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Traditional uses, phytochemistry, pharmacology and toxicology of *Lamiophlomis rotata* (Benth.) Kudo: a review

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Lamiophlomis rotata (Benth.) Kudo is a herbaceous plant of the family Lamiaceae, subfamily Lamioideae. Approximately, 127 chemical constituents have been isolated and identified from *L. rotata*, including iridoids, flavonoids, phenylethanoid glycosides, polysaccharides, and organic acids. These chemical constituents have extensive pharmacological properties, which include anti-nociceptive, haemostatic, anti-inflammatory, anti-tumour, immunomodulatory, antioxidant, and cardio-protective activities. Documentation of its historical use in traditional medicine and contemporary phytochemical and pharmacological research indicate that *L. rotata* has significant potential in therapeutic and health care applications. Both whole extracts and individual chemical components isolated from this plant exhibit a wide range of biological activities that warrant further investigation. These investigations can be assisted by careful review of existing traditional knowledge from diverse cultural backgrounds. A new search for chemical and biological markers and reinforced protection of the germplasm resources of *L. rotata* are also important to ensure targeted and sustainable use of this medicinal resource. The aim of this review was to provide comprehensive information on the botanical characteristics, traditional uses, ethnopharmacology, chemical and pharmacological properties, toxicity profile, and conservation status of *L. rotata*, to improve understanding of its mechanisms of action so that novel therapeutic agents may be developed from this plant.

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1. Introduction

Lamiophlomis rotata (Benth.) Kudo is a herbaceous plant in the family Lamiaceae, subfamily Lamioideae.[1] *Lamiophlomis* is a monotypic genus, represented by *L. rotata*. There are significant differences in the chemical constituents in plants between the genera *Lamiophlomis* and *Phlomis*, therefore, the genus *Lamiophlomis*, which was originally assigned to the genus *Phlomis*, was later re-assigned.[2] The formal Chinese name of *L. rotata* is Duyiwei (独一味), or Dubutong (独步通) in Chinese dialect.[3,4] *L. rotata* is also known as Daba, Gaguola or Dabuba in Tibetan folk medicine,[4] and as Dabage or Dagama in traditional Mongolian medicine. This herb has been widely used as a traditional Tibetan medicine, traditional Mongolian medicine, and traditional Chinese medicine for thousands of years.[3] It is well known for treating traumatic injury, traumatic haemorrhage and rheumatic arthralgia, as well as diabetes resulting from haemostatic imbalances. The phytochemical and pharmacological studies of the genus *Lamiophlomis* have drawn much attention since 1987. Thus far, the compounds isolated from *L. rotata* have included iridoids, flavonoids, phenylethanoid glycosides, polysaccharides, and organic acids. Modern pharmacological studies have demonstrated that these compounds possess anti-nociceptive, haemostatic, anti-inflammatory, anti-tumour, immunomodulatory, cardio-protective, anti-bacterial, antioxidant, anti-fatigue, anti-ulcer, and memory-boosting activities.[5–11]

The aim of the review was to provide comprehensive information on the botanical characteristics, distribution, traditional uses, ethnopharmacology, chemical constituents, pharmacological activities, and toxicity profile of *L. rotata*,

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gained from both historical and recent publications. It is hoped that this compiled body of knowledge will provide a strong foundation for further studies on the mechanisms of action of this medicinal plant, and guide the development of novel therapeutic agents.

2. Botanical characterisation and distribution

L. rotata is a perennial herbaceous plant which is erect, with horizontally thickened rhizomes, that grows to 2.5–10 cm in height and 0.5–1.1 cm wide. Its leaves are diamond-shaped and decussate, and they grow up to 6–13 cm long and 7–12 cm wide. The leaf apex can be obtuse, rounded or acute. The leaves have crenate leaf margins. The cymes are densely arranged in a short-scabbed head shape or spike-like inflorescences of 3.5–7 cm in length. The bracts are lanceolate, oblanceolate or linear, and grow to 1–4 cm long and 1.5–6 mm wide. The calyx is tubular, approximately 10 mm in length and 2.5 mm in width, and is pubescent along the external veins. The corolla is tube-shaped and about 1.2 cm long; puberulent on the outside and more densely puberulent within the middle of the tube. The flowering-fruiting season (in the northern hemisphere) for *L. rotata* is from June to September. The representative pictures of *L. rotata* are shown in Fig. 1.

Fig. 1 *L. rotata* from *Jingzhubencao* (Qing Dynasty, AD 1848) (A), the aerial parts of *L. rotata* (B), and *Lamiophlomis* herba (C).

L. rotata is mainly distributed in China, Nepal, Sikkim and Bhutan, where they grow wild on the meadows or hills, at 2700 to 4500 metres above sea level.[1] In China, *L. rotata* is mainly found in the western regions such as Gansu, Qinghai, Sichuan, Yunnan, and the Tibet provinces/autonomous regions. Among them, Tibet and the Maqu county of Gansu are the main growing areas of *L. rotata*, and it is here that high quality medicinal material is produced.[4]

3. Traditional uses and ethnopharmacology

L. rotata has been used in traditional Tibetan medicine for more than a thousand years, with significantly therapeutic effects described for traumatic injury, traumatic haemorrhage and rheumatic arthralgia, as well as for diabetes resulting from haemostatic imbalances. In traditional Tibetan medicine, *L. rotata* is described to exert its curative functions by promoting blood circulation, relieving swelling and pain, and removing blood stasis. The earliest record of *L. rotata* use in China appeared in the *Yuewangyaozhen* (AD 700), where it was used for marrow supplementation and yellow water after the oedema treatment.[4] Later, its use was recorded in famous medicinal writings, including the *Sibuyidian* (AD 765), where its functions, usage and compatibility with other medications were considered.[4] A detailed and systematic description of the ecological environment of *L. rotata* and its morphology was recorded in as early as 1848, in the *Jingzhubencao* (Qing Dynasty, AD 1848). In 1978, *L. rotata* was included in the local standards of Tibetan medicine in six provinces (Tibet, Qinghai, Sichuan, Gansu, Yunnan and Xinjiang). In 1995, the Ministry of Health included it in the Pharmaceutical Standards of the Ministry of Health of the People's Republic of China (volume 1).

In order to improve its clinical efficacy, *L. rotata* is also prescribed as a critical ingredient in combination with other

Table 1 Traditional medicine uses of *L. rotata* in China[a]

Preparation names	Compositions	Traditional and clinical uses	Origins
Duyiwei pian	*Lamiophlomis* herba 1000 g	Treatment of analgesia, fracture, hemostasis, sprain, rheumatism, arthralgia pain, metrorrhagia, dysmenorrhea, painful gum	*Chinese Pharmacopoeia* 2015
Duyiwei capsule	*Lamiophlomis* herba 1000 g	Treatment of analgesia, fracture, hemostasis, sprain, rheumatism, arthralgia pain, metrorrhagia, dysmenorrhea, painful gum	*Chinese Pharmacopoeia* 2015
Xiaotong plaster	*Lamiophlomis* herba, *Curcumae longae* rhizoma, *Bubalus bubalis* Linnaeus, *etc*	Treatment of sprain, hyperosteogeny, periarthritis, strain of lumbar muscles	*Chinese Pharmacopoeia* 2015
Dabage plaster	*Lamiophlomis* herba, *Salviae miltiorrhizae* Radix et Rhizoma, and *Pyrrosiae folium*, *etc.*	Treatment of traumatic injury	*Mongolian pharmacy*[17]
Wuyang powder	*Lamiophlomis* herba, Fel Ursi, *etc*	Treatment of traumatic injury. Detumescence, acesodyne	*Mongolian pharmacy*[17]

[a] All the names of crude drug in column are identified properly according to Chinese Pharmacopoeia 2015.

