[26]
24		Isoorientin-4'-O-glucoside	44257975	610.5 g/mol	$C_{27}H_{30}O_{16}$	R, F	[2, 18]
25		Isovitexin	162350	432.4 g/mol	$C_{21}H_{20}O_{10}$	R, F, S, L	[25]
26		Apigenin	5280443	270.24 g/mol	$C_{15}H_{10}O_5$	R, F	[25]
27		Vitexin	5280441	432.4 g/mol	$C_{21}H_{20}O_{10}$	F	[2]
28		Kurarinone	11982640	438.5 g/mol	$C_{26}H_{30}O_6$	R	[22]
29		Acacetin	5280442	284.26 g/mol	$C_{16}H_{12}O_5$	R	[18]
30		Saponarin	441381	594.5 g/mol	$C_{27}H_{30}O_{15}$	R, F, S, L	[19]
31		Quercetin	5280343	302.23 g/mol	$C_{15}H_{10}O_7$	R, F, S, L	[19]
32		Kaempferol	5280863	286.24 g/mol	$C_{15}H_{10}O_6$	R, F, S, L	[19]
33	Phenylpropanoids	Erythrocentaurine	191120	176.17 g/mol	$C_{10}H_8O_3$	R, F, S, L	[18]
34		2-methoxyanofinic acid	5319400	234.25 g/mol	$C_{13}H_{14}O_4$	R, F, S, L	[19]
35		Ferulic acid	445858	194.18 g/mol	$C_{10}H_{10}O_4$	R, F, S, L	[19]
36	Alkaloids	Guanosine hydrate	135705230	301.26 g/mol	$C_{10}H_{15}N_5O_6$	R	[18]
37		Gentianine	354616	175.18 g/mol	$C_{10}H_9NO_2$	R, F	[27, 28]
38		Gentianidine	362908	163.17 g/mol	$C_9H_9NO_2$	R	[27]
39		Gentianal	171304	193.20 g/mol	$C_{10}H_{11}NO_3$	R, F	[28]
40		Gentianaine	135438604	141.12 g/mol	$C_6H_7NO_3$	R	[18]
41		Gentianamine	442535	205.21 g/mol	$C_{11}H_{11}NO_3$	R	[18]
42	Other compounds	Sucrose	5988	342.30 g/mol	$C_{12}H_{22}O_{11}$	R, F, S, L	[19]
43		Gentianose	117678	504.4 g/mol	$C_{18}H_{32}O_{16}$	R	[18]
44		Citric acid	311	192.12 g/mol	$C_6H_8O_7$	R, F, S, L	[19]
45		Benzoic acid	243	122.12 g/mol	$C_7H_6O_2$	R	[18]

Corresponding molecular structures refer to PubChem and Figure 2. R, Root; F, Flower; S, Stem; L, Leaf.

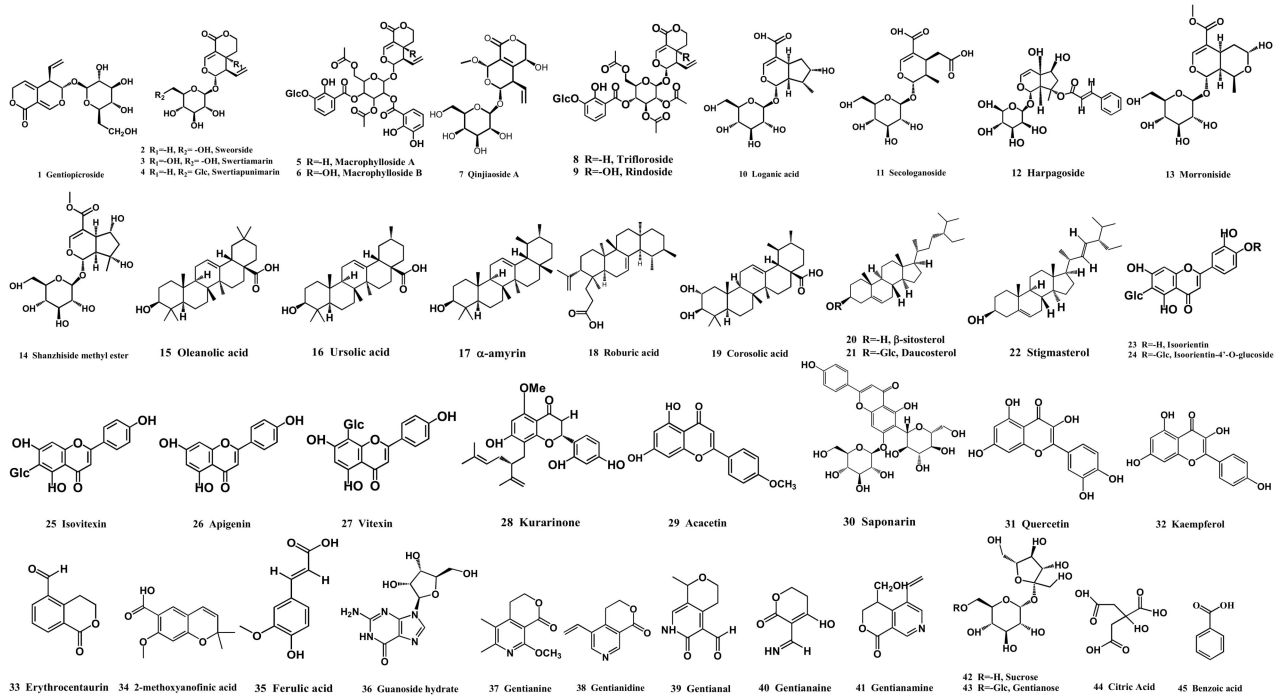

Figure 2 The chemical structures of major phytochemicals isolated from *G. macrophylla*

of C-3 structure oxidation degree, ring formation, and B ring connection location, flavonoids can be divided into flavonoids, flavonols, dihydroflavonols, dihydroflavonols, isoflavones, dihydroisoflavones, chalcones, dihydrochalcones, orange ketones (aukol), flavanols and other components [30]. They have been widely reported to display marked in vitro and in vivo anti-inflammatory and anti-oxidant properties [32]. 2-Phenylchromogen serves as the fundamental parent nucleus. They mainly exist in the flower part of *G. macrophylla*, and the content was rich, the main active ingredients were isoorientin and isovitexin, and it has anti-inflammatory and antitumor activities. In addition to the iridoid terpenoids and flavonoids, *G. macrophylla* also contains triterpenoids, steroids, phenylpropanoids, alkaloids and other components. Triterpenoids, steroids, phenylpropanoids and alkaloids were rarely found in *Gentiana* plants. Terpenoids and steroidal components were produced by the meglutaric acid pathway. Most of the triterpenoids found in *G. macrophylla* were tetracyclic triterpenes and pentacyclic triterpenes, which were optically active. The glycosides synthesized with sugar were called triterpenoid saponins, and triterpenoid saponins were also called acid saponins because of their acidic polyligated carboxyl group (-COOH) [30]. The main active ingredients are Roburic acid, Oleanolic acid and Ursolic acid, which have anti-inflammatory, anti-tumor and anti-hepatitis effects. The structure of these components contains cyclopentane parallel polyhydrophenanthrene parent nucleus, the main active components β-sitosterol and Daucosterol. Phenylpropanoids are a class of naturally occurring chemicals that comprise one or more C_6-C_3 units. The cinnamic acid pathway was responsible for the synthesis of simple phenylpropanoids, coumarins, and lignans. The alkaloids in *G. macrophylla* have terpenoid properties. The primary source of these alkaloids was iridoid. In the process of extraction and separation, ammonia was used to treat gentiopicrin, which was very unstable in chemical properties and reacted with ammonium hydroxide to form alkaloids [33]. Under the influence of human intestinal bacteria, gentiopicroside can be rapidly metabolized and transformed into gentianine and gentianal [34]. Blood pressure is lowered and blood sugar is raised as a result of these active substances [2].

