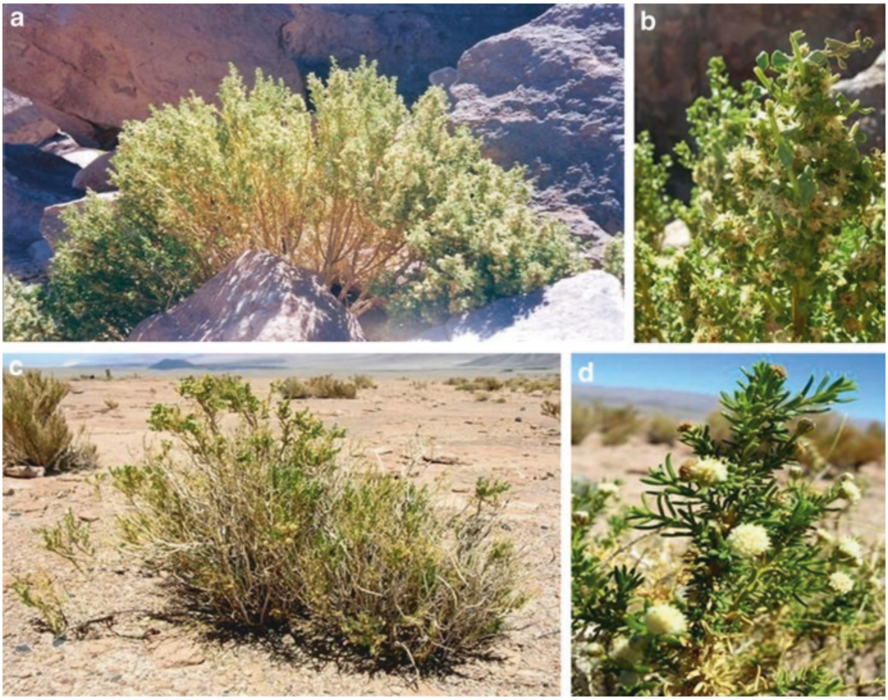
Baccharis tola Phil., *B. boliviensis* (Wedd.) Cabrera

María Inés Isla, Mariana Leal, Silvana L. Carrizo, and Iris C. Zampini



Baccharis tola ex *Baccharis incarum* (a. and b.) and *Baccharis boliviensis* (c. and d.). Photos: I Catiana Zampini, during the sample collection. Antofagasta de la Sierra, Catamarca, Argentina

M. I. Isla (✉) · M. Leal · S. L. Carrizo · I. C. Zampini
Instituto de Bioprospección y Fisiología Vegetal (INBIOFIV, CONICET- Facultad de Ciencias Naturales e Instituto Miguel Lillo-Universidad Nacional de Tucumán), San Miguel de Tucumán, Argentina
e-mail: misla@csnat.unt.edu.ar; zampini@csnat.unt.edu.ar

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Abstract The genus *Baccharis,* with approximately 500 species, is one of the largest genera of the family Asteraceae. Species of this genus are distributed mainly in the warm temperate and tropical regions of Brazil, Argentina, Colombia, Chile and Mexico. In Argentina, 96 species have been described. *Baccharis tola* and *Baccharis boliviensis* are used in traditional medicine, in Argentina. They are popularly known as "tola", "tolilla", "lejía" or "romerillo". The occurrence and identification of flavonoids and terpenoids have been reported from these species. The scientific validation of its medicinal properties as antioxidants, anti-inflammatory and antibiotics/antifungal agents has been done. Some phytotherapeutic formulations for topical applications have been developed with the ethanolic extract of *B. tola.* Both *B. boliviensis* and *B. tola* seem to be promising species for regional development, in these countries, although farther studies are needed in order to elaborate the technology for its sustainable domestication and subsequent cultivation.

Keywords *Baccharis boliviensis* · *Baccharis tola* · Argentine medicinal plant · Anti-inflammatory · Antibiotic · Antioxidant · Antifungal

1 Introduction

The present chapter shows the advances aimed at exploring the medicinal potential of two Argentinian *Baccharis* species. The ultimate aim is to promote the conservation and sustainable use of this valuable natural resource.

