



Review

Phytochemistry, pharmacology, quality control and future research of *Forsythia suspensa* (Thunb.) Vahl: A review



Zhaoyi Wang^{a,1}, Qing Xia^{b,1}, Xin Liu^a, Wenxue Liu^a, Wanzhen Huang^a, Xue Mei^a, Jun Luo^a, Mingxu Shan^a, Zhiqiang Ma^{a,*}, Ruichao Lin^{a,*}

^a Beijing Key Lab for Quality Evaluation of Chinese Materia Medica, School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing 100102, China

^b Biology Institute of Shandong Academy of Sciences, Key Laboratory for Drug Screening Technology of Shandong Academy of Sciences, Shandong Provincial Engineering Laboratory for Biological Testing Technology, Key Laboratory for Biosensor of Shandong Province, Jinan 250014, China

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ABSTRACT

Ethnopharmacological relevance: *Forsythiae Fructus* (called Lianqiao in Chinese), the fruit of *Forsythia suspensa* (Thunb.) Vahl, is utilized as a common traditional medicine in China, Japan and Korea. It is traditionally used to treat pyrexia, inflammation, gonorrhoea, carbuncle and erysipelas. Depending on the different harvest time, *Forsythiae Fructus* can be classified into two forms, namely Qingqiao and Laoqiao. The greenish fruits that start to ripen are collected as Qingqiao, while the yellow fruits that are fully ripe are collected as Laoqiao. Both are applied to medical use. This review aims to provide a systematic summary of *F. suspensa* (*Forsythia suspensa* (Thunb.) Vahl) and to reveal the correlation between the traditional uses and pharmacological activities so as to offer inspiration for future research.

Materials and methods: All corresponding information about *F. suspensa* was searched by Scifinder and obtained from scientific databases including Springer, Science Direct, Wiley, Pubmed and China Knowledge Resource Integrated (CNKI). Local dissertations and books were searched as well.

Results: According to classical Chinese herbal texts and Chinese Pharmacopoeia, *Forsythiae Fructus* dominantly displays heat-clearing and detoxifying effects in TCM prescriptions. In modern research, more than 230 compounds were separated and identified from *F. suspensa*. 211 Of them were isolated from fruits. Lignans and phenylethanoid glycosides are considered as the characteristic and active constituents of this herb, such as forsythiaside, phillyrin, rutin and phillygenin. They exhibited anti-inflammatory, antioxidant, antibacterial, antiviral, anti-cancer and anti-allergy effects, etc. Currently, there is no report on the toxicity of *Forsythiae Fructus*, despite slight toxicity of forsythiaside reported in local publications. Compared to Laoqiao, Qingqiao contains higher levels of forsythiaside, forsythoside C, cornoside, rutin, phillyrin, gallic acid and chlorogenic acid and lower levels of rengyol, β -glucose and S-suspensaside methyl ether.

Conclusion: Heat-clearing actions of *Forsythiae Fructus* are based on the anti-inflammatory and antioxidant properties of lignans and phenylethanoid glycosides. Detoxifying effects attribute to the antibacterial, antiviral and anti-cancer activities of *Forsythiae Fructus*. And traditional Chinese medicine (TCM) characteristics of *Forsythiae Fructus* (bitter flavor, slightly cold nature and lung meridian) supported its strong anti-inflammatory effects. In addition, the remarkable anti-inflammatory and antioxidant capacities of *Forsythiae Fructus* contribute to its anti-cancer and neuroprotective activities. The higher proportion of lignans and phenylethanoid glycosides in Qingqiao than Laoqiao might explain the better antioxidant ability of Qingqiao and more frequent uses of Qingqiao in TCM prescriptions. For future research, more *in vivo* experiments and clinical studies are encouraged to further clarify the relation between traditional uses and modern applications. Regarding to Qingqiao and Laoqiao, they remain to be differentiated by all-round quality control methods, and the chemical compositions and clinical effects between them should be compared.

* Corresponding authors.

E-mail addresses: mazq1968@sina.com (Z. Ma), linrch307@sina.com, linrch307@126.com (R. Lin).

¹ These authors contributed equally to this study and share first authorship.