There was an experiment, high performance liquid chromatography (HPLC) was used to detect the changes in the active constituents (longanic acid, sweroside, gentiopicroside, and swertiamarin) and Inductively Coupled Plasma-Atomic Emission Spectrometry was used for mineral nutrients in *G. macrophylla* during flower development. The research results show that biomass of the flower was considerable during flower development, in which the contents of longanic acid and gentiopicroside were at the highest levels, sweroside and swertiamarin in the flowers reached 6.06 and 1.25 times higher than those in roots [35]. In this case, the flowers of *G. macrophylla* could be used as a potential medicinal plant part.

Pharmacological activities

Anti-inflammatory activity

The anti-inflammatory action can stop the inflammatory response, which stops inflammation from happening, stops it from spreading, and gets rid of all the symptoms that come with inflammation. Thus, there is a great necessity for this activity. According to the literature, there are many studies on the anti-inflammatory effect of *G. macrophylla*, among which the four studies included here show that *G. macrophylla* has a strong anti-inflammatory effect. When rats were administered the *G. macrophylla* water extract orally at a daily dose of 100 mg/kg body weight, the prostaglandin E2 levels in the inflammatory tissues, sole thickness, and ankle circumferences of feet were significantly decreased [36]. The carrageenan-induced rat paw edema and xylene-induced mouse ear edema models were used to study anti-inflammatory activity. The water extracts of the flowers of *G. macrophylla* and *G. straminea* inhibited significantly, in a dose-dependent manner, the increase of rat paw edema induced by carrageenin. It can be seen from this, that the extracts of *G. macrophylla* and *G. straminea* possessed antinociceptive and anti-inflammatory activities. The mechanism may be the iridoid glycoside existing in *G. macrophylla* could alleviate the arthritis induced by collagen in rats through underlying mechanisms modulated in imbalance between the cytokines secretion of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) through the decrease in cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) overexpression [37]. Studies have shown that roburic acid can regulate nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, inhibit the secretion of pro-inflammatory factors nitric oxide and IL-6, and thus play an anti-inflammatory role [38]. To a certain extent, iridoids from

the flower of *Gentiana macrophylla* Pall. (GMI) can reduce the arthritis index of mice with collagen-induced arthritis (CIA), improve the histopathological changes of joint synovium, inhibit the secretion of inflammatory factors TNF-α, IL-1β, and IL-6 in serum, and reduce the expression levels of matrix metalloproteinase 1 (MMP1) and matrix metalloproteinase 3 (MMP3) in synovium [39]. Studies have shown that GMI can inhibit the ear swelling of mice induced by xylene, the increase of capillary permeability of mice induced by acetic acid, and the formation of cotton ball granuloma in mice. It can also inhibit the release of inflammatory mediators such as TNF-α and interleukin-1 [40]. The above research shows that the anti-inflammatory effect of GMI may be related to inhibiting the production of inflammatory cytokines. In summary, we found that the roots and flowers of Gentiopicrin have anti-inflammatory effects, and the mechanism of action is probably related to gentiopicrin.

Antioxidant activity

The antioxidant activity experiments showed that iridoid terpenes and phenylpropanoids could remove free radicals in different degrees, and the scavenging rate of sweroside was as high as 80.13%, showing excellent antioxidant activity. The change in reaction rate of the free radical model over time showed that the scavenging rate of samples decreased from large to small. It was positively correlated with 1, 1-diphenyl-2-picrylhydrazyl solution concentration. The analgesic effect of *G. macrophylla* was not determined by one chemical substance, but by the interaction of many substances. Therefore, the pharmacological effect can't be judged by the content of a specific substance [41]. *G. macrophylla* iridoid glucoside iridoid glucoside can effectively combat the peroxidation damage caused by inflammation in rats and has an obvious antioxidant effect [40]. Swertiamarin can play an anti-oxidative stress role by activating nuclear factor erythroid-2-related factor 2 and having a protective effect on ischemic brain tissue [42]. The results of the 2,2-diphenyl-1-picrylhydrazyl and nitroblue tetrazolium antioxidant assays clearly show that the total flavonoids from *G. macrophylla* display strong antioxidant activity [32]. The role of antioxidants is mainly reflected in delaying aging, protecting cells and tissues, enhancing resistance, and reducing the risk of disease. Overall, antioxidants play a vital role in the human body and have positive implications for maintaining human health and disease. From the above four studies, it can be seen that iridoid and phenylpropanoid components have antioxidant effects.

Analgesic activity

Using medications to interfere with the central nervous system and produce an analgesic effect is the fundamental concept behind analgesia. The analgesic activity of *G. macrophylla* has been the subject of experimental investigations; however, its mechanism of action has not been the subject of any research. The extract of *G. macrophylla* flower can increase the threshold time of hot plate pain, significantly reduce the number of body twistings caused by acetic acid, and prolong the latency time of photoelectric tail swinging, which indicates that the extract of *G. macrophylla* flower has analgesic effects [43]. Research has shown that the ethanol extract of *G. macrophylla* can reduce the degree of auricle swelling in xylene model mice and inhibit acute inflammation, which was inhibited to some extent in the rat model. The alcohol extract of *G. macrophylla* can also increase the pain threshold of mice and reduce the number of body twists caused by glacial acetic acid [44]. From the two studies above that *G. macrophylla* extract possesses analgesic properties.