2 Taxonomic Characteristics

The genus *Baccharis,* with approximately 500 species, is one of the largest genera of the Family Asteraceae. Species of this genus are distributed mainly in the warm temperate and tropical regions of Brazil, Argentina, Colombia, Chile and Mexico. *Baccharis* spp. are abundant in Argentina, where 96 species have been described (Abad and Bermejo 2007). In this chapter, *Baccharis tola* (ex *B. incarum*) and *Baccharis boliviensis* are included.

***Baccharis tola* Phil. var. *incarum* (Wedd.) Joch. Müller** has as synonyms: *B. incarum* (Wedd.) Perkins (The Plant List, 2020). This species is known by the Aymara-Quechua names of "tola", "t'ula", "ñakat'ula", "ñakat'ola", "ñaka", "femala ñaka", "pacha thaya", "waka t'ula"; also, with the Spanish names of "baila buena", "tola", "tola macho", "tola hembra", "sacha tola", "tola lejía", "lejía", "le,a lejia" (Beck, 1985; De Lucca 1987; De Lucca and Zalles 1992; Galafassi, 1997; Cazés Camarero 2000; Villagrán et al. 2003; Borgnia et al. 2006). The denomination of “lejía” have their etymology in the Latin *aqua lixiva*: water in which alkalis or their carbonates have dissolved. According to Murillo (1861), “several species of the genus *Baccharis*, contain in their ashes a large amount of potash”. For these reasons, *B. tola* ashes serve to peel quinoa and corn.

***Baccharis boliviensis* (Wedd.) Cabrera**. Synonyms: *Psila boliviensis* (Wedd.) Cabrera, *Heterothalamus boliviensis* Wedd. and *Baccharis boliviensis* var. *latifolia* (R.E.Fr.) Cabrera, among others (The Plant List, 2020). *B. boliviensis* is known by the Aymara names of “kulkuma”, “kulkut’ula” and the Quechua names of “peskotola” or “tola”, also with Spanish names “romero”,“manzanilla”, “tola”, “tola limón”, “tolilla”, “tolita”, “tola chica”,“tola de pájaro”, “chijua”, “chisqua”, “romerillo”, “monte alpaca”, “monte de paloma”. The name “tola de pájaro” or “monte paloma” refers to the birds nesting in this bush, due to its leafy and low foliage. In Quechua, *peskko* means bird, so it is called “peskotola” because when this species blooms it is filled with birds that eat its flowers. The name “tola limón” owes its etymology to the color provided by this dye species, green and yellow. The name “manzanilla” is due to the similarity of its flowers with those of orchard chamomile (Lira 1945; Haber 1992; Cazés Camarero 2000; Villagrán et al. 2003; Borgnia et al. 2006).

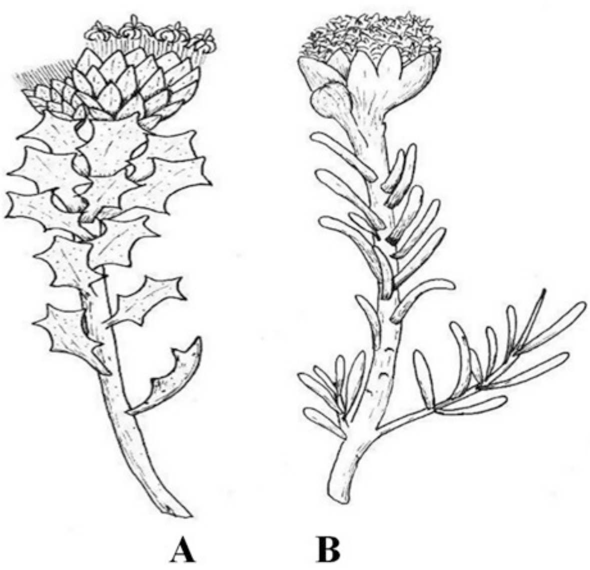

Fig. 1 Parts employed in popular medicine of (**a**) *B. tola*; (**b**) *B. boliviensis*. Pictures: M Leal

3 Crude Drug Used

Plant parts used for crude drug production are: leaves, branches, and flowers (Fig. 1). In general, the crude drug is the dried biomass that is processed into powder. In very few cases the fresh drug is used.

