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Botanical, Chemical, and Pharmacological Characteristics of Lomatogonium rotatum: A Review

A Review on Lomatogonium rotatum

Lili Dai, Ronggui Eni, Ming-Hai Fu, Gen-Na Ba

Abstract

Lomatogonium rotatum (L.) Fries ex Nym (LR), a dry whole grass belonging to the family Gentianaceae, is widely used to treat liver diseases in Mongolian medicine. In Mongolian medicine, LR, also known as *Digeda*, is a rare medicinal herb with low yield and widespread clinical use. Currently, it is included in over 25 traditional Mongolian medicine prescriptions that help reduce heat, dispel *xieri*, enhance stomach function, and heal wounds. Recent studies have shown that LR contains a variety of metabolites, including flavonoids, xanthone compounds, terpenoids, organic acids, steroids, and alkaloids. In addition, its anti-hepatitis B, anti-inflammatory, anti-acute liver injury, anti-obesity effects have been proven by pharmacological studies. In this review, we have summarized the ecological resources, traditional pharmacodynamics, chemical constituents, and pharmacological actions of LR. We have also provided a theoretical basis for future applied research and new product development.

Key Words: Mongolian medicine; Lomatogonium rotatum; Chemical composition; Pharmacological action; Research progress

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Core Tip: As a highly distinctive Mongolian medicinal herb, LR is traditionally used to prevent and treat liver and gall diseases. However, its clinical application value and further development are limited by strict requirements on its growing environment, high demand for medicinal materials, decrease in wild resources, and insufficient scientific and technological availability in ethnic minority areas. Currently, a total of 38 compounds have been isolated and identified from LR, with flavonoids, xanthones, and terpenoids being the main metabolites. Pharmacological studies have mainly focused on hepatitis, liver injury, and weight loss, but mechanisms of pharmacological activity remain elusive and further comprehensive *in vivo* and *in vivo* experimental designs are needed to elucidate.

INTRODUCTION

Lomatogonium rotatum (L.) Fries ex Nym (LR) is a dry whole grass belonging to the family Gentianaceae. LR, also known as *Habirigen-Digeda* or *Temuri-Digeda*, is a commonly used Mongolian medicine to treat liver diseases. In traditional Mongolian medicine, LR is believed to clear heat, remove *xieri*, strengthen the stomach, treat poisoning, and heal wounds. It is widely used to prevent and treat influenza and fever, hepatobiliary disease, typhoid fever, and jaundice. It also has a therapeutic effect on heatstroke symptoms [1-2]. In addition, it is clinically effective in the prevention and treatment of liver and gallbladder diseases. Recent chemical and pharmacological studies have shown that LR contains organic compounds (xanthones), swertiamarin, oleanolic acid, luteolin, and other metabolites that play a role in enhancing the liver and biliary tract functions [3].

1. MORPHOLOGY, RESOURCES, AND BREEDING

1.1 Floral morphology of LR

LR is a 30- to 50-cm-high annual herb with an erect stem, four prisms, and a few branches. The leaves are sessile and opposite, and the leaf blades are narrowly lanceolate, 1.5- to 3-cm long, 0.4- to 0.6-cm wide, and apically acute, with a wider base. It has five calyces, deep, lanceolate lobes, and an equally long corolla. The corolla has five deeply lobed segments; the lobes are spheric and obtuse, with a toothed tube on each side of the base (Figure 1). The plant usually grows on hillsides and wetlands at an altitude of 2500 m. After picking the grass in the autumn flowering season, adherent soil and moisture are removed, and it is mashed or sun-dried before use.