1. Introduction

Forsythia suspensa (Thunb.) Vahl. (Family Oleaceae) is an ornamental shrub, the fruits of which are used as the well-known TCM “Forsythiae Fructus” (FF) (连翘 in Chinese). The TCM characteristics of FF are summarized as bitter in flavor, with a mild cold nature and lung, heart or intestinum meridian distributions (Pharmacopoeia Commission of PRC, 2015), those characteristics are parallel to the characterisation of anti-inflammatory TCM, according to Chen and Zhang (2014). In Shennong’s herbal, FF was used for the treatment of pyrexia, inflammation, gonorrhoea, carbuncle and erysipelas (Cho et al., 2011). Two forms of FF are available, the greenish fresh ripe fruit called “Qingqiao” and the yellow fully ripe one called “Laoqiao”. Both of them serve as official sources of FF, nevertheless, Qingqiao is used more frequently in TCM prescriptions (Jia et al., 2015). The major producing areas of FF are Hebei, Shaanxi, Shanxi, Shandong, Anhui, Henan, Hubei, Jiangsu (cultivated) and Sichuan Provinces (Editorial Board of Flora of China, 1978).

In the 2015 edition Chinese Pharmacopoeia, 114 Chinese medicinal preparations containing FF are listed, such as Shuanghuanglian oral solution, Yinqiao Jiedu tablet, Niu Huang Shangqing tablets, etc (Pharmacopoeia Commission of PRC, 2015). Modern researches reveal its anti-inflammatory (Kim et al., 2003), antioxidant (C.C. Chen et al., 1999), antibacterial (Han et al., 2012), anti-cancer (Hu et al., 2007), anti-virus (Ko et al., 2005), anti-allergy (Hao et al., 2010), neuroprotective (S. Zhang et al., 2015) effects, etc. Although only the fruit is used as TCM, some studies reported the phytochemistry and pharmacological effects of leaves (Ge et al., 2015; Q. Zhang et al., 2015), flowers (Takizawa et al., 1981) and seeds (Zhang et al., 2002) of *F. suspensa*. Therefore, we now provide a systematic overview of the available information of *F. suspensa*, including traditional uses, botany, phytochemistry, pharmacology, toxicity, pharmacokinetics and quality control. Also, the possible future directions of research are discussed.

2. Traditional uses

In classical Chinese herbal texts, FF is recorded as useful in the treatment of rat fistula, scrofula, carbuncle, malignant ulcer, gall tumor, heat and poison (Shennong’s herbal, Bencao Chongyuan, Bencao Zhengyi, Zhenglei Bencao). According to many ancient classics, this medical herb is considerably effective on clearing the heat of heart channel and releasing the dampness-heat of spleen and stomach. It is also therapeutic for the treatment of stranguria, oedema, qi stagnancy and blood stasis (Bencao Yanyi, Yaoxing Bencao, Rihua Bencao, Bencao Buyi). Furthermore, FF was used as the Holy Medicine for Ulcer of Twelve Channels (Bencao Beiyao, Bencao Congxin). It is able to clear pathogenic fever away from the body, treat boils and influenza virus, suppress bacteria, diuresis and hepatic damage and relieve vomiting (Chen et al., 2004). In the Chinese Pharmacopoeia, preparations containing FF are mainly used for heat-clearing and detoxifying (Pharmacopoeia Commission of PRC, 2015). Some of the prescriptions are summarized in Table 1.

3. Botany

F. suspensa (Weeping Forsythia) is an ornamental deciduous shrub native to China, growing to a height of about 3 m (Fig. 1). It has hollow internodes with spreading or pendulous branchlets that are yellow-brown or gray-brown in colour. Leaves are usually simple, but sometimes 3-foliolate. Leaf blades are ovate, broadly ovate, or elliptic-ovate and $2\text{--}10 \times 1.5\text{--}5 \text{ cm}^2$ in size with a rounded to cuneate base and an acute apex. Both sides of the leaves are green, glabrous with sharply or coarsely serrate margins. The petioles are glabrous and 0.8–1.5 cm in length. Flowers grow severally in leaf axils, and the pedicel is 5–6 mm in length. Calyxes are green and the lobes are oblong, ciliate, (5-) 6–7 mm in length. Corollas are yellow, and the lobes are obovate-

