Berberis microphylla G. Forst.

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Fruits of *Berberis microphylla* G. Forst. (Photo: Victor Fajardo)

Abstract The genus *Berberis* includes about 500 different species, which commonly grow in Europe, the United States, South Asia, some northern areas of Iran and Pakistan and South America. Plant species of the genus *Berberis* (Berberidaceae) are of particular phytochemical interest because they have been found to be important sources of alkaloids. In Chile, the Berberidaceae family is represented only by the *Berberis* genus, which includes 50 species. Only some of them have been chemically studied, as they are an important source of bisbenzyl-isoquinoline alkaloids (BBIAs), which are biogenetically derived from tyrosine. Various species of the

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Á. Máthé, A. Bandoni (eds.), *Medicinal and Aromatic Plants of South America Vol. 2*, Medicinal and Aromatic Plants of the World 7,
https://doi.org/10.1007/978-3-030-62818-5_7

genus *Berberis* have been used in folk medicine for the treatment of some diseases, highlighting its hypoglycemic value. The roots of *Berberis* (especially *B. microphylla*) have a high content of alkaloids, especially berberine, which appears to be responsible for its beneficial effects. Several studies have determined that the use of this natural product reduces the glycemic levels in healthy subjects and diabetes.

Keywords "Calafate" · Benzylisoquinoline alkaloids (BIAs) · Bisbenzylisoquinoline alkaloids (BBIAs) · Anthocyanins · Folk medicine

1 Introduction

In recent years, some species of *Berberis* from Chile and Argentina have been studied due to interesting biological properties related to their alkaloids and polyphenols content. *Berberis microphylla*, is a native plant commonly known as "calafate" that grows wildly in Southern of Chile and Argentina, and used by aboriginal ethnic groups in traditional medicine. Therefore, research has been focused on identification and isolation of new compounds in the *Berberis* genus with prominent biological activity.

2 Taxonomic Characteristics

Berberis microphylla G. Forst. of common name "calafate" is a thorny evergreen shrub endemic to Argentine and Chilean Patagonia. It is a species belonging to the subfamily Berberidoideae, the family Berberidaceae.

For a long time, the name *Berberis buxifolia* was the most commonly used name for this species, but in accordance with the rules of botanical nomenclature, presently, an older, less frequently used name, *Berberis microphylla* must be used. Other authors have subdivided it into numerous entities, but after field and herbarium studies Landrum in 1999, has published that cannot verify any satisfactory specific divisions. Other binomials assigned to *Berberis microphylla*, with corresponding authors are: *Berberis buxifolia* Lam., *Berberis inermis* Pers., *Berberis heterophylla* Juss. ex Poir., *Berberis cuneata* DC., *Berberis marginata* Gay, *Berberis buxifolia* var. *spinosissima* Reiche, *Berberis heterophylla* var. *pluriflora* Reiche, *Berberis buxifolia* Lam. var. *gracilior* Albov, *Berberis buxifolia* var. *papillosa* C.K. Schneid., *Berberis buxifolia* var. *nuda* C.K. Schneid., *Berberis buxifolia* var. *antarctica* C.K. Schneid., *Berberis antucoana* C.K. Schneid., *Berberis parodii* Job, *Berberis michay* Job, *Berberis barilochensis* Job (Landrum 1999).

Photo 1 The typical root of yellow color of *Berberis microphylla*, used to prepare aqueous decoctions and to be drunk as hypoglycemic agent especially as a popular medicine

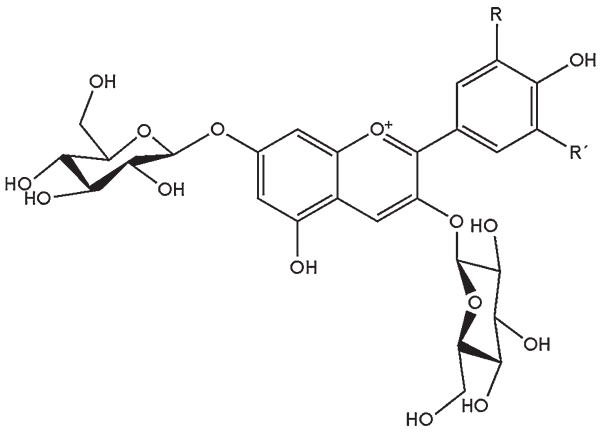
3 Crude Drug Used

Normally a root decoction is prepared with boiling water (photo 1).

