Journal of Ethnopharmacology 228 (2019) 26–39

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

Fabiana imbricata Ruiz et Pav. (Solanaceae), a review of an important Patagonian medicinal plant

Guillermo Schmeda-Hirschmann[a,b,*], Cristina Theoduloz[c]

[a] Laboratorio de Química de Productos Naturales, Instituto de Química de Recursos Naturales, Universidad de Talca, Casilla 747, Talca, Chile
[b] Fraunhofer Chile Research Foundation - Centre for Systems Biotechnology (FCR-CSB), Av. del Condor 844, Piso 3, Huechuraba, Santiago de Chile, Chile
[c] Laboratorio de Cultivo Celular, Facultad de Ciencias de la Salud, Universidad de Talca, Talca, Chile

ARTICLE INFO

Keywords:
Fabiana imbricata
Solanaceae
South American crude drug
Sesquiterpenes
Gastroprotective
Diuretic

ABSTRACT

Ethnopharmacological relevance: *Fabiana imbricata* (Solanaceae) is a Patagonian medicinal plant with a long tradition of use. The aim of this review is to provide an integrative overview of the traditional uses, chemistry, bioactivity and chemical profiling of the crude drug.

Materials and methods: The information was collected from scientific databases searching with the keywords *Fabiana imbricata*, *Fabiana* species, *Fabiana* (Solanaceae) and includes local literature and books.

Results: The indications of use reported in literature show little variation from the data published as early as 1889. The chemical studies showed a rich diversity in metabolites including phenolics, coumarins, flavonoids, phenylpropanoids, terpenes, alkaloids and sugars. Bioactivity studies supported the traditional use as diuretic and also the potential of the crude drug as a gastroprotective agent. The plant can be used as a source of compounds with effect on gastric ulcers and shows enzyme inhibitory activity. While the germination rate of the plant is very low, protocols were developed for the rapid in vitro propagation of the species. The toxicity of the crude drug extracts was low and did not show clastogenic effect in human lymphocytes. Further research is needed to disclose the potential of the *F. imbricata* sesquiterpenes on other relevant biological targets.

1. Introduction

The genus *Fabiana* (Solanaceae) comprises 15 species, occurring in dry areas of the Patagonia and in the mountains of central and southern Andes (Cuello et al., 2011). Some species belonging to this genus are used in South American traditional medicine. The classic work of Reiche (http://images.mobot.org/efloras/FloraData/060/PDF/V05/Volume5-Fabiana.pdf) cited eight species for Chile. Alaria and Peralta (2013) updated the taxonomy of the genus for Chile in seven species: *F. bryoides* Phil., *F. denudata* Miers, *F. imbricata* Ruiz & Pav., *F. ramulosa* (Wedd.) Hunz. & Barboza, *F. squamata* Phil., *F. stephanii* Hunz. & Barboza and *F. viscosa* Hook. & Arn., the latter being the single endemic species. The latest revision of the vascular flora of Chile indicates a total of eight species of the *Fabiana* genus, including *F. densa* J. Remy (Rodríguez et al., 2018).

The Argentinean *F. bryoides*, *F. punensis*, *F. densa* and *F. patagonica* have been investigated from the ethnopharmacological point of view, looking for antioxidant, anti-inflammatory and genotoxic effects of aqueous and alcoholic extracts (Cuello et al., 2011). The diuretic effect of *F. patagonica* was reported and it was suggested to be associated with oleanolic acid (Alvarez et al., 2002). The antimicrobial effect of Argentinean species occurring in the highlands, including *F. bryoides*, *F. densa* and *F. punensis* was reported by Zampini et al. (2009). The diterpenes *ent*-beyer-15-en-18-*O*-succinate and *ent*-beyer-15-en-18-*O*-oxalate were isolated from *Fabiana densa* var. *ramulosa* and showed antibacterial activity (Erazo et al., 2002). The most common species in central Chile is *Fabiana imbricata* and is used in traditional medicine since pre-Hispanic times (Mösbach, 1992; Murillo, 1889).

The aim of this review is to update the information available on the ethnobotany, bioactivity, chemistry, propagation and chemical profiling of the crude drug. We revised all information on *Fabiana imbricata* available in ScienceDirect.com, SciFinder, Google Scholar, Chilean books and literature including Murillo (1889) and following references up to present. We excluded all information that was not clearly validated/supported by voucher herbarium specimens (except Murillo´s compilation). We selected books that are supported by scientific literature or first-hand data. We did not include all books and articles reporting the same information on the traditional use of the plant

* Corresponding author at: Laboratorio de Química de Productos Naturales, Instituto de Química de Recursos Naturales, Universidad de Talca, Casilla 747, Talca, Chile.
E-mail address: schmeda@utalca.cl (G. Schmeda-Hirschmann).

https://doi.org/10.1016/j.jep.2018.09.020
Received 3 July 2018; Received in revised form 3 September 2018; Accepted 11 September 2018
Available online 12 September 2018
0378-8741/

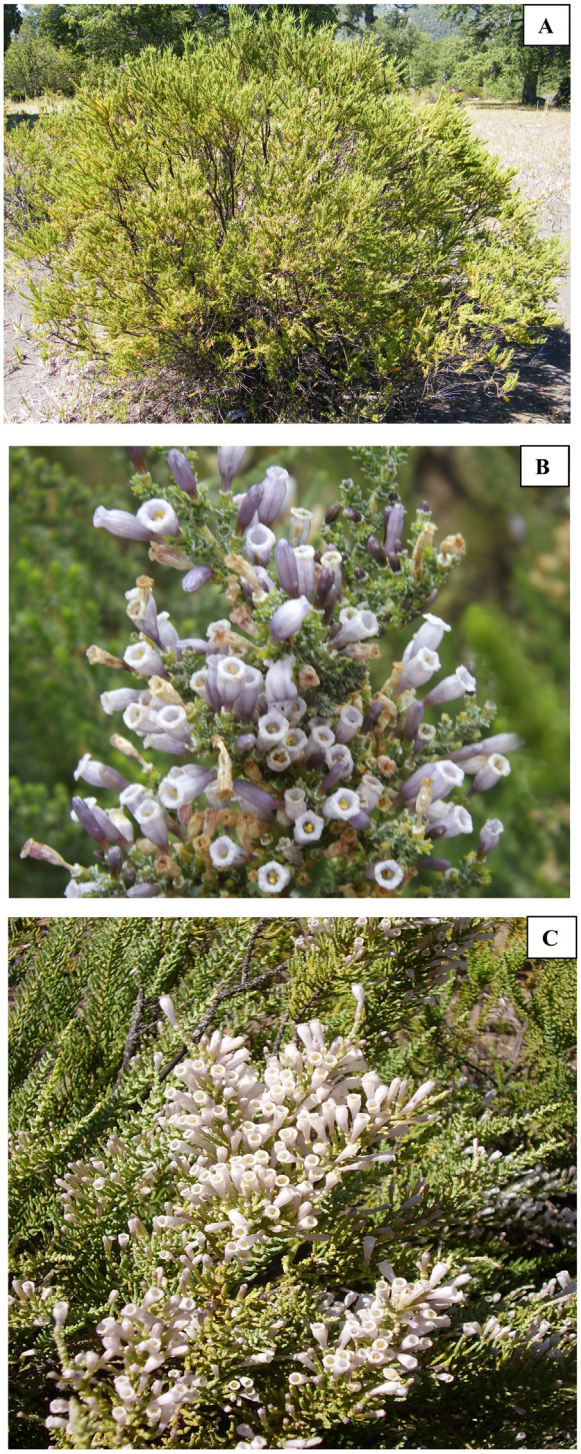


Fig. 1. *Fabiana imbricata* growing in the Andean slopes in central Chile (A) and the flowering tops with lilac (B) and white (C) flowers.