1.2 Resources and geographical distribution of LR

LR for medicinal use primarily grows in the wild. However, the yield is low because of environmental factors and excessive mining, necessitating artificial breeding, which also has a low yield. A survey found wild LR in Xilingol League, Horqin, and Hulun Buir of the Inner Mongolia Autonomous Region, but observed a decreasing growth trend year on year [4]. The shortage of LR has led to the use of *Viola yedoensis* Makino of the family Violaceae as a substitute medicine in most Mongolian hospitals. It is, therefore, crucial to immediately protect and direct increasing efforts toward improving resources required for growing LR. Currently, several challenges, such as the low germination rate of group embryos and the low success rate of inoculation, which affect the large-scale cultivation of LR, continue to persist in artificial cultivation and domestication of the plant [4]. Li *et al* conducted a field investigation and found that the plant shows optimum growth during the dry season in February, with an average temperature of -13 to 18°C and precipitation of 6-19 mm. The vegetation growth types include temperate grasses, mixed grasses meadow, halophytic meadow, temperate deciduous shrub, and broad-leaved forest. [5]. According to the literature, LR is widely distributed in Inner Mongolia, Gansu, Yunnan, Xinjiang, Qinghai, Tibet, Sichuan, and other regions [6], usually on grassy slopes of hillsides and shrublands below an altitude of 4200 m [7]. Li *et al* pointed out that LR is scattered in shrubland, alpine meadows, grassland wetlands, flat meadow grasslands associated with rivers, and alpine and hillside meadows in Xilingol, Inner Mongolia, Heilongjiang, Hebei, and other regions [4].

1.3 Characteristics of breeding and pollen viability of LR

Li *et al* set up fixed points in the field to monitor the morphology and characteristics of LR organs, dynamics during flowering, and types of pollinators. A systematic inspection and measurement of its growth and reproduction were conducted by calculating pollen viability, pollinable characteristics such as stigma, estimation of pollen-to-ovule ratio, and hybridization index (OCI), and artificially controlled pollination [7]. The results demonstrated that the flowering time of a single LR flower was 6-7 days and that the flowering time of a single plant could be classified into a common bud stage followed by the initial flowering, blooming, wilt, and litter periods. During this process, the open stigma was always higher than the anther, and the pollen vitality and stigma receptivity were relatively strong at 2-3 days after anthesis. In addition, the researchers also observed that the breeding system was mainly outcrossing, and some were self-compatible, which may require insect thrips as the primary pollinators. In the case of bagging without pollination after emasculation, the seed setting rate of the fruit was 0, indicating a lack of fusion reproduction [8]. Zhu *et al* investigated the effects of different storage times and temperatures and the use of gibberellin reagents on promoting the flowering and growth rates of LR seeds. They found that changes in outdoor temperature and gibberellin immersion significantly promoted the germination and flowering of LR seeds [9].

Similarly, Li *et al* intervened in the LR germination rate by adopting different temperatures and germination sites. They found that the highest germination index was on sand, under which condition the rot rate of the seeds was the lowest. Furthermore, the germination rate was highest at 40°C. Therefore, the optimal conditions for LR seed germination may be the temperature of 40°C and planting on sand [10].

2. TRADITIONAL APPLICATIONS

LR is a typical medicinal plant used for internal applications to prevent and treat various liver and gallbladder diseases. In 1998, it was recorded in the Drug Standard (Mongolian Medicine Volume) of the Ministry of Health. The plant helps degrade *xieri* and clears heat. In Mongolian medicinal prescriptions, LR is either combined with *Herpetospermum caudigerum* Wall and *Ixeris Chinensis* (Thunb.) Nakai to formulate a Lidan powder containing 28 medicinal herbs, or it is used alone to degrade the *xieri* heat of the gallbladder. In addition, it is used as a prescription combination of Digeda-15, Digeda-20, and Digeda-25 to treat common clinical diseases such as liver and gallbladder heat, redness, yellow appearance of the eye and skin, gallbladder stasis, and stasis of *xieri*, which may lead to organ injury [11]. In addition, Digeda-4, a combination of LR and *Coptidis rhizoma*, *Gardenia jasminoides* Ellis, and *Dianthus superbus* L., is used to reduce problems such as inflammation, sore throat, liver and gallbladder heat, blood heat, thirst, and irritability [2]. Furthermore, LR is used as an adjuvant, subordinate, or auxiliary medicine in several compound preparations. There are a total of 24 Mongolian medicine prescriptions that include LR, including three where LR is used as a monarch medicine, four where LR is used as a minister medicine, 16 as assistant medicines, and one as a guide medicine.

3. CHEMICAL COMPOSITION

Research on the pharmacodynamic substances and chemical components of LR is still in the initial stages. To date, 38 compounds have been isolated and identified, mainly including flavonoids and xanthones, with a small number of iridoids, alkaloids, steroids, organic acids, amongst others.