Chinese herbs such as *Curcuma longa*, *Salvia miltiorrhiza*, and *Pyrrosia lingua* (Table 1).

In traditional Chinese medicine, *L. rotata* has a long history of use in treating injuries from falls, muscle and bone pain, joint swelling and pain, dysmenorrhea, metrorrhagia.[4] For instance, it was recorded in the *Sichuanzhongyaozhi* that *L. rotata* had been used to treat injuries from falls, muscle pain, joint swelling and pain, dysmenorrhea, and metrorrhagia.[12] *Lamiophlomis* originates from the root, rhizome or whole herb of *L. rotata* (recorded in the *Zhonghuabencao*[13]). Its early collection for use as a traditional Chinese medicine is documented in the *Chinese Pharmacopoeia* (2000). Since then, *L. rotata* has also been recorded to have significant therapeutic effects in traumatic injury, traumatic haemorrhage and rheumatic arthralgia in the *Chinese Pharmacopoeia* (2015).[14] Generally, *L. rotata* is used directly in the clinic without any prior processing, and commonly for pain relief. However, processing the herb in vinegar and wine may increasing its flavonoid content and enhance its analgesic effects.[15,16]

In traditional Mongolian medicine, there are only a few records of *L. rotata* usage, where *L. rotata* was described to remedy analgesia, detumescence, traumatic injury, and promote wound healing and porosis in a process known as removing "*Huangshui*".[17]

4. Phytochemistry

Phytochemical investigations of *L. rotata* have led to the isolation of 127 compounds, including iridoids, flavonoids, phenylpropanoid glucosides, polysaccharides, and organic acids.[27,34,42] These structures are shown in Fig. 2–10.

4.1 Iridoids

The main compounds isolated from the aerial regions and rhizomes of *L. rotata* are iridoids (Table 2). To date, 47 iridoids have been isolated. Li *et al.* showed that the main substance responsible for the analgesic effect of *L. rotata* was iridoid glycosides.[18–20] The simple compounds 8-*O*-acetyl shanzhiside methyl ester (**1**), shanzhiside methyl ester (**2**), loganin (**23**), and phloyoside II (**38**) were detected in total iridoid glycosides, and could significantly inhibit foot pain and swelling caused by acetic acid. Yi *et al.*[21] isolated an additional four iridoid glycosides from an *n*-butanol extract from the rhizomes of *L. rotata* in 1997, and identified these as 8-*O*-acetyl shanzhiside methyl ester (**1**), 6-*O*-acetyl shanzhiside methylester (**4**), penstemoside (**5**), and 7,8-dehydropenstemoside (**35**) by spectral analysis and chemical methods. A further ten iridoid glycosides components were identified by four independent groups in ethanol extracts of *L. rotata*. These include sesamoside (**3**), 6′-*O*-β-D-glucopyranosylphlorigidoside C (**8**), 6′-*O*-α-D-galactopyranosylphlorigidoside C (**9**), 6′-*O*-β-D-glucopyranosylsesamoside (**10**), 6′-*O*-α-D-galactopyranosylsesamoside (**11**), phlorigidoside C (**12**), 6′-*O*-β-D-glucopyranosylbarlerin (**13**), 6′-*O*-α-D-galactopyranosylbarlerin (**14**), 6′-*O*-α-D-galactopyranosylshanzhiside methyl ester (**15**), and shanzhisin methyl ester gentiobioside (**16**).[27,28,34,41] More recently, in 2018, Zhang *et al.*[24] isolated three new iridoid glycosides from *L. rotata*, namely, barlerin-6″-hydroxy-2″,6″-dimethylocta-2″,7″-dienate ester (**27**), 7-dehydroxy-zaluzioside (**33**), and 6β-*n*-butoxy-7,8-dehydropenstemonoside (**34**). Their structures were characterised by high-resolution mass spectrometry, and one-dimensional and two-dimensional nuclear magnetic resonance (NMR) spectroscopy. It was found that 6β-*n*-butoxy-7,8-dehydropenstemonoside (**34**) and 8-*epi*-7-deoxy-loganin (**25**), and 7,8-dehydropenstemonoside (**36**) significantly inhibited NF-κB activation upon lipopolysaccharide stimulation.[22,23] In 1990, Yi *et al.*[25] separated lamiophlomiol A (**39**) and lamiophlomiol B (**6**) from the ethanol extracts from the rhizomes of *L. rotata*. This was followed by identification of lamiophlomiol C (**7**) in 1992.[26] The structures of the three lamiophlomiols are similar. They all have epoxy structures at the C-7 and C-8 sites of the iridoid skeleton. Lamiophlomiol A (**39**) and lamiophlomiol B (**6**) are isomeric and cannot be completely separated but their structures were confirmed by spectroscopy and chemical

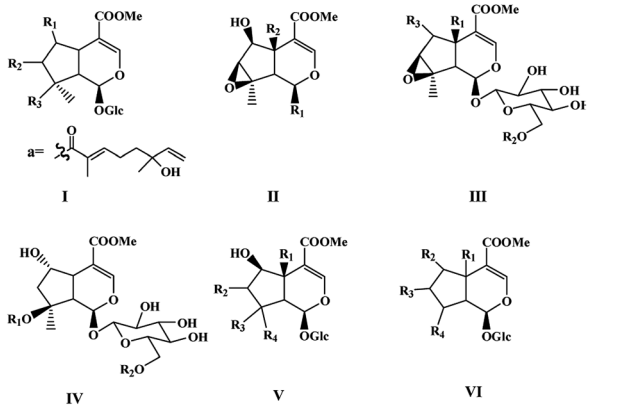

Fig. 2 The skeletal structures of iridoids from *L. rotata*.

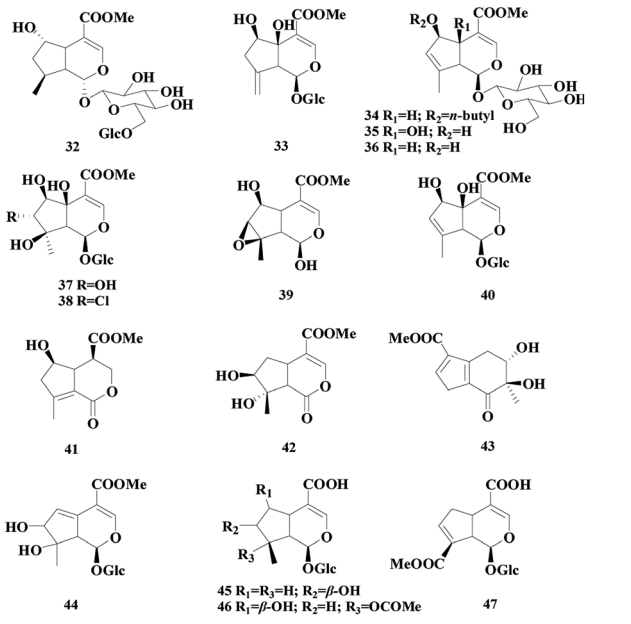

Fig. 3 The structures of compounds **32**–**47** from *L. rotata*.