Hepato-protective activity

According to recent pharmacological research, *G. macrophylla* root ethanol or water extract can be used as protective agent for liver damage. According to an experimental investigation, *G. macrophylla* root water extract reduced oxidative stress and had a protective impact on acute liver injury in mice generated by carbon tetrachloride (CCl_4), and 70% (v/v) ethanol extract of *G. macrophylla* root could, via oxidation resistance, mitigate acute liver damage brought on by alcohol [45, 46]. The study on the protective effect of *G. macrophylla* water decoction on CCl_4 induced acute liver injury in mice showed that *G. macrophylla* can enhance the expression of interleukin-10 (IL-10) in carbon tetrachloride damaged liver tissue, and IL-10 was an important cytokine mediating the hepatoprotective effect of *G. macrophylla* [47]. High, medium, and low doses of water extract of *G. macrophylla* could decrease the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the serum of CCl_4-induced acute liver injury mice, decrease the content of malondialdehyde (MDA) in the liver, and enhance the activity of superoxide dismutase (SOD). Pathological sections showed that *G. macrophylla* extract could significantly reduce the degree of liver lesions in model animals [45]. The model group mice were intragastrically administered 200 μL of a 50% (v/v) ethanol aqueous solution. The mice in the normal control group were given the same amount of water. The outcomes demonstrated that, in a dose-dependent way, the *G. macrophylla* the ethanol extract markedly reduced alcohol-induced liver damage. Following the administration of *G. macrophylla* extract, the damaged hepatic tissue structure was restored and the amount of collagen deposition decreased. In the meantime, the extract of *G. macrophylla* significantly and dose-dependently reduced the levels of MDA, AST, and ALT in blood serum – indicators of liver damage. Furthermore, the extract of *G. macrophylla* also improved liver index and body weight. Thus, by preventing c-Jun-NH2-terminal kinase and P38 phosphorylation and further reducing the start of inflammation, the extract of *G. macrophylla* reduced alcoholic liver disease [48]. Our objective was to examine the impact of *G. macrophylla* root ethanol extract (at 100 and 300 mg/kg body weight) on human parvovirus (B19)-nonstructural protein (NS1)-exacerbated liver injury in NZB/W F1 mice. Hematoxylin-eosin staining and immunoblotting were used to evaluate the liver tissues. The results indicate that the *G. macrophylla* root extract significantly reduced the expressions of urokinase plasminogen activator and hepatic matrix metalloproteinase-9 (MMP-9) in response to B19-NS1-exacerbated liver inflammation ($P < 0.05$) [49]. These results point to *G. macrophylla* root extract's potential as a treatment for B19-NS1-exacerbated liver inflammation in systematic lupus erythomatosus (SLE) patients. It was discovered that camphaloside possesses a potent antispasmodic impact on gastrointestinal tract and biliary smooth muscle spasmodic discomfort. Hence, swertiamarin might be one of the ways that *G. macrophylla* shields the liver from harm. The liver can also be shielded by gentiopicroside. Gentiopicroside underwent a series of metabolic processes, including deglycosylation, oxidation, n-heterocyclic acid production, sugar esterification, and other processes, to produce active ingredients that exerted the hepato-protective effects of gentiopicroside [34]. On the other hand, when mice were given intragastric administration with isoorientin at a dose of 15 mg/kg, the liver tissue culture experiment revealed that it exhibited strong liver protective activity [50].

Bacteriostatic activity

G. macrophylla can stop the growth of many different types of bacteria and has potent antibacterial action. The three literatures indicate that this phenomenon was the subject of extensive research. The aqueous acetone extract of *G. macrophylla* roots was fractionated using LC-UV-mass spectrometry and the bioassay co-directed method, yielding three novel chromene derivatives; kurarinone, kushenol I, and 2-methoxyanofinic acid. Studies have demonstrated the efficacy of 2-methoxyanofinic acid, its methyl ester, kurarinone, and kushenol I in inhibiting the fungal disease *Cladosporium cucumerinum* in plants. The growth of the human pathogenic yeast *Candida albicans* was also suppressed by the methyl ester and kurarinone [22]. Using bioassay-guided fractionation and structural elucidation techniques, four antifungal bisphosphocholines were found in *G. crassicaulis*. All four *Gentiana* species (*G. crassicaulis*, *G. macrophylla*, *G. dahurica*, and *G. straminea*) included bisphosphocholines, with irlbacholine being the main component, and ranged from 2.0 to 6.2 mg per gramme of dried material, according to a subsequent chemical examination of 56 samples of four "Qinjiao" species. With minimum inhibitory

concentrations (MIC) of 0.63, 1.25, 10.0, and 5.0 μg/mL for *Aspergillus fumigatus*, *Candida albicans*, *Candida glabrata*, and *Cryptococcus neoformans*, respectively, irlbacholine demonstrated strong in vitro antifungal activity [51]. The *G. macrophylla* methanol extract had strong antibacterial activity against all of the tested bacterial strains, according to an evaluation of its antimicrobial activity against bacterial strains recovered from wound burns. There was a range of 60 to 240 μg/mL in the MIC values. *S. epidermidis* was found to have the lowest MIC whereas *E. coli* had the highest MIC [52]. As a result, it was evident that the *G. macrophylla* extract strongly inhibits the growth of bacteria. Its role may be through irlbacholine to achieve antibacterial effect.

Gastrointestinal tract-protective activity

Frequent belly pain and bloating, heartburn, indigestion/dyspepsia, nausea and vomiting, diarrhoea, and constipation are among the main symptoms of common gastrointestinal illnesses. The isolated iridoid and flavonoid components of *G. macrophylla* show gastrointestinal tract-protective properties. The examination of the biological activity of four gentian decoctions (*G. algida*, *G. decumbens*, *G. macrophylla*, and *G. triflora*) showed that they were highly effective in stimulating the stomach's ability to create mucus, acid, and enzymes. This ability was mostly ascribed to iridoids and flavonoids [53]. Gentiopicroside, which was derived from *G. macrophylla*a, was proactively administered to mice (male Kunming mice (28 ± 3 g)) via intragastric administration once a day for three days in a row. Following the final intragastric injection, mice were given 70% ethanol to produce a gastric ulcer on the third day. The results showed that gentiopicroside protects mice's stomach mucosa from damage caused by ethanol [54]. In rats with gastrointestinal motility disorders brought on by stress stimulation, gentiopicroside was administered as a treatment in the investigation of the gastric motility mechanism of *G. macrophylla*. The outcome of the trial indicates that gentiopicroside accelerated intestinal propulsion and stomach emptying. Additionally, it markedly raised gastrin and lowered somatostatin levels in plasma. Additionally, it inhibited the expression of vasoactive intestinal peptide (VIP) receptor 2 in the duodenum and increased the expression of motilin receptor in the gastric antrum, duodenum, jejunum, and ileum [55]. In the study of gentiopicroside therapy for cholestatic liver injury induced by α-naphthalene isothiocyanate in mice, experimental data demonstrated that gentiopicroside significantly upregulated the hepatic mRNA levels of synthesis enzymes (cytochrome P450, family 8, subfamily B, polypeptide 1 (Cyp8b1) and Sterol 27 Hydroxylase (Cyp27a1)) and transporters (Multidrug Resistance-Associated Protein 4 (Mrp4), Multidrug Resistance-Associated Protein 1 (Mdr1) and Organic Solute and Steroid Transporter-Beta (Ost-β)), as well as ileal bile acid circulation mediators (Apical Sodium Dependent Bile Acid Transporter (Asbt) and Fibroblast Growth Factor 15 (Fgf15)), accompanied by a decrease in serum and hepatic bile acid levels [56]. It is evident that iridoid terpenoids and flavonoids can protect the gastrointestinal tract, and the roots and flowers of *G. macrophylla* contain iridoid terpenoids and flavonoids, so this outcome is feasible.