because they are repeating the data provided by Murillo and other authors. If the same information was published in mainstream journals and low impact journals, we included here the references from mainstream journals. This review is focused on traditional uses, pharmacology and chemistry and did not include floristic studies in the distribution area of the plant neither ecological work on the plant communities where the species occurs.

2. Traditional uses

The Solanaceae *Fabiana imbricata* Ruiz et Pav., known under the common names of “pichi” or “pichi romero” is a shrub common in the western Andean slopes of southern South America and in Patagonia. The shrub can be up to 3 m in height, with small leaves and light violet or white flowers (Fig. 1). *Fabiana imbricata* occurs from the Provincia de Mendoza to Chubut in Argentina, including the Patagonia steppe where it forms shrublands. In Chile, it can be found from Atacama to the Región de los Ríos, covering a wide range of dry, mediterranean landscapes to the more rainy places in southern Chile (de Torrres Curth et al., 2012). It grows in poor quality soils and is a typical plant of the sclerophilous forest of central Chile. The plant has a characteristic aroma and the aerial parts are covered with a bitter exudate. The infusion or decoction of the aerial parts has been used for different purposes in Chilean and Patagonian traditional medicine. The most common contemporary uses are as a diuretic, digestive and for kidney diseases.

The *F. imbricata* shrublands are relevant floristic communities in Patagonia, where it is known as “palo piche” or “palo de piche”. The distribution of the species in the Argentinean Patagonia is influenced both by rainfall and fire, following the changes associated with El Niño Southern Oscillation (de Torres Curth et al., 2012). Ethnobotanical studies on *F. imbricata* in the Argentinean Patagonia covers the ecology, cultural uses of the plant by the Mapuche-Tehuelche and an integrative approach of the plant selection by the Native Americans and rural people. In a revision of the Mapuche medicinal plants, Molares and Ladio (2009a) updated the information on Mapuche ethnobotany from 1955 to 2007 using articles published from Argentina and Chile. *Fabiana imbricata* grows all over the Mapuche traditional territory and the uses are nearly the same in Argentina and Chile (Molares and Ladio, 2009a, 2014). The authors concluded that the Mapuche medicinal plants form a solid nucleus of knowledge that is shared by the communities and reflects the different growth habitats in some areas of Patagonia. However, some differences in the indications of use can be found according to the different environment and access to alternatives (Estomba et al., 2006). *Fabiana imbricata* is recommended for liver diseases, as a laxative, to expel intestinal parasites, for general digestive disorders and as an emetic. The bitter taste of the plant and the strong smell are considered important and suggest using lower doses of the crude drug in infusions and decoctions (Molares and Ladio, 2009b). Molares and Ladio observed that plants used for digestive illnesses presented higher flavor and aroma as descriptors in Mapuche-Tehuelche communities in Argentinean Patagonia and showed that plants used to treat diseases of the gastrointestinal system present high consensus of taste and smell (Molares and Ladio, 2009b, 2014).

In Mapuche rural and semi-rural populations in Argentina, the collection of plants for medicinal uses is higher in more isolated places, following the interactions between traditional knowledge and living conditions (Eyssartier et al., 2013). In this study, *F. imbricata* is reported for renal and respiratory diseases. The relation of forest conservation and traditional uses of plants in Argentinean Patagonia was revised by Molares et Ladio (2012). The study shows correlations between the ethnoclassification of *Nothofagus* forests and recollection patterns of medicinal plants. In forests dominated by *N. antarctica*, which are closer to the settlements, *F. imbricata*, known as “palo piche” was the most cited medicinal plant species. It is used as diuretic, blood depurative, for liver ailments and for hair washing (Molares and Ladio, 2012). The *N. antarctica* forest is associated with a higher frequency of citations for plants used for hepatic and gastrointestinal diseases, as well as for genitourinary complains, being *F. imbricata* the species with highest relative importance.

Written records on the use of this plant in Chile can be traced back to the description of Murillo (1889) who was later incorporated into most of the books on medicinal plants of Chile. Murillo (1889) (p. 136–141) reports the traditional use of the plant in Chile during the

second half of the XIX century, including the observations of the naturalists Ruiz et Pavon and Claudius Gay about the veterinary use of *F. imbricata* to treat sheep and goat infected with the liver parasite known as "pirigüines" (*Fasciola hepatica*) and since ancient times for urinary affections (Murillo, 1889). In the same work, the successful use of a light decoction of this plant to treat gonorrhoea as well as the effect on chronic inflammation, including cystitis was reported. The author believed that the effect of the crude drug was due to the resin occurring in the small leaves, twigs and stem bark and suggests to employ the aerial parts. Some experiences on the diuretic effect of the plant decoction and resin were described in the original work and the results of the experiences are presented below (Murillo, 1889).

> *"Decoction (60/500) (60 g crude drug in 0.5 L water) in 4 portions, 2000 g of urin. Excess over the mean physiological value - 330 g, considered normal: 1670 g.*
>
> *Second experience: infusion (60/500), once, 540 g urine. No differences with mean values.*
>
> *Third and fourth experience: with maceration, no differences with mean values.*
>
> *Fifth experience, bark decoction (30 g/500 mL), 1900 g urine, some 230 g excess.*
>
> *Sixth-seventh experience: The plant resin, ingested, in about 1.2–3 g in two doses, during 2 days, produced an increase of 150 g in the mean urine value until 400 g considering the urine from the former day.*
>
> *Eigth-ninth experience. With aqueous extract, the urine amount was increase to 1900 g taking 2 g of extract in two doses in 2 h interval.*
>
> *Tenth experience. 45 g of powdered plant taken in 5 h (no information is given about the way of administration or if the powder should be taken with some food or swallowed with water, for instance). The increase over mean physiological urine values was 80 g, the total excreted was 1750 g"* (Murillo, 1889).

Mösbach (1992) recorded the use of plants by the Mapuche culture in southern Chile. As a missionary, he worked with the Mapuche people in the years 1920–1940. His work was published in 1992 after revision of his notes and update in his voucher herbarium specimens. *Fabiana imbricata* was reported to be used as a decoction of the twigs resin for bladder and urinary tract affections and as anthelmintic for sheep liver parasites known as "pirhuines" (*Fasciola*). The author also mentions the common name "tola" for the plant growing in northern Chile. However, this name applies for other *Fabiana* species and to several Asteraceae with small resinous leaves.