Table 2 Iridoids isolated from *L. rotata* (1–31)

No.	Name	Skeletons	R_1	R_2	R_3	R_4
1	8-*O*-Acetyl shanzhiside methyl ester	**I**	OH	H	OCOMe	—
2	Shanzhiside methyl ester	**I**	OCOMe	H	OH	—
3	Sesamoside	**II**	OGlc	OH	—	—
4	6-*O*-Acetyl shanzhiside methyl ester	**I**	OH	H	OH	—
5	Penstemoside	**VI**	α-OH	α-OH	H	β-Me
6	Lamiophlomiol B	**II**	H	OH	—	—
7	Lamiophlomiol C	**II**	OH	OH	—	—
8	6′-*O*-β-D-Glucopyranosylphlorigidoside C	**III**	H	β-D-Glc	α-OH	—
9	6′-*O*-α-D-Galactopyranosylphlorigidoside C	**III**	H	α-D-Gal	α-OH	—
10	6′-*O*-β-D-Glucopyranosylsesamoside	**III**	OH	β-D-Glc	α-OH	—
11	6′-*O*-α-D-Galactopyranosylsesamoside	**III**	OH	α-D-Gal	α-OH	—
12	Phlorigidoside C	**III**	H	H	α-OH	—
13	6′-*O*-β-D-Glucopyranosylbarlerin	**IV**	Ac	β-D-Glc	—	—
14	6′-*O*-α-D-galactopyranosylbarlerin	**IV**	Ac	α-D-Gal	—	—
15	6′-*O*-α-D-Galactopyranosylshanzhiside methyl ester	**IV**	H	α-D-Gal	—	—
16	Shanzhisin methyl ester gentiobioside	**IV**	OH	β-D-Glc	—	—
17	6′-*O*-Syringyl-deoxysesamoside	**III**	H	Syringyl	β-OH	—
18	5-Deoxysesamoside	**III**	H	H	β-OH	—
19	Phlomiol	**V**	OH	β-OH	α-Me	β-OH
20	Lamalbid	**V**	H	β-OH	α-Me	β-OH
21	Schismoside	**V**	H	β-OH	α-OH	β-Me
22	Chlorotuberoside	**V**	H	α-Cl	α-Me	β-OH
23	Loganin	**VI**	H	H	β-OH	β-Me
24	7-*epi*-Loganin	**VI**	H	H	α-OH	β-Me
25	8-*epi*-7-Deoxyloganin	**VI**	H	H	H	α-Me
26	5-Hydroxy-loganin	**VI**	OH	H	β-OH	β-Me
27	Barlerin-6″-hydroxy-2″,6″-dimethylocta-2″,7″-dienate ester	**I**	*O*-a	H	Acetyl	—
28	6-*O*-Syingyl-barlerin	**I**	*O*-Syingyl	H	Acetyl	—
29	5-Deoxypulchelloside I	**VI**	H	α-OH	α-OH	β-Me
30	5-Desoxylamiide	**I**	H	β-OH	β-OH	—
31	Deoxypulchelloside I	**I**	β-OH	β-OH	H	—

analysis. Twelve compounds 6′-*O*-syringyl-deoxysesamoside (**17**), 5-deoxysesamoside (**18**), phlomiol (**19**), lamalbid (**20**), schismoside (**21**), chlorotuberoside (**22**), 7-*epi*-loganin (**24**), 5-hydroxy-loganin (**26**), 6-*O*-syingyl-barlerin (**28**), 5-deoxypulchelloside I (**29**), 5-desoxylamiide (**30**), and deoxypulchelloside I (**31**) have also been identified in *L. rotata*.[22–24] Ethanol extracts from the rhizomes of *L. rotata* have also been shown to contain 6α-dihydrocornic methyl ester-6′-*O*-β-D-glucopyranoside (**32**) and 7,8-dehydropenstemoside (**35**),[22,23] as well as phloyoside I (**37**), phloyoside II (**38**), 7,8-dehydropenstemoside (**40**), and gentioside (**44**). In 2015, researchers focusing on the aerial region of *L. rotata* by silica gel, MCI chromatography and gel chromatography, preparative thin layer chromatography, preparative high-performance liquid chromatography and recrystallisation, further identified lamiophlomiol D (**41**), lamiophlomiol E (**42**), and lamiophlomiol F (**43**). Loganic acid (**45**), 8-*O*-acetylshanzhiside (**46**), 10-methylixoside (**47**) from *L. rotata* and confirmed these structures by ^{1}H-NMR and ^{13}C-NMR spectral data.[24–30]

Among the iridoids, 8-*O*-acetyl shanzhiside methylester (**1**), shanzhiside methyl ester (**2**) and 6-*O*-acetyl shanzhiside methyl

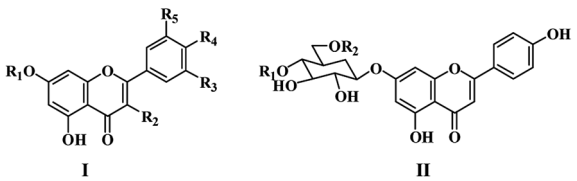

Fig. 4 The skelectal structures of flavonoids from *L. rotata*.

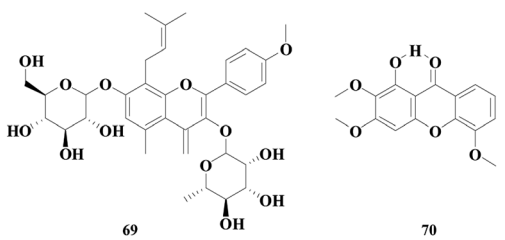

Fig. 5 The structures of compounds **69**–**70** from *L. rotata*.

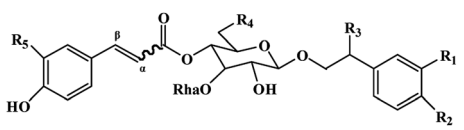

Fig. 6 The skeletal structures of phenylethanoid glycosides from *L. rotata*.

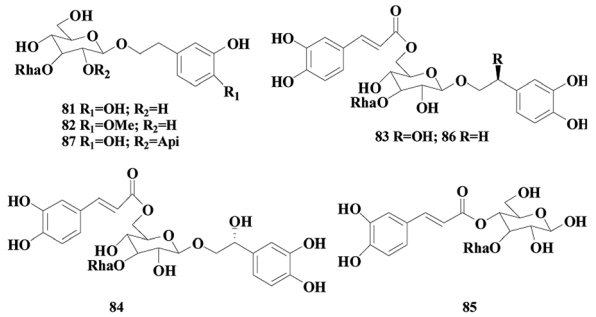

Fig. 7 The structures of compounds 81–87 from *L. rotata*.

ester (**4**) were detected at higher concentrations compared to the other components in *L. rotata*. Both shanzhiside methyl ester and 8-*O*-acetyl shanzhiside methyl ester have been used as a quality control indicators of *L. rotata* content in the *Pharmacopoeia of P. R. China* (2015).[3]

