

Original Research Article

Traditional uses, chemical constituents and pharmacological effects of *Boschniakia rossica*: A systematic review

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Abstract

Purpose: To undertake a review on the morphology, traditional uses, phytochemistry and pharmacology of *Boschniakia rossica*, a plant with a long history of usage in Chinese traditional medicine.

Methods: Available literature on the ethnopharmacological uses of *B. rossica* from 1967 to 2018 were selected via various databases, such as ScienceDirect, NCBI, Springerlink, Taylor & Francis and CNKI.

Results: A variety of phytochemical studies demonstrated that *B. rossica* contains more than 100 chemical constituents, among which boschnaside, boschniakine, 7-deoxy 8-epiloganic acid, (4R)-4-hydroxymethyl-boschnialactone are predominant. Studies showed that isolates and crude extracts of *B. rossica* exhibit a wide spectrum of in vitro and in vivo pharmacological effects such as anti-aging, anti-tumor, anti-oxidant, anti-inflammatory and immune enhancement. It was revealed that iridoids, carbohydrates and glycosides are perhaps responsible for most of the biological activities shown by this plant. However, the bio-active compounds and their underlying mechanisms of action have not yet been investigated in detail.

Conclusion: *B. rossica* has received tremendous research attention. Phytochemical and pharmacological studies have provided scientific bases for validation of the traditional uses of the plant.

Keywords: *Boschniakia rossica*, Traditional herb, Pharmacology, Chemical components, Boschnaside

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INTRODUCTION

Boschniakia rossica Fedtsch. et Flerov (Figure 1) belongs to *Orobanchaceae*. It is a perennial parasitic herb which lives on the roots of plants belonging to the genus *Alnus*, for example *Alnus japonica*. The whole herb is used as medicine which in China, is called “no old herb” because of its medicinal properties. The distribution area of

B. rossica is a very limited in the world: it is found only in Korea, Japan, Russia’s Siberia Mountains and northeast China. In China, it is distributed mainly at 1350- 2000 m above sea level in the Changbai Mountains and on the northern mountainous area of Daxinganling [1]. *Boschniakia rossica* has rare natural distribution due to its parasitic characteristics, it belongs the

second-class of national protected plants in the list of rare and endangered plants in China [2].



Figure 1: *B. rossica*. (A) fresh whole herb; (B) dry whole herb. The roots are underground, while the stems and spikes are above the ground. The leaves are dense near the base of the stem and sparse upward

B. rossica is a highly parasitic and precious medicinal plant, the aerial parts of which contain boschnialactone, boschnaside, boschniakine and boschnialinic acid. The rhizome contains mannitol and alkaloids. *Boschniokia rossica* is available and collected between May and August every year. After drying by airing or in the sun, it is cut into sections. Most people take *B. rossica* in the form of soup or infuse it into their bodies. It possesses multiple functions which are recorded in Chinese traditional books. These include; kidney invigoration, aphrodisiac qualities, hemostatic activity, and enhancement of longevity [2]. Clinically, *B. rossica* is used to treat kidney problems, chills, waist and knees pain, chronic constipation, cystitis, functional uterine hemorrhage, nephritis, prostatitis, as well as kidney and bladder hemorrhage. Although its dried herb is used as a tonic in China, Korea and Japan, the basic principle involved in this

application has not yet been elucidated. Studies have shown that *B. rossica* exhibited free radical scavenging, anti-lipid peroxidation, anti-tumor, anti-inflammatory and immunity-enhancing properties [3].

METHOD

The available literatures on the ethno-pharmacological uses of *B. rossica* from 1967 to 2018 were selected via several databases-such as Science Direct, NCBI, Springer link, Taylor & Francis and CNKI. The main chemical compositions and pharmacological activities were reviewed based on the collected literatures, with the aim of providing beneficial information for the development and clinic applications of *B. rossica*.

RESULTS AND DISCUSSION

Phytochemistry

Varieties of natural compounds have been isolated from different parts of *B. rossica* through chromatography. These include phenylpropanoid glycosides, iridoids, polysaccharides, organic acids and alkaloids. The main chemical compositions of the plant are shown on Tables 1 and 2. In addition to chemical composition, nutrient and mineral element contents of *B. rossica* have been determined by automatic amino acid analyzer and atomic absorption spectrometry, respectively. The results showed 6.55 % amino acid content, out of which essential amino acids accounted for 36.18 % [4]. In addition, there were 17 amino acids, and more than 7 of these are essential to humans [5]. Inorganic elements include K, Na, Ca, Mg, Fe, Zn, Mn, Cu, Ni and Cr. The contents of first eight inorganic elements were 20.436, 2.275, 0.820, 0.994, 0.236, 0.036, 0.034 and 0.016 mg/g, respectively [4,6,7]. Water-soluble polysaccharides have been isolated and purified from *B. rossica*, and their molecular weights and monosaccharide compositions have been studied [8,9].