Pacheco et al. (1977) (p. 197–198) recorded the same uses as Murillo (1889). According to Muñoz et al. (1981), several preparations from the different plant parts are used in Chilean traditional medicine. The air-dried powdered twigs are sieved to obtain a powder. An infusion of about 4% from the aerial parts, or a light decoction of the aerial parts, as well as the aqueous extract are used. An alcoholic tincture was prepared placing the plant in ethanol in a plant:ethanol 1:5 ratio. All preparations are considered digestive and as an appetizer. The most common use of all preparations is for genito-urinary diseases, including bladder troubles, as a diuretic, to treat cystitis and gonorrhoea. It is also recommended for chronic bronchial affections and tuberculosis. The tea was used to heal liver abscesses. San Martin (1983) described the popular knowledge on medicinal plant uses in central Chile and reported the infusion of *F. imbricata* to treat kidney and urinary tract troubles. Houghton and Manby (1985) recorded the traditional use of "pichi" flowering tops as a diuretic by the Mapuche people. Montes and Wilkomirsky (1985) describe the use of the plant as a diuretic (p. 16) and as an excellent drug for the urinary system. The use comprises the diuretic, balsamic, antiseptic and sedative activity (p. 166). It is also considered as a good liver stimulant and cholagoge. The same information was later included in Muñoz et al. (2001) (p. 121–122). Other uses of the crude drug includes diuretic, balsamic, antiseptic and sedative. The crude drug is used as a 1 or 2% infusion of twigs and bark (aerial parts). Muñoz (1992) revised the Chilean information on *F. imbricata* and compiled the chemical studies carried out at that time. *Fabiana imbricata* has been included as one of the ingredients of a patent for skin care (Pillai et al., 1998). Schilcher et al. (2007) refer to *F. imbricata* as a plant used to treat diseases of the genito-urinary system.

3. Chemical studies

The information on the metabolites isolated and identified in the plant so far is summarized according to the chemical groups. The structures with the literature references are shown in Tables 1, 2. For the occurrence of the different compounds in other plant sources see the Dictionary of Natural Products on DVD (2018).

3.1. Chemical constituents

3.1.1. Alkanes

Knapp et al. (1972) identified the alkanes **1–8** from the aerial tops of *F. imbricata* by GC-MS. The uneven alkanes (C23-C31) were the main constituents of the mixture with lower amount of the even *n*-alkanes (C24-C28).

3.1.2. Fatty acids

The fatty acids (FA) **9–17** of the plant were identified as the corresponding methyl esters by GC-MS. The compounds were mainly C_{22}-C_{30} FA with C_{23}-C_{29} FA as less abundant compounds (Knapp et al., 1972).

3.1.3. Sugars

Richtmeyer (1970) described ten carbohydrates (compounds **18–27**) from the aqueous extract of the crude drug. The pentose xylose **18**, the hexose galactose **19**, the C5 polyalcohol arabinitol **20**, the C6 polyalcohols galactitol **21** and mannitol **22**, the cyclic polyol myo-inositol **23**, the C7 mannoheptulose **24** and perseitol **25**, the C8 D-glycero-D-manno-octulose **26**, and the disaccharide primeverose **27** were isolated and identified from the extract.

3.1.4. Anthraquinones

The study of a plant sample purchased in New York as *F. imbricata* afforded the anthraquinones physcion **28** and erythroglaucin **29** (Knapp et al., 1972). However, we never found physcion and erythroglaucin in samples of *F. imbricata* collected in central Chile.

3.1.5. Phenolics

The simple phenolic acetovanillone **30** was reported by Knapp et al. (1972). The same compound and the related *p*-hydroxyacetophenone **31** and its acetate **32** were isolated by Schmeda-Hirschmann and Papastergiou (1994) from central Chile samples. The compound **31** and the glucoside **33** were identified in infusions of the plant (Quispe et al., 2012).

3.1.6. Coumarins

The coumarin scopoletin **34** was reported from the first investigations on *F. imbricata*, including the studies of Knapp et al. (1972), Schmeda-Hirschmann and Papastergiou (1994) and Quispe et al. (2012). The glucoside **35** was identified in the infusion of the crude drug (Quispe et al., 2012).

3.1.7. Caffeoylquinic acids

Chlorogenic acid (3-*O*-caffeoylquinic acid) **36** is a constituent of the crude drug infusion (Quispe et al., 2012).

3.1.8. Flavonoids

The flavonols kaempferol **37**, quercetin **38** and quercetin-3-*O*-

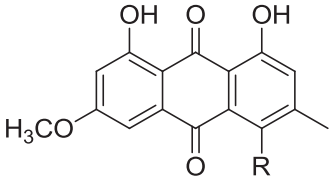
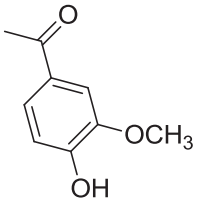
Table 1
Compounds identified in *Fabiana imbricata*.

Compounds identified in *Fabiana imbricata*.

	Compound	Reference
	Alkanes	
1	*n*-tricosane (C_{23})	Knapp et al., 1972.
2	*n*-tetracosane (C_{24})	
3	*n*-pentacosane (C_{25})	
4	*n*-hexacosane (C_{26})	
5	*n*-heptacosane (C_{27})	
6	*n*-octacosane (C_{28})	
7	*n*-nonacosane (C_{29})	
8	*n*-hentriacontane (C_{31})	
	Fatty acids	
9	Docosanoic acid (C_{22})	Knapp et al., 1972.
10	Tricosanoic acid (C_{23})	
11	Tetracosanoic acid (C_{24})	
12	Pentacosanoic acid (C_{25})	
13	Hexacosanoic acid (C_{26})	
14	Heptacosanoic acid (C_{27})	
15	Octacosanoic acid (C_{28})	
16	Nonacosanoc acid (C_{29})	
17	Triacontanoic acid (C_{30})	
	Sugars	
18	D-xylose	Richtmeyer, 1970.