4.2 Flavonoids

The flavonoids can be classified by their skeletal structures into apigenin, luteolin and quercetin [**2**] (Fig. 4). Through silica gel column and polyamide column chromatography, followed by the hydrochloric acid-magnesium powder reaction test and spectral data analyses, Zhang *et al.* identified five flavonoids in ethanol extracts from the aerial regions of *L. rotata*, namely, luteolin (**48**), luteolin-7-*O*-glucoside (**49**), quercetin (**50**), quercetin-3-*O*-glucoside (**51**), and apigenin-7-*O*-neohesperidoside (**52**).[31] Three flavonoid glycosides, luteolin-7-*O*-β-D-glucopyranoside (**53**), apigenin-7-*O*-β-D-glucopyranoside (**54**), and luteolin-7-*O*-(6″-*O*-β-D-apiofuranosyl)-β-D-glucopyranoside (**55**) have also been identified in *n*-butanol extracts of *L. rotata*, and this is the first report of the isolation of this family of compounds from *L. rotata*.[32]

A further seven flavonoids have been isolated and identified from the 70% ethanol extracts of *L. rotata*, including apigenin-7-*O*-β-D-(6″-*p*-coumaroyl)-glucopyranoside (**56**) apigenin (**57**), apigenin-7-*O*-(6″-*O*-β-D-apiofuranosyl)-β-D-glucopyranoside (**58**), 4′-(*p*-carbonylphenyl)-luteolin (**59**), luteolin-7-*O*-β-D-(6″-*O*-acetyl)-glucopyranoside (**60**), apigenin-7-*O*-β-D-(6″-*O*-*p*-*E*-coumaroyl)-glucopyranoside (**61**), and apigenin-7-*O*-β-D-(4″,6″-di-*O*-*p*-*E*-coumaroyl)-glucopyranoside (**62**).[33]

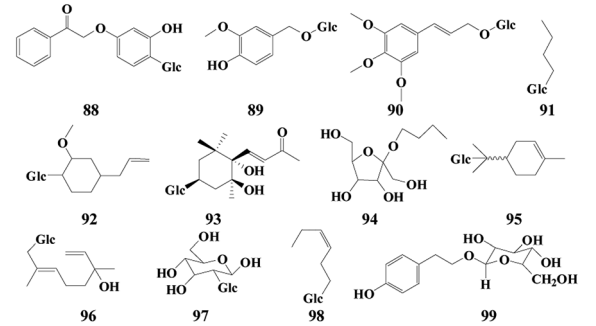

Fig. 8 The structures of compounds 88–99 from *L. rotata*.

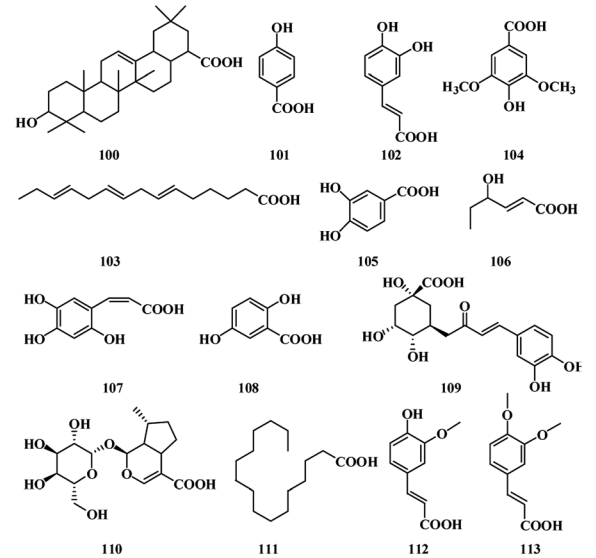

Fig. 9 The structures of compounds 100–113 from *L. rotata*.

Among these flavonoids, apigenin-7-*O*-β-D-glucopyranoside, luteolin-7-*O*-β-D-glucopyranoside and luteolin-7-*O*-(6″-*O*-β-D-apiofuranosyl)-β-D-glucopyranoside were found in higher concentrations compared to the other components.[34] Using high performance liquid chromatography-electrospray/quadrupole time-of-flight tandem mass spectrometry (UPLC-ESI-TOF MS) identified rutin (**63**) in *L. rotata*.[35]

In 2008, Li *et al.*[36] studied the chemical constituents of ethanol extracts from the aerial regions of *L. rotata*, and confirmed the structure of the following flavonoids by chemical and spectral methods (Table 3): luteolin (**48**), apigenin-7-*O*-(6″-(*E*)-*p*-coumaroyl)-β-D-galactopyranoside (**64**), tricin (**65**), acacetin (**66**), and genkwanin (**67**). Luteolin (**48**) and tricin (**65**) profoundly inhibit the release of nitric oxide (NO) by murine macrophages, which may account for the anti-inflammatory activity of *L. rotata*. Finally, isorhamnetin (**68**) and icariin (**69**) were identified in the ethanol extract of *L. rotata* in 2008 whilst

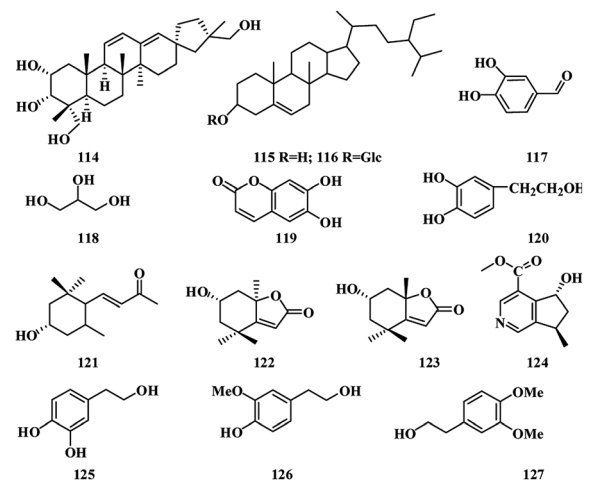

Fig. 10 The structures of compounds 114–127 from *L. rotata*.

Table 3 Flavonoids isolated from *L. rotata* (**48–68**)

No.	Name	Skeletons	R_1	R_2	R_3	R_4	R_5
48	Luteolin	**I**	H	H	H	OH	H
49	Luteolin 7-*O*-glucoside	**I**	H	H	OGlc	OH	H
50	Quercetin	**I**	H	OH	OH	OH	H
51	Quercetin-3-*O*-glucoside	**I**	H	OGlc	OH	OH	H
52	Apigenin-7-*O*-neohesperidoside	**I**	Neohesp	H	H	OH	H
53	Luteolin-7-*O*-β-D-glucopyranoside	**I**	Glc	H	OH	OH	H
54	Apigenin-7-*O*-β-D-glucopyranoside	**I**	Glc	H	H	OH	H
55	Luteolin-7-*O*-(6″-*O*-β-D-apiofuranosyl)- β-D-glucopyranoside	**I**	Api–Glc	H	OH	OH	H
56	Apigenin-7-*O*-β-D-(-6″-*p*-coumaroyl)-glucopyranoside	**II**	H	*p*-Coumaroyl	—	—	—
57	Apigenin	**I**	H	H	H	OH	H
58	Apigenin-7-*O*-(6″-*O*-β-D-apiofuranosyl)-β-D-glucopyranoside	**I**	Glc–Api	H	H	OH	H
59	4′-(*p*-Carbonylphenyl)-luteolin	**I**	H	H	*O*-*p*-Carbonylphenyl	OH	H
60	Luteolin-7-*O*-β-D-(6″-*O*-acetyl)-glucopyranoside	**I**	Acetyl-Glc	H	OH	OH	H
61	Apigenin-7-*O*-β-D-(6″-*O*-*p*-*E*- coumaroyl)-glucopyranoside	**II**	H	*p*-*E*-Coumaroyl	—	—	—
62	Apigenin-7-*O*-β-D-(4″,6″-di-*O*-*p*-*E*-coumaroyl)-glucopyranoside	**II**	*p*-*E*-Coumaroyl	*p*-*E*-Coumaroyl	—	—	—
63	Rutin	**I**	H	Rha–Glc	OH	OH	H
64	Apigenin7-*O*-(6″-(*E*)-*p*-coumaroyl)-β-D-galactopyranoside	**I**	Gal	H	*p*-Coumaroyl	OH	H
65	Tricin	**I**	H	H	OMe	OH	OMe
66	Acacetin	**I**	H	H	H	OMe	H
67	Genkwanin	**I**	Me	H	H	OH	H
68	Isorhamnetin	**I**	H	OH	OMe	OH	H

