



Review

Lycium ruthenicum studies: Molecular biology, Phytochemistry and pharmacology



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ABSTRACT

Lycium ruthenicum has been used as ethnic medicine and nutraceutical food. Existing studies of *L. ruthenicum* can be classified into three areas: (1) those in which molecular biology methods were used to study its origin, genetic variation and relationships with other species; (2) those in which phytochemical methods were used to extract, isolate, and identify compounds; and (3) those in which pharmacological methods were used to study active compounds. The purpose of this paper is to provide an overview of *L. ruthenicum* studies. This review will provide a useful bibliography for further investigations and applications of *L. ruthenicum* in medicines and foods.

1. Introduction

There is an overwhelming amount of research on berry fruits, and the dried fruits of *Lycium* plant (Fructus lycii, wolfberries, goji berries) are popular in Asia and other countries (Seeram, 2008). There are approximately 80 species of *Lycium* L. (Solanaceae) in the world (Hitchcock, 1932; Levin & Miller, 2005; Miller, 2002), and seven species and three varieties are found in China (Board, 1994). However, only three species (*L. barbarum*, *L. chinense* and *L. ruthenicum*) are used as medicine, and they are referred to as goji berries in China. There have been used as medicine and functional foods for at least 2000 years (Ulbricht et al., 2014; Zeng, Wu et al., 2014). Nearly 90% of all commercially available goji berries are *L. barbarum* (Zhong, Shahidi, & Naczki, 2013), and this species has been widely cultivated in northwest China for more than 600 years (Chen, Liu, Zhu, & Wang, 2013), especially in Ningxia province. In addition, Goji (*L. barbarum* L.) leaves as a functional tea or as dietary are a rich source of bioactive compounds with functional properties (Mocan et al., 2017). *L. ruthenicum*, a wild perennial thorny shrub, inhabits northwestern China (Han, Ye, & Suo, 2014). Its resistant to drought and salt stress makes it an ideal plant under conditions of soil desertification and for alleviating the degree of soil salinity-alkalinity, which is very important for the ecosystem (Zheng et al., 2011). It is used as medicine and has had a

great influence on the development of Minority Medicine (Tian et al., 2016). Additionally, it is used as nutritional food and can be eaten as fruit or used as a raw material for beverages (Jin, Liu et al., 2015; Lv, Wang, Yang, Huang, & Wang, 2013).

L. ruthenicum has been described in the Tibetan medical classics *Jing Zhu Ben Cao* and *Si Bu Yi Dian* for the treatment of heart disease, abnormal menstruation and menopause (Dierma & Mao, 2012; Yutuo, 1987). It has also been described in *Pharmacography of Uighur* for the treatment of urethral and ureteral stones, tinea and furuncle, and gingival bleeding (Liu, 1999). Modern pharmacology research has confirmed that *L. ruthenicum* has many pharmaceutical effects such as antioxidant (Hu, Zheng, Li, & Suo, 2014), anti-fatigue (Ni et al., 2013), immuno-enhancement (Gong, Wu, & Li, 2015), radio-resistance (Duan et al., 2015), and anti-aging (Tian, Jiang, & Fan, 2015) effects. Its berries contain abundant anthocyanins (Zheng et al., 2011), which are a kind of water-soluble natural pigment. The pigments extracted from the berries are widely used as natural food colorants (Hu et al., 2014). Additionally, *L. ruthenicum* is endemic to northwestern China. It is important for controlling erosion because of its high tolerance to salt, drought, strong winds, cold temperatures and petroleum contamination (Chen et al., 2013; Jalali, Akbarian, Rhoades, & Yousefzadeh, 2012; Xi, Zhang, Mao, & Yan, 2003; Zhang, Yin, & Pan, 2013). Therefore, *L. ruthenicum* plays important roles in ethnic medicine, nutritional food and

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the restoration of desert ecosystems.

The aim of this paper is to provide an overview of *L. ruthenicum* research, focusing on its genetics, chemical composition and pharmacology. The most relevant results from the published studies are summarized, analyzed and discussed.