Heart-protective activity

Searching the database, we discovered that there aren't many publications or research on *G. macrophylla*'s potential heart-protective benefits. Using the left ventricle (LV) of NZB/W F1 mice fed a high-cholesterol diet as a model, this study examines whether ethanol extract of *G. macrophylla* has anti-apoptotic effects. The morphology and apoptotic status of the ventricular tissues were assessed using microscopy and the Terminal deoxynucleotidyl transferase dUTP nick end labeling assay. Using immunoblotting, the levels of apoptotic indicators were ascertained. Thus, by inhibiting both intrinsic and extrinsic apoptotic pathways, the ethanol extract of *G. macrophylla* was able to drastically diminish the cholesterol-aggravated apoptosis of LV in NZB/W F1 mice. Furthermore, in LV tissues, the ethanol extract of *G. macrophylla* markedly elevated the levels of anti-apoptotic proteins and cardiac insulin-like growth factors-1 survival signaling. As a result, the ethanol extract of *G. macrophylla* was to help reduce the heart damage caused by high cholesterol in SLE patients [57]. As well, isoorientin has the therapeutic effect on cardiovascular disease [2]. This study has demonstrated the need for additional development in subsequent experimental investigations, as this position is highly deserving of notice.

Antineoplastic activity

The cause of cancer is that the body receives a variety of factors that lead to abnormal genetic changes and eventually form tumors. In vivo, *G. macrophylla* total glycosides were shown to have an anticancer impact on mice injected with the human hepatocellular carcinoma cell SMMC-7721. The data demonstrated that the tumor inhibition rates were 27.1%, 35.8%, and 37.1%, respectively, at medication concentrations of 10, 20, or 40 g/kg. It is established that the total glycosides of *G. macrophylla* can extend the survival period of tumor-bearing mice and have a certain inhibitory effect on transplanted tumors. The mechanism might have anything to do with immunity augmentation [58]. The well-known oncogene Neuro-oncological Ventral Antigen 2 was shown to be induced by hypoxia in endothelial cells and to be inhibited by treatment with flavonoids from *G. macrophylla*. In addition, treatment with *G. macrophylla* flavonoids reduced hypoxia-evoked non-small cell lung cancer cell invasion and proliferation as well as hypoxic H1299 and A549 cells-evoked M2 macrophage polarisation in vitro; furthermore, treatment with *G. macrophylla* flavonoids inhibited the formation of non-small cell lung cancer tumours in vivo [59]. As a result, in the future, the flavonoids that were isolated from *G. macrophylla* might play a significant role in tumour inhibition.

Antiarthritic activity

In treated adjuvant-induced arthritis (AIA) rats, gentiopicroside was able to suppress tumor necrosis factor alpha induced proliferation and migration of rheumatoid arthritis fibroblast-like synoviocytes cells and significantly reduce joint swelling and arthritic index scores. These reductions were accompanied by corresponding decreases in synovial inflammatory cell infiltration, synovial hyperplasia, and bone erosion. Gentiopicroside 200 mg/kg decreased the thymus index but did not affect body weight or spleen index. These results suggest that gentiopicroside can suppress the ROS-NF-κB-NLRP3 axis to ameliorate the symptoms of rheumatoid arthritis [60]. To create the animal model (CIA), type II collagen from chicken was administered intraperitoneally into male C57BL/6J mice. The study was conducted in vitro using synoviocytes that resembled rheumatoid fibroblast-like synoviocytes. In vivo and in vitro experiments confirmed that CD147 was the main target of gentiopicroside in attenuating rheumatoid arthritis symptoms for the first time. The CD147/p38/NF-κB pathway may be involved in the regulation of Gentiopicroside's anti-rheumatic actions and inhibitory effects on matrix metalloproteinase (MMP) secretion [61]. Gentiopicroside protects rat articular chondrocytes against interleukin-1 beta-induced inflammatory response. Its protective properties and mechanisms were investigated using immunohistochemistry, western blotting, and reverse transcriptase-polymerase chain reaction. The results of this investigation showed that gentiopicroside had a strong protective effect against the inflammatory response caused by IL-1β in rat articular chondrocytes [62]. Gentiopicroside may therefore be a viable therapeutic approach for the management of osteoarthritis.

Immunoregulatory activity

Immune regulation refers to the interaction between immune cells and immune molecules in the immune system, as well as with other systems such as the neuroendocrine system so that the immune response is in the most appropriate form to maintain the body at the most appropriate level. Concanavalin A (ConA) was utilized to stimulate splenic T lymphocyte proliferation. Both in vitro and in vivo tests were used to examine the impact of ConA on the growth of splenic T cells. The experimental results showed that the n-butanol site inhibited the proliferation of spleen T lymphocytes induced by

ConA in rats. It was proven that the n-butanol extract of *G. macrophylla* could regulate immunity [63]. Gentianine A has anti-allergic shock and anti-histamine abilities [25]. From the above studies, it is not difficult to find that the extract of *G. macrophylla* is likely to be used as an immunomodulator.

Other activity

Gentiana A has the effect of increasing blood sugar. In the experiment, 30 min after intraperitoneal injection of *Gentiana* A, blood sugar increased, and the increase effect was positively correlated with the dose. Meanwhile, liver glycogen decreased significantly [45]. A water extract of *G. macrophylla* can reduce blood pressure in rabbits [64]. Isoorientin from *Gentiana veitchiorum* Hemsl. flower extract showed significant suppression of melanin content [32]. Studies have shown that swertiamarin has an anti-diabetic effect, which was due to the production of its metabolite gentianine [65]. The flavonoids isoorientin and isovitexin showed strong acetylcholinesterase inhibitory activity, with median inhibitory concentrations of 50.26 μm and 8.36 μm, respectively [30]. Additionally, there were antiviral and cardio-cerebrovascular protective properties in the *G. macrophylla* extract.