4 Major Chemical Constituents and Bioactive Compounds

Baccharis tola Previous phytochemical studies on the leaves and top parts (aerial parts) of *B. tola* described the isolation and structural elucidation of diterpenes, triterpenes, flavonoids and other phenolic compounds. Flavones such as 5,4′-dihydroxy-6,7,8,3′-tetramethoxyflavone; 5,4′-dihydroxy-3′,3,6,7,8-pentamethoxy flavone; 5,7,4′-trihydroxy-6,8,3′-trimethoxyflavone; 5,7,4′-trihydroxy-3′,3,6,8-tetramethoxyflavone; 3′,4′,5,7-tetrahydroxyflavone; 3′,4′,5,7-tetrahydroxy-3,6-dimethoxyflavone; 3′,4′,5,7-tetrahydroxy-3,6,8-trimethoxyflavone; 3,3′,4′, 5,5′,7-hexahydroxyflavone (myricitin) and derivatives compounds have been identified (Faini et al. 1982; Zampini et al. 2006, 2007, 2009a; Herrera et al. 2007; Nuño et al. 2012; Carrizo et al. 2020). Phenolic acids such as chlorogenic, ferulic, quinic, dicaffeoyl quinic, and 1-caffeoyl-5-feruloylquinic were identified (Zampini et al. 2007; Nuño et al. 2012; Simirgiotis et al. 2016; Carrizo et al. 2020). Other simple phenolic compounds such as scopoletin; 4-hydroxy-3-methoxyacetophenone were also identified (San Martín et al. 1980). Terpenoid compounds, such as erythroxylol-A; oleanolic acid; erythroxylol-A oxide; *ent*-beyer-14-en-18-ol; 19-hydroxy-13-epimanoyl oxide, bacchalineol; barticulidiol, bincatriol, hawtriwaic acid, solidagoiol A and derivatives compounds, and *ent*-clerodane derivatives compounds were identified (San Martín et al. 1980, 1983, 1985; Givovich et al. 1986; Simirgiotis et al. 2016; Carrizo et al. 2020).

Baccharis boliviensis Terpenoids and flavonoids were mainly isolated from aerial parts of this species. Labdanes, clerodanes (Gonzaga Verdi et al. 2005) and *ent*-clerodanes were identified (Zdero et al. 1986,1989; Carrizo et al. 2020). Flavones, such as 5,4′-dihydroxy-6,7,8-trimethoxyflavone (xanthomicrol), 5,4′-dihydroxy-6,7,8,3′-tetramethoxyflavone, 5,4′-dihydroxy-3,3′,5′,7-tetramethoxyflavone, 5,3′-dihydroxy-6,7,8,4′-tetramethoxyfllavone, 5,4′-dihydroxy-3,6,7,8,3′-pentamethoxy-fllavone, 5,3′-dihydroxy-3,6,7,8,4′-pentamethoxyflavone, 7,4′-dihydroxy-5,6,8-trimethoxyflavone, 4′,5,7-trihydroxy-3′,3,6,8-tetramethoxyflavone, 5,7,3-trihydroxi-6,8,3′,4′-tetramethoxyflavone, 3′,4′,5,7-tetrahydroxyflavone, 3′,4′,5,7-tetrahydroxy-3,6-dimethoxyflavone, 3′,4′,5,7-tetrahydroxy-3,6,8-trimethoxyflavone, 3′,4′,3,5,7-pentahydroxyflavone, 3′,4′,5,7-tetrahydroxy-6-methoxyflavone-3-rhamnoside, 5,6,7,3′,4′-pentahydroxyflavone, 3,3′,4′,5,5′,7-hexahydroxyflavone (myricitin) and derivatives compounds; flavanones, such as 5,7,3′,4′-tetrahydroxyflavanone (eriodictiol), 7-*O*-glucoside eriodictiol and 3′,4′,5,7- tetrahydroxy-6-methoxyflavanone were identified (Morales et al. 1990; Cazón et al. 2002; Gonzaga Verdi et al. 2005; Zampini et al. 2007, 2009a; Calle et al. 2012; Carrizo et al. 2020). Chlorogenic, isochlorogenic, ferulic, *O*-dicaffeoylquinic, 1-caffeoyl-5-feruloylquinic acid and quinic acids were isolated and identified by HPLC-MS and UHPLC-OT-MS from the methanolic and ethanolic extract of *B. boliviensis* aerial parts collected in Antofagasta de la Sierra, Catamarca, Argentina (Cazón et al. 2000; Carrizo et al. 2020).

