Berberis darwinii Hook.

Victor Fajardo Morales, Marisel Araya, and Loreto Manosalva

Fruits and flowers of *Berberis darwinii* Hook. (Photos: V Fajardo)

Abstract *Berberis darwinii* Hook. has its natural origin in both slopes of the Andes Mountains, in Southern Chile and Argentina, but the species has been naturalized also in other continents. In traditional medicine, it is used by the Mapuche ethnic group for the treatment of inflammatory processes, feverish states and stomach pain. The secondary metabolites in *B. darwinii*, primarily alkaloids and polyphenols, show a great diversity. There are several scientific reports and ethnographic antecedents about the traditional uses. From a medicinal point of view, this seems to be a promising plant species.

V. Fajardo Morales (✉) · M. Araya · L. Manosalva
Faculty of Science, Universidad de Magallanes, Punta Arenas, Chile
e-mail: victor.fajardo@umag.cl

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_8

Keywords "Michay" · Benzylisoquinoline alkaloids · Anthocyanins · Hydroxycinnamic acids · Flavonols · Folk medicine

1 Introduction

Berberidaceae is a plant family of about 15 genera and 650 species that is widespread in the Northern Hemisphere. With the single genus of *Berberis,* it extends into temperate South America and the Andean region. Fruits of *B. darwinii* are consumed either in a raw state or cooked. It is popular and used in preserves: although acidic, still they have a very pleasant flavor. The fully ripe fruit loses most of its acidity and makes very pleasant eating. Due to its relatively broad ecological range, and content of berberine-alkaloids in its roots and stems, with favorable reported pharmacological activities (antimicrobial, antidiarrhea, anti-inflammatory, antitumor effects, antituberculosis, etc.), it is also used in traditional medicine.

2 Taxonomic Characteristics

Berberis darwinii Hook. is an evergreen thorny shrub, commonly known as ¨michay¨ belonging to the subfamily Berberidoideae, family Berberidaceae. The family Berberidaceae, was first established by A.L. Jussieu in 1789 as *Berberides* and was considered as one of the most primitive families of Angiosperms having a high number of disjunction or discontinuous genera.

Synonyms *Berberis costulata* Gand. (Landrum 1999), *Berberis knightii* (Lindl.) K. Koch, *Mahonia knightii* Lindl. (Rodríguez et al. 2018).

Since the times of the native peoples it has received different popular names, among which it is possible to mention "michay" (Hoffmann 2005; Rodríguez et al. 2018) and "quelung" (Rodríguez et al. 2018). The generic name is the Arabic name for the fruit of these plants; the specific name in honor of Charles Darwin (Muñoz 1980).

3 Crude Drug Used

In natural medicine, the most frequent use of *Berberis darwinii* is in decoctions and infusions. Leaves and fruit-infusion are used against inflammation, the roasted and powdered root bark is used as a wound healing agent and through decoction of leaves a soft and febrifugal purgative is obtained (Bisheimer 2012; Cordero et al. 2017).

4 Chemical Constituents and Bioactive Compounds

Berberis darwinii contains different types of phytochemicals in its stems, fruits, leaves and roots. Of primary importance is the presence of different alkaloids and polyphenols (Núñez et al. 2018a, b). The phenolic profiles, antioxidant activity, and inhibitory effects of (enzymes α-glucosidase, α-amylase, and pancreatic lipase) of three Argentinean Patagonia berries were investigated by Chamorro et al. (2019). The most complex polyphenol profile among the studied species was found in the *Berberis darwinii* samples (Maza and Miniati 1993; Chamorro et al. 2019): delphinidin-3-*O*-glucoside, delphinidin rutinoside, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, petunidin hexoside, petunidin rutinoside, peonidin hexoside, peonidin rutinoside, malvidin-3-*O*-glucoside and malvidin rutinoside; the following hydroxycinnamic acids: caffeoylglucaric acid, caffeoylquinic acid, dicaffeoyl glucaric acid, caffeoylquinic acid, feruloylquinic acid, caffeoyl glucaric acid, dicaffeoylquinic acid; and flavonols: quercetin hexoside, quercetin glucuronide, quercetin rutinoside, quercetin acetylhexoside, quercetin rhamnoside, isorhamnetin rutinoside, isorhamnetin acetylhexoside and isorhamnetin acetylhexoside.