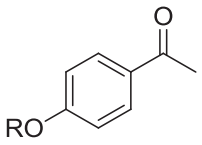
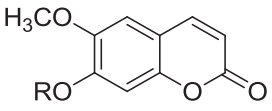
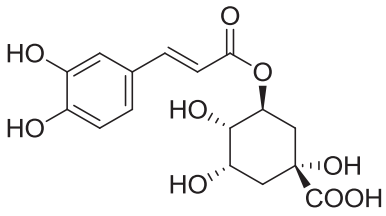
(*continued on next page*)

Table 1 (*continued*)

19 D-galactose		
20 D-arabinitol		
21 Galactitol		
22 D-mannitol		
23 *myo*-inositol		
24 D-mannoheptulose		
25 D-glycero-D-galacto-heptitol (perseitol)		
26 D-glycero-D-manno-octulose		
27 6-*O*-β-D-xylopyranosyl-D-glucose (primeverose)		
Anthraquinones		
		Knapp et al., 1972.
R		
28 H	Physcion	
29 OH	Erythroglaucin	
Phenolics		
		Knapp et al., 1972; Schmeda-Hirschmann and Papastergiou, 1994.
30 Acetovanillone (Apocynin)		

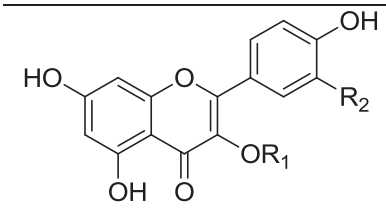
(*continued on next page*)

Table 1 (*continued*)

			Schmeda-Hirschmann and Papastergiou, 1994; Quispe et al., 2012.
	R		
31	H	*p*-hydroxy acetophenone	
32	Acetate		
33	Glucose		
Coumarins			
			Knapp et al., 1972; Schmeda-Hirschmann and Papastergiou, 1994.
	R		
34	H	scopoletin	
35	Glucose	scopoletin glucoside	
Caffeoylquinic acids			
			Quispe et al., 2012.
36	Chlorogenic acid (3-*O*-caffeoylquinic acid)		
Flavonoids			

(*continued on next page*)

Table 1 (*continued*)



Hörhammer et al., 1973; Razmilic et al., 1994; Quispe et al., 2012.

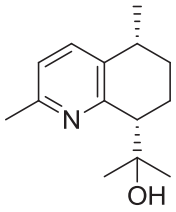
	R_1	R_2	
37	H	H	Kaempferol
38	H	OH	Quercetin
39	Rutinose	OH	Rutin

40 Rhamnose-dihexose* OH

41 Dirhamnose hexose* OH

*exact placement of the sugars not determined

Alkaloids

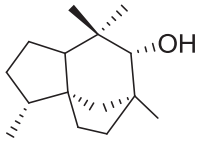


Edwards and Elmore, 1962; Schmeda-Hirschmann and Papastergiou, 1994.

42 Fabianine

Sesquiterpenes

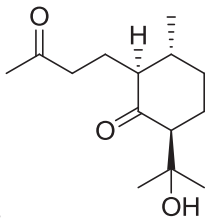
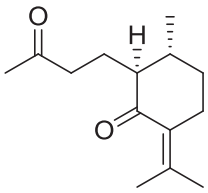
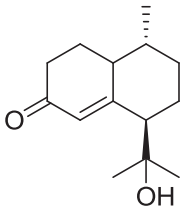
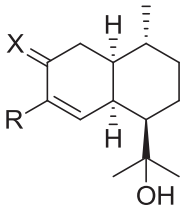
Schmeda-Hirschmann and Papastergiou, 1994.



43

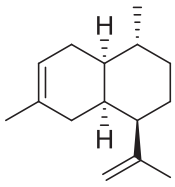
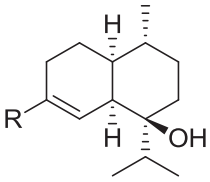
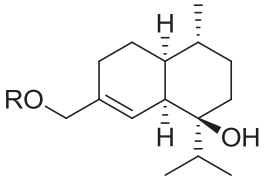
(*continued on next page*)

Table 1 (*continued*)

44		Schmeda-Hirschmann and Papastergiou, 1994. 3-methyl-6-(1-hydroxy-1-methylethyl)-2-(3-oxobutyl) cyclohexanone
45		Schmeda-Hirschmann and Papastergiou, 1994. 3-methyl-6-(1-methylethylidene)-2-(3-oxobutyl) cyclohexanone
46		Schmeda-Hirschmann and Papastergiou, 1994. Armerillone
		Schmeda-Hirschmann and Papastergiou, 1994. (compounds **48**, **49**, **51**) Brown, 1994a. (compounds **47**-**50**)
	R X	
47	CH_3 H_2	fabiaimbricatan 4-amorphen-11-ol
48	CHO H_2	15-oxo fabiaimbricatan 11-hydroxy-4-amorphen-15-al
49	COOH H_2	fabiaimbricatan-15-oic acid 11-hydroxy-4-amorphen-15-oic acid
50	CH_2OMalonate H_2	
51	CH_3 O	3-oxo fabiaimbricatan 4-amorphen-11,15-diol, 15-malonate ester

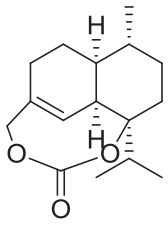
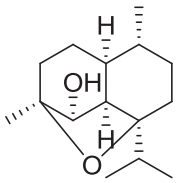
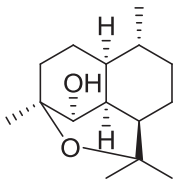
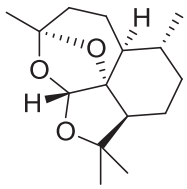
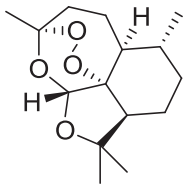
(*continued on next page*)

Table 1 (*continued*)

52			Brown and Shill, 1994. 3,11-amorphadiene
			Brown, 1994a.
	R		
53	CH_3	4-muurolen-7-ol	Chamomillol
54	CHO	7-hydroxy-4-muurolen15-al	Pernetal
55	COOH	7-hydroxy-4-muurolen15-oic acid	Pernetic acid
			Brown, 1994a.
	R		4-muurolen-7,15-diol, 15-malonate ester
56	malonate	Pernetyl malonate	4-muurolen-7,15-diol, 15-*trans*-cinnamate ester
57	*trans*-cinnamate	Pernetyl cinnamate	4-muurolen-7,15-diol, 15-*cis*-cinnamate ester
58	*cis*-cinnamate	Pernetyl cinnamate (cis)	4-muurolen-7,15-diol, 15-(2-phenylacetate) ester
59	2-phenylacetate		

(*continued on next page*)

Table 1 (*continued*)

60		Brown, 1994a. 4-muurolen-7,15-diol, 7,15-carbonate
61		Brown, 1994a. 4,7-epoxy-5-hydroxymuurolane
62		Brown, 1994a. 4,11-epoxy-5-hydroxyamorphane
63		Brown, 1994b. Fabianane
64		Ngo and Brown, 1999. Peroxyfabianane from 4-amorphen-11-ol

rhamnoglucoside (rutin) **39** were identified from the aerial parts of the plant by Hörhammer et al. (1973). In the infusion of the aerial parts, Quispe et al. (2012) identified rutin, quercetin-*O*-rhamnose-dihexoside **40** and quercetin-dirhamnoside hexoside **41**.

3.1.9. Alkaloids

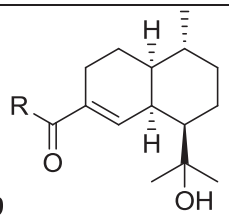
The alkaloid fabianine **42** was isolated by Edwards and Elmore (1962) from the aerial tops of the plant. The compound was obtained from samples collected in central Chile (Schmeda-Hirschmann and Papastergiou, 1994) and is the only alkaloid reported so far from the plant.