5 Morphological Description

Baccharis tola Intricate-resinous bush, no more than half a meter high. It has rounded branches, very glandulous and densely leafy to the apex. The leaves are alternate, sessile, oblanceolate-spatulated, obtuse at the apex (rarely acute) and attenuated at the bottom, whole or with one or two triangular teeth on each side, dotted-glandular and, generally, covered with resin droplets, 6–12 mm long by 2–4 mm wide. At the ends of very short and sessile twigs, it has numerous solitary chapters. The feminine chapters have bell-shaped engagement of 5–6 mm high by 4 mm in diameter, filarial in 4–5 series, numerous flowers with filiform corolla. The masculine chapters have the same involvement as the feminine ones, numerous flowers with corolla pentasecta and style of very short branches, not separated, white crested and widened pappus at the apex of the bristles. The fruit is an acyloid, glabrous achene, 2.2 mm long; white and deciduous pappus (Cabrera, 1978).

Baccharis boliviensis Shrubs 0.3–1 m high, erect, bunny bush 30–100 cm tall, with thin twigs, sides, glabrous, glandulous-dotted, densely leafy to the apex. The leaves are alternate, sessile, linear lanceolate or elliptical, acute or semi-blunt, whole, glabrous and dotted-glandular on both sides. It presents numerous chapters, arranged in paucicephal terminal tops. It presents feminine chapters with bell-shaped involvement of about 3 mm high by 4 mm in diameter, filarial in 2–3 series, the oblong obtuse external with laciniated hyaline margin, resinous on the back, the interiors, acute lanceolate. Hemispheric receptacle, covered with lanceolate, hyaline, as long as flowers, deciduous, numerous flowers, female with briefly linked corolla, 1 mm long tube and 0.5 mm ligule, white pappus, longer than the corolla, achenes sericeous-pubescent oblanceolate, 1.5 mm long. It also presents male chapters with bell-shaped engagement of 2–2.5 mm in height by 3 mm in diameter, filarial in 2 series, oblong, obtuse, hyaline in the margin and resinous in the back, flowers with deeply pentalobate corolla, short style branches and little separated (Cabrera, 1978).

6 Geographical Distribution

Baccharis tola is geographically distributed in the high mountains and highlands of Southern Peru and Bolivia, Northern Chile and Northwestern Argentina from Provinces of Jujuy to La Rioja and San Juan (Cabrera, 1978). In Argentine grows between 1900 and 4800 m.a.s.l.

Baccharis boliviensis is distributed geographically in Southern Peru and Bolivia, Northern Chile and Northwestern Argentina (Jujuy, Salta, Tucumán and Catamarca) at 1500–4700 m.a.s.l.

Both species are characteristic of the phytogeographic province of Puna and high streams of Prepuna (Cabrera, 1978; Cuello 2006; Carilla et al. 2018). At present, there is no information about the cultivation and domestication of *B. boliviensis* or *B. tola.*

7 Ecological Requirements

B. tola and *B. boliviensis* grow under conditions of high ultraviolet light, low temperature, high salinity and low atmospheric pressure (Cabrera, 1978).

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

B. tola In Argentina, Chile and Bolivia is widely used as a medicine. Roasted and boiled leaves are used as an infusion for fever, to combat cough, bronchitis, pneumonia, flu and colds, digestive disorders and "empachos" (indigestion), purgative, sweaty, stomatic. It is prepared as a poultice for stomatic pain. The decoction is used against dysentery. The infusion and decoction of the aerial parts of *B. tola* are used in traditional medicine for the treatment of ulcers, burns and wounds, to restore blood circulation and reduce inflammatory processes, as antiseptic and anti-inflammatory and to relieve muscle and bone pain. The leaves and stems are macerated in ethanol for seven days and the solution is rubbed to relieve rheumatism and inflammation. It is appreciated for the resin it contains, in cases of bruises, wounds and to consolidate dislocations and cracks, since it is very sticky and is used in the form of strips or patches (Castro et al. 1982; De Lucca and Zalles, 1992; Wickens, 1993; Abad and Bermejo, 2007). According to Galafassi (1997), it has veterinary use, it is medicinal for cattle, it is used to smoke cattle, donkeys and forage it when they are sick. *B. tola* is also used in human food: the resin is consumed as sweet in the winter (Aldunate et al. 1981); lumps on the branches (gills, sometimes called fruits) serve as a lemon substitute. In its roots live a parasitic plant (*Ombrophytum subterraneum* (Asplund) Hansen, Balanophoraceae) that forms a radical thickening or "sichas" that are edible (Muñoz Pizarro, 1973; Aldunate et al. 1981; Wickens, 1993). It is also consumed as fodder by camelids, goats and sheep (Alzirreca and Cardozo, 1991; Haber, 1992; Wickens, 1993). On the other hand, *B. tola* is used to dye wool and the whole plant is used as fuel, it is a hardwood and is considered the best wood in the mountains (Beck, 1985; Vidaurre et al. 2006).