On the other hand, many isoquinoline bases have been identified in *Berberis darwinii*, among them the alkaloids berberine, magallanesine, dihydrorugosinone, rugosinone, nuevamine, santiagonamine and chiloenamine (Valencia et al. 1984a, b, c, 1985). A general aspect to highlight in any studied *Berberis*, is the presence of the berberine alkaloid, a situation that is also reflected in *Berberis darwinii*. Berberine bearing special quaternary ammonium salt in the benzylisoquinoline alkaloid core, is a major active component of some Chinese herbal medicines, and multiple therapeutic actions of berberine analogs have been continuously reported including antimicrobial, antidiarrhea, anti-inflammatory, antitumor effects, antituberculosis activities, etc. (Seng et al. 2019).

It is important to mention that some alkaloids of *Berberis darwinii* have been of particular interest among organic chemists. Similarly, various heterocyclic bases, natural products containing the isoindolin-1-one system such as (±)-nuevamine, (±)-lennoxamine and magellanine are very important since their extensive occurrence in nature is known. These architecturally sophisticated chemical structures include five-eight membered rings fused with different aromatic moieties and differently oxygenated substituents. Thus, analogs of these pentacyclic systems incorporating a skeleton of isoindolin-[1,2-*a*]-5-one are of great interest in drug research because of their biological activity (Vázquez-Vera et al. 2017). Therefore, their unique structural features have recently attracted the attention of many organic research groups and several synthetic strategies have been pursued towards these attractive and challenging synthetic targets. (±)-Nuevamine was the first naturally occurring isoindole-[1,2-*a*]-isoquinolinone, whose chemical structure is very interesting from a pharmacological perspective, due to the potential and promising biological activity of many of its analogs, *e.g.* as anti-inflammatory, antimicrobial, antileukemic and antitumor properties (Mertens et al. 1993).

5 Morphological Description

"Michay" is a moderately branched shrub that grows 1–3 meters high. Leaves abundant, variously shaped, margins entire or with fewer than 10 teeth per side, born from 3 to 5 in the armpits of strong thorns, smooth, shiny coriaceous, sessile, with toothed-spiky edge 1–2 cm long, dark green, the underside is somewhat lighter, new shoots have a reddish tone. The inflorescence a raceme; style on fruit 1–3 mm long. Flowers gathered in clusters, with 6 orange sepals, located on two levels; 6 petals, 6 stamens and a pistil in the shape of a small bottle, with discoid stigma. The fruit is a round berry that during the ripening process goes from green to black, passing through red; it contains 3–4 seeds (Muñoz 1980; Landrum 1999).

6 Geographical Distribution

Berberis darwinii is a native shrub to temperate forest of Southern South America (Chalcoff et al. 2006), specifically it is located in southern Chile, from Ñuble to Aysen (Muñoz 1980), and mountains areas of the Argentinean Patagonia (Landrum 1999); however, it has been distributed in Europe and other continents after its Discovery by Charles Darwin (Sykes 1982; Habtemariam 2013). In addition, it is important to note that *B. darwinii* is considered as an invasive species in New Zealand, because the plant invades and persists in different light environments, from grazed pasture to intact forest (Mc Alpine and Jesson 2007), where prolific seed production and seed dispersal in high light environments is considered a key feature contributing to the success of this species' invasion (Mc Alpine and Jesson 2008).

7 Ecological Requirements

Berberis darwinii is highly tolerant to drought, frost and shade (Timmins and Mackenzie 1995), and can also occupy a wide range of soil types in relation to its texture (sandy and clay soil) and pH (acid, neutral and basic), as well as, it can grow in nutritionally poor soils (Allen 1991).

A good bee plant, and birds also love its fruit and will happily eat it before it reaches full maturity. If you want to experience the fully ripe fruit, then it might be necessary to find ways of keep the birds off the plants.