3.2. Terpenes

3.2.1. Sesquiterpenes

The plant is rich in sesquiterpenes with a large structural diversity. Most of them belong to the γ-amorphene or α-muurolene skeletons, differing in the stereochemistry of the isopropyl group at C-7. Different oxidation patterns at C-15 and esterification of the alcohol function at C-15 increases the chemical diversity. The tricyclic sesquiterpene alcohol **43** and the diketones **44** and **45** were isolated from plants collected at the Andean slopes of Región del Maule, in central Chile (Schmeda-Hirschmann and Papastergiou, 1994). The norcadinane **46** is related to compound **44**. The γ-amorphene derivatives **47**–**51** were identified in samples from the Región del Maule (**48**, **49** and **51**) (Schmeda-Hirschmann and Papastergiou, 1994) and from Cajón del Maipo, at the Andean slopes of the Región Metropolitana (compounds

Table 2
Terpenes from *Fabiana imbricata* and semisynthetic derivatives investigated as gastroprotective agents.



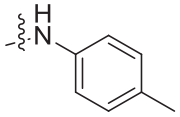
49

11-Hydroxy-4-amorphen-15-oic acid

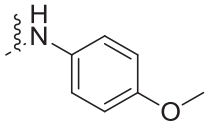
R

49 OH

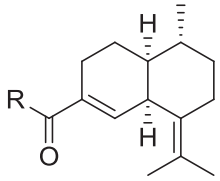
65 OCH_3



66 *p*-toluidine



67 *p*-anisidine



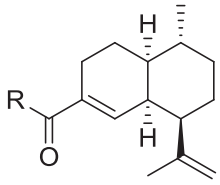
4,7(11)-Amorphadien-15-oic acid; [4,7(11)-cadinadien-15-oic acid]

R

68 OH

69 *p*-toluidine

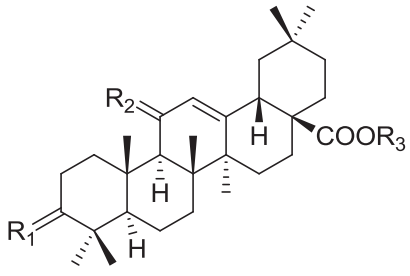
4,11-amorphadien-15-oic acid; [4,11-cadinadien-15-oic acid]

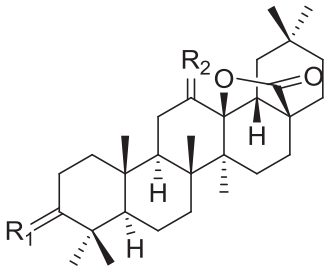


R

70 OH

71 *p*-toluidine





(*continued on next page*)

Table 2 (*continued*)

	R_1	R_2	R_3		R_1	R_2
72	H, β-OH	H_2	H Oleanolic acid	**79**	O	O
73	H, β-OAc	H_2	H	**80**	H, β-OH	H, α-OH
74	H, β-OH	H_2	CH_3			
75	H, β-OAc	H_2	CH_3			
76	O	H_2	H			
77	O	H_2	CH_3			
78	O	O	H			

47–50) (Brown, 1994a). The sesquiterpene hydrocarbon **52** was obtained from the Cajón del Maipo sample (Brown and Shill, 1994). Interestingly, the *F. imbricata* population from Cajón del Maipo also synthesizes a large variety of α-muurolene derivatives, including the compounds **53–59** and the tricylic sesquiterpenes **60–62** (Brown, 1994a, 1994b). A special mention merits the secoamorphane fabianane **63** (Brown, 1994b) because of some similarities with artemisinine. Autooxidation of 4-amorphen-11-ol and fabianane can led to the endoperoxide **64** (Ngo and Brown, 1999).

3.2.2. Triterpenes

The triterpene oleanolic **72** was described as a constituent of the crude drug (Hegnauer, 1973) and was isolated by several authors (Knapp et al., 1972; Schmeda-Hirschmann and Papastergiou, 1994). Other triterpenes occurs in the crude drug in lower amounts (Schmeda-Hirschmann, unpublished data).

3.2.3. Infusion constituents and crude drug analysis

The crude drug contains among its secondary metabolites the flavonoid rutin, the coumarin scopoletin, oleanolic acid and several sesquiterpenes. The aqueous infusions and decoction of the plant aerial parts was investigated for a fast characterization of the constituents. The main compounds from the infusion as determined by HPLC and HPLC-MS techniques were *p*-hydroxyacetophenone **31** and its glucoside **33**, scopoletin **34** and the glucoside **35**, chlorogenic acid **36**, rutin **39** and the triglycosides **40** and **41** (Quispe et al., 2012).

Rutin was quantified in 10 samples of the plant (Fischer et al., 2011). The total flavonoid content, expressed as rutin percent was in the range of 1.3–5.3%. The scopoletin content in three commercial samples of *F. imbricata* aerial parts was determined by TLC and reported in a congress to be in 0.25–0.55% (Poukens-Renwart and Angenot, 1990). In the TLC Atlas of plant crude drugs, Wagner and Bladt (2009) include the characterization of *F. imbricata* based on the coumarins scopoletin, its 7-*O*-primveroside, isofraxidin and its 7-*O*-glucoside, rutin, quercetin 3-*O*-glucoside, chlorogenic and isochlorogenic acids.

The main compounds in the infusion are metabolites with several proved biological effects. Chlorogenic acid (Naveed et al., 2018), rutin (Hosseinzadeh and Nassiri-Asl, 2014), quercetin (Carvalho et al., 2017), scopoletin (Benoit et al., 2012; Ferreira et al., 2017) and oleanolic acid (Pollier and Goossens, 2012; Yin, 2012) are compounds of growing interest both as health promoting and for their potential therapeutic applications.

4. Bioactivity studies

Extracts from the aerial parts of *F. imbricata* showed several biological activities. The ethanol:water 7:3 extract inhibited the enzyme β-glucuronidase with an IC_{50} of 6.2–10 μg/mL (Schmeda-Hirschmann et al., 1994). After solvent partition of the extract, affording a $CHCl_3$, *n*-BuOH and aqueous fraction, the effect was higher in the $CHCl_3$ fraction, with percent inhibition of 69%, 23% and 17%, respectively at 10 μg/mL. Scopoletin **34** was identified as the main compound with effect on the enzyme and showed a non-competitive inhibition of the enzyme with a K_i value of 4×10^{-5} M. The same extract presented an $IC_{50} > 50$ μg/mL towards the enzyme xanthine oxidase (XO) and was considered inactive (not interesting) as a source of XO inhibitors (Schmeda-Hirschmann et al., 1992).

The diuretic effect of the crude extract was assessed at 250 mg/kg in rats and resulted in a 47.8% increase in urine output, compared with untreated animals. Hydrochlorothiazide (25 mg/kg) was used as a reference compound (Schmeda-Hirschmann et al., 1994). Intravenous administration of the extract at 5 mg/kg in normotensive rats did not elicit relevant changes in blood pressure (Schmeda-Hirschmann et al., 1992). A report published in a homoeophatic journal describes positive results of *F. imbricata* on diseases related with kidney, gallbladder, bladder and prostate by oral administration mainly in the 4x-12x form of drops (Mehnert, 1989).