1-hydroxy-2,3,5-trimethoxyxanthone (**70**) was identified in the polyethylene-soluble fraction of the ethanol extract.[37]

4.3 Phenylethanoid glycosides

Seventeen phenylethanoid glycosides (**71-87**) have been isolated and identified from *L. rotata* (Table 4). Lamiophlomioside A (**72**), cistanoside C (**73**), 6′-β-D-apiofuranosyl cistanoside C (**74**), and *cis*-lamiophlomiside A (**75**) were identified in the *n*-buthanol extracts of both the rhizomes and aerial regions of *L. rotata*.[32,34–40] Leucosceptoside B (**71**), alyssonoside (**79**), and isoverbascoside (**86**) were isolated and purified from *L. rotata* by high-speed counter-current chromatography combined with macroporous resin (MR) column separation. Wang *et al.*[32] used electrospray mass spectrometry (ESI-MS), ^{1}H-NMR, ^{13}C-NMR and other modern spectroscopy methods to isolate and identify three phenylethanol glycosides in the *n*-butanol extract from the rhizomes and aerial region of *L. rotata*, namely, forsythoside B (**76**), betonyosides A (**77**), and verbascoside (**78**).

A further six phenylethanoid glycosides have been isolated and identified in the 70% ethanol extracts of *L. rotata* by spectral analyses, including *via* UV, IR, MS, ^{1}H-NMR, ^{13}C-NMR and 2D-NMR. These include campneoside II (**80**), decaffeoylverbascoside (**81**), cistanoside E (**82**), betonyoside B (**83**), betonyoside C (**84**), and cistanoside F (**85**).[34] Most recently, Pan *et al.*[29] isolated and purified 50% ethanol extracts from *L. rotata* by silica gel, Ozone-Depleting Substances (ODS), and sephadex LH-20, and isolated markhamioside A (**87**) from *L. rotata* for the first time in 2018.

4.4 Polysaccharides

The eleven main polysaccharides identified in *L. rotata* include salviifoside A (**88**), vanillyl-*O*-β-D-glucopyranside (**89**), icariside H1 (**90**), *n*-butyl-β-D-fructopyranoside (**91**), eugenyl-*O*-β-D-

Table 4 Phenylethanoid glycosides isolated from *L. rotata* (**71–80**)

No.	Name	R_1	R_2	R_3	R_4	R_5	αβ moiety
71	Leucosceptoside B	OH	OMe	H	OApi	OMe	*E*
72	Lamiophlomioside A	OMe	OH	H	OApi	OMe	*E*
73	Cistanoside C	OMe	OH	H	OH	OH	*E*
74	6′-β-D-Apiofuranosyl cistanoside C	OMe	OH	H	OApi	OH	*E*
75	*cis*-Lamiophlomiside A	OMe	OH	H	OApi	OMe	*Z*
76	Forsythoside B	OH	OH	H	OApi	OH	*E*
77	Betonyosides A	OH	OH	OH	OH	OMe	*E*
78	Verbascoside	OH	OH	H	OH	OH	*E*
79	Alyssonoside	OH	OH	H	OApi	OMe	*E*
80	Campneoside II	OH	OH	OH	OH	OH	*E*

glucopyranoside (**92**), 5β,6α-dihydroxy-3β-(β-D-glucoyranosyloxy)-7-megastigmen-9-one (**93**), *n*-butyl-β-D-fructofuranoside (**94**), (±)-α-terpineol-8-*O*-β-D-glucopyranoside (**95**), (2*Z*)-2,6-dimethyl-6-hydroxyocta-2,7-dienyl-*O*-β-D-glucopyranoside (**96**), β-D-glucopyranoside-(2→1)-β-D-glucopyranoside (**97**), and (*Z*)-3-hexenyl glucopyranoside (**98**). These were identified by UV, infrared, MS, ^{1}H-NMR, ^{13}C-NMR, 2D-NMR and other spectral analysis techniques in ethanol extracts of the aerial regions of *L. rotata*.[34] Mei *et al.*[42] used silica gel, MCI chromatography, and preparative HPLC to study extracts from the aerial regions of *L. rotata* and by analysing the physical and chemical properties and spectral data, isolated salidroside (**99**) for the first time in 2014. This compound is likely to contribute to the anti-fatigue and anti-oxidative damage properties of *L. rotata*.[30,42]

4.5 Organic acids

Fourteen organic acids (**100–113**) have been isolated and identified from *L. rotata*. Zhang *et al.*[34] isolated and identified the first four organic acid compounds from the aerial regions of *L. rotata*, namely, oleanolic acid (**100**), 4-hydroxybenzoic acid (**101**), caffeic acid (**102**), and (7*E*,10*E*,13*E*)-hexadeca-7,10,13-trienoic acid (**103**). Zhang *et al.*[33] studied the chemical constituents in the ethanol fraction of *L. rotata*, and according to their physical and chemical properties and spectral data analyses, identified syringic acid (**104**) and 3,4-dihydroxybenzoic acid (**105**) in 2011. Mei *et al.*[42] isolated three additional organic acid compounds from the ethanol fraction of *L. rotata*, namely, (*E*)-4-hydroxyhex-2-enoic acid (**106**), *cis*-2,4,5-trihydroxycinnamic acid (**107**), and 2,5-dihydroxy-benzoic acid (**108**). In 2018, Zan *et al.*[35] identified chlorogenic acid (**109**) from *L. rotata* by using high performance liquid chromatography-electrospray/quadrupole time-of-flight tandem mass spectrometry (UPLC-ESI-TOF MS). It was the first time 8-epideoxyloganic acid (**110**) was obtained from the ethanol extract of *L. rotata* by Hao Y, in 2011.[43] According to published pharmacological research, both the low and high doses of 8-epideoxyloganic acid have significant analgesic and haemostatic activities, while high doses of 8-epideoxyloganic acid have anti-inflammatory properties.[43] Finally, *n*-hexadecanoic acid (**111**) was isolated and identified in the 50% ethanol extract from *L. rotata*[29,61] and fumalic acid (**112**) and 3,4-dimethoxycinnamic acid (**113**) were simultaneously identified by high-performance liquid chromatography in 2013.[44]

