COMMENT
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Oriental Medicine

Safety of *Lycium barbarum* L.: more information needed

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Figure 1 The whole plant of Goji and its medicinal site

The earliest use of *Lycium barbarum* L. (Goji fruits) as a medicinal plant was at around 2,300 years ago, and nowadays it is used as a medicinal food (Figure 1) [1, 2]. There have been some reports on the antifertility effects and fertility-promoting or aphrodisiac effects [3–5]. The famous Chinese herbalist Li Shizhen first recorded the pro-fertility efficacy of *Lycium barbarum* L. in *Compendium of Materia Medica* in the 16th century [6]. *Lycium barbarum* L. also has many other effects, such as the antioxidant function, anti-cytotoxicity, anti-fatty acid toxicity, neuroprotective and anticancer effects, and so on [7]. *Lycium barbarum* L. is rich in vitamins, zeaxanthin, carotenoid and other ingredients [8].

Despite the long history and well-documented multiple benefits, some related adverse reactions of *Lycium barbarum* L. cannot be easily overlooked. The traditional records had already featured a warning stating that *Lycium barbarum* L. is contraindicated for pregnant women [6]. The patients suffering from cold, fever, inflammation, or diarrhea are advised not to use [9]. Excessive heavy metal and pesticide residues have been a major problem in Chinese medicinal materials [10]. Some caution is advised with samples of unknown origin. The adverse effects of overdose Goji fruits also should be attached importance. When the dogs taken Goji fruits at a dose of 120 g/kg orally or 30 g/kg intraperitoneally, they will suffer from vomiting. The rabbits may show drowsiness at doses of 80 g/kg (orally) or 60 g/kg (i.p.) [11]. In a research, rats with high doses (5 and 10 g/kg) orally for 14 days, subacute toxicity occurred as an increase in the weight of heart, liver and lungs was observed. However, there was no sign of any irreversible pathological damage or mortality in the rats [12]. There have been allergic reactions reported including urticaria-like or papular rashes [13].

With the usage of *Lycium barbarum* L. is becoming common, there is the potential risk of causing herb-drug interactions. Recently, it reported a case of *Lycium barbarum* L. interact with flecainide, which further caused warfarin overdose and a life-threatening pleomorphic arrhythmia [14]. This highlights the challenge of daily uses of *Lycium barbarum* L., especially for the patients with chronic diseases who take medicine for a long time. Constituents of *Lycium barbarum* L. could be a substrate, inhibitor, or inducer of drug metabolism enzyme systems or transport proteins as previous studies have shown that *Lycium*

barbarum L. strongly inhibit the activity of cytochrome (CYP) 450 enzymes (more than 75%) and a moderate inhibitory effect on CYP2D6 (50–60%). There are at least four cases of warfarin poisoning caused by *Lycium barbarum* L., in part because it inhibits the activity of CYP2C9 enzymes, a warfarin-related enzyme [15–17]. The international standard ratio increased significantly after admission, so patients who used warfarin should avoid Goji use. A 75-year-old woman, who underwent mitral valve replacement three years ago, was treated with oral warfarin to keep the international standard ratio within target range (2.5–3.5). Two years ago, she was treated for premature atrial contractions with flecainide (100 mg twice daily). She recently drank Goji fruit tea (1–2 cups a day) to prevent new coronavirus infection. However, she suffered from dizzy, nausea, and extreme fatigue. On admission, the electrocardiogram revealed pleomorphic ventricular tachycardia, which further was diagnosed as flecainide poisoning [14]. Flecainide is an antiarrhythmic agent by blocking the Na^+ channel with a narrow therapeutic window. CYP2D6 is one of the main enzymes in the metabolism of flecainide. Impaired CYP2D6 activity is associated with a 21% decrease in intermediate metabolizer and a 41% decrease in poor metabolizer [18]. Because of the narrow therapeutic window of flecainide, it is very easy to cause drug poisoning.

More than 200 different components, including polysaccharides, vitamins, betaine, carotenoids, phenylpropanoids, flavonoids, polyphenols and alkaloids have been identified in *Lycium barbarum* L. which component contributes to the herb-drug interactions have not been reported. So far, there was no side effects or drug interactives reported about the *Lycium barbarum* polysaccharides. Researchers found that dietary betaine supplementation could enhance cholesterol synthesis by increasing the levels of 3-hydroxy-3-methylglutaryl-CoA reductase and CYP7A1. However, no reports about the effects of betaine on other drug metabolizing enzymes [19]. CYP2C9 is considered one of the most abundant and significant CYP enzymes, accounting for approximately 20% of the total hepatic CYP content. Some ingredients are able to exhibit inhibiting effects on CYP2C9; such as some flavonoids interfere with CYP2C9, and several rare but dangerous bleeding episodes due to application of ginkgo have been reported, but no flavonoids in *Lycium barbarum* were reported [20–22], phenylpropanoids are possible inhibitors of CYP2C9, which have been shown to interact with many prescription medications, such as ethinylestradiol, cyclosporin, midazolam, triazolam, and terfenadine [23]. Whether these components in *Lycium barbarum* affect CYP2C9 also not been researched.

To sum up, *Lycium barbarum* L. showed antioxidant function, anti-cytotoxicity, anti-fatty acid toxicity, neuroprotective, anticancer effects, which showed a promising use in the supplements field. However, the potential risk of causing herb-drug interactions should cause our caution, especially for patients taking flecainide and warfarin.

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Competing interests
The authors declare no conflicts of interest.

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Abbreviations
CYP, cytochrome.

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