In summary, we know that the main pharmacological effects of *G. macrophylla* were anti-inflammatory, antioxidant, analgesic, hepatoprotective, bacteriostatic, Gastrointestinal tract-protective, heart-protective, anti-tumor, antiarthritic, immunomodulatory and other effects, and its mechanism research mainly focuses on iridoid and flavonoid components. The pharmacological effects were summarized in Figure 3, the possible mechanisms for the main pharmacological actions of *G. macrophylla* were summarized in Figure 4, and the characteristics of the relevant to the pharmacological action

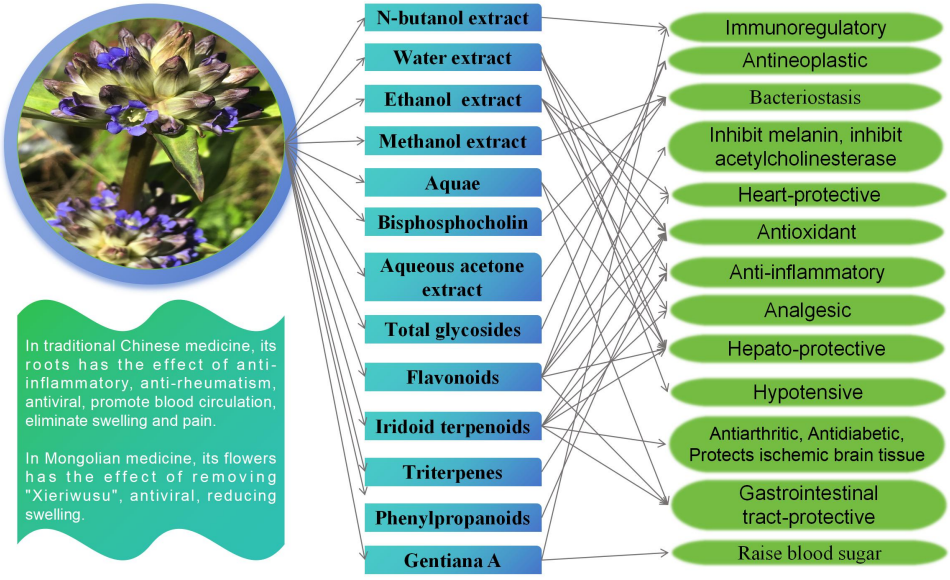

Figure 3 Multiple pharmacological effects of *G. macrophylla*

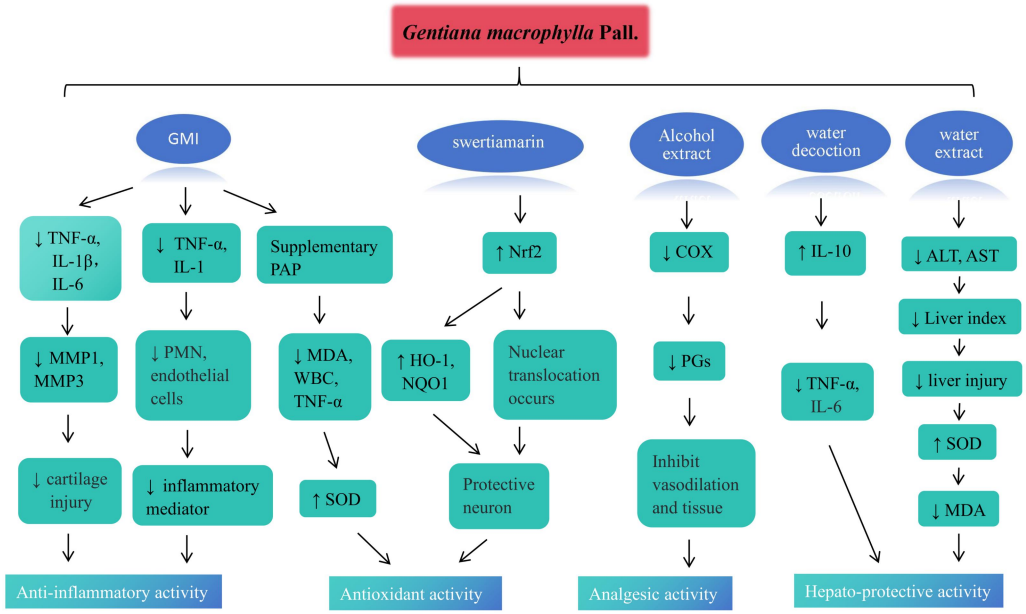

Figure 4 Possible mechanism for the main pharmacological action of *G. macrophylla*. GMI, iridoids from the flower of *Gentiana macrophylla* Pall.; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; Nrf2, nuclear factor erythroid-2-related factor 2; COX, cyclooxygenase; IL-10, interleukin-10; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MMP1, matrix metalloproteinase 1; MMP3, matrix metalloproteinase 3; MDA, malondialdehyde; WBC, White blood cells; SOD, superoxide dismutase; HO-1, Heme oxygenase-1; PGs, prostaglandins; IL-1, interleukin-1; PAP, partialpasture; PMN, Polymorphonuclear neutrophil; NQO1, NAD(P)H:quinone oxidoreductase 1.

and mechanisms of actions of *G. macrophylla* were showed in Table 4 [36–41, 44–49, 51, 54–63].

Quality control

The purpose of quality control for medicinal materials was to guarantee their efficacy and safety, as well as to uphold the industry's positive development. Therefore, it was crucial to ensure the quality monitoring of medical ingredients. According to the quality standard of *G. macrophylla* in the *2020 edition of the Chinese Pharmacopoeia*, using high-performance liquid chromatography, the total amount of gentiopicroside and Loganic acid shall not be less than 2.5% according to the calculation of dry products. Yang et al. established an ultra-UPLC method for the simultaneous determination of seven components of *G. macrophylla*, which can be better used for the detection of *G. macrophylla* [66]. The contents of these four components were ascertained in *G. macrophylla* from various regions using the HPLC evaporative light sacttering detection method. The findings demonstrated that *G. macrophylla* from the Qinling area of Shanxi Province had substantial concentrations of four iridoid glycosides, suggesting that the *G. macrophylla* grown in this area was of higher quality [18]. To evaluate its quality, the HPLC fingerprint of 14 batches of *G. macrophylla* from various harvesting times and sources was identified, compared, and determined, establishing the fingerprint of *G. macrophylla* [67]. To optimize the quality standard method of *G. macrophylla*, using HPLC and the HPLC mass spectrum approach, eight components of *G. macrophylla* were identified in flowers and roots in a straightforward, precise, and dependable manner, Table 5 displays the chemical components content in *G. macrophylla* [2]. The aforementioned four studies demonstrate that, about *G. macrophylla* quality control, the majority of the active ingredients investigated are iridoid components. Since the detection of a single active ingredient was not a reliable indicator of overall efficacy, it was important to take a multifaceted approach to quality control. As a result, alternative active ingredients may serve as the foundation for future research on *G. macrophylla* quality control.