4.6 Other compounds

Additional compounds that do not fall into the categories described in the sections above that have been identified by MS, ^{1}H-NMR, ^{13}C-NMR, 2D-NMR and other spectral analysis techniques in *L. rotata* are notohamosin B (**114**), β-sitosterol (**115**), β-daucosterol (**116**), 3,4-dihydroxybenzaldehyde (**117**), and glycerol glycerin (**118**).[34] 6,7-dihydroxycoumarin (119) was identified by ESI-MS and ^{1}H-NMR from the rhizomes of *L. rotata* for the first time in 2011.[33] In 2015, Yin *et al.*[30] used silica gel, macroporous resin, MCI chromatography, preparative HPLC, recrystallisation and other methods to separate compounds from *L. Rotata* based on their spectral data and physicochemical properties, and identified five compounds, namely, 3,4-dihydroxyphenylethanol (120), 3β-hydroxy-5α, 6α-epoxy-7-megastigmen-9-one (**121**), loliolide (**122**), isololiolide (**123**), and rhexifoline (**124**). Finally, hydroxytyrosol (**125**), homovanillyl alcohol (**126**), and 3,4-dimethoxyphenethyl alcohol (**127**) were simultaneously identified by high-performance liquid chromatography in *L. rotata* in 2013.[44]

5. Pharmacological activities

5.1 Anti-nociceptive activity

The analgesic activity of a purified, water-soluble *L. rotata* extract was studied in several pain models in rat and mice, including formalin-induced pain (phase I acute pain and phase II centrally-sensitised pain), neurogenic pain caused by spinal nerve ligation, and pain caused by bone cancer. The analgesic effects of cycloalliterpenes extracts and cycloalliterpenes monomers with different flavonoid content were investigated after formalin-induced pain in mice. Gardenioside methyl and 8-*O*-acetyl gardenioside methyl were administered to the spinal cord to determine the analgesic site. Oral administration of the water-soluble extract inhibited the first phase of central pain caused by formalin, as well as the hyperalgesia caused by spinal nerve ligation and bone cancer pain in rats. The analgesic effect was dose-dependent, with a maximum inhibition rate of 82%, 50% and 54%, at the median effective dose of 133.7, 236.5 and 242.9 mg kg^{-1}, respectively. Continuous administration of the *L. rotata* extract for seven days did not produce analgesic tolerance in the neurogenic pain model in rats. The analgesic activity of cycloallyl ether terpene glycosides increased with its increasing concentrations within the extract, while high doses of flavonoids (1000 mg kg^{-1}) had no analgesic effect. Therefore, in the formalin-induced pain model in mice, the content of total cycloallyl iridoid glycosides in cycloallyl ether was positively correlated with the analgesic activity through pain. Further, administration of methylgeniocide and 8-*O*-acetyl methylgenioside to the spinal cord inhibited formalin-induced phase II pain in rats with a dose-dependent inhibition rate of 70–80%.

There have also been studies that provide evidence for an analgesic effect of iridoid glycosides from *L. rotata* (IGLR) in a spared nerve injury (SNI) model. The rat SNI model was established by transversely intact peroneal and distal branches of the sciatic nerve and intact sural branches. After nerve injury, the rats were treated with different concentrations of IGLR for 14 days, whilst normal saline was administered to the negative control group. Significant mechanical abnormalities and decreased paw withdrawal mechanical threshold (PMWT) scores were observed on the first day after SNI. IGLR treatment significantly reduced SNI-induced mechanical pain, and significantly reduced the levels of nitric oxide (NO), tumour necrosis factor-a (TNF-α), interleukin-1beta (IL-1β), nitric oxide synthase (NOS), and cyclic guanosine monophosphate (cGMP), whilst increasing levels of IL-10. IGLR also inhibited *N*-methyl-D-aspartate receptor (NMDAR) and protein kinase C (PKCγ) protein expression, and reduced inducible NOS (iNOS) and protein kinase G type I (PKGI) mRNA levels. These results suggest that IGLR produce anti-neuropathic pain effects by

partial inhibition of the NO/cGMP/PKG and NMDAR/PKC pathways and by altering the levels of cytokines in the spinal cord.[45]

5.2 Haemostatic activity

In traditional Chinese medicine, *L. rotata* has been widely been used and proven to have haemostatic effects. The aqueous extract of Herba *L. rotata* (HLRE) has an effect on several haemagglutination parameters, including prothrombin time (PT), thrombin time (TT), fibrinogen content (FIB) and activated partial thrombin time (APTT) when administered at different doses (high, 3 g kg^{-1} medium, 1.5 g kg^{-1} and low, 0.75 g kg^{-1}) for a duration of 7, 14, or 21 days to rats. After seven days and 14 days of administration, TT was significantly shortened ($p < 0.05$) and the FIB value significantly increased ($p < 0.05$) at all three doses of HLRE compared with controls. After 21 days of administration, TT in the high and middle HLRE dosage groups remained shorter than TT in the control group ($p < 0.05$), whereas only the high dose group sustained higher FIB values compared with the controls ($p < 0.05$). A negative and linear correlation between TT and FIB values were observed throughout the experiment ($p = 0.002$). Therefore, this study showed that a dose- and time-dependent haemostatic effect is present within the aqueous extract of *L. rotata* and this may be mediated through shortening TTs and increasing FIB content.[46]

In another study, Jia *et al.*[11] used a polyamide chromatographic column and a macroreticular resin column to purify ethanol extracts of *L. rotata*, and obtained flavones, total secoiridoid glycosides, and high-polarity compounds. Mice were administered with 2 g kg^{-1} of these purified compounds for three days before haemostatic effects were compared by a capillary coagulation test (after nicking the animals' tails). Compared with the control group that was administered physiological saline, the alcohol extract (2 g kg^{-1}) and the secoiridoid glycoside (2 g kg^{-1}, ig)-containing extract of *L. rotata* reduced the bleeding time after tail amputation by 37.4% and 49.3% respectively, and reduced the clotting time by 23.1% and 28.0%, respectively. All these fractions exhibited similar effects as the positive control drug, *Yunnan Baiyao*. In addition, the ethanol extract that contained iridoid glycosides in *L. rotata* had a haemostatic effect in mice after intra-gastric injection, leading researchers to conclude that fractions containing iridoid glycosides in *L. rotata* regulate blood haemostasis.

5.3 Anti-inflammatory activity

The anti-inflammatory effects of *L. rotata* injection (LRI) were studied in a model of granuloma formation and ear oedema in mice. To determine the anti-inflammatory activity of LRI *in vitro* and *in vivo*, the phagocytic function of macrophages was detected by phagocytosis of neutral red, and the production of IL-1 was detected by thymocyte co-stimulation. At the 0.45, 0.9, and 1.8 g kg^{-1} doses of LRI, dose-dependent inhibition of xylene-induced ear oedema was observed. At the 0.225 and 0.45 g kg^{-1} doses of LRI, protection from of cotton pellet-induced granuloma formation was 43.87–68.16% and 13.26–43.33%, respectively. Furthermore, LRI increased peritoneal macrophage phagocytosis and reduced lipopolysaccharide (LPS)-induce IL-1β production. This study showed that LRI has anti-inflammatory effects during both chronic and acute inflammation.[46]

The anti-inflammatory effects of *L. rotata* ointment have also been demonstrated in models of xylene-induced ear swelling, in acetic acid-induced abdominal capillary permeability, and during carrageenan- or adjuvant-induced foot swelling. Mice treated with 4.5, 3.0, and 1.5 g kg^{-1} of *L. rotata* ointment daily for five consecutive days had decreased capillary permeability in their abdominal cavity and reduced swelling reactions in their ears and feet, indicating marked anti-inflammatory effects of *L. rotata*. It is proposed that the anti-inflammatory effects are associated with inhibition of histamine synthesis and release, as well as the regulation of production of prostaglandins and other inflammatory mediators.[67]