4 Major Chemical Constituents and Bioactive Compounds

From a chemical point of view, *Berberis microphylla* shows a pattern of accumulation of alkaloids (from stems and roots), anthocyanins and flavonoids (from fruits). Fruits of "calafate" were studied in order to know the phenolic composition and antioxidant activity and also compared with data obtained for other berry fruits from southern Chile, including "maqui" (*Aristotelia chilensis*) and "murtilla" (*Ugni molinae*). Polyphenolic compounds in "calafate" fruits were essentially present in glycosylated form, 3-glucoside conjugates being the most abundant anthocyanins. The anthocyanin content in "calafate" berries and flavonol levels are comparable with those found in "maqui"; however, "maqui" shows lower flavan-3-ol concentration than "calafate". "Maqui" and "calafate" show high antioxidant activity, which correlates highly with total polyphenol content and with anthocyanin concentration (Ruiz et al. 2010). Fig. 1 shows the different anthocyanins found in *Berberis microphylla (*Pomilio 1973; Ruiz et al. 2014*)*.

The root and bark of this species are characterized by producing a very special arrangement of isoquinoline alkaloids, all of which are biogenetically derived from the aminoacid tyrosine (Fajardo et al. 1979a, b). Figure 2 considers only those alkaloids that would be present in aqueous decoctions used by some people living in the Southern region of Chile and Argentina. It includes protoberberine alkaloids, with common names: berberine (main alkaloid of *Berberis* species in the world), jatrorrhizine, columbamine, palmatine, isocorydine, jatrorrhizine, palmatine, reticuline, scoulerine and tetrahydroberberine (Fajardo 1987; Freile et al. 2003; Manosalva et al. 2016).



1. R = R` = OH (delphinidin-3,7-β-O-diglucoside)
2. R = H; R` = OH (cyanidin-3,7-β-O-diglucoside)
3. R = OH; R` = OCH_3 (petunidin-3,7-β-O-diglucoside)
4. R = H; R` = OCH_3 (peonidin-3,7-β-O-diglucoside)
5. R = R` = OCH_3 (malvidin-3,7-β-O-diglucoside)

Fig. 1 Anthocyanins in fruits of *Berberis microphylla* G. Forst

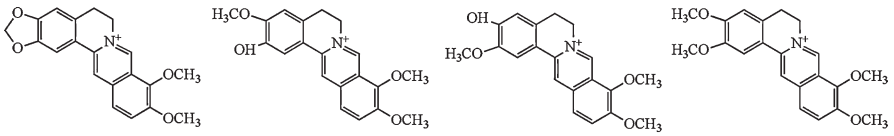


Fig. 2 Main protoberberines alkaloids from stems and roots of *Berberis microphylla* G. Forst

The first report related to bisbenzylisoquinoline alkaloids in *Berberis microphylla* was calafatine (Fajardo et al. 1979a, b). Later, *B. microphylla* has yielded the bisbenzylisoquinolines, chillanamine and (−)-osornine (Fig. 3). Alkaloid chillanamine is the likely precursor of osornine and calafatine (Leet et al. 1983). In the course of an investigation of the alkaloids of *B. microphylla* collected near the town of Punta Arenas, in Chilean Patagonia, were isolated two amorphous bisbenzylisoquinoline N-oxides (Leet et al. 1984).

Damascos et al. (2008) found a significant quantity of Zn and low content of Na and Br in these berries.

