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Review

Ethnopharmacology, phytochemistry, and pharmacology of *Cornus officinalis* Sieb. et Zucc

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Ursolic acid (PubChem CID: 64945)
Oleanolic acid (PubChem CID: 10494)
Cornuside (PubChem CID: 11228694)
Sweroside (PubChem CID: 161036)
7-O-Galloyl-D-sedoheptulose (PubChem CID: 42636959)
Gallic acid (PubChem CID: 370)
β-Sitosterol (PubChem CID: 222284)
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ABSTRACT

Ethnopharmacological relevance: *Cornus officinalis* (Cornaceae), known in Chinese as "Shanzhuyu," is a frequently used traditional Chinese medicine. It tastes sour and is astringent and slightly warm in nature. Its fruits have long been used to treat kidney deficiency, high blood pressure, waist and knee pain, dizziness, tinnitus, impotence, spermatorrhea, menorrhagia, and other diseases in China. The main distribution areas are Shanxi and Gansu.
Aim of the study: This review focused on the ethnopharmacological uses of the herb. We also focus on the phytochemical, pharmacological, and toxicological studies on *C. officinalis.* The recent analytical methods developed for the quality control of the herb's constituents are also reviewed. Additionally, future trends and prospects in the study of this herb are proposed.
Materials and methods: Information on *C. officinalis* was gathered by searching the internet (PubMed, ScienceDirect, Wiley, ACS, CNKI, Scifinder, Web of Science, Google Scholar, and Baidu Scholar) and libraries.
Results: This review compiled the ethnopharmacological uses, including the classic prescriptions and historical applications. Approximately 300 chemical compounds have been isolated and identified from *C. officinalis*. The major active components of the plant are organic acids and iridoids, among which morroniside and loganin have been extensively investigated. The fruit of the plant has been used in treating many diseases in traditional medicine. Scientific studies indicated the herb's wide range of pharmacological activities, such as hepatic and renal protection, antidiabetes activity, cardioprotection, antioxidation, neuroprotection, antitumor activity, anti-inflammation, analgesic effects, antiaging activity, antiamnesia, antiosteoporosis, and immunoregulation. The analytical methods developed for the quantitative and qualitative determination of various compounds in the herb were further reviewed.
Conclusions: In this paper, we reviewed various studies conducted on *C. officinalis*, especially in areas of its ethnopharmacological use, as well as on its phytochemistry, pharmacology, and modern analytical methods used. Some of the herb's ethnomedical indications have been confirmed by the herb's pharmacological effects, such as its hepatic and renal protection and the antidiabetic effects. In particular, the crude extract and its chemical composition have exerted good therapeutic effect in diabetic treatment. *C. officinalis* entails additional attention on its pharmacological effects and drug development to expand its effective use clinically. Many advanced technologies are used for quality testing, but the detection component is exceedingly scarce for synthetically evaluating the quality of *C. officinalis* herbs. Thus, further research is necessary to investigate the quality control and toxicology of the plant, to further elucidate its clinical use, and to control herbal quality.

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1. Introduction

Cornus officinalis Sieb. et Zucc. (CO), also called Asiatic dogwood, is a deciduous tree belonging to the Cornaceae family. It is well distributed in Tianmu Mountain, Funiu Mountain, and Qinling Bashan Mountain in China (Bai et al., 2014). In China, CO and *C. chinense* are used as traditional Chinese medicine (TCM). Furthermore, this tree is widely distributed in eastern Asia, mainly in China, as well as Korea and Japan (Ma et al., 2014). The optimum growing environment of this plant includes an average annual temperature of 8–17.5 °C, fertile soil, soil that is deep with good drainage, good loam and sandy soil, and an annual precipitation of 600–1500 mm (http://baike.so.com/doc/4370533-4576418.html).

The fruit of CO (Chinese: 山茱萸) is a primary medicine that was first recorded in Shen Nong's Materia Medica (Shen-Nong-Ben-Cao-Jing) about 2000 years ago (Ma et al., 2014). The fruit has long been used to nourish the liver and kidney and treat diabetes and other diseases. Because this herb was included in the Chinese Pharmacopoeia in 1963, more than 20 prescriptions containing CO have been used to treat various hepatic and renal diseases in China (Ding et al., 2008). The most well-known prescription is the Liuwei Dihuang pill, which is effective in treating renal diseases and preventing and curing many diseases, especially disorders of the immune and endocrine systems, such as diabetes, dizziness, and tinnitus (Xie et al., 2008).

Modern pharmacological studies have shown that CO and its active components exhibit a broad range of pharmacological activities against diseases, such as diabetes, and cardioprotective, antioxidative, anti-inflammatory, antiaging, neuroprotective, and antibacterial effects (Cao et al., 2009). Most of these activities are consistent with those reported for the CO used as traditional medicine. CO has also been used to treat different diseases in Korea and Japan, such as Paeng-Jo-Yeon-Nyeon-Baek-Ja-In-Hwan (PJBH) and Ba-Wei-Di-Huang-Wan (Bawei-DHW). PJBH is used to activate brain function, promote memory, and lengthen the life span in Korea, whereas Bawei-DHW, also known as Hachi-Mi-Ji-O-Gan in Japanese, is used to treat diabetes and urinary frequency (Adams et al., 2007; Koo et al., 2004; Lee et al., 2016).