The important phytochemical components of *B. rossica* that have received research interest are phenylpropanoid glycosides, iridoids, polysaccharides and the resinous exudates which are dispensed on prescription in the indigenous medicines of China, Japan, Korea. Therefore, the spikes, leaves, bark and stem of *B. rossica* are the most frequently investigated targets for screening active compounds. Figure 2 shows the structures of some chemical constituents of *B. rossica*.

Biological activities

Various studies have reported the anti-aging, anti-tumor and hepatoprotective effects of *B. rossica* extracts in animal models (Table 3). These activities might be related to the anti-inflammatory, free radical scavenging and SOD-enhancing effects of the plant. Other studies have suggested that iridoids, polysaccharides and glycosides are the major bioactive compounds in *B. rossica*.

Immune-enhancing effects

It has been shown that ethanol extracts of *B. rossica* increased immune function *in vitro* and *in vivo*. Mice spleen cells and sheep red blood cells

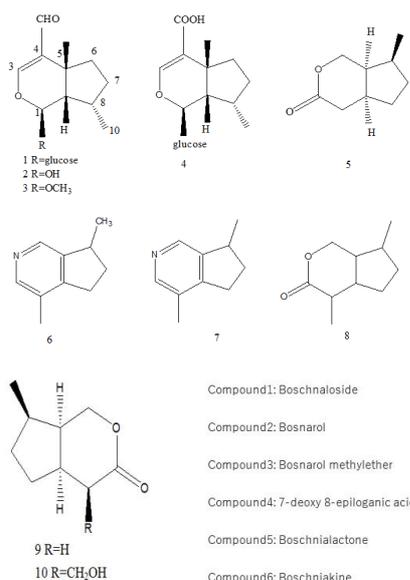
of treatment group increased significantly compared with control group, and two had positive correlation [29]. Rat Kupffer cells cultured *in vitro* and treated with carbon tetrachloride had significantly higher phagocytic rate and phagocytic index when exposed to ethanol extract *B. Rossia* ethanol extract [30]. In another research, three polysaccharides were isolated and purified from the water extract of *B. rossica*, and their effects on macrophage activation were also investigated *in vitro*, including phagocytosis of macrophages, NO production and TNF- α secretion. The results indicated that *B. rossica* polysaccharides mediated macrophage activation and promoted the production NO and TNF- α , thereby contributing to immune-stimulation [9].

Table 1: Chemical constituents of *B. rossica*

Class	Chemical constituent	Source	References	
Volatile oils	All-cis-iridomyrmecin (1)	Whole herb	[10, 11]	
	All-cis-iridomyrmecin (2)	Whole herb	[10, 11]	
	All-cis-dihydronepetalactone (3)	Whole herb	[10, 11]	
	All-cis-isodihydrone petalactone (4)	Whole herb	[10, 11]	
	Boschnialactone (5)	Whole herb	[10, 11]	
	Neoboschnialactone (6)	Whole herb	[10, 11]	
	1-Heanol (7)	Whole herb	[12]	
	Cis-8-mintene (8)	Whole herb	[12]	
	Pulegine (9)	Whole herb	[12]	
	N-hexylvinyl (10)	Whole herb	[12]	
	Dihydro-carvone (11)	Whole herb	[12]	
	Tetradecane (12)	Whole herb	[12]	
	Heptadecane (13)	Whole herb	[12]	
	Cis-caryophyllene (14)	Whole herb	[12]	
	Octadecane (15)	Whole herb	[12]	
	Geraniol (16)	Whole herb	[12]	
	Lavanduol (17)	Whole herb	[12]	
	Ethyl-tren- α -heptanoate (18)	Whole herb	[12]	
	4-methyl-azabicyclo(2,2,2)octane acid (19)	Whole herb	[12]	
	N-pentadecane (20)	Whole herb	[12]	
	3 α - acetyloleanolic acid (21)	Whole herb	[13, 14]	
	Oleanolic acid (22)	Whole herb	[13, 14]	
	β -sitosteryl (23)	Whole herb	[13, 14]	
	7-deoxy-8-epiloganic acid (24)	Root, stem	[15]	
	(4R)-4-hydroxymethyl-boschnialactone (25)	Root, stem	[16]	
	(24S)-3 β -hydroxy-24-ethylcholest-5-en-7-one (26)	Whole herb	[16]	
	(24R)-3 β -hydroxy-24-ethylcholest-5-en-7-one Methyl p-coumarate (27)	Whole herb	[16]	
	4,5,6-three hydroxyl odone (28)	Whole herb	[11, 17]	
	Boschnialinic acid (29)	Whole herb	[11, 17]	
	Organic acids	Decahydronaphthoic acid (30)	Whole herb	[18]
		3,5-Dimethoxybenzoic acid (31)	Whole herb	[18]
		Palmitic acid (32)		[18]
		Linoleic acid (33)		[18]
10-methyl-heptadecanoic acid (34)			[18]	
9,12-octadecadienoic acid (35)			[19]	
9,17-octadecadienoic acid (36)			[19]	
5,8,11-heptadecatrienoic acid (37)			[19]	
Gallic acid (38)			[17, 20]	
Cinnamic acid (39)			[17, 20]	
Caffeic acid (40)			[17, 20]	