5 Morphological Description

Shrub up to *ca*. 2 m high, glabrous or the twigs and young growth pubescent to minutely papillate-puberulent; twigs reddish brown, tan, or gray, with longitudinal ridges, the bark smooth, with age slightly fibrous; spines 3-parted, the arms 3–12 mm

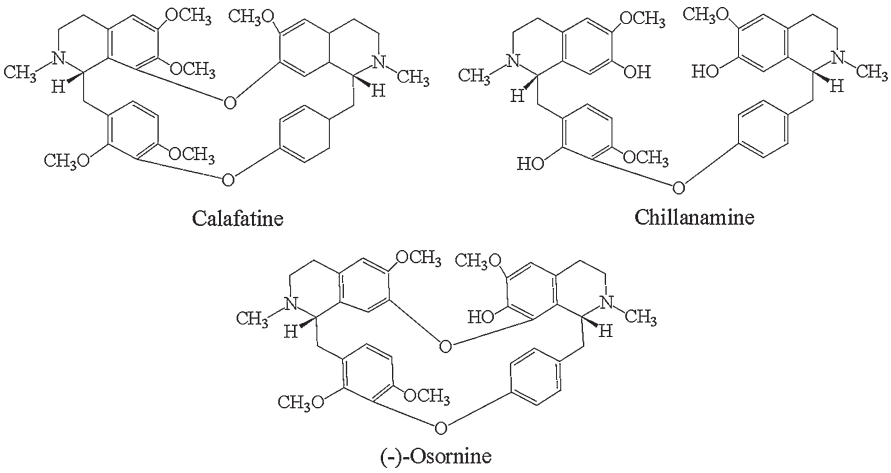


Fig. 3 Main bisbenzylisoquinolines from stems and roots from *Berberis microphylla* G. Forst

long, or often the lateral arms absent or insignificant, especially near the branch tips; bracts ovate to broadly rounded, 1–2 mm long, membranous to submembranous, reddish brown to yellowish tan. Leaves obovate, oblanceolate, or oblong, the blade 5–18 mm long, 1.5–9 mm wide, 2–3.3 times as long as wide, membranous to submembranous, drying gray-green, dull to slightly lustrous above, the margin normally entire; apex acute to rounded, usually without an apiculum; base acute to acuminate; petiole in living leaves usually insignificant (Landrum 2003). Style short; stamens with or without tooth-like appendages; spines 3- parted or simple; inflorescence usually a solitary flower; leaves obovate or oblanceolate to ovate, obtuse to subacute, with sharp rigid apical spine, attenuate at base into short petiole, the margin thickened, entire, coriaceous, glabrous, bright green above, pale beneath, with prominent yellowish veins. Berry subglobose, pruinose, lunate, smooth, dark brown. Flowers October to January (Moore 1983).

6 Geographical Distribution

Berberis microphylla is a native species, endemic to Southwestern South America, from the Andes of Curicó at central Chile at 2500 m.a.s.l. in Tierra del Fuego (Landrum 1999). In Patagonia, *B. microphylla* grows wild in the under-forest, steppe, and forest–steppe ecotones (Correa 1984; Bottini et al. 2000).

7 Ecological Requirements

According to our own experience, working for 40 years in Chilean and Argentine Patagonia, it is possible to mention that *Berberis microphylla* grows in slopes, valleys, canyons and banks of bodies of water. Some authors published that this often growing in the Magellanic subpolar forest ecoregion, in coastal scrub, *Nothofagus* forest margins and clearings, moister areas in grass steppes, and along streams and rivers (Radice and Arena 2015).

8 Traditional Use (Part(s) Used) and Common Knowledge

Berberis microphylla roots have been used by the people in the Austral zone of Chile, for years in folk medicine to treat diabetes because it is thought that they exhibit hypoglycemic activity. Its roots are also used to reduce high levels of cholesterol. Despite the interesting biological activities reported for these roots, there are no scientific studies to support this assumption. It is important to mention that *Berberis microphylla* was used by indigenous people for the treatment of fever, inflammations, stomachaches, diarrhea and urinary tract infection (Zin and Weiss 1998). Additionally, the Aonikenk people used yellow scraping of the bark as tobacco, due to its hallucinogen effect, probably caused by the alkaloid berberine, whereas the fruit of the plant was used by Kawésqar people as a source of food (Domínguez et al. 2012). Aónikenk or Tehuelches, inhabited Patagonia, north of the Strait of Magellan, characterized by being a nomadic land people. The ancient Kawésqar or Alakalufes inhabited the fjords and canals of the extreme south of the South American continent. According to Martínez Crovetto (1968), the Onas in Patagonia used the fruits (named as "kór") as food, and the wood (named as "mich" or thorn) to make arrows.