oblong or oblong, $1.2\text{--}2.0 \times 0.6\text{--}1.0 \text{ cm}^2$ in size, and the corolla tubes are subequal to calyx lobes. Pistils in flowers are 5–7 mm with 3–5 mm stamens or about 3 mm with 6–7 mm stamens. The fruits (capsules) are ovoid to long ellipsoid, coronoid at top, $1.2\text{--}2.5 \times 0.6\text{--}1.2 \text{ cm}^2$ in size with scattered lenticels. The stalks are 0.7–1.5 cm in length. Qingqiao is mostly indehiscent, externally greenish-brown to brown, texture hard; seeds numerous, yellowish-green to brown, slender, winged on one side. Laoqiao is dehiscent starting from apex or into two segments, the outer surface yellowish-brown to reddish-brown, the inner surface mostly pale yellowish-brown, smooth, with a longitudinal septum, its texture brittle; seeds brown, mostly fallen off. This plant flowers from March to April and fruits from July to September. *F. suspensa* grows in thickets or grassy areas on slopes, valleys and gullies at 300–2200 m. In China, it is produced in Hebei, Shaanxi, Shanxi, Shandong, Anhui, Henan, Hubei, Jiangsu (cultivated) and Sichuan Provinces. The fruits are used as antipyretic and antidote (Editorial Board of Flora of China, 1978).

FF is the dried fruit of *Forsythia suspensa* (Thunb.) Vahl. (Oleaceae) (Fig. 1). The herbal medicine is either collected in autumn when nearly ripe, but still greenish, foreign matter removed, steamed thoroughly and dried under the sun (known as Qingqiao), or collected when fully ripe, foreign matter removed, dried under the sun (known as Laoqiao) (Pharmacopoeia Commission of PRC, 2015).

4. Phytochemistry

Nowadays, 237 compounds have been found in *F. suspensa*, including 46 lignans (1–46), 31 phenylethanoid glycosides (47–77), 11 flavonoids (78–88), 80 terpenoids (89–168), 20 cyclohexylethanol derivatives (169–188), six alkaloids (189–194), four steroidal (195–198) and 39 other compounds (199–237). Among them, two components (21–22) were isolated from the flowers of *F. suspensa*, 19 components (94–100, 107–111, 115–117, 198, 233–235) were isolated from the leaves of *F. suspensa*, four constituents (194, 211–213) were separated from the seeds of *F. suspensa*. 211 Components were isolated from FF, involving 21 (13–18, 23–24, 29–30, 38, 43, 54–55, 69–70, 74–76, 187–188) out of Qingqiao and 17 (44–45, 62–68, 91, 114, 180, 189–192, 196–197, 207) out of Laoqiao, while the rest did not specify whether isolated from Qingqiao or Laoqiao. The names and structures of 1–237 compounds are listed as follow.

4.1. Lignans

Lignans are the characteristic substances of *F. suspensa*. In summary, lignans of *F. suspensa* display anti-inflammatory, antioxidant, anti-cancer, anti-virus and anti-allergy effects, etc. 46 Lignans (1–46) were isolated from this herb in total. They are sorted into six groups, including furofurans (1–19), dibenzylbutane (20), dibenzylbutyrolactones (21–24), tetrahydrofurans (25–36), neolignans (37–42) and aryl naphthalenes (43–46). Among them, two dibenzylbutyrolactones (21–22) were separated from the flowers of *F. suspensa*. The others were isolated from the fruits.

Three furofuran lignans including (+)-pinoselinol (1), (+)-phillygenin (2) and phillyrin (forsythin) (3) were separated in 1977 (Nishibe et al., 1977a). (+)-Pinoselinol monomethyl ether- β -D-glucoside (4) was isolated in 1997 (Liu et al., 1997). Guo reported the isolation and identification of six furofuran lignans involving (+) epipinoselinol (5), (+)-1-hydroxy-6-epipinoselinol (6), (+)-1-hydroxy-6-epipinoselinol-4'-O- β -D-glucopyranoside (7), (+)-1-hydroxypinoselinol (8), (+)-1-hydroxypinoselinol-4'-O- β -D-glucoside (9) and (+)-1-hydroxypinoselinol-4'-O- β -D-glucoside (10) in 2006 (Guo, 2006). 7'-Epi-8-hydroxypinoselinol (11) was found in 2008 (Chang et al., 2008), and pinoselinol (12) was discovered in 2010 (Xue et al., 2010). Six more furofurans, (+)-8-hydroxyepipinoselinol-4-O- β -D-glucopyranoside (13), (+)-epipinoselinol-4'-O- β -D-glucopyranoside (14), (+)-epipinoselinol-4-O- β -D-glucopyranoside (15) (Yan et al., 2014b),

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