The antifeedant activity of the main constituents *p*-hydroxyacetophenone **31**, scopoletin **34**, rutin **39**, the sesquiterpene fabiaimbricatan-15-oic acid **49** and oleanolic acid **72**, was assessed towards the greenbug *Rhopalosiphum padi* and the corn earworn *Heliothis zea* using artificial diets. The sesquiterpene **49** and oleanolic acid presented toxic effect against the aphid at concentrations up to 3.0 mM. The insect behavior suggested antifeedant effect. Rutin, scopoletin and *p*-hydroxyacetophenone were toxic for the greenbug but none of them was a feeding deterrent on *H. zea* (Schmeda-Hirschmann et al., 1995).

The main terpenes of the *F. imbricata* exudate, namely the sesquiterpene **49** and the triterpene oleanolic acid **72** were individually evaluated for gastroprotective effect in animal models. The sesquiterpene **49** was assessed as a gastroprotective agent in HCl/EtOH-induced gastric lesions in mice at the single oral doses of 25, 50 and 100 mg/kg. The dose-response experiments proved **49** to be active, reducing gastric lesions by 19.4%, 42.3% and 68.7% at 25, 50 and 100 mg/kg, respectively. Structural modification of the sesquiterpene by chemical means afforded the derivatives **65–71** that were compared

at 100 mg/kg. The best gastroprotective effect was found for 11-hydroxy-4-amorphen-15-*p*-toluidinamide **66** reducing the gastric lesions by 80% but with a ten-fold increase in cytotoxicity compared with the parent compound (Reyes et al., 2005).

The main triterpene of the aerial parts of *F. imbricata* is oleanolic acid (OA). This compound presents gastroprotective effect in rats with low toxicity (Astudillo et al., 2002). A single oral dose of OA at 50, 100 and 200 mg/kg inhibited gastric lesions induced by ethanol, aspirin and pylorus ligature. In the Shay and aspirin models, the effect of OA in the selected concentrations was comparable to that of ranitidine at 50 mg/kg. The OA derivatives **73–77** were compared as gastroprotective agents at 200 mg/kg in the HCl/EtOH-induced ulcers in mice. OA and its methoxylated (**74**) and acetylated (**73** and **75**) derivatives proved to be active in the animal models but their effect was not significantly higher than OA itself (Astudillo et al., 2002). OA presented curative effect on acetic acid-induced gastric ulcers in rats (Rodríguez et al., 2003). Sanchez et al. (2006) used human gastric epithelial adenocarcinoma cells (AGS, ATCC CRL-1739) and human lung fibroblasts (MRC-5, ATCC CCL-171™) cells to assess the cytoprotective effect of OA and six derivatives against the damage induced by sodium taurocholate (NaT). The same cell lines were used to evaluate the ability of OA and its derivatives to stimulate the synthesis of cellular reduced glutathione (GSH) and prostaglandin E_2 content, as well as the stimulation of cell proliferation for ulcer wound healing (Sanchez et al., 2006). All the assayed compounds displayed a significant cytoprotective effect in AGS cells after incubation with NaT. None of the studied compounds stimulated the GSH synthesis in AGS cell cultures. Compounds **72**, **73**, **75** and **79** increased the prostaglandin E_2 content in AGS cells. Concerning the cell proliferation assays, a significant stimulating effect was observed for compounds **74** and **80** on AGS cells, and for **72** and **80** on MRC-5 fibroblasts.

Other activities should be expected for the *F. imbricata* compounds, including possible effect on *Plasmodium* protozoa. The similarity of the rearranged sesquiterpenes Fabianane **63** (Brown, 1994b) and peroxyfabianane **64** (Ngo and Brown, 1999) with artemisinin (Liu, 2017) merit further investigation. *Fabiana imbricata* is much more abundant in the Argentinean Patagonia. The chemistry and bioactivity of samples from Argentina should be assessed because there are remarkable differences in the chemistry and bioactivity of other species collected in both sides of the Andes, including the currants *Ribes magellanicum* (Jiménez-Aspee et al., 2016) and the fruits from *Geoffroea decorticans* (Jiménez-Aspee et al., 2017; Costamagna et al., 2016).

4.1. Oral toxicity and clastogenic effect

Oral acute toxicity tests in rats and mice using crude EtOH:H_2O 7:3 extract of *F. imbricata* at 1.0 and 5.0 g/kg did not show neither behavioral changes, nor macroscopic damage in organs after necropsy when the animals were euthanized seven days after oral administration. In the range of 0.10–0.50 mg/mL, the extract did not increase chromosome damage in human lymphocytes in vitro. In an acute toxicity test on mice, intraperitoneal administration of OA showed no toxicity at doses up to 600 mg/kg. According to the pharmacological evidence from the Chilean collections of the plant (Schmeda-Hirschmann et al., 1994), *Fabiana imbricata* is a safe crude drug in the amounts used in traditional medicine. In the field work carried out in the Argentinean Patagonia (Molares and Ladio, 2009a, 2009b, 2012, 2014), there is no information suggesting toxicity from “palo piche” or “palo de piche”.

5. Cultivation and micropropagation

At present, there is no major concern on the conservation status of *F. imbricata*. The native populations are widespread in the western Andean slopes and in the Patagonia. The plant grows on poor quality soils, with limited water supply. Urbanization of rural and semi-rural areas of Chile may have an impact in the wild growing populations of *F. imbricata*. However due to the abundance of this resource, there should be enough material for a potential sustainable collection.

A study on traditional micropropagation was published (Razmilic et al., 1994) and a massive propagation method for *F. imbricata* by means of the temporary immersion system (TIS) technique. The study included callus cultures, cell suspensions and biomass production by the TIS (Schmeda-Hirschmann et al., 2004). The content of the main constituents of the plant aerial parts (OA, rutin, chlorogenic acid and scopoletin) was compared with that of the micropropagated plantlets. Fischer et al. (2011) reported propagation assays for several Chilean medicinal plants, including *F. imbricata*. According to this group, the seed germination rate was very low (3%). Therefore, micropropagation seems to be a choice method for the rapid propagation of this medicinal plant.

6. Conclusions

The Chilean crude drug *Fabiana imbricata* shows activity as diuretic and their main constituents presents gastroprotective effect in animal models of induced gastric lesions. The extract also inhibits the enzyme β-glucuronidase. The plant shows high diversity of chemical constituents, ranging from non-polar waxes, fatty acids and terpenes, to highly polar constituents such as phenolics and sugars. The chemical profile of the infusions and the variations observed in the content of the main compounds from the lyophilized aqueous extracts shows the need of standardization of the plant material, including good practices from the harvesting in wild growing populations and the selection of best germplasm for cultivation trials. The emphasis in the research work is clearly different in Argentina and Chile. Most ethnobotanical work has been carried out in Argentina, while pharmacological and chemical studies were undertaken with plant samples collected in Chile.