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

Berberis darwinii is recognized as a healing plant, where leaves and fruits have been used by the ethnic group due to effects febrifuge, astringent and anti-inflammatory (Hirschmann et al. 2019). *B. darwinii* also is known for stomach pains, indigestion, and colitis (Montes and Wilkomirsky 1987). In addition, the fruits of this berry have been consumed raw and cooked, *e.g*. in pastry as decorative, juices, sweets and syrups (Cordero et al. 2017).

9 Modern Medicine Based on Its Traditional Medicine Uses

Berberis darwinii has an important pharmacological activity for its potential in the treatment of pathologies associated with inflammation (Núñez et al. 2018a), where the most important active compound is berberine present in high concentrations in root extracts (Núñez et al. 2018b). So, *B. darwinii* shows anti-inflammatory action by inhibiting the production of superoxide anion, the expression of tumor necrosis factor-alpha (TNFα), and interleukin-1-beta (IL-1β) in monocytes activated by lipopolysaccharide (Alarcón et al. 2014). Moreover, it has been shown that the therapeutic potential of the stem-bark extract of *B. darwinii* for Alzheimer's disease, is due to the presence of berberine, which is a potent inhibitor of acetylcholinesterase (ACHE) enzyme thereby increasing the lifespan of the neurotransmitter, acetylcholine (Habtemariam 2011).

10 Conclusions

A search in the SciFinder has resulted more than 20,000 scientific reports on species of the genus *Berberis* or compounds related to isoquinoline alkaloids, i.e. berberine ("berberine" as keyword). It can also be perceived that there is a growing interest in studying plant extracts and/or pure compounds of this genus, which in traditional medicine have demonstrated biological activity. More progress is needed, especially tests that can lead to the development of medicines and their use in humans. In the case of *Berberis microphylla* and *B. darwinii* and other species of the same genus, one of the points under discussion is the optimal effective dose for applicability, as side effects 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

Alarcón D, Paredes M, Ramos D (2014) Los extractos acuoso y metanólico de *Berberis darwinii* H. (Berberidaceae) inhiben respuestas celulares innatas en monocitos humanos tratados *in vitro*. BLACPMA 13(1):81–91

Allen RB (1991) A preliminary assessment of the establishment and persistence of *Berberis darwinii* Hook., a naturalized shrub in secondary vegetation near Dunedin, New Zealand. N Z J Bot 29:353–360

Bisheimer M (2012) Flores de la Patagonia Argentina. Flores nativas y exóticas presentes en los ambientes cordilleranos y precordilleranos de la Patagonia argentina. 1° ed. – Neuquén: Serie Patagonia. Ed. Eduardo Marcelo Fernández, Neuquén, Argentina, p 240

Chalcoff V, Aizen M, Galetto L (2006) Nectar concentration and composition of 26 species from the temperate forest of South America. Ann Bot 97:413–421

Chamorro M, Reiner G, Theoduloz C, Ladio A, Schmeda-H G, Gómez S, Jiménez F (2019) Polyphenol composition and (bio) activity of *Berberis* species and wild strawberry from the Argentinean Patagonia. Molecules 24:3331

Cordero S, Abello L, Gálvez F (2017) Plantas silvestres, comestibles y medicinales de Chile y otras partes del mundo. Guía de campo. Ed. Corporación Chilena de la Madera, Concepción, Chile, 292 pp

Habtemariam S (2011) The therapeutic potential of *Berberis darwinii* stem-bark: quantification of Berberine and *in vitro* evidence for Alzheimer's disease therapy. Nat Prod Commun 6(8):1089–1090

Habtemariam S (2013) The hidden treasure in Europe's garden plants: case examples; *Berberis darwinii* and *Bergenia cordifolia*. Med Aromat Plants 2(4):1–5

Hoffmann A (2005) Flora Silvestre de Chile, Zona Araucana Árboles, arbustos y enredaderas leñosas. V ed.. Ed. Fundación Claudio Gay, Santiago, Chile, 257 pp

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

Maza G, Miniati E (1993) Anthocyanins in Fruits, Vegetables and Grains. Ed. CRC, New York, USA, 362 pp

Mc Alpine K, Jesson I (2007) Biomass allocation, shade tolerance and seedling survival of the invasive species *Berberis darwinii* (Darwin's barberry). N Z J Ecol 31(1):1–12