Baccharis boliviensis The aerial part is used as a medicinal product in Argentina, Chile, Bolivia and Peru. The infusion is used as an antispasmodic, febrifuge and helps liver function. The resin is used in patches, plasters or poultices to heal fractures and, in general, to relieve muscle aches. It is used as an anti-inflammatory, antipyretic, and antiseptic, to heal wounds, burning and ulcers, for rheumatism, stomach pain, gastric protector, liver and prostate illness (Abad and Bermejo, 2007). It is also a good fuel and is preferred as firewood since they heat clay ovens better. It constitutes a forage resource for grazing llamas and sheep (Villagrán et al. 2003; Vidaurre et al. 2006).

9 Modern Medicine Based on its Traditional Medicine Uses

Several studies using different methods have demonstrated the health benefits attributable to these *Baccharis* species. These reports also describe the development and characterization of phytopharmaceutical products.

Antimicrobial Activity The ethanolic extracts (ethanol 60° and 80°) of *Baccharis boliviensis* and *B. tola* inhibited the growth of one or more of the following antibiotic resistant strains: *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Morganella morganii,* and *Pseudomonas aeruginosa*. Ethanol extracts (tinctures) of aerial parts of these species showed the highest levels of antibacterial activity on methicillin, oxacillin and gentamicin resistant *Staphylococcu*s *aureus* with MIC values from 20 to 150µg/ml (Feresin et al. 2000; Eraso et al. 2002; Mahady 2005; Zampini et al. 2006, 2007, 2009a, b). *Baccharis boliviensis* were more active than *B. tola* on *Enterococcus faecalis*. The ethanolic extracts exhibited stronger activity and broader spectrum of action than aqueous extracts. The extracts show a bactericidal effect. Moderate anti-*Trypanosoma cruzi* activity for 5,4′-dihydroxy-3,6,7,8,3′-pentamethoxyflavone isolated from *Baccharis* species was demonstrated (González et al. 1990). *B. tola* and *B. boliviensis* were actives on *Candida* species and on dermatophytes fungi species, principally on *Microsporum canis* and *Trichophyton rubrum* (CIM < 100µg/ml), (Carrizo et al. 2010, 2020; Carrizo 2011). These results are relevant considering that *T.rubrum* is the etiological agent of 80-93% of all clinical infections produced by dermathophytes.

The presence of antibacterial activity and antifungal activity in *B. tola* and *B. boliviensis* extracts against bacteria and fungi resistant to commercial products give support to their traditional use and would seem promising for the treatment of infections in humans and animals.

Antioxidant Capacity The antioxidant capacity of *Baccharis boliviensis* and *Baccharis tola* aerial parts alcoholic extracts collected at 3800 m.a.s.l. in the Argentine Puna were studied (Herrera et al. 2007; Zampini et al. 2006, 2007, 2008, 2009a). Extracts of both *Baccharis* species exerted high hydrogen donating ability in the presence of DPPH radicals. The TEAC values of 15,000 and 7833μmol Trolox equivalent/100 g dry weight to *B. boliviensis* and *B. tola,* respectively, were found (Zampini et al. 2008). The tinctures were active as scavengers of reactive oxygen species such as superoxide anion and hydroxyl radical (Zampini et al. 2008). In the non-enzymatic system of O_2^- generation, extracts were scavengers of superoxide radicals with IC_{50} values between 10 and 20μg of total phenolic compounds/ml. *B. boliviensis* and *B. tola* extracts were also effective hydroxyl radical scavengers with IC_{50} values of 6 and 13.5, respectively. *B. tola* was the best H_2O_2 scavenger with IC_{25} values of 30μg/ml (Zampini et al. 2008).

Numerous studies have linked xanthine oxidase activity to inflammatory process. This enzyme produces superoxide anion radical and uric acid from xanthine and elicits the upregulation of inflammatory markers (Romagnoli et al. 2010). The xanthine oxidase inhibitory effect of ethanolic extracts was described by Zampini et al. (2008).