2. Molecular biology

Most *Lycium* species are found in southern South America, southern African and southwestern North America. In addition, a number of species are distributed in the Mediterranean and across Asia, and one species is apparently native to Australia (Levin, Shak, Miller, Bernardello, & Venter, 2007). Researchers studying the biogeographical history of *Lycium* have relay on chloroplast DNA (cpDNA) analysis, which has been frequently used to reconstruct the phylogenetic relationships of a wide range of land plants. The analysis showed that *Lycium* almost certainly originated in American, and it suggested a single dispersal from the Americas to southern Africa, Australia and Eurasia (*Lycium chinense*, *L. europaeum*, *L. barbarum* and *L. ruthenicum*). The Eurasian species are monophyletic (Fukuda, Yokoyama, & Ohashi, 2001; Levin & Miller, 2005; Miller, 2002; Miller, Levin, & Feliciano, 2007), and are most widely distributed in China. RAPD was used to construct a phylogeny, and the common bands in the fingerprints generated from the OPC-2 and OPAM-2 (Sequences (5'-3'): GTG AGG CGTC and ACT TGA CGG G, respectively) primers indicated that homologous sequences are present in *Lycium*. The unique bands illustrate that the individual species have their own characteristics, such as unique bands at 480 bp and 580 bp in the *L. chinense* and *L. ruthenicum* RAPD fingerprint generated from OPC-2, respectively (Yin, Fang, Liang, Wong, & Ha, 2005; Zhang, Leung, Yeung, & Wong, 2001).

L. ruthenicum is an endangered and medically important species. RAPD, SRAP, cpDNA and SSR were successfully used to study its genetic diversity and genetic structure (Chen, Zeng, Yonezawa, Ren, & Zhong, 2014; Liu et al., 2012; Zhang et al., 2001; Chen & Zhong, 2014). At the species level, it has a relatively high genetic diversity ($He = 0.2112$) compared to the average solanaceae plant ($He = 0.0940$) (Hamrick & Godt, 1996). However, it has a relatively low genetic diversity compared to *L. chinense* ($He = 0.3792$), which is widely distributed species in China (Zhao et al., 2010). Additionally, the genetic differences were found mainly within populations, in which gene exchange was relatively high (Chen, Zeng, Yonezawa, Ren, & Zhong, 2014; Liu et al., 2012). In addition, this species has weak phylogeographic structure, as suggested by the chloroplast DNA genetic structure ($G_{ST} = 0.351$, $N_{ST} = 0.304$, $N_{ST} \leq G_{ST}$). The divergence times of different lineages were consistent with the rapid uplift phase of the Qinghai-Tibetan Plateau and the initiation and expansion of deserts in northern China, which suggest that the origin and evolution of *L. ruthenicum* were strongly influenced by Quaternary environment changes (Chen, Zeng et al., 2014).

Gene expression was analyzed for *L. barbarum* and *L. ruthenicum*, which indicated that no candidate reference gene was consistently expressed across different tissues or species. *EF1a* was the most stable reference genes in *L. ruthenicum* fruits. Additionally, *H2B1* and *GAPDH1 + PGK1* for *L. ruthenicum* and *SAMDC2 + H2B1* for *L. barbarum* were the best single and/or combined reference genes (Zeng, Liu et al., 2014). The expression patterns of both regulatory and structural genes and the transcriptional ratio of branch node structural genes F3'5'H/F3'H may determine the phenotypic difference in anthocyanin biosynthesis between *L. ruthenicum* and *L. barbarum* fruits (Zeng, Liu et al., 2014). In addition, 1913 up-regulated and 536 down-regulated genes that showed at least a twofold change were identified by high throughput RNA-sequencing analysis of *L. ruthenicum* with and without UV-B exposure, and the activities of antioxidant enzyme related genes, the secondary metabolism genes and defense response genes were down-regulated. The analysis also illustrated that UV-B stress could affect several biological pathways related to biotic and abiotic stress

(Chen, Feng et al., 2014). Virus-induced gene silencing (VIGS) is a power approach for conducting loss of function assays to study gene function in plants. VIGS has shown that there is a difference in silencing efficiency due to genetic background. *L. ruthenicum* was found to be more susceptible than *L. barbarum*. Additionally, TRV-based VIGS could be used to silence endogenous genes of the related *L. barbarum* and *L. ruthenicum* (Liu, Sun et al., 2014; Liu, Zeng et al., 2014).