Mc Alpine K, Jesson I (2008) Linking seed dispersal, germination and seedling recruitment in the invasive species *Berberis darwinii* (Darwin's barberry). Plant Ecol 197:119–129

Mertens A, Zilch H, Koenig B, Schaefer W, Poll T, Kampe W, Seidel H, Leser U, Leinert H (1993) Selective non-nucleoside HIV-1 reverse transcriptase inhibitors. New 2,3-dihydrothiazolo[2,3-a]-isoindol-5(9bH)-ones and related compounds with anti-HIV-1 activity. J Med Chem 36:2526–2535

Montes M, Wilkomirsky T (1987) Medicina Tradicional Chilena. Ed. de la Universidad de Concepción, Concepción, Chile, 205 pp

Muñoz M (1980) Flora del Parque Nacional Puyehue. Ed. Universitaria. Santiago, Chile, 557 pp

Núñez D, Balboa N, Quilaqueo N, Alvear M, Paredes M (2018a) Evaluación de la Actividad Inmunomoduladora de Extractos Metanólicos y de Alcaloides de *Berberis darwinii* H. (Berberidaceae). Int J Morphol 36(2):454–459

Núñez D, Balboa A, Carvajal F, Alvear M, Paredes M (2018b) Efecto del extracto de alcaloides de *Berberis darwinii* Hook. sobre respuestas celulares innatas en fagocitos murinos. BLACPMA 17(3):259–269

Rodríguez R, Marticorena C, Alarcón D, Baeza C, Cavieres L, Finot V, Fuentes N, Kiessling A, Mihoc M, Pauchard A, Ruiz E, Sánchez P, Marticorena A (2018) Catálogo de las plantas vasculares de Chile. Gayan Botanica 75(1):1–430

Schmeda-Hirschmann G, Jiménez-Aspee F, Theoduloz C, Ladio A (2019) Patagonia berries as native food and medicine. J Ethnopharmacol 241:111979

Seng Q, Wang H, Wei W, Guo T, Wang Y, Li Y, Song D (2019) Synthesis and biological evaluation of berberine derivatives as a new class of broad-spectrum antiviral agents against Coxsackievirus B. Bioorg Chem 9(95):103490

Sykes W (1982) Checklist of Dicotyledons naturalized in New Zealand 15. Annonales, Berberidales, Cactales, Fagales, some Geraniales, Juglandales, Laurales, Rutales, Salicales, Sapindales, Tiliales, Nyctaginaceae, and Zygophyllaceae. N Z J Bot 20:333–341

Timmins S, Mackenzie I (1995) Weeds in New Zealand protected natural areas database. Department of Conservation Technical Series No. 8. Wellington, Department of Conservation. New Zealand, 287 pp

Valencia E, Weiss I, Shamma M, Urzua A, Fajardo V (1984a) Dihydrorugosinone, a pseudobenzylisoquinoline alkaloid from *Berberis darwinii* and *Berberis actinacantha*. J Nat Prod 47(6):1050–1051

Valencia E, Patra A, Freyer A, Shamma M, Fajardo V (1984b) Santiagonamine: a new aporphinoid alkaloid incorporating a phenanthridine skeleton. Tetrahedron Lett 25(30):3163–3166

Valencia E, Freyer A, Shamma M, Fajardo V (1984c) Nuevamine, an isoindoloisoquinoline alkaloid, and lennoxamine, an isoindolobenzazepine. Tetrahedron Lett 25(6):599–602

Valencia E, Fajardo V, Freyer A, Shamma M (1985) Magallanesine: an isoindolobenzazocine alkaloid. Tetrahedron Lett 26(8):993–996

Vázquez-Vera O, Sánchez-Badillo J, Islas-Jácome A, Rentería- Gómez M, Pharande S, Cortés-García C, Rincón-Guevara M, Ibarra I, Gámez-Montaño R, González-Zamora E (2017) Efficient Ugi-3CR / aza Diels-Alder / Pommeranz-Fritsch protocol towards novel Aza-analogues of (±)-Nuevamine, (±)-Lennoxamine and Magallanesine: a diversity oriented synthesis approach. Org Biomol Chem 15:2363–2369