Acknowledgements

We acknowledge support from Fraunhofer Chile Research Foundation - Centre for Systems Biotechnology (FCR-CSB), Santiago de Chile

Conflicts of interest

The authors have none to declare.

Author's contribution

Both authors designed the study, carried out the literature survey and wrote the paper.

References

Alaria, A., Peralta, I., 2013. Las especies de *Fabiana* Ruiz et Pav. (Solanaceae) que crecen en Chile. Chloris Chilensis. Año 16 N°1, 24 pp. URL: http:// www.chlorischile.cl ⟨http://ri.conicet.gov.ar/bitstream/handle/11336/3185/Fabiana_Chloris_Chilensis_16_2013.pdf?Sequence=1&isAllowed=y⟩.

Alvarez, M.E., Maria, A.O.M., Saad, J.R., 2002. Diuretic activity of *Fabiana patagonica* in rats. Phytother. Res. 16, 71–73.

Astudillo, L., Rodríguez, J., Schmeda-Hirschmann, G., 2002. Gastroprotective activity of oleanolic acid derivatives on experimentally induced gastric lesions in mice. J. Pharm. Pharmacol. 54, 583–588.

Benoit, G., Sanni, G.J., Brimer, L, A., 2012. Review Scopoletin – a coumarin phytoalexin with medicinal properties. Crit. Rev. Plant Sci. 31, 47–56.

Brown, G.D., 1994a. The sesquiterpenes of *Fabiana imbricata*. Phytochemistry 35, 425–433.

Brown, G.D., 1994b. Fabianane, an unusual secoamorphane from *Fabiana imbricata*. J. Nat. Prod. 57, 328–330.

Brown, G.D., Shill, J., 1994. Isolation of 3,11-amorphadiene from *Fabiana imbricata*. Planta Med. 60, 495–496.

Carvalho, D., Paulino, M., Polticelli, F., Arredondo, F., Williams, R.J., Abin-Carriquiry, J.A., 2017. Structural evidence of quercetin multi-target bioactivity: a reverse virtual screening strategy. Eur. J. Pharm. Sci. 106, 393–403.

Costamagna, M.S., Zampini, I.C., Alberto, M.R., Cuello, S., Torres, S., Perez, J., Quispe, C., Schmeda-Hirschmann, G., Isla, M.I., 2016. Polyphenol rich fraction from *Geoffroea*