3.1 Flavonoids

Flavonoids are abundant in most herbaceous plants, especially in higher plants, and possess a plethora of biological activities. According to the literature, LR contains about 16 flavonoids, including luteolin [12], apigenin, 5,7,3',4',5'-pentahydroxy flavonoids, quercetin, kaempferol, luteolin-7-O-glucoside, apigenin-7-O-glucoside [13], swertisin [14], swertianolin [15], isoorientin, mangiferin, isovitexin [16], carinoside A [17], carinoside B, carinoside C, and carinoside D [18] (Table 1, Figure 2).

3.2 Xanthones

Ten xanthone compounds have been identified in LR: 6, 8-dihydroxy-1, 2-dimethoxy xanthone [19], 1,8-dihydroxy-3,4,5-trimethoxyxanthone, 1-hydroxy-3,7,8-trimethoxy xanthone, 8-hydroxy-1,3,5-trimethyl xanthone, 1-hydroxy-3,5,8-trimethoxy xanthone [13], 1,8-dihydroxy-4,5-dimethoxy-6,7-methylenedioxy xanthone, 5-O-D-gluco-pyranosyl-1,3,8-trihydroxy-5,6,7,8-tetrahydroxanthone, 1,3,5,8-tetrahydroxy-5,6,7,8-tetrah-ydroxanthone [20], 1,2,6-trihydroxyl xanthone-8-O-β-D-glucoside, and 1,4,8-trimethoxyxanthone--6-O-β-D-glucoronyl-(1→6)O-β-D-glucoside[21] (Table 1, Figure 2).

3.3 Terpenoids

Terpenoids are a class of compounds derived from methylcarboxylic acid with ≥2 isoprene units in the basic carbon frame. According to the literature, three iridoids (i.e., swertiamarin [22-25], ursolic acid 3 β-hydroxy-ursol-11, 12-ene-28, 13β-lactone [14], and amarogentin [16,26]), as well as two pentacyclic triterpenes, oleanolic acid [20], 2a-hydroxyoleanolic acid [13], lomacarinoside A, and lomacarinoside B [27] are present in LR (Table 1, Figure 2).

3.4 Other compounds

LR also contains organic acids, steroids [14], alkaloids [28-29], and other compounds (erythrocentaurin), in addition to the above-mentioned metabolites [13]. However, current research on this aspect is inadequate, warranting further studies (Table 1 and Figure 2).

3.5 Study on the extraction process of LR

Chen *et al* [30] investigated the primary factors affecting total flavonoid extraction in LR using single-factor experiments. They then optimized the extraction method for the total flavonoids in LR by an orthogonal test using the rutin concentration as the standard and formulated the optimal extraction process for the total flavonoids. The results demonstrated that the optimal parameters for total flavonoid extraction from LR were: ethanol concentration, 60%; solvent volume, 150 mL; extraction time, 8 h; total flavonoid extraction rate from LR, about 3.47%.

In addition, single-factor experiments were conducted to explore the effects of the ethanol percentage and volume used for extraction, the ultrasonic extraction time, and the liquid-to-sample ratio on the total saponin concentration extracted from LR. Response surface methodology was used to optimize the experimental conditions for ultrasonic extraction of LR, resulting in a gradual increase in the total saponin extraction yield. The experimental results demonstrated that the optimal experimental conditions for the extraction of total saponins from LR were as follows: average volume content fraction of ethanol, 77%; average liquid-to-solid ratio, 40 mL/g; ultrasound duration, 33 min. Under these conditions, the researchers found that the average total saponin concentration extracted from LR was 27.36 mg/g, which was close to the theoretically predicted value [31]. However, the optimization of the extraction process, using 65% ethanol, a solid-to-liquid ratio of 20 mL/g, and an extraction time of 20 min, defined by Liu *et al*'s study is considered the best method [32].

3.6 Fingerprint and mineral elements of LR

Sun *et al* [33] used high-performance liquid chromatography to determine the fingerprint of LR plants from 15 different places and cultivation areas. The results showed 15 common peaks, of which the five most common were swertiamarin, isoorientin, swertisin, apigenin, and luteolin. In addition, Deng *et al* measured the mineral elements in two *Lomatogonium* species using inductively coupled plasma-optical emission spectrometry (ICP-OES). finding 21 mineral elements in *Lomatogonium macranthum* and 18 elements in *Lomatogonium carinthiacum*. Both *Lomatogonium* species had relatively high Ca, Mg, and Fe contents while the greatest difference was seen in the Co concentrations and the least difference was found in the T1 contents [34].