The effect of *L. rotata* granules was investigated in a model of formaldehyde-induced persistent gingival inflammation in mice by M. Li in 2008.[48] After causing inflammation, *L. rotata* granules were administered continuously for 5 days at three doses (high, 1.0 g kg; middle, 2.0 g kg; and low, 4.0 g kg^{-1}), or were treated with 100 mg kg^{-1} of aspirin for 4 days, once a day. The daily food intake was recorded by measuring feed and cage weights, and the amount of food ingested before and after treatment was taken as an indicator of relief from gingival inflammation-induced pain. The intake of *L. rotata* granules in the high and middle dosage groups were higher than that in the model control group on days 4, 5 and 6 after induction of inflammation, indicating a dose-dependent effect of *L. rotata* granules on relieving persistent gingival inflammation.[48]

5.4 Anti-tumour activity

The alcohol extracts from *L. rotata* containing either ethereal oils, flavones, secoiridoid glycoside or high-polarity compounds were tested using an MTT (A method for detecting cell survival and growth) proliferation assay to explore the anti-tumour activities of these components. Five concentrations of the extract were prepared from an initial concentration of 25 mg mL^{-1} by performing dilutions in DMSO. The rate of proliferation inhibition by the different concentrations of each component was tested on SGC-7901 human gastric cancer cells, BEL-7402 liver cancer cells, and HL-60 leukaemia cells, and the corresponding hemi-inhibitory concentration (IC_{50}) values calculated by logarithmic linear regression. The IC_{50} values of ethereal oil on SGC-7901, BEL-7402 and HL-60 were 78.25 μg mL^{-1}, 113.25 μg mL^{-1} and 121.00 μg mL^{-1} respectively, which were lowest compared with IC_{50} values of the other components, and markedly lower than the IC_{50} values of total ethanol extracts. These results indicate a strong, dose-dependent inhibitory effect of ethereal oils on the proliferation of cancer cell lines *in vitro*, and that ethereal oil possessed more anti-tumour activity than the total ethanol extract or other components of *L. rotata*.[11]

The petroleum ether extract of *L. rotata* (PEELR) has also been shown to induce apoptosis in a concentration-dependent manner, which was quantified by flow cytometric detection of

early apoptotic cells staining positive for annexin V and propidium iodide. The PEELR significantly inhibited the colony formation ability of the Tca8113 cell line ($p < 0.05$) compared with the group that did not receive treatment. The PEELR also induced increased apoptosis ($p < 0.01$) and decreased the ratio of Bcl-2/Bax expression ($p < 0.01$) compared to controls. These results indicate that the anti-tumour activity of PEELR on the Tca8113 cell line occurs as a result of reduced proliferation and increased apoptosis regulated *via* the Bcl-2 pathway, and this anti-tumour effect warrants further clinical investigation.[49]

5.5 Immunomodulatory activity

Saponin from *L. rotata* was injected at a dose of 50 mg kg^{-1} and 10 mg kg^{-1} into the abdominal cavity for five consecutive days to test its effect on innate immunity, specifically, on its ability to affect the number of phagocytic cells and their phagocytic rate. Saponin from *L. rotata* markedly improved the phagocytosis rate, phagocytic count, erythrocyte active-rosetting rate, and the rates of positive acetylase staining of macrophages, indicating an enhancement of innate immune cell activity.[8]

L. rotata also has an effect on the immune responses of patients infected with *Mycobacterium tuberculosis*. Peripheral blood mononuclear cells (PBMC) (isolated by dextran-diatrizoine density gradient centrifugation) from 20 patients with pulmonary tuberculosis and from 15 healthy controls were stimulated for 72 h, after which culture supernatants were collected to quantify γ-interferon (IFN-γ) and IL-4 levels by enzyme-linked immunosorbent assay (ELISA). The addition of *L. rotata* to these cultures effectively promoted the secretion of IFN-γ by PBMC from both tuberculosis patients and healthy controls ($p < 0.05$) but there were no differences in IL-4 levels ($p > 0.05$). Therefore, *L. rotata* could play a protective immunological role in patients infected with *Mycobacterium tuberculosis* by regulating the balance of Th1/Th2 cytokines.[50]

5.6 Other effects

In addition to the above activities, *L. rotata* has also cardio-protective, anti-bacterial, antioxidant, anti-fatigue, anti-gastric ulcer, and memory-boosting activities.

5.6.1 Cardio-protective effects. Doses of *L. rotata* in the range of 0.01–2.0 mg mL^{-1} were found to inhibit cardio-contractility, cardiac output, and heart rate on isolated hearts. There was a dose-dependent effect on cardio-contractility with a maximal inhibitory effect of close to 36.4%. These inhibitory effects were partially antagonised by atropine. Therefore, compounds in *L. rotata* may be useful for controlling cardiac excitability and angina.[47]

5.6.2 Anti-bacterial properties. The bacteriostatic effect of *L. rotata* was compared to penicillin, gentamicin, kanamycin, and chloramphenicol, by measuring bacterial growth on filter paper. *L. rotata* was bacteriostatic for Group B *Streptococcus* and *Aerobacterium aerogenes*, reducing the average diameter of the bacteriostasis diagram to 0.8 cm and 0.6 cm, respectively. The average diameters of *L. rotata* saponin-treated bacteriostatic diagrams were 1.0 cm, 0.8 cm for *Pseudomonas aeruginosa*, 0.7 cm for *Aerobacterium*, 1.0 cm for *Bacillus subtilis*, and 1.2 cm for Group B Streptococcus, respectively. The leaf extracts of *L. rotata* could also inhibit the growth of *Bacillus gasoformans* and *Streptococcus haemolyticus*. Of note, the effect of saponin from *L. rotata* on restraint of *Bacillus gasoformans* growth was significant and similar to that achieved by regular antibacterial agents.[8]

5.6.3 Antioxidant properties. All the regions of *L. rotata* with described medicinal properties contained stable and high superoxide dismutase (SOD) activity, reaching 150.87 U g^{-1} in some cases, providing an excellent source of H_2O_2-detoxifying enzymes. In addition, a higher peroxidase (POD) activity of 236.76 μmol g^{-1}, whilst a higher efficiency of the Ascorbate–glutathione (AsA–GSH) cycle was achieved, leading to lower levels of Malondialdehyde (MDA) accumulation of 1.22 μmol g^{-1}. These results suggest that *L. rotata* may enhance resistance to cellular stress due to its high-efficiency antioxidant activities.[51]

5.6.4 Anti-fatigue properties. Mice that received an alcohol extract of *L. rotata* showed extended weight-loaded swimming times under standard temperature and pressure and hypoxia, when compared with mice that received saline ($p < 0.05$). Their performance was better than mice that received water-soluble extracts from the herb gingko tablet, but weaker than mice that received dihydrocortisone. The alcohol extract of *L. rotata* also extended the lives of mice to a similar extent achieved by dihydrocortisone ($p > 0.05$). These results demonstrate the anti-fatigue properties of *L. rotata*.[10]

5.6.5 Oral ulcers. In oral ulcer models, induced by either acetic acid in rats or by phenol in New Zealand rabbits, oral mucosal administration of *L. rotata* had anti-ulcer effects. The rates of ulcer healing in rats were 44.4% and 33.3% respectively after receiving high-dose (1.5 g kg^{-1}) and medium-dose (1.0 g kg^{-1}) *L. rotata* extracts for six days, which were significantly higher than rates observed in the control group that. The *L. rotata* extracts resolved inflammation and reduced swelling significantly, leading to healing of ulcers – these outcomes may be related to their ability to improve blood circulation in the oral mucosa.[52]