Table 4 Characteristics of the 24 included studies relevant to the pharmacological action and mechanisms of actions of *G. macrophylla*

Pharmacological effects/included studies	Study type	Extract	Characteristics of the sample	Interventions	Duration	Primary results
1. Anti-inflammatory						
Yu et al., 2004 [36]	In vivo	Ethanol extract	80 wistar male rats	Control group: normal saline (180 mg/kg); positive control: prednisone at a one-third dose (250 mg/kg) of the Semi-lethal dosage value; *G. macrophylla* extract orally at a dose of 100 mg/kg.	28 days	When treated with the *G. macrophylla* extract, all animals had survived at the day 28, and the body weights were significantly increased. It works better than prednisone.
Jia et al., 2012 [37]	In vivo	Ethanol extract	96 mice (Institute for Cancer Research mice and Sprague-Dawley (SD) rats)	Control group: water treatment; positive drug group: aspirin treatment (100 mg/kg); extract isolated from *G. macrophylla* group: intragastrically administered three doses (600, 300, 150 mg/kg); extract isolated from *G. straminea* group: intragastrically administered three doses (600, 300, 150 mg/kg).	7 days	The inhibition percentage of *G. macrophylla* on xylene-induced ear edema in mice was equal to *G. straminea* in high dosage, and both herbal extracts significantly inhibited acetic acid-induced vascular permeability in mice in a dose-dependent manner ($P < 0.001$). The analgesic effect of *G. macrophylla* was higher than that of aspirin (100 mg/kg) at the dose of 15 mL/kg ($P < 0.05$).
Chen et al., 2017 [38]	In vitro	Roburic acid	RAW264.7 macrophage cells	RAW264.7 cells were pre-treated with roburic acid for 1 h, then stimulated with lipopolysaccharide (200 ng/mL) for 24 h. L-N6-(1-iminoethyl) lysine was used as a positive control.	25 h	Roburic acid reduced production of nitric oxide and IL-6, and the expression of inducible nitric oxide synthases.
Jia et al., 2018 [39]	In vivo	Iridoids	50 male C57BL /6J mice	Normal group and CIA model group (equal volume of normal saline), dexamethasone group (0.25 mg/kg), iridoids group (30 mg/kg) and iridoids group (15 mg/kg) were given intragastric administration.	28 days	Iridoids from the flower of *G. macrophylla* markedly down-regulated the levels of TNF-α, IL-1β and IL-6 in the serum. Western blot test indicated that iridoids notably inhibited the expression of MMP1 and MMP3.

Table 4 Characteristics of the 24 included studies relevant to the pharmacological action and mechanisms of actions of *G. macrophylla* (*continued*)

Pharmacological effects/included studies	Study type	Extract	Characteristics of the sample	Interventions	Duration	Primary results
Niu et al., 2013 [40]	In vivo	Total iridoid glycosid	50 female mice	Blank control: normal saline; positive control: aspirin 200 mg/kg; total iridoid glycoside doses (200, 400 and 800 mg/kg).	5 days	Compared with the negative control group, total iridoid glycosid inhibited xylene-induced ear swelling, acetate-induced increase in capillary permeability, and cotton ball granuloma formation in mice, and it could significantly reduce the volume of exudate, reduce the content of white blood cells, MDA and TNF-α in exudate and the level of MDA in serum, and increase the activity of SOD in exudate and serum.
2. Antioxidant activity						
Lin et al., 2013 [41]	In vivo	Ethanolic extract	30 male SD rats and 60 male mice	Model group: normal saline; ethanolic extract group: 2 g/(kg·d); aspirin group: 0.02 g/(kg·d).	4 days	Ethanolic extract group can reduce the degree of auricle swelling in xylene inflammation model mice ($P < 0.01$), and can inhibit the acute inflammation of cyclopropanetin model rats, increase the pain threshold of mice, and reduce the number of body twisting caused by ice acetic acid.
Niu et al., 2013 [40]	In vivo	Total Iridoid glycosid	50 male SD rats	Blank control: normal saline; positive control: aspirin 200 mg/kg; total iridoid glycoside doses (200, 400 and 800 mg/kg).	1 week	The content of MDA in serum and exudate of balloon synovitis induced by egg white increased, while the activity of SOD decreased. The total iridoid glycosid significantly decreased the content of MDA in serum and exudate of balloon synovitis and increased the activity of SOD.
3. Analgesic activity						
Li et al., 2006 [44]	In vivo	Water extract; alcohol extract	60 mice	Blank control group: normal saline; positive control group: aspirin (0.2 g/kg); wild water extraction group, wild alcohol extraction group, cultivated water extraction group, cultivated alcohol extraction group: 10 g/kg.	1 week	Compared with the normal saline group, four groups of extract were significant differences in anti-inflammatory, analgesic and other pharmacological effects ($P < 0.01$).
4. Hepato-protective activity						
Kang et al., 2012 [45]	In vivo	Water extract	60 male mice	Control group and model group: distilled water; bifendate group: 6.8 mg/kg; aqueous extract Low, medium, and high dose groups: 2, 4, and 8 g/kg.	10 days	Compared with model group, high, medium and low doses of water extract (8, 4, 2 g/kg) groups could decrease the activities of ALT and AST in serum of CCL_4-induced acute liver injury mice ($P < 0.01$, $P < 0.05$), decrease the content of MDA in liver, and enhance the activity of SOD ($P < 0.01$, $P < 0.05$).

Table 4 Characteristics of the 24 included studies relevant to the pharmacological action and mechanisms of actions of *G. macrophylla* (*continued*)

Pharmacological effects/included studies	Study type	Extract	Characteristics of the sample	Interventions	Duration	Primary results
Zhang et al., 2014 [46]	In vivo	Ethanolic extract	60 male Institute for Cancer Research mice	7:00–8:00, positive control: tiopronin (30 mg/kg) 0.1 mL/10 g; ethanolic extract each dose group (1, 2, 4 g/kg): 0.1 mL/10 g; Normal control group and model group: normal saline. 19:00–20:00, except normal control group, the other groups: 50% ethanol (12.5 mL/kg).	12 days	Compared with model group, ethanolic extract medium and high dose groups significantly decreased the activities of ALT and AST and MDA contents ($P < 0.05$), and increased the activity of SOD ($P < 0.05$).
Su et al., 2010 [47]	In vivo	Water decoction	40 mice	Blank group and model group: normal saline (4 g/kg); two drug groups: water decoction (4 g/kg).	1 week	Compared with the model group, ALT and TNF-α levels were decreased ($P < 0.05$), while IL-10 expression levels were increased ($P < 0.05$).
Cui et al., 2019 [48]	In vivo	Root extract	50 mice	Model group: 50% (v/v) ethanol aqueous solution (200 μL for each); control normal group: equal volumes of water. Root extract group: 50% (v/v) ethanol aqueous solution (200 μL for each) once daily at 10:00 a.m., after 1 h, sequentially was treated with 20, 40 and 100 mg/kg of root extract by gastric gavage.	19 days	The level of MDA, AST and ALT (indicators of liver damage) in blood serum were significantly controlled by root extract with a dose-dependent manner, moreover, body weight and liver index were also improved after administration of root extract.
Sheu et al., 2017 [49]	In vivo	Ethanolic extract	32 female mice	Control group: normal saline (180 mg/kg); positive control group: one-third dose (250 mg/kg) of the Semi-lethal dosage value; extract of *G. macrophylla* group (100 mg/kg).	8 weeks	Ethanolic extract significantly decreased B19-NS1-exacerbated liver inflammation ($P < 0.05$), and it also significantly reduced the B19-NS1-exacerbated MMP-9 and urokinase plasminogen activator expressions.
5. Bacteriostatic activity						
Ren et al., 2020 [51]	In vitro	Irlbacholine	56 *Gentiana* samples	The dried powdered plant material (1.0 g) of 56 *Gentiana* was accurately weighed and extracted with 10 mL of MeOH (HPLC grade) under ultrasonication at room temperature for 1h, followed by centrifugation at 2,850 rpm for 30 min. The supernatant was transferred to a volumetric flask. The extraction procedure was repeated for the second time. The combined supernatants were reconstituted to a final volume of 25 mL. Then, 1 μL of the solution was injected into the Liquid Chromatograph Mass Spectrometersystem.	1.5 h	Irlbacholine exhibited potent in vitro antifungal activity, chemical analysis of 56 *Gentiana* samples showed that bisphosphocholines were present in all four *Gentiana* species.
6. Gastrointestinal tract-protective activity						