9 Modern Medicine Based on its Traditional Medicine Uses

In recent years, some studies have corroborated the medicinal use of *B. microphylla*, attributing interesting pharmacological and antimicrobial properties based on the presence of isoquinoline alkaloids. In this context, root extracts of *Berberis microphylla* showed hypoglycemic effects and stimulate glucose uptake in Hep G2 cells with and without resistance by activating AMPK protein (Furrianca et al. 2017). As well, leaves, stems and roots extracts of *Berberis microphylla* possess important antimicrobial activity against human Gram positive pathogenic bacteria. It is interesting that the root extract showed similar activity against *Bacillus cereus* and *Bacillus epidermidis* when compared to ampicillin and cephalothin, commercial antibiotics (Manosalva et al. 2016). Muñoz et al. (2013) found a mild antitrypanosomal activity of extracts of this species.

On the other hand, berberine and its derivatives are used in pharmacy or as a dye substance (Romeo and Sánchez 2005). Related to the used of pure berberine, it has been used in traditional Chinese medicine and Ayurvedic medicine and current research evidence support its use for various therapeutic areas (Singh and Mahajan 2013). It is widely available as a dietary supplement in the different countries and has demonstrated efficacy in the treatment of type 2 diabetes mellitus (Pang et al. 2015). By the way, the genus *Berberis*, also, is used since ancient times for curing eye disease (Srivastava et al. 2015). In addition, there has been a growing interest in the commercial use of *Berberis microphylla* fruits, being consumed fresh or processed as marmalades and jams, in non-alcoholic beverages and in ice creams (Arena et al. 2018). It is known that in Chilean-Argentinean Patagonia the "calafate" syrup is used familiarly and commercially to prepare a "calafate" liquor, which is sold as "calafate sour" (a mixture of syrup with grape brandy, lemon juice and sugar).

10 Conclusions

There is a growing interest to study extracts of plants and/or pure compounds, which historically have shown some biological activity about which many related papers have been published. It should be mentioned that even greater progress is required in this process, especially in relation to trials that may lead to the production of drugs and their use in human beings. In the case of *Berberis microphylla* and other species of the genus *Berberis*, one of the points under discussion is to determine the optimum effective dose for the functions for which its applicability has been indicated and to avoid the collateral effects that might occur. Similarly, highly reliable clinical trials should be conducted.

Acknowledgments This work has been supported by the Vice-Rectory of Research and the Faculty of Sciences of the University of Magallanes, Chile.

References

Ahrendt LWA (1961) *Berberis* and *Mahonia.* A taxonomic revision. J Linnean Soci Botany 57(369):1–410

Arena M, Lencinas M, Radice S (2018) Variability in floral traits and reproductive success among and within populations of *Berberis microphylla* G. Forst., an underutilized fruit species. Sci Hortic 241:65–73

Bottini M, Greizerstein E, Aulicino M, Poggio L (2000) Relationships among genome size, environmental conditions and geographical distribution in natural populations of NW Patagonian species of *Berberis* L. (Berberidaceae). Ann Bot 86:565–573

Correa MN (1984) Berberidaceae. In: Flora Patagónica IV, vol. VIII. Ed. INTA. Buenos Aires, Argentina, pp 325–348

Damascos MA, Arribere M, Svriz M, Bran D (2008) Fruit mineral contents of six wild species of the North Andean Patagonia, Argentina. Biol Trace Elem Res 125(1):72–80

Domínguez E, Aguilera O, Villa-Martínez R, Aravena J, Henríquez JM (2012) Ethnobotanical survey of Kalau Island, ancestral Kawesqar territory, Magallanes region, Chile. Anales del Instituto de la Patagonia 40:19–35

Fajardo V (1987) Estudio químico de las especies chilenas del género *Berberis*. Revista Latinoamericana de Química 18(1):46–50

Fajardo V, Urzúa A, Cassels B (1979a) Calafatine, an unusual bisbenzylisoquinoline alkaloid. Heterocycles 12(12):1559