5.6.6 Anti-gastric ulcer. Rats with gastric ulcer treated with ranitidine or a water-soluble extract of *L. rotata* exhibited different responses compared to rats treated with normal saline ($p < 0.05$). The *L. rotata* extract exerted similar effects to ranitidine, namely, by reducing the acidity and volume of gastric juices to inhibit the rate of ulcer formation (to greater than 53.3%). These results indicate that *L. rotata* could protect the gastric mucosa by inhibiting both gastric juice and gastric acid production.[53]

5.6.7 Memory-boosting functions. The effects of *L. rotata* and piracetam on learning and memory were studied in a model where scopolamine and ethanol were used to cause impairments in learning, memory acquisition, and recall in mice. Both doses of *L. rotata* extracts (0.5 g kg^{-1} and 1.0 g kg^{-1}) and piracetam (0.2 g kg^{-1}) accelerated the response time to injury upon stimulation, significantly reduced the number of errors made by the mice, and shortened their response times upon receiving an electric shock ($p < 0.05$ compared with the model group). The efficacy of *L. rotata* and piracetam were similar ($p > 0.05$),

indicating that *L. rotata* could alleviate learning and memory impairment in mice.[54]

6. Toxicology

Despite its long history of use as a traditional Tibetan medicine, a traditional Mongolia medicine, and a traditional Chinese medicine, the potential toxicity of *L. rotata* has not been well addressed. *L. rotata* is listed for medicinal and normal consumption use, and whilst systematic evaluations of the plant's systemic toxicity and safety are lacking, no major side effects have yet been reported.

In a study where mice received 20 mL kg^{-1} of *L. rotata* extract by intravenous injection, they experienced convulsion, breathing difficulties and vomiting, and died within 1–2 minutes. However, at post mortem, no significant differences were found between the treated mice and mice that received saline ($p > 0.05$). The median lethal dose (LD_{50}) was established to be 711.0 mg kg^{-1} (equivalent to a crude drug concentration of 4.7 g kg^{-1}) in this study, with a confidence limit of 95% at 612.9–824.9 mg kg^{-1}. Of mice that received 18.0 g kg^{-1} for 14 days, only some showed symptoms of restricted movements, fast breathing, and somnolence after an hour but they did not die. There was an average weight increase of 35.7% in these mice, but no significant pathological changes were detected upon euthanasia. As the total gavaged dose would be equivalent to 102 multiple-doses in adults, these results indicate a low level of toxicity for *L. rotata*.[55] In a separate study, mice that received phenylethanoid glycosides from *L. rotata* (1.5 g kg^{-1} *via* intraperitoneal injection for 30 days) showed no damage in their hearts, lungs, thymi, testes, uterus, stomach or intestines, nor did they have abnormal appearances.[56] Finally, when iridoid glycosides capsule of *L. rotata* was tested for toxicity, diarrhoea and less spontaneous activity were found in mice that received the 172 mg kg^{-1} and 430 mg kg^{-1} doses, in a dose-dependent manner. These adverse reactions to *L. rotata* capsule require further investigation.[57]

7. Conservation status

L. rotata is a common herb that grows in the wild that is of important medicinal and economic value in traditional Tibetan medicine and traditional Chinese medicine. In addition to being administered as a single drug, *L rotata* is also prepared into various formulations, including granules, capsules, tablets, dispersible tablets, soft capsules, and dripping pills. With the increase in usage of *L rotata*, over-exploitation has led to significant reductions on the growth of *L. rotata* in the wild in Gansu, Qinghai and Sichuan, such that *L. rotata*, is now a class II-endangered and protected plant species in Tibet.[58] *Lamiophlomis* is the dried whole herb of *L. rotata*, as described in the *Chinese Pharmacopoeia* 2005.[14] However, due to the destruction of grasslands from collectors digging for the roots of *L. rotata*, in recent years, the digging of entire plants has been forbidden. In order to protect the ecological environment of the alpine grassland, *Lamiophlomis* is the dried parts of *L. rotata* in the *Chinese Pharmacopoeia* 2015.[3,59] In summary, wild resources of *L. rotata* have been severely degraded and whilst the ban on digging up *L. rotata* by the roots has been fully implemented, there are still no specific protection measures in place, and wild *L. rotata* resources faces significant pressure.

Therefore, there is an urgent need to establish the necessary protective measures for use and conservation of wild *L. rotata*. This could be achieved by strengthening the Legislation of Tibetan medicine on resource protection, and by raising awareness. Secondly, the search for alternative varieties with similar therapeutic effects could be encouraged. Finally, *L. rotata* could be conserved by wild tending – there is therefore an urgent need to establish a germplasm bank of Tibetan medicine to protect the germplasm resources.[60–64]

8. Conclusion and perspectives

Based on the analysis and evaluation of literature ranging from historical records to modern scientific publications, *L. rotata*, proves to be one of the most important and frequently used traditional Tibetan medicine and traditional Chinese medicine with an excellent safety record. Historically, *L. rotata* has been effectively used for treating traumatic injury, traumatic haemorrhage and rheumatic arthralgia; and also used to promote blood circulation, stop bleeding, dispel wind and relieve pain in clinical practice. As an ingredient, *L. rotata* is used in many health products including health drinks, soap, wine, mouth rinses, and biological toothpastes.[65–69]

Approximately 127 chemical constituents have been isolated and identified from *L. rotata*, including iridoids, flavonoids, phenylethanoid glycosides, polysaccharides, and organic acids. The crude extracts as well as individual compounds isolated from *L. rotata* show significant anti-nociceptive, haemostatic, anti-inflammatory, anti-tumour, immunomodulatory, cardio-protective, anti-bacterial, antioxidant, anti-fatigue, skin-protective, anti-gastric ulcer, and memory-boosting activities.[70–72] Modern phytochemical and pharmacological studies have provided insights into some of *L. rotata*'s mechanisms of action and demonstrated its potential for further development as an anti-tumour and anti-fatigue agent.

In conclusion, there are two important aspects to be considered in the further development and investigations of *L. rotata's* medicinal properties. The first is to search for chemical and biological markers from *L. rotata*, to guide research into its mechanisms of action, and to guide new drug discovery and quality assurance. For instance, in addition to its pharmacological and therapeutic properties, the marker compounds for quality control were changed from 'luteolin' to 'shanzhiside methyl ester and 8-*O*-acetyl shanzhiside ethyl ester', which were identified as major effective iridoid glycosides (IGs). IGs are pharmacologically active ingredients that can be used for quality control.[24] Currently, only shanzhiside methyl ester and 8-*O*-acetyl shanzhiside methylester have been selected as chemical markers for evaluating the quality of *L. rotata* in the Chinese Pharmacopoeia 2015.[3] There is therefore a need to develop more chemical and biological markers that better reflect the quality of *L. rotata* preparations.

The second consideration is the protection of germplasm resources and the sustainable use of *L. rotata*. In addition to protecting limited wild growth, *L. rotata* could be cultivated on a large scale on suitable mountains or plains to enable plant regeneration. Collection could also be limited to the aerial regions of the plant. The preservation of *L. rotata* is critical for the continued development of effective drugs targeting coagulation, hypertension, and cardiovascular disease. There is an urgent need to establish a cohesive plan for future utilisation and protection of this important medicinal resource.

Conflicts of interest

There are no conflicts to declare.

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