Table 4 Characteristics of the 24 included studies relevant to the pharmacological action and mechanisms of actions of *G. macrophylla* (*continued*)

Pharmacological effects/included studies	Study type	Extract	Characteristics of the sample	Interventions	Duration	Primary results
Yang et al., 2018 [54]	In vivo	Gentiopicroside	60 mice	Normal control group and negative control: saline (2.5 mL/kg); positive control: cimetidine (100 mg/kg); three gentiopicroside groups: gentiopicroside (20, 40, and 80 mg/kg).	3 days	Oral administration of gentiopicroside significantly increased heat shock protein-70 and glutathione levels and SOD activity, normalized epidermal growth factor and vascular endothelial growth factor levels, and decreased the levels of TNF-α, IL-6 and MDA, and myeloperoxidase activity in gastric tissue.
Ruan et al., 2015 [55]	In vivo	Gentiopicroside	60 SD rats	Control group; model group; positive control (2.5 mg/kg); gentiopicroside (40, 80, 160 mg/kg).	1 week	Gentiopicroside increased gastric emptying and intestinal propelling obviously. However, gentiopicroside failed to improve the hypofunction of guinea pigs ileums pre-treated with atropine sulfate.
Tang et al., 2016 [56]	In vivo	Gentiopicroside	100 mice (C57BL/6J)	Mice were treated with gentiopicroside (130 mg/kg, ig). On the third day, mice were given a single dose of alpha-naphthylisothiocyanate (75 mg/kg).	5 days	Gentiopicroside can change bile acids metabolism which highlights its importance in mitigating cholestasis, resulting in the marked decrease of intracellular bile acid pool back toward basal levels.
7. Heart-protective activity						
Huang et al., 2015 [57]	In vitro	Root extract	The LV of NZB/W F1 mice	The morphology and apoptotic status of ventricular tissues were determined by microscopy and Terminal deoxynucleotidyl transferase dUTP nick end labeling assay. Levels of apoptotic biomarkers were determined by immunoblotting.	12 weeks	Root extract is considered to be beneficial in alleviating cholesterol-aggravated cardiac damage in SLE.
8. Antineoplastic activity						
Wang et al., 2010 [58]	In vivo	Total glycosides	150 mice	Model group (medicinal soybean oil); positive drug 5-Fu group (100 mg/kg); total glycosides small, medium, large dose group (10, 20, 40 g/kg).	10 days	The tumor inhibition rates were 27.1%, 35.8% and 37.1% when the drug concentration was 10, 20 and 40 g/kg, respectively. Thymus index and spleen index were compared with those of model group ($P < 0.05$). The life extension rates were 24.7%, 55.6% and 71.8%, respectively.

Table 4 Characteristics of the 24 included studies relevant to the pharmacological action and mechanisms of actions of *G. macrophylla* (*continued*)

Pharmacological effects/included studies	Study type	Extract	Characteristics of the sample	Interventions	Duration	Primary results
Ma et al., 2024 [59]	In vivo	Flavonoids	24 mice (BALB/c)	(1) miR-512-5p mimic or the controls (sh-NC) + phosphate buffered salin (PBS), (2) sh-circ_0059665 + PBS, (3) sh-NC + flavonoids, (4) sh-circ_0059665 + flavonoids. The subcutaneous tumor volume $\text{Volume} = \frac{\text{Length} \times \text{Width2}}{2}$ was measured every 3 days. At day 22, the mice were sacrificed, the tumors were weighed, and collected for subsequent analysis. A549 cells were placed in the anoxic chamber for 3 days incubation: (1) normal + sh-NC + PBS, (2) hypoxia + sh-NC + PBS, (3) hypoxia + sh-circ_0059665 + PBS, (4) hypoxia + sh-NC + flavonoids, (5) hypoxia + sh-circ_0059665 + flavonoids.	22 days	Flavonoids treatment in hypoxic environments suppressed non-small cell lung cancer cell proliferation, invasion and M2 macrophage polarization via the circ_0059665/ miR-512-5p/Neuro-oncological Ventral Antigen 2 axis.
9. Antiarthritic activity						
Wang et al., 2020 [60]	In vivo	Gentiopicroside	SD male rats	Control group (0.1 mL either complete Freund's adjuvant or PBS); AIA group; dexamethasone group (0.2 mg/kg); gentiopicroside groups (100 mg/kg and 200 mg/kg). On days 15 to 28 post-immunization: control and AIA group: 0.5% sodium carboxymethyl cellulose; dexamethasone (0.2 mg/kg); gentiopicroside groups (100 mg/kg and 200 mg/kg).	28 days	Gentiopicroside was able to significantly reduce the swelling of joints and arthritic index scores, with corresponding reductions in synovial inflammatory cell infiltration, synovial hyperplasia, and bone erosion in treated AIA rats. Gentiopicroside 200 mg/kg reduced thymus index in AIA rats, but had no effect on spleen index and body weight.
Jia et al., 2022 [61]	In vivo	Gentiopicroside	30 male mice (C57BL/6J)	Control group (saline), CIA group, methotrexate group (2 mg/kg), and two doses of gentiopicroside groups (20 or 40 mg/kg). From day 13, the immunized groups were intragastrically administered daily with methotrexate or gentiopicroside.	42 days	Gentiopicroside treatment attenuated synovitis and cartilage destruction in CIA mice.
Zhao et al., 2015 [62]	In vitro	Gentiopicroside	Rat articular chondrocytes	Gentiopicroside (50, 500 and 1,500 μg/mL); normal control: without gentiopicroside; blank control: without cells.	76 h	50, 500, and 1,500 μg/mL of gentiopicroside exhibited no significant toxicity to chondrocytes ($P > 0.05$) after 24 h. Gentiopicroside showed inhibition in the IL-1β-induced release of MMPs while increasing Collagen type II expression.
10. Immunoregulatory activity						

Table 4 Characteristics of the 24 included studies relevant to the pharmacological action and mechanisms of actions of *G. macrophylla* (*continued*)

Pharmacological effects/included studies	Study type	Extract	Characteristics of the sample	Interventions	Duration	Primary results
Dong et al., 2006 [63]	In vivo	Effective part of *G. macrophylla*	Wistar male rats	Normal group and model group: potable water; Tripterygium glycoside group: 15 mg/kg; petroleum ether part, ethyl acetate part, N-butanol part (QZ) and water soluble part groups: 400 mg/kg.	15 days	Petroleum ether part, QZ and water soluble part have anti-inflammatory effects on local inflammation and immune inflammation caused by Fowlard complete adjuvant. QZ can inhibit the proliferation of spleen T lymphocytes induced by Con A in vivo.