4. INVESTIGATION OF LR PHARMACOLOGICAL ACTION

4.1 Effects of LR powder on hepatitis B

Bai *et al* [35] investigated the anti-hepatitis B effect of LR powder and found that LR had relatively low cytotoxicity to HepG2 cells, with some inhibitory effect on the number of hepatitis B virus (HBV) DNA copies in the cells. In addition, *in vitro* experiments showed that LR is able to counteract HBV to some degree. This may be because LR acts against HBV by directly inducing apoptosis, thereby blocking HBV replication in HepG 2 cells.

4.2 Anti-inflammatory effects of LR

Ethyl acetate has been found to be the active component responsible for the anti-inflammatory effect of LR, which has significant antibacterial activity against both Gram-positive and Gram-negative bacteria such as *Escherichia coli*, *Staphylococcus alba*, drug-resistant *Staphylococcus aureus*, *S. aureus*, and *Pseudomonas aeruginosa* [36]. LR also contains several anti-inflammatory compounds, including sweroside, swertiamarin, and luteolin. Chen *et al* reported that swertiamarin had anti-inflammatory, antioxidant, and anti-fibrotic effects in rats with smoking-exposed prostate dysfunction [37]. Aziza *et al* also reported that luteolin had strong anti-inflammatory effects in both *in vivo* and *in vitro* experiments [38].

4.3 Anti-acute liver injury effect

LR extracts with different polarities were reported to have pharmacological effects on acute liver injury [39]. In a drug interaction study of LR prescription medication, an LR water extract was found to significantly protect liver function in rats with carbon tetrachloride (CCl_4)-induced liver astrocyte damage [40]. In a further study, the urine of rats with liver injury was analyzed after LR administration, showing 19 common peaks, one of which was the drug itself, 14 were metabolites passed through the body, and the rest were endogenous components of urine [41]. In addition, the study found that the Digeda-4 decoction had a protective action in mice with pyloric ligation-induced liver injury. It has been suggested that LR may affect the protein expression of MRP3 and MRP4 by regulating the nuclear receptors CAR and PXR, resulting in liver protection [42]. An experimental metabolomics study found that LR administration restored several disturbed metabolic pathways, including those involving linoleic acid and glycerolipid metabolism. The use of another eight metabolites as potential biomarkers was proposed to help clarify the liver protective mechanism of LR [43]. Zhao *et al* also proposed that the liver protective activity of LR may be related to metabolites in rat plasma and liver [44].

4.4 Anti-obesity effect

Baol *et al* [45] investigated the effect of LR on weight loss based on the function of bitter receptors in rats with obesity induced by a high-fat and high-energy diet. The LR extract significantly reduced body weight, Lee's index, epididymal fat, perirenal fat, and mesenteric fat deposition in the rats. It also reduced serum triglyceride and total cholesterol levels to a certain extent, indicating its potential for lipid-lowering, cholesterol-lowering, and weight-loss effects. Chemical analysis demonstrated that flavonoids, glycosides, and alkaloids were the primary components of LR, and the main source of bitterness was base substances. The effects of LR on fat metabolism and its bitter receptor activation mechanism require further investigation.

CONCLUSION

As a highly distinctive Mongolian medicinal herb, LR is traditionally used to prevent and treat liver and gallbladder diseases. However, its clinical application value and further development are limited by the strict requirements of its growing conditions, high demand for medicinal materials, decrease in natural resources, and insufficient scientific and technological expertise in ethnic minority areas. To date, a total of 38 compounds have been isolated and identified from LR, with flavonoids, xanthones, and terpenoids being the main metabolites. While pharmacological studies on LR have mainly focused on hepatitis, liver injury, and weight loss, the mechanisms of its pharmacological activity remain elusive and further comprehensive *in vivo* and *in vivo* experimental studies are necessary. Thus, our study may provide a foundation for further research on LR and its clinical applications.

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