Table 2: Chemical constituents of *B. rossica* (contd)

Class	Chemical constituent	Source	References
Alkaloids	P-coumaric acid (41)		[13]
	Actinidine (42)		[10]
	Boschniakine (43)		[10, 11]
	Trans-2,3-dimethylindoline (44)		[21]
	7-methyl-6,7-dihydro-5H-1-pyridine (45)		[21]
	2-phenyl-5-isopropyl -1,3,4-oxadiazoles (46)		[21]
Glycosides	8-Epi-iridodial glucoside (47)		[22]
	Boschnarol (48)		[14]
	Daucosterol (49)	Whole herb	[14]
	Boschnaloside (50)	Whole herb	[15]
	Boschnarol methylether (51)		[15]
	β -sitosterol-3-O- β -D-glucoside (52)	Whole herb	[17]
	Rossicaside A (53)	Whole herb	[23]
	Rossicaside B (54)		[13]
	Rossicaside C (55)	Whole herb	[13]
	Rossicaside D (56)	Whole herb	[13]
	Rossicaside E (57)	Whole herb	[23]
	Rossicaside F (58)		[24]
	Acteoside (59)	Whole herb	[25]
Carbohydrate	Glucose (60)	Whole herb	[8, 9, 26-28]
	Xylose (61)	Whole herb	[8, 9, 26]
	Mannose (62)	Whole herb	[8, 9]
	Galactose (63)	Whole herb	[8, 9, 28]
	Rhamnose (64)	Whole herb	[26]
	Arabinose (65)	Whole herb	[9, 26, 28]
	Fucose (66)	Whole herb,	[27, 28]
	Sucrose (67)	inflorescence	[20]
	Galacturonic acid (68)	Whole herb,	[26, 27]
	Glucuronic acid (69)	inflorescence	[9]
	amino acids (70)	Whole herb	[5]
	Mineral elements (71)		[4, 6, 7]

**Figure 2:** Chemical structure of partial components from *B. rossica*

Anti-aging and memory-enhancing effects

The dried herb and stem of *B. rossica* have been used as anti-senile agents in China for many years. In the past few decades, a series of studies have confirmed the anti-aging and memory-enhancing ability of *B. rossica* extracts, as well as the underlying mechanisms. A 50 % ethanol extract of *B. rossica* was administered to rats whose nucleus basalis of Meynert had been destroyed by the injection of ibotenic acid. This administration resulted in significant mitigation of the decreases in correct responses caused by destruction of the nucleus basalis of Meynert, suggesting that *B. rossica* might be a useful source of therapeutic drug for senility [31]. Further studies on the mechanism involved in the invigorating and anti-senile actions of *B. rossica* revealed the 50 % ethanol extract exhibited free radical scavenging activity. The concentrations showing 50 % inhibition of 1, 1-diphenyl-2-picrylhydrazil radical, superoxide radical and

hydroxyl radical were 0.003, 0.06 and 9.67 %, respectively [32]. The extract increased SOD activity, decreased MDA content, and inhibited the MAO activity in brain tissue. It was observed under microscope that *B. rossica* extract reversed mitochondrial degeneration of mitochondrion and had obvious protective effect on brain tissue of senile rats [33,34]. In addition, *B. rossica* extract has been shown to exert anti-hypoxia and anti-fatigue effects in normal mice [35]. *Boschniakai rossica* extract increased the expression of nestin in hippocampus neural stem cells nestin in AD model rats, and improved learning ability and memory in the AD rats [36]. It reduced the activation of glial cells, thereby protecting the neurons, and it enhanced the ability of learning and memory of rats with Alzheimer's disease [37].