AIA, adjuvant-induced arthritis; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; B19, human parvovirus; CCL_4, carbon tetrachloride; CIA, collagen-induced arthritis; Con A, Concanavalin A; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-10, Interleukin-10; MDA, malondialdehyde; MMPs, Matrix metalloproteinases; NS1, nonstructural protein; PBS, Phosphate buffered saline; QZ, N-butanol part; sh-NC, miR-512-5p mimic or the controls; SLE, Systemic lupus erythematosus; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; LV, left ventricle; MMP1, matrix metalloproteinase 1; MMP3, matrix metalloproteinase 3; *G. macrophylla*, *Gentiana macrophylla* Pall.; SD, Sprague-Dawley.

Table 5 The chemical components content in *G. macrophylla*

	Content (%)							
	Iridoid					Flavonoids		
Botany parts	Gentiopicroside	6'-O-β-D-glucosyl gentiopicroside	Loganic acid	Sweroside	Swertiamarin	Isovitexin	Isoorientin	Isoorientin-4'-O-glucoside
Flowers	3.53–6.29	0.82–1.45	1.30–2.28	1.10–1.97	0.84–1.49	0.40–0.71	1.24–2.20	0.49–0.86
Rhizomes	4.56–7.04	0.52–0.80	–	0.90–1.38	0.55–0.85	–	–	0.58–0.89

Discussion

The Gentiaceae family comprises over 700 species and 80 genera that are extensively dispersed over all continents, with the northern hemisphere's temperate and cold temperate zones being their primary distribution areas. China has 22 genera, the majority of which are found in the country's southwest mountain region. The most common species were *Gentian*, *Swertia*, and *Lomatoaonium*. With more than 400 species, the *Gentiana* genus was the largest in the Gentianaceae family and was extensively distributed throughout the world's temperate alpine regions. There were 247 species in China, most of which were found in shrublands, alpine meadows, and marshes. Many species have been used medicinally for thousands of years and have a broad spectrum of pharmacological properties [68, 69]. However the yearly production of *G. macrophylla* started to decrease in the 1950s and 1960s. As a result, *G. macrophylla* was now mostly grown in the Qinling area in Shanxi Province, where artificial cultivation has been done [18].

Gentian plants generally contain iridoid and schizocyclic iridoid components and derivatives. These components were one of the main chemical components of *Gentian* plants, and also the characteristic chemical components of *Gentian* plants, and were of great significance in chemical taxonomy. *Gentiana manshurica*, *G. macrophylla*, *Gentiana rhodantha*, *Gentiana rigescens* Franch., *Gentiana scabra*, *Gentiana* contain gentiamarin, swertiamarin and other components, and these two components were also the main pharmacological active components of *Gentiana* plants. In addition to the above components, some straight chain and branched chain saturated aliphatic hydrocarbons, alkyl benzene and terpene volatile oils were isolated from *Gentiana lutea*, and *Gentiana punctata*. *G. macrophylla* was a kind of medicine with great value. The substantial therapeutic value of *G. macrophylla* has been shown in numerous studies to date; nevertheless, additional study is required to prove its potential medical usage. The roots of *G. macrophylla* were mostly utilized in traditional Chinese medicine, but the blooms were also frequently used in Mongolian medicine. The chemical components of *G. macrophylla* are still largely unexplored in current research. Further research is required to examine the additional chemical components of *G. macrophylla* because, in addition to the ones that have been found, we have just scratched the surface of what this organism is capable of *G. macrophylla* had a lot of bioactive components. The fact that the alkaloids in *G. macrophylla* were produced from iridoid, which was distinct from other *Gentian* plants, and possesses terpenoid characteristics warrants particular consideration. Iridoid terpenoid components represented by gentiopicroside and Loganic acid were the main components of the root of *G. macrophylla*, which have anti-inflammatory, antioxidant, hepatoprotective, analgesic, antibacterial and promote gastrointestinal tract activities. The flower mainly contains isoorientin and isovitexin as the representatives of flavonoids., which have anti-tumor, liver protection, heart protection, inhibition of acetylcholinesterase and inhibition of melanin. At present, the activity studies of *G. macrophylla* mainly focus on iridoid components, in addition to a few studies of flavonoids and triterpenoids. If we want to study *G. macrophylla* more deeply and want to find more value, we need to study flavonoids in addition to studying iridoid components. Because its content is the largest in *G. macrophylla* except for iridoid components, and some research results show that flavonoids have a variety of activities, which has scientific research value. The flavonoids were concentrated in flowers. If you want to study these components, then flowers of *G. macrophylla* was an essential research medicine.

The active components of *G. macrophylla* have progressively come to light through the application of contemporary scientific research techniques to the study of traditional Chinese medicine. Following the identification of novel pharmacological effects of *G. macrophylla*, including anti-tumor properties, the potential for its clinical application appears to be extensive, but further clarification is required about the pharmacodynamic evaluation, action targets, route mechanisms, and other pharmacological effects of this plant. Furthermore, research on this aspect is currently lacking and it is unclear how *G. macrophylla*'s pharmacological effect relates to its underlying material base. There were several fake *G. macrophylla* as

the market for therapeutic products expanded. It was worthwhile to research quality control to ensure the calibre of pharmaceutical supplies. The lack of research in this field makes quality control an especially challenging issue. A broad approach to quality control is necessary the identification of a single active ingredient was not a reliable predictor of overall efficacy. Flavonoids are concentrated in *G. macrophylla*, so they may be the main quality control components in *G. macrophylla*. With the development of society and the progress of technology, the deeper pharmacodynamic material basis of *G. macrophylla* and the mechanism of action of disease prevention and treatment will be continuously clarified and discovered. It is believed that through multi-dimensional and deeper research, people's understanding of all aspects of *G. macrophylla* will continue to improve.

Conclusions

It is worth noting that this study is the first systematic review of *G. macrophylla*. *G. macrophylla*, as a precious medicinal material, was widely used in different ethnic medicines, and its clinical effect was good. As the research on *G. macrophylla* has received more and more attention, this article reviews the basic source, traditional use, chemical components, pharmacological activities, and quality control of *G. macrophylla*, to provide a reliable basis for future research and development.

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