Aqueous extracts exhibit also antioxidant activity on ABTS cation radical, on the production of reactive oxygen species (ROS) and inhibit the expression of hsp72 in human neutrophils stimulated by different agents (Pérez-García et al. 2001; Zampini et al. 2009a). The oxidation of red blood cells (RBC) by molecular oxygen with the azo-compound AAPH as a free radical initiator was inhibited by *B. tola* infusion (Rojo et al. 2009). The ethanolic and aqueous extracts from aerial parts of *B. tola* and *B. boliviensis* could be exploited as natural medicine to reduce oxidative stress and for the prevention and treatment of hyperuricemia.

Anti-Inflammatory Activity Inflammatory and pathogenic conditions activate secretory phospholipase A2 (sPLA2), cyclooxygenase (COX) and lipoxygenase (LOX), two key enzymes in the synthesis of prostanoids and eicosanoids from polyunsaturated fatty acids, which are involved in various inflammatory process. Nitric oxide (NO) is one of the inflammatory mediators that is synthesized by inducible nitric oxide synthase (iNOS) in macrophages and is induced by different inflammatory stimuli such as bacterial endotoxic and inflammatory cytokines (Achike and Kwan, 2003). Although NO is required in immunological defense mechanisms and to maintain the dilation of blood vessels, high concentrations of NO can cause oxidative damage. Data obtained suggest that the inhibition of NO and prostaglandin (PG) production by *B. tola* extracts in macrophages occurs at the level of enzyme expression and/or enzyme activity. Hydroalcoholic extracts from *B. tola* and *B. boliviensis* were showed also inhibition of COX-2 activity. *B. tola* extract also decreases the COX-2 protein expression (43%). The induction of RAW 264.7 cells into an inflammatory state by treatment with lipo-polysaccharides (LPS) caused a significant increase in NO production. Pretreatment of cells with the *B. tola* and *B. boliviensis* extracts inhibited NO overproduction in a concentration-dependent manner with IC_{50} values of 167 and 195μg/ml, respectively. The iNOS protein expression was significantly decreased by *Baccharis tola* (58%). *B. boliviensis* and *B. tola* were inhibitors of sPLA2 activity (IC_{50} around 200μg/ml) and LOX activity (IC_{50} around 300μg/ml) (Alberto et al. 2009, Torres Carro et al. 2015, 2017, 2019). Therefore, these extracts might be an important therapeutic target to treat various inflammatory diseases or for cancer chemoprevention. It was also demonstrated that the dichloromethane extracts of *B. tola* have an anti-inflammatory effect with anti-edema action (44.54% inhibition) in the carrageenan-foot edema test in rats (Pérez et al. 1995). Intraperitoneal administration of extracts was performed 30 min before subcutaneous injection of 0.1 ml of 1% v/v i-carrageenan in normal saline (Pérez et al. 1995).

Phytotherapeutic Formulations A standardized extract of *Baccharis tola* with antimicrobial, antioxidant and anti-inflammatory activities were included in a topical phytopharmaceutical formulation (Hydrogel/Carbopol W934) (Nuño et al. 2012). The formulation showed antimicrobial and antioxidant activities *in vitro* assays. The hydrogel showed microbiological, chemical, physical and functional stability during storage at room temperature. Studies that measure drug release as a determination of bioavailability were also carried out. The results demonstrated the release of two bioactive compounds (chlorogenic acid and 4′,5-dihydroxy-3′,3,6,7,8-pentamethoxyflavone) from the phytotherapeutic preparation. In consequence, the preparation applied topically could be used to treat skin and soft tissue infection produced by methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus faecalis* strains and opens new opportunities for the use of active natural ingredients in the cosmeceutical field as anti acne and antioxidant agent.

Recently, *B. tola* and *B. boliviensis* were cited to have medicinal properties that make these species economically attractive in Argentina by its medicinal properties (Cantero et al. 2019).

10 Conclusions

Baccharis tola and *B. boliviensis* that grow in arid regions of Argentina, are species popularly used as medicinal plants. They are reported to show scientifically validated antibacterial, antifungal, antioxidant and anti-inflammatory activity. Both species are promising for the development of pharmaceutical and cosmetic products. The sustainable use of *Baccharis* species could be favorable for the regional economies. Therefore, it is important to promote their domestication (cultivation) and the development of value chains for their production.

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