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Traditional use, chemical constituents, and pharmacological activity of *Maytenus laevis* Reissek

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Review

Abstract

Background: Species of the genus *Maytenus* are recognized for their uses in pain and cancer-related conditions. The purpose of the literature review was to compile scientific information on the traditional uses, chemical constituents, and pharmacological activities of *Maytenus laevis* Reissek.

Methods: The scientific name *Maytenus laevis* and its synonyms, in combination with "traditional uses" OR ethnobotany OR "chemical constituents" OR "chemical composition" OR phytochemistry OR "biological activities" OR "pharmacological activities" OR pharmacology, were searched in the main databases. Seventy papers were selected according to research type and relevance.

Results: *M. laevis* is known by the common name ''chuchuhuasi'' and is traditionally used for the treatment of rheumatism and cancer, although it is also used as a sexual enhancer. Its chemical constituents are pyridine-derived alkaloids, triterpenes, sterols, iridoids and phenolic compounds, and are of great pharmacological interest, but only anti-inflammatory, antibacterial, antiparasitic and anticancer activities have been proven in preclinical studies. In addition, different studies point to its growth in Peru, due to it being confused with other species of the genus *Maytenus*.

Conclusions: Reports on its chemical composition indicate the therapeutic potential of this species. However, there is little information on its pharmacological effects at the preclinical and clinical levels. Therefore, further research could verify its correct distribution and scientific validation of its traditional uses. In addition, specific chemical markers could be used to differentiate it from other species.

Keywords: *Maytenus laevis*, *Maytenus javensis*, *Monteverdia laevis*, traditional use, chemical constituents, pharmacological activities.

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Background

The family Celastraceae is distributed in the continents of America, Africa, and Asia. In addition, it is composed of approximately 106 genera and 1,300 plant species (Kouamé *et al.* 2020). They are small trees, shrubs or lianas and are used in traditional medicine through the oral consumption of aqueous extracts or hydroethanolic macerates of the leaves, stem, bark, and root; for the treatment of rheumatoid arthritis, skin infections and autoimmune diseases (Bazzocchi *et al.* 2017, Camargo *et al.* 2020, Veloso *et al.* 2017).

In plant species of the Genus *Maytenus*, more than 300 compounds of biological importance have been detected (Zhang *et al.* 2020). It consists of 76 identified species and are used by communities for gastric diseases and cancer. Phytochemical studies have made it possible to identify flavonoids, pentacyclic triterpenes (friedelane-, oleane-, lupane-, and ursane-type), sesquiterpenes, alkaloids and condensed tannins. Antiulcer, anti-inflammatory, contraceptive, antioxidant, antimicrobial, antiviral, and antiparasitic activities have been reported (Biral *et al.* 2017, Guimarães *et al.* 2020, Lei *et al.* 2020, Niero *et al.* 2011, Veloso *et al.* 2017, Zhang *et al.* 2020). Recent research has confirmed the activity of the hexanic extract from the bark of *Maytenus guianensis* against leishmaniasis. Its effectiveness would be mediated by the inhibition of amastigotes through the production of cytokines such as IL-12 and TNF-α (Macedo *et al.* 2019). Also, it has been reported that the methanolic extract of the leaves of *Maytenus robusta* generated a decrease in liver inflammation; decreasing the concentration of myeloperoxidases, TNF, and IL-6 (Thiesen *et al.* 2017).

In Latin America, the species of the Genus *Maytenus* grow in the countries of Bolivia, Brazil, Colombia, Ecuador, Venezuela, and Peru. Depending on the disease, the communities use the barks or roots in preparations with water or hydroethanolic macerates. The extracts are used as antirheumatic, antidiarrheal, antimalarial, anti-Leishmania, anticancer and as an aphrodisiac (Malaník *et al.* 2019). The most widely used species is *Maytenus macrocarpa* and is often confused with *Maytenus ebenifolia*, *Maytenus krukovii*, *Maytenus laevis*, among other species, due to its growth in similar areas and its traditional utility (Malaník *et al.* 2019).