Fajardo V, Urzúa A, Torres R, Cassels B (1979b) Metabolitos secundarios de *Berberis buxifolia*. Revista Latinoamericana de Química 10:131–134

Freile M, Giannini F, Pucci G, Sturniolo A, Rodelo L, Pucci O, Balzaretti V, Enriz R (2003) Antimicrobial activity of aqueous extracts and of berberine isolated from *Berberis microphylla*. Fitoterapia 74:702–705

Furrianca M, Alvear M, Zambrano T, Fajardo V, Salazar L (2017) Hypoglycemic effect of *Berberis microphylla* G Forst. Root extract. Trop J Pharm Res 16(9):2179–2184

Landrum L (1999) Revision of *Berberis* (Berberidaceae) in Chile and adjacent southern Argentina. Ann Mo Bot Gard 86:793–834

Landrum L (2003) Berberidaceae. In: Marticorena C, Rodríguez R (eds): Flora de Chile. Ed. Universidad de Concepción, Concepción, Chile 2(2):1–23

Leet J, Fajardo V, Shamma M (1983) Some dimeric Benzylisoquinoline alkaloids with an unusual oxygenation pattern. J Nat Prod 46(6):908–912

Leet J, Freyer A, Minard R, Shamma M, Fajardo V (1984) Stereochemistry of Bisbenzylisoquinoline N-oxides. Calafatine 2α-N-oxide and Calafatine 2β-N-oxide. J Chem Soc Perkin Trans 1:651–652

Manosalva L, Mutis A, Urzúa A, Fajardo V, Quiroz A (2016) Antibacterial activity of alkaloids fraction from *Berberis microphylla* G Forst. And study of synergism with ampicillin and cephalothin. Molecules 21(1):76

Martínez Crovetto RN (1968) Estudios Etnobotánicos. IV. Nombres de plantas y su utilidad según los indios Onas de Tierra del Fuego. Etnobiológica (3):1–20

Moore D (1983) Flora of Tierra del Fuego. Ed. Anthony Nelson (England) and Missouri Botanical Garden, USA, pp 66–68

Muñoz OM, Maya JD, Ferreira J, Ph C, San Martin J, López-Muñoz R, Morello A, Kemmerling U (2013) Medicinal plants of Chile: evaluation of their anti-*Trypanosoma cruzi* activity. Zeitschrift fuer Naturforschung, C: J Biosci 68(5/6):198–202

Pang B, Zhao L, Zhou Q, Zhao T, Wang H, Gu C, Tong X (2015) Application of Berberine on treating type 2 diabetes mellitus. Int J Endocrinol 2015:905749

Pomilio A (1973) Anthocyanins in fruits of *Berberis buxifolia*. Phytochemistry 12:218–220

Radice S, Arena M (2015) Environmental effect on the leaf morphology and anatomy of *Berberis microphylla* G. Forst. Int J Plant Biol 6:5677

Romeo R, Sánchez A (2005) Aportes Botánicos de Salta - Ser. Flora Berberidaceae Juss 7:9):1–9):8

Ruiz A, Hermosín-Gutiérrez I, Mardones C, Vergara C, Hertlitz E, Vega M, Dorau C, Winterhalter P, von Baer D (2010) Polyphenols and antioxidant activity of calafate (*Berberis microphylla*) fruits and other native berries from southern Chile. J Agric Food Chem 58(10):6081–6089

Ruiz A, Mardones C, Vergara C, von Baer D, Gómez-Alonso S, Gómez V, Hermosín Gutiérrez I (2014) Isolation and structural elucidation of Anthocyanidin 3,7-β-O-diglucosides and caffeoyl-glucaric acids from calafate berries. J Agric Food Chem 62(29):6918–6925

Singh I, Mahajan S (2013) Berberine and its derivatives: a patent review (2009 – 2012). J Exp Opin Therap Patent 23(2):215–231

Srivastava S, Srivastava M, Misra A, Pandey G, Rawat AKS (2015) A review on biological and chemical diversity in *Berberis* (Berberidaceae). EXCLI J 14:247–267

Zin J, Weiss C (1998) La Salud por Medio de Plantas Medicinales, 8th edn. Don Bosco, Santiago, Chile, pp 70–71