Anti-tumor effects

The water extract of *B. rossica* increased the activities of SOD, GSH-PX and, CAT, and raised TNF- α content of rat liver at the early stage of chemical carcinogenesis; it also reduced GST activity of GST and MDA level arising from increased pre-cancerous lesions [38].

Studies have shown that ethanolic extract of *B. rossica* increased the tumor growth inhibition ratio, and the serum T-AOC, while decreasing serum MDA content [39]. It promoted the apoptosis of tumor cells and inhibited the proliferation of A549 lung carcinoma cells [40]. Further studies showed that the phenylpropanoid glycosides from *B. rossica* extract significantly increased P53, Bax and Fas expressions, and decreased Bcl-2 expression, thus exerting anti-lung cancer effect by inducing cell cycle arrest and apoptosis [41].

Iridoid glucosides from *B. rossica* in H₂₂-bearing mice significantly reduced xenograft tumor mass, and significantly increased mice spleen index and serum levels of IL-2 and T-AOC, while decreasing the levels of TNF- α and MDA [42]. It has been reported that iridoid glucosides from *B. rossica* inhibited the expression of PCNA of tumor cells, induced tumor cell apoptosis, decreased Bcl-2 protein expression, and increased Bax protein expression, indicating that inhibition of tumor cell proliferation and induction of tumor cell apoptosis may be part of the mechanisms involved in the anti-tumor effect of iridoid glucosides [43].

Rhizome polysaccharide of *B. rossica* [BRP] showed antitumor effect *in vivo* at early metaphase of liver cancer [44]. It was seen that BRP alone or in combination with 5-FU

significantly inhibited sarcoma-180 tumor growth and increased the spleen index in a dose-dependent manner. A synergistic effect was observed in boosting various immunity functions such as stimulating lymphocytes proliferation, increasing NK cell cytotoxicity, enhancing serum IL-2 and TNF- γ secretions, as well as augmenting CD⁴⁺ and CD⁸⁺ spleen T lymphocytes subsets [45,46]. The BRP inhibited the proliferation of Hep2 cells in a time- and dose-dependent manner. Cell cycle analysis revealed that exposure to BRP.

Hepatoprotective effect

Studies on the hepatoprotective effect of *B. rossica* extract have reported that it reduced the formation of thiobarbituric acid- reactive substances, conjugated dienes and old lipofuscin, and restored SOD activity to normal value [48].

Ethanol extract of *B. rossica* protected the liver against chemically-induced injuries in animal models. Using a rat model of pig serum-induced liver fibrosis, it was shown that *B. rossica* extract significantly reduced serum procollagen type III and collagen type IV levels, and RT-PCR revealed that TGF- β 1 mRNA expression was also reduced. Thus *B. rossica* prevented rat liver fibrosis by inhibiting the activation of hepatic stellate cells and synthesizing collagen [49]. It has been shown that administration of *B. Rossica* ethanolic extract resulted in an anti-fibrogenic role in DMN-induced liver fibrosis in rats through its anti-oxidative effect and inhibition of hepatic stellate cell activation [50].

In CCl₄-induced liver injury in rats, pre-administration of *B. rossica* extract not only reversed the significant changes hepatic oxidative stress, xenobiotic metabolizing enzymes and pro-inflammatory mediators induced by CCl₄, but it also restored liver cytochrome P450 2E1 level and function [51,52].

The iridoid glucosides, phenylpropanoid glycosides and polysaccharides of *B. rossica* extract showed strong activity against D-Gal, LPS and CCl₄-induced liver injury. Iridoid glucosides from *B. rossica* significantly reduced serum ALT and AST levels in LPS-induced liver injury mice, reduce the caspase-3 and caspase-8 activation levels of liver tissue, and decreased liver DNA fractures. These effects may involve mechanisms related to its inhibition of liver cell apoptosis [53,54]. Moreover, the extract increased the anti-oxidative status of the liver, and exerted protective effects on acute liver injury induced by D-galactamine in mice [55].