This review compiles scientific research on the traditional uses, chemical constituents, and pharmacological activities of *Maytenus laevis*, with the aim of detailing the key points for future research on this plant species and avoiding its confusion with other species.

Materials and Methods

The systematic collection of scientific information was obtained from the Scopus, Web of science, ScienceDirect, PubMed Central® and Scielo databases, in addition to the Peruvian repository ALICIA. The following search strategy was used: ("*Maytenus laevis*" OR "*Maytenus javensis*" OR "*Monteverdia laevis*") AND ("traditional uses" OR ethnobotany OR "chemical constituents" OR "chemical composition" OR phytochemistry OR "biological activities" OR "pharmacological activities" OR pharmacology). The collection was carried out from December 1, 2021, to August 15, 2022. Manuscripts dating from 1964 to 2022 were obtained. Subsequently, the repeated titles were eliminated, and the documents were filtered according to the type of research and relevance. 70 documents were selected (45 original articles, 4 review articles, 3 books and 18 theses).

Results and Discussion

Traditional use

The plant species *Maytenus laevis* is an erect tree 25 m high, its bark is reddish and hard. It has leaves 10 cm long, entire, perennial, petiolate and coriaceous. It's distributed in Brazil, Ecuador, Colombia, and Venezuela (Fig. 1) (Ramírez Aste 2004). *M. laevis* receives the vernacular name ''chuchuhuasi'', a term from the native Shipibo-Konibo language: "chochowasa" or "chochohoasha". However, ethnobotanical studies indicate nominal variants at the time of their recognition by the communities (Table 1). This situation generates confusion with other species of the Genus *Maytenus*. In addition to its botanical resemblance and traditional use (Cauper Pinedo 2019, Cuartas Muñoz & García Vergara 2017, Ramírez Aste 2004).

Most communities use different parts of the tree for their preparations. Depending on the ethnomedicinal use, they select the root or the leaves in the form of an infusion or decoction; and the stem or bark macerated with the alcoholic beverage called "aguardiente". The extracts are administered orally, although they are usually applied topically and in "baths" (Camargo Camargo & Villegas Caro 2015, González *et al.* 2000c, Lagos 2015). The water and the "aguardiente" extract polar and moderately polar molecules, thus obtaining a variety of metabolites that have different effects. For example, the aqueous and alcoholic extracts of the species of the Genus *Maytenus* contain phenolic compounds, triterpenes, sesquiterpenes, and alkaloids that generate antitumor, antiseptic, anti-inflammatory, analgesic, antibacterial, antioxidant, antiulcer, antipathogenic, and antiproliferative activities (Zhang *et al.* 2020).

Figure 1. Geographical distribution of *Maytenus laevis* (A) and *Maytenus macrocarpa* (B) around the world. Dots of different shades are observed indicating the frequency with which it is reported (Photo: Global Biodiversity Information Facility)

Table 1. Traditional names of *Maytenus laevis*

Traditional names	**Reference**
"chuchuhuasca"	Evans 1983
"chuchuasha curi-caspi"	González *et al.* 2000c
"chuchuhuaza"	Alvarado Cabrera 2006, Bussmann *et al.* 2018, Camacho Martínez 2013, González Villa 2015
"chuchuhuaso"	Bravo Gallardo 2010
"chuchuaza"	Yesid *et al.* 2011
"chuchuuaso"	Yesid *et al.* 2011
"chugchuguao"	Yesid *et al.* 2011
"chuchuguasi"	Yesid *et al.* 2011
"chuchuhuasha"	Camargo Camargo & Villegas Caro 2015, Iannicelli *et al.* 2018
"chuchuhuasi"	Bussmann *et al.* 2016, Camargo Camargo & Villegas Caro 2015, Ceutorick *et al.* 2011, Iannicelli *et al.* 2018
"