About 305 compounds, such as alkaloids, iridoids, flavones, polysaccharides, organic acid, terpenoids, and essential oils, have been isolated and identified from CO. Among these components, iridoids have been well studied and exhibited primary bioactivities. In 2009, Wang et al. investigated the function of morroniside (300–500 μM) in SH-SY5Y cells and found that the compound reduces superoxide dismutase (SOD) activity and determined the percentage of cells undergoing H_2O_2-induced apoptosis. Thus, morroniside inhibits oxidative-stress-induced neurotoxic processes (Wang et al., 2009). In the Pharmacopoeia of P.R. of China (2015), morroniside and loganin are listed as indicators of content determination for herb quality control.

The present review discusses the recent views regarding the ethnopharmacology, phytochemistry, pharmacology, and toxicology of CO and the increasing data supporting the utilization of CO as a common drug. Although CO presents many synonyms (http://www.theplantlist.org/tpl1.1/search?q=Cornus+officinalis), we used CO as the plant name throughout this review, except in instances where we indicated whether or not a synonym was used. The Chinese traditional prescriptions, chemical compositions, and bioactivities of the herb are presented in tabular form.

2. Botany and ethnopharmacology

2.1. Botany

CO is a deciduous tree that grows to a height of 4–10 m and displays a greyish brown bark. The opposing leaves are papery, ovate-lanceolate, or ovate-elliptic, with a length of 5.5–10 cm and width of 2.5–4.5 cm. Each leaf exhibits an acuminate apex and a broad cuneate or nearly circular base, with an entirely green base above without hair and a pale green region below diluted by dense, white, pubescent axillary veins and light-brown hair tufts. On the umbel branch side, four bracts showing the following characteristics are present: ovate, thick papery to leathery, and approximately 8 mm in length. They are purple and slightly pubescent on both sides, and they fall after flowering. The flowers display four glabrous calyx lobes that are broadly triangular with long faceplates. The flowers also display four petals with a yellow lanceolate tongue that is 3.3 mm long. These petals display an outward antiroll. The flower also shows an oblong red to purple drupe with a length of 1.2–1.7 cm and a diameter of 5–7 mm. Flowering occurs from March to April, and fruiting occurs from September to October (http://frps.eflora.cn/frps/Cornus%20officinalis).

The CO grows at an altitude of 400–1500 m. The tree thrives in the Shanxi, Sichuan, Henan, Anhui, and Zhejiang provinces (Ma et al., 2014), but it also distributed across Korea and Japan (http://frps.e-flora.cn/frps/Cornus%20officinalis).

2.2. Ethnopharmacology

CO is a tonic with functions of nourishing the liver and kidney and is often used in TCM (Ma et al., 2014). The original plant was described in Shen-Nong-Ben-Cao-Jing, the oldest classical medicine book written in the Hou-Han Dynasty, and Wu-Pu-Ben-Cao written in the Wei dynasty. The latter manuscript states that CO protects the kidney, which is the essence of the four viscera. In the same era, Shanzhuyu was believed to be CO, as written in the Ming-Yi-Bie-Lu (Mikage and Hutagi, 2008). Afterward, CO was listed in Ben-Cao-Gang-Mu, a known book from the Ming Dynasty compiled by the Chinese pharmacologist Shizhen Li. In this book, CO was described to promote a healthy liver and kidney and was widely used in many TCM prescriptions (Liu et al., 2011).

The CO fruit has been present in the Pharmacopoeia of P.R. of China since 1963. At present, CO is among the 42 national key protected wild species of animals and plants (Hou et al., 2013). More than 20 prescriptions include CO as the principal and active component, as listed in the Chinese pharmacopoeia and approved by the state administration of TCM of P.R. of China (National Pharmacopoeia Committee, 2015). For example, Liu Wei Di Huang Wan and Mai Wei Di Huang Wan are commonly used to treat chronic inflammation, oxidative stress, revitalize the kidney and liver, and treat diabetes. The prescription of Liu Wei Di Huang Wan is used to formulate pills, including rehmanniae radix praeparata, wine-prepared corni fructus, moutan cortex, dioscoreae rhizoma, poria, and alismatis rhizoma. These formulations prevent renal fibrosis and protected glomerular mesangial cells by upregulating cytoglobin expression and suppressing multiple pathways involving TGF-β/SMADS, MAPK, and NF-kB signaling (Xu et al., 2017).

Currently, CO is a broadly used shrub medicine worldwide and can be used in medicine, food sanitation, and cosmetics to improve a person's health and prevent illness (Cao et al., 2013). The combination of its traditional pharmacological effects and modern research techniques, exploring the underlying mechanism of action of the plant, lays the foundation for its clinical application. The Pharmacopoeia of P.R. of China also contains many prescriptions for treating various diseases. The preparations for CO are listed in Table 1, whereas the plant morphology is presented in Fig. 1.

3. Phytochemistry

Currently, approximately 300 chemical components have been isolated and identified from CO. These components include 21 flavonoids, 10 triterpenes, 30 tannins, 4 saccharides, 33 monoterpenes and sesquiterpenes, 39 iridoids (Table 2), essential oils (Table 3), and 15 other compounds. The chemical structures of the primary compounds are shown in Fig. 2.