3. Phytochemistry

Lycium typically produces many seeds, yellow to red (sometimes black), fleshy berries (Levin & Miller, 2005). The compounds found in berry fruits mainly include carotenoids, vitamin C and phenolic compounds such as anthocyanins, phenolic acids, stilbenes, and flavonols (Szajdek & Borowska, 2008; Toyoda-Ono et al., 2004). *L. ruthenicum* mainly grows in the salinized desert of northeast of China, it has black berries that are used as a nutritional food and folk medicine. Chemical composition research illustrated that the compounds in *L. ruthenicum* include flavonoids (Wu, Lv, Wang, & Wang, 2016; Zhang, Chen, Zhao, & Xi, 2016; Zhao, Xu, Ji, & Li, 2014), anthocyanins (Jin, Liu, Yang et al., 2015; Jin, Liu, Guo et al., 2015; Jin, Zhao et al., 2015; Tian et al., 2016; Wu et al., 2016; Zhao et al., 2014; Zheng et al., 2011), polysaccharides (Lv et al., 2013; Peng, Xu, Yin, Huang, & Du, 2013; Peng, Lv et al., 2012; Peng, Song et al., 2012), phenolic acids (Wu et al., 2016; Zhang et al., 2016; Zhao et al., 2014), carotenoids (Peng et al., 2005; Zhang et al., 2016), alkaloids (Jin, Zhao et al., 2015; Wu et al., 2016; Zhao et al., 2014), essential oils (Altintas, Kosar, Kirimer, Baser, & Demirci, 2006), and fatty acids (Chi, Xiao, Dong, Yang, & Hu, 2016).

3.1. Flavonoids

The total flavonoid (TF) is significant differences between gouji genotypes. The TF levels ranged from 36.1 to 54.7 mg rutin equivalents (RE)/g fresh weight (FW). *L. barbarum* (Ningji No.1) has the highest levels (54.7 ± 3.2 mg RE/g FW), while *L. ruthenicum* has the lowest (36.1 ± 2.8 mg RE/g FW). *L. barbarum* (Baihua) (48.2 ± 5.3 mg RE/g FW), *L. chinense* (45.3 ± 2.6 mg RE/g FW), *L. yunnanense* (43.9 ± 2.9 mg RE/g FW), *L. barbarum* (42.6 ± 4.3 mg RE/g FW) has significantly higher TF contents than *L. barbarum* var. auranticarpum (38.5 ± 3.8 mg RE/g FW), *L. chinense* var. potaninii (37.2 ± 3.5 mg RE/g FW) (Zhang et al., 2016). Forty-six flavonoids, include thirty-seven anthocyanins, were isolated and identified in the fruits of *L. ruthenicum* (Table 1). Quercetin-rhamno-di-hexoside (934.3 ± 87.7 μ g/g FW) is the most abundant flavonoid (Zhang et al., 2016). Anthocyanins, a class of flavonoids, are widespread in *L. ruthenicum* fruits (Jin, Liu et al., 2015).

3.1.1. Anthocyanins

Anthocyanins, natural pigments found in plants, are responsible for brilliant colors (red, blue and purple) (Zhao et al., 2014). So colors are changed along with plasma treatment influences on anthocyanins stability, such as in cloudy pomegranate juice (Bursać et al., 2016) and chokeberry juice (Kovačević et al., 2016). Anthocyanins have been widely used in the fields of medicine, cosmetics and natural food coloring. Research has shown that *L. ruthenicum* fruits, which are black, contain abundant, and they are the main active ingredients in this species. And anthocyanins contents in dried *L. ruthenicum* from different origins are different (Tian et al., 2016). These anthocyanins have attracted great interest from many researchers. Researchers have isolated and identified 37 anthocyanins from *L. ruthenicum* fruits (Table 1), including derivatives of peonidin, petundin, pelargonidin, cyanidin, malvidin, and delphinidin (Jin, Liu, Yang et al., 2015; Jin, Liu, Guo et al., 2015; Jin, Zhao et al., 2015; Tian et al., 2016; Wu et al., 2016; Zhao et al., 2014; Zheng et al., 2011). There are many *cis-trans* isomeric anthocyanins in the fruits (Jin, Liu, Yang et al., 2015). Petundin

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