Table 3: Pharmacological activities of *B. rossica*

Activity	Extract used	Plant part used	References
Immune-enhancing effect	Ethanol, polysaccharide	Whole herb	[9, 29-30]
Anti-aging and memory-enhancing effect	Ethanol, water	Whole herb	[31-37]
Anti-tumor effect	Water & ethanol, iridoid glucosides, polysaccharide, Phenylpropanoid glycosides	Whole herb root	[38-47]
Hepatoprotective effect	Ethanol, water, n-butanol, phenylpropanoid glycoside, iridoid glucoside, Polysaccharide	Whole herb	[48-60]
Anti-oxidative effect	Polysaccharide, water	Whole herb	[61-64]
Anti-inflammatory effect	Water, CH ₂ Cl ₂	Whole herb	[65-66]
Safety	Polysaccharide	Whole herb	[67, 69]

In addition, activity screening results showed that phenylpropanol glycosides of *B. rossica* inhibited triglyceride accumulation HepG2 cells [56].

Different doses of polysaccharides from *B. rossica* had different degrees of lowering effects in mice blood ALT and AST levels, and they reduced MDA content in liver tissue to varying degrees. They reduced liver tissue NO, and improved the activity of SOD in liver tissue. Histological studies on mice liver using H&E staining showed that the polysaccharides reduced the degree of liver cell swelling and, inflammatory cell infiltration [57]. Moreover, these data, *Boschniakia rossica* ethanol extract inhibited the proliferation of rat hepatic stellate cell-T6 cultured *in vitro* in a dose- and time-dependent manner. Flow cytometry analysis showed that the hepatic stellate cell-T6 treated with the *B. rossica* ethanol extract was arrested in Go/G1 [59,60].

Further investigations are needed to fully elucidate the exact mechanisms.

Anti-oxidative effect

Anti-oxidative effect was exhibited by water extract of *B. rossica* in the early stage of chemical hepato-carcinogenesis in rat livers [61]. *Boschniakia rossica* alleviated pathological changes in myocardial cells infected with coxsackie virus B 3 and significantly reduced MDA content in myocardial cells, while increasing the activity of superoxide dismutase [62]. The anti-lipid peroxidation effect of BRP has been investigated, and it was shown that BRP exerted high total antioxidant capacity in a concentration-dependent manner, and concentration-dependently inhibited lipid peroxidation of liver homogenate and liver mitochondria induced by H₂O₂, Fe²⁺ and ·OH [63,64]. These results suggest that BRP has anti-lipid peroxidation effects *in vitro*.

Anti-inflammatory effect

Aqueous extract of *B. rossica* has strong anti-inflammatory effect. Studies have shown that it inhibited carrageenan-induced foot swelling, controlled the release of inflammatory media PGE, and inhibited mouse celiac capillary permeability induced by acetic acid [65]. Both CH₂Cl₂ and H₂O extracts of *B. rossica* exhibited inhibitory effect in carrageenan-, histamine- and hot scald-induced hind paw edema, adjuvant-induced arthritis in rats and cotton pellet-induced granuloma formation in mice. They exhibited inhibitory effect on formation of preneoplastic hepatic foci in early stage of rat chemical-hepatocarcinogenesis. Both extracts exerted anti-inflammatory effect in rats and mice [66]. It has been reported that BRP inhibited xylene-induced ear swelling in mice, and the number of leukocytes and neutrophil in blood of mice with ear swelling. Dextran-induced rat paw swelling was remarkably reduced by BRP [67].

Anti-atherosclerosis effect

B. rossica significantly reduced the content of cholesterol, triglycerides, low density lipoprotein cholesterol, and MDA in serum of atherosclerosis rats, and increased the activity of high-density lipoprotein cholesterol and, superoxide dismutase. *B. rossica* significantly reduced atherosclerosis-induced damage in rabbit aortic endothelial cells, inhibited smooth muscle cell proliferation, and reduced monocytes adhesion, through a mechanism involving regulation of lipid metabolism, resistance to free radical oxidative damage, and prevention of aortic intima injury [68].

CONCLUDING REMARKS

Boschniakia rossica has received increasing research interest in recent years, and phytochemical and pharmacological studies have

validated its traditional uses. The various organic and aqueous extracts of *B. rossia* possess an array of pharmacological activities, including immune-enhancing, anti-aging, anti-tumor, hepatoprotective and antioxidant effects due to the presence of various iridoids, carbohydrates and glycosides in this plant. These compounds could serve as leads in the search for novel medicinal agents. There is a need to investigate the biochemical and physiological mechanisms underlying the properties of *B. rossia*, especially its cardioprotective, hepatoprotective and neuroprotective activities. Further studies on *B. rossia* should be designed to investigate the molecular mechanism(s) of action of isolated phytoprinciples using specific biological screening models and clinical trials, and also to discover novel leads from them. Moreover, studies should be extended to standardize the various extracts of *B. rossia* for the purpose of their use in specific herbal formulations. Further safety verification and clinical trials should be performed before *B. rossia* can be integrated into medicinal practice.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

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