decorticans fruits flour affects key enzymes involved in metabolic syndrome, oxidative stress and inflammatory process. Food Chem. 190, 392–402. https://doi.org/10.1016/j.foodchem.2015.05.068.
Cuello, S., Alberto, M.R., Zampini, I.C., Oredoñez, R.M., Isla, M.I., 2011. Comparative study of antioxidant and anti-inflammatory activities and genotoxicity of alcoholic and aqueous extracts of four *Fabiana* species that grow in mountainous area of Argentina. J. Ethnopharmacol. 137, 512–522.
De Torres Curth, M.I., Ghermandi, L., Biscayart, C., 2012. Are *Fabiana imbricata* shrublands advancing over northwestern Patagonian grasslands? A population dynamics study involving fire and precipitation. J. Arid Environ. 83, 78–85.
Dictionary of Natural Products on DVD, 2018. CRC Press, Taylor&Francis.
Estomba, D., Ladio, A., Lozada, M., 2006. Medicinal wild plant knowledge and gathering patterns in a Mapuche community from North-western Patagonia. J. Ethnopharmacol. 103, 109–119.
Eyssartier, C., Ladio, A.H., Lozada, M., 2013. Traditional horticultural and gathering practices in two semi-rural populations of Northwestern Patagonia. J. Arid Environ. 97, 18–25.
Edwards, O.E., Elmore, N.F., 1962. Fabianine. Canad. J. Chem. 40, 256–264.
Erazo, S., Zaldívar, M., Delporte, C., Backhouse, N., Tapia, P., Belmonte, E., Delle Monache, F., Negrete, R., 2002. Antibacterial diterpenoids from *Fabiana densa* var. ramulosa. Planta Med. 68, 361–363.
Ferreira, I.C.F.R., Natália Martins, N., Lillian Barros, L., 2017. Phenolic compounds and its bioavailability: in vitro bioactive compounds or health promoters? Adv. Food Nutr. Res. 82, 1–44.
Fischer, S., Berti, M., Wilckens, R., Baeza, M., Pastene, E., Inostroza, L., Tramón, C., Gonzalez, W., 2011. Characterization and propagation of some medicinal plants in the central-south region of Chile. Ind. Crops Prod. 34, 1313–1321.
Hegnauer, R., 1973. Chemotaxonomie der Pflanzen, Band 6. Springer Verlag, Basel AG.
Hörhammer, L., Wagner, H., Wilkomirsky, M.T., Iyengar, M.A., 1973. Flavonoide in einigen Chilenische Heilpflanzen. Phytochemistry 12, 2068–2069.
Hosseinzadeh, H., Nassiri-Asl, M., 2014. Review of the protective effects of rutin on the metabolic function as an important dietary flavonoid. J. Endocrinol. Investig. 37, 783–788.
Houghton, P.J., Manby, J., 1985. Medicinal plants of the Mapuche. J. Ethnopharmacol. 13, 89–103.
Jiménez-Aspee, F., Theoduloz, C., Soriano, M., del, P.C., Ugalde-Arbizu, M., Alberto, M.R., Zampini, I.C., Isla, M.I., Simirgiotis, M.J., Schmeda-Hirschmann, G., 2017. The native fruit *Geoffroea decorticans* from the arid northern Chile: phenolic composition, antioxidant activities and in vitro inhibition of pro-inflammatory and metabolic syndrome associated enzymes. Molecules 22, 1565. https://doi.org/10.3390/molecules22091565.
Jiménez-Aspee, F., Valdés, S.T., Schulz, A., Ladio, A., Theoduloz, C., Schmeda-Hirschmann, G., 2016. Antioxidant activity and phenolic profiles of the wild currant *Ribes magellanicum* from Chilean and Argentinean Patagonia. Food Sci., Nutr. 4, 595–610.
Knapp, J.E., Farnsworth, N.R., Theiner, M., Schiff, P.L., 1972. Anthraquinones and other constituents of *Fabiana imbricata*. Phytochemistry 11, 3091–3092.
Liu, C.-X., 2017. Discovery and development of Artemisinin and related compounds. Chin. Herbal. Med. 9, 101–114.
Mehnert, H., 1989. Fabiana imbricata. Br. Homoeopath. J. 78, 115.
Molares, S., Ladio, A., 2009a. Ethnobotanical review of the Mapuche medicinal flora: use patterns on a regional scale. J. Ethnopharmacol. 122, 251–260.
Molares, S., Ladio, A., 2009b. Chemosensory perception and medicinal plants for digestive ailments in a Mapuche community in NW Patagonia, Argentina. J. Ethnopharmacol. 123, 397–406.
Molares, S., Ladio, A., 2012. Mapuche perceptions and conservation of Andean *Nothofagus* forests and their medicinal plants: a case study from a rural community in Patagonia, Argentina. Biodivers. Conserv. 21, 1079–1093.
Molares, S., Ladio, A., 2014. Medicinal plants in the cultural landscape of a Mapuche-Tehuelche community in arid Argentine Patagonia: an eco-sensorial approach. J. Ethnobiol. Ethnomed. 10 (61), 14.
Montes, M., Wilkomirsky, M.T., 1985. Medicina Tradicional Chilena. Editorial de la Universidad de Concepción, Concepción, Chile.
Mösbach, E.W., 1992. Botanica Indigena de Chile. In: Aldunate, C., Villagrán, C. (Eds.), Museo Chileno de Arte Precolombino. Fundación Andes and Editorial Andrés Bello. Santiago de Chile.
Muñoz, M., Barrera, E., Meza, I., 1981. El uso medicinal y alimenticio de plantas nativas y naturalizadas en Chile. Publicación Ocasional N° 33, Museo Nacional de Historia Natural, Santiago de Chile, Chile.
Muñoz, O., Montes, M., Wilkomirsky, T., 2001. Plantas medicinales de uso en Chile. Química y farmacología. Vicerrectoria de Asuntos Académicos. Universidad de Chile, Santiago de Chile.
Muñoz, O., 1992. Química de la flora de Chile. Departamento Técnico de Investigación, Universidad de Chile.
Murillo, A., 1889. Plantes medicinales du Chili. Exposition Universelle de Paris, Section Chilienne. Biblioteca Nacional, Paris.
Naveed, M., Hejazi, V., Abbas, M., Kamboh, A.A., Khan, G.J., Shumzaid, M., Ahmad, F., Babazadeh, D., Fangi, X.F., Modarresi-Ghazani, F., WenHua, L., XiaoHui, Z., 2018. Chlorogenic acid (CGA): a pharmacological review and call for further research. Biomed. Pharmacother. 97, 67–74.
Ngo, K.-S., Brown, G.D., 1999. Autoxidation of 4-amorphen-11-ol and the biogenesis of nor- and seco-amorphane sesquiterpenes from *Fabiana imbricata*. Tetrahedron 55, 15109–15126.
Pacheco, P., Chiang, M.T., Marticorena, C., Silva, M., 1977. Química de las plantas chilenas usadas en medicina popular I. Universidad de Concepción, Concepción, Chile.
Pillai, S., Gottlieb, K.A., Brinker, A.M., Mahajan, M., Rawlings, A.V., 1998. Cosmetic compositions containing phytovitamin D. United States Chesebrough-Pond's USA Co., Division of Conopco, Inc., (Greenwich, CT), Patent N° 5776461.
Pollier, J., Goossens, A., 2012. Oleanolic acid. Phytochemistry 77, 10–15.
Poukens-Renwart, P., Angenot, L., 1990. Concerning the standardization of *Fabiana imbricata*. Planta Med. 56, 595 (Conference paper).
Quispe, C., Viveros Valdez, E., Schmeda-Hirschmann, G., 2012. Phenolic constituents of the Chilean herbal tea *Fabiana imbricata* R. et P. Plant Foods Hum. Nutr. 67, 242–246.
Razmilic, I., Schmeda-Hirschmann, G., Dutra-Behrens, M., Reyes, S., Lopez, I., Theoduloz, C., 1994. Rutin and scopoletin content and micropropagation of *Fabiana imbricata*. Planta Med. 60, 140–142.
Reyes, M., Schmeda-Hirschmann, G., Razmilic, I., Theoduloz, C., Yañez, T., Rodriguez, J., 2005. Gastroprotective activity of sesquiterpene derivatives from *Fabiana imbricata*. Phytother. Res. 19, 1038–1042.
Richtmeyer, N.K., 1970. The isolation of D-manno-heptulose, perseitol, D-glycero-D-manno-octulose, and other compounds from pichi tops (*Fabiana imbricata* Ruiz & Pav.). Carbohydr. Res. 12, 233–239.
Rodríguez, R., Marticorena, C., Alarcón, D., Baeza, C., Cavieres, L., Finot, V.L., Fuentes, N., Kiessling, A., Mihoc, M., Pauchard, A., Ruiz, E., Sánchez, P., Marticorena, A., 2018. Catálogo de las plantas vasculares de Chile. Gayana Bot. 75, 1–430.
Rodríguez, J.A., Astudillo, L., Schmeda-Hirschmann, G., 2003. Oleanolic acid promotes healing of acetic acid-induced chronic gastric ulcers in rats. Pharmacol. Res. 48, 291–294.
San Martin, J., 1983. Medicinal plants in Central Chile. Econ. Bot. 37, 216–277.
Sanchez, M., Theoduloz, C., Schmeda-Hirschmann, G., Razmilic, I., Yañez, T., Rodriguez, J., 2006. Gastroprotective and ulcer-healing activity of oleanolic acid derivatives: in vitro-in vivo relationships. Life Sci. 79, 1349–1356.
Schilcher, H., Kammerer, S., Wegener, T., Volkmann, D., 2007. Erkrankungen des Urogenitaltrakts. Leitfaden Phytotherapie, Third ed. Urban & Fischer, München.
Schmeda-Hirschmann, G., Jordan, M., Gerth, A., Wilken, D., Hormazabal, E., Tapia, A.A., 2004. Secondary metabolite content in *Fabiana imbricata* plants and *in vitro* cultures. Z. Naturforsch. 59C 48–54.
Schmeda-Hirschmann, G., Román, P., Theoduloz, C., Donoso, C., Corcuera, L., 1995. Effect of *Fabiana imbricata* constituents on *Rhopalosiphum padi* and *Heliothis zea*. Phytother. Res. 9, 219–221.
Schmeda-Hirschmann, G., Loyola, J.I., Dutra-Behrens, M., Reyes, S., Hubert, E., Rodríguez, M., Rodríguez, J., 1994. ß-Glucuronidase inhibition and diuretic activity of *Fabiana imbricata* (Solanaceae). Phytother. Res. 8, 485–487.
Schmeda-Hirschmann, G., Papastergiou, F., 1994. Sesquiterpenes from *Fabiana imbricata*. Phytochemistry 36, 1439–1442.
Schmeda-Hirschmann, G., Loyola, J.I., Sierra, J., Retamal, R., Rodriguez, J., 1992. Hypotensic effect and enzyme inhibitory activity of Mapuche medicinal plant extracts. Phytother. Res. 6, 184–188.
Wagner, H., Bladt, S., 2009. Plant Drug Analysis: A Thin Layer Chromatography Atlas. Springer Verlag, New York.
Yin, M.-C., 2012. Anti-glycative potential of triterpenes: a mini-review. BioMedicine 2, 2–9.
Zampini, I.C., Cuello, S., Alberto, M.R., Ordoñez, R.M., D'Almeida, R., Solorzano, E., Isla, M.I., 2009. Antimicrobial activity of selected plant species from "the Argentine Puna" against sensitive and multi-resistant bacteria. J. Ethnopharmacol. 124, 499–505.