Review

Phytochemistry and pharmacology of *Fagopyrum dibotrys* (D. Don) H. Hara: A review

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Accepted 11 April, 2012

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*Fagopyrum dibotrys* (D. Don) H. Hara, a widely used traditional Chinese herb, belongs to the family of *Polygonaceae*, and possesses a wide range of ethnomedicinal uses. In recent decades, a great number of chemical and pharmacological studies have been done on *F. dibotrys*. More than 80 compounds including flavonoids, organic acids, sterides, essential oil and amino acids, as well as vitamins have been found in the herb, with many of them being isolated for the first time from *Fagopyrum Mill*. Currently, the effective compounds or effective parts have been screened for the pharmacological activity of this herb to exhibit anti-tumor effect, anti-inflammatory, analgesic, antibacterial and other activities. This review aims at providing a comprehensive work about the phytochemistry and pharmacological action of *F. dibotrys*. Future efforts should concentrate more on *in vitro* or *in vivo* studies and clinical trials in order to confirm traditional uses. Especially, the efficacy of *F. dibotrys* should be further researched in the treatment of anti-tumor and lung abscess.

Key words: *Fagopyrum dibotrys*, phytochemistry, pharmacological action.

INTRODUCTION

*Fagopyrum dibotrys* (D. Don) H. Hara (Figure 1) belongs to the genus *Fagopyrum* and family *Polygonaceae*, a widely distributed genus. Wild species of *Fagopyrum* grows best in the temperate and hilly regions of countries in China, India, Nepal, Vietnam, Thailand and the Himalayan region (lian, 1998; Wu et al., 2010).  

Jinqiaomai, the roots of this herb, is one of the most commonly used traditional Chinese herbs, and is also widely accepted as a health product in the Western countries in recent years, owing to its remarkable and reliable biological activities, especially in the treatment of lung ailments (Liu et al., 1981; Gao and Meng, 1993; Peng et al., 1996). The therapeutic use of the herb was first cited in Dian Nan Ben-Cao (1436 a.d., Ming Dynasty), a classical masterpiece of Traditional Chinese Medicine (TCM). The traditional uses recorded for this herb are numerous, and mainly medicinal (Liu et al., 1981; Xu et al., 1982; Samaiya and Saxena,1989; Zhang et al.,1999; Zhao et al., 2002; Huang, 2008; Pharmacopoeia Commission of People's Republic of China, 2010). Several kinds of Chinese pharmaceutical preparations have been developed, including capsules, tablets and syrups. In brief, jinqiaomai and jinqiaomai-containing medicinal preparations are now receiving considerable attention worldwide, and many scientific studies have been carried out in chemistry, clinical trial,
safety, as well as in pharmacology.

In recent decades, researches on this genus, mainly based on its botanical, phytochemical and pharmacological aspects have taken place. Due to the variability in the thematic of the studies and the extension of this genus, the purpose of this review is to summarize the phytochemistry and pharmacological properties of this herb in order to facilitate and guide future researches.

PHYTOCHEMISTRY

The phytochemical study of *F. dibotrys* can be dated back to 1951 with rutin first isolated from the plant (Imai and Furuya, 1951). So far, more than 80 compounds have been separated and structurally identified from this herb, among them, flavonoids and organic acid are with the largest content, in fact, they are the main components responsible for the pharmacological activity (Gonzalez et al., 2011).

Recently, from the polar extracts of the roots of cultivated *F. dibotrys*, some new flavonoids compounds have been isolated, which was given the trivial names luteolin (Shao et al., 2005), rutin (Imai and Furuya, 1951; Tian et al., 1997; Wang et al., 2005), quercetin (Tian et al., 1997; Zhao et al., 2011), isorhamnetin, quercitrin (Tian et al., 1997; Zhao et al., 2011), pratol, luteolin-7,4′-dime-thylether, rhamnetin, 3,6,3′,4′-tetrahydroxy-7-methoxyflavon (Wu et al., 2008), and hesperidin (Yan et al., 2006). Meanwhile, 3,4-dihydroxybenzoic acid, gallicacid, (-)-epicatechin, (-)-epicatechin-3-O-gallate acid ester, procyanidin B-2, and procyanidin C-1 from the alcoholic extract of the plant were isolated (Zhang et al., 1994). The main component was procyanidin B-2 (0.19%). 5,7,3′,4′-tetrahydroxyflavan-3-ol-dimmer was also isolated from *F. dibotrys* (Liu et al., 1983).

Organic acids have been known to be important constituents of this herb. Four phenolic acid derivatives were isolated from the plant. The chemical structures were elucidated as trans-p-hydroxy cinnamic methyl ester, 3,4-dihydrox benzamid, protocatechuic acid, and protocatechuic acid methyl ester (Shao et al., 2005). Benzoic acid, p-hydroxy-benzoic acid (Tian et al., 1997), succinic acid (Tian et al., 1997; Zhao et al., 2011), and syringic acid (Zhao et al., 2011) have also been isolated from this herb. Moreover, diboside A and lapathoside A from acetone-water mixture extract of root of *F. dibotrys* were isolated by Wang et al. (2005). At the same time, steride compounds were isolated from the roots of *F. dibotrys*, such as hecogenin (Liu et al., 1983), β-sitosterol (Liu et al., 1983; Tian et al., 1997; Wu et al., 2008; Zhao et al., 2011) and β-daucosterol (Yan et al., 2006; Zhao et al., 2011). Extraction of essential oil from *F. dibotrys* by using steam distillation and analysis by GC-MS identified 43 compounds (Bai et al., 2007). Among the 43 species, there were 13 kinds of hydrocarbon compounds and 30 oxygenated hydrocarbon derivatives. N-hexadecanoic acid was the main constituents, accounting for 10.34% of the volatile fraction. The seeds of the herb possess 18 amino acids, a number of essential inorganic substances and vitamins, such as, asparaginic acid, threonine, glutamic acid, serine, sodium, calcium, selenium, vitamins B1, B2, VPP, VP, etc. (Zhang et al., 1999; Zhao et al., 2002; Wang et al., 2011). The content of glutamic acid is the highest. A range of other compounds have also been isolated from the herb along with the aforementioned constituents, including glycerol monop-almitate, n-butyl-β-D-fructopy-ronoside, glutinol (Shao et al., 2005), glutinone (Shao et al., 2005; Zhao et al., 2011), daucosterol, 5,5′-di-c-furaldehyde dimethyl ether, (Tian et al., 1997), eriodictyol, acid-4-o-glucoside, p-hydroxyl-benzaldehyde, 3,5-dimethoxy benzene carbonic, N-trans-coumaroyl tyramine, emodin (Zhao et al., 2011), and shakuchirin (Liu et al., 1998).

In addition, luteolin (1), pratol (2), rhamnetin (3), luteolin-7,4′-dime-thylether (4), 3,6,3′,4′-tetrahydroxy-7-methoxyflavon (5), hesper-iden (6), 3,4-dihydoxy benzamide (7), protocatechuic acid methyl ester (8), glutinone (9), glutinol (10), n-butyl-β-D-fructopy-ronoside (11), trans-p-hydroxy cinnamic methyl ester (12), eriodictyol (13), 3,5-dimethoxy benzene carboxic acid-4-O-glucoside (14), and N-trans-coumaroyl tyramine (15) are isolated from *Fagopyrum Mill* genus for the first time. Syringic acid (16) is isolated from this plant for the first time. The structures of the major components (1 to 16) are depicted in Figure 2.

Pharmacological action

Anti- tumor effect

Many *in vivo* and *in vitro* experiments have demonstrated that Fr4 is regarded to be the most promising anticancer compound in *F. dibotrys* (Ling et al., 1996; Chen et al., 2000, 2002, 2003, 2005, 2006). The main anti-tumor constituent is 5,7,3′,4′-tetrahydroxyflavan-3-ol-dimmer (Figure 1) (Liu et al., 1983). Down regulation of the telomerase activity in tumor cells might be contributed to Fr4 induced apoptosis. At the same time, component (E) is the most active agent against the DNA of cancer cells among the extracts from *F. dibotrys* (Ma et al., 1989). Component (E) inhibits cancer cell growth by directly or indirectly influencing the metabolism of DNA, especially in low concentrations and probably plays the major role. Moreover, the extract has notable inhibitory effects against tumor invasion and metastasis (Liu and Han, 1998).

Anti-inflammatory and analgesic activity

An organic extract from this herb presented topical anti-inflammatory activity on chronic inflammation in animal models (Cheng et al., 2009). Additionally, the extract markedly decreased the amount of mice which had
Antibacterial activity

The results indicated that all the extracts have strong antibacterial activities in vitro, and the extracts have high inhibition on Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Bacillus thuringiensis, Diplodocus Catarrhalis, Sclerophthora macrospora, Candida albicans, Pestalotia funereal, Rhizoctonia solani, Sclerotinia sclerotiorum, Curvularia lunata (walk) boed, Gibberelle zae (schw) and Trichoderma viride (Feng et al., 2006). Furthermore, ethanol extracts exhibited a wide spectrum of antibacterial activity, thus confirming the previous result (Ai et al., 2002).

Other study concluded that the lung injury induced by Klebsiella pneumonia is related to toll-like receptor2/4 (TLR2/4), myeloid differentiation primary response gene 88 (MyD88) mRNA and nuclear factor kappa B inhibitor protein (IkB-α). A decrease in the excessive expression of TLR2/4, MyD88 mRNA and IkB-α might be obtained by the effect of F. dibotrys on lung injury (Dong et al., 2011).

On the other hand, in vitro antibacterial test result demonstrated that the extract showed remarkable inhibition to the beta-hemolytic Streptococcus and Pneumococcus, but proved weak antimicrobial effect to S. aureus and Pseudomonas aeruginosa and was ineffective against K. pneumoniae and E. coli. The protection in vivo to the mice infected with Streptococcus pneumoniae by the extract’s effects on bacteria was obvious (Wang et al., 2005). Phenolic acids and flavonoids compounds were the major base of antimicrobial function (Wang et al., 2005). In spite of these recent studies, the identity of the active antibacterial ingredients of F. dibotrys as well as its mechanisms of action is still questionable.

Other pharmacological action

Within the concentration of 20 to 60 g/kg, the extract could significantly decrease the activities of rat serum alanine transaminase (ALT), and aspartate transaminase (AST), and was capable of protecting the liver from
Figure 2. The structures of the major components: a) luteolin, b) pratol, c) rhamnetin, d) luteolin-7,4′-dime-thylether, e) 3,6,3′,4′-tetrahydroxy-7-methoxyflavon, f) hesperidin, g) 3,4-dihydroxy benzamide, h) protocatechuic acid methyl ester, i) glutinone, j) glutinol, k) n-butyl-β-D-fructopyronoside, l) trans-p-hydroxy cinnamic methyl ester, m) eriodictyol, n) 3,5-dimethoxy benzene carbonic acid-4-O-glucoside, o) N-trans-coumaroyl tyramine, p) syringic acid.
Figure 2. Contd.
chemical damage (Shu et al., 2005). The extracts of this herb (dose of 0.45 to 1.8 g/kg) reduced the times of coughing by the ammonia-induced cough in mice and also enhanced the secretion of phenol red in mice (dose of 0.90 to 1.8 g/kg). Meanwhile, the acute toxicity study of the maximum dosage of the extracts suspension for administering to mice was 810 g/kg (Bao et al., 2009). Additionally, the 70% ethanol extracts showed remarkable antioxidation activity with IC\textsubscript{50} of 0.324 mg/ml (Wang et al., 2009). Besides, it can inhibit mutagenicity of daunomycin and methanesulfonate in strains TA98 and TA100.

It did not induce the increase of micronucleus rate in NIH mice marrow polychromatic erythrocytes and chromosome aberration in cholesterin. It did not cause the adverse effects on the NIH mice reproductive ability and embryo, growth, development and deformity of the fetus appeararoes, bone, and internal organs (Ma et al., 1989, 1990, 1991a, b). It is worth noting that the crude aqueous acetone extracts exhibited high antioxidiant activity (SC\textsubscript{50} 10.95 g/ml) in 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay. 3-methyl-gossypetin 8-α-β-d-glucopyranoside and diboside A together with other known antioxidant phenolic compounds play an important role for the antioxidant activity of \textit{F. dibotrys} (Wang et al., 2005).

CONCLUSION

So far, a lot of progress has been made in the study of phytochemistry; more than 80 chemical components have been separated and identified in this plant, with many of them being isolated for the first time from \textit{F. Mill}. In recent decades, modern pharmacological studies have demonstrated that the herb possesses not only very comprehensive pharmacological actions but also wide clinical applications.

Molecular biological technology has also been applied in the study of the pharmacology of this herb, which opened a new approach for the study of pharmacological mechanism of \textit{F. dibotrys}. It should be noted that pharmacological studies of Fr4 and component (E) from \textit{F. dibotrys} have been paid extensive attention in recent years, and exhibited better therapeutic effects in antitumor treatment. However, the pharmacological studies have focused mainly on crude extracts, and many of the constituents responsible for different pharmacological actions remain unknown. More studies are needed to prove clinical efficacy and reveal the exact mechanism of action.

ACKNOWLEDGEMENT

This work was supported by the Foundation from the Education Department of Heilongjiang Province, China (Grant No. 12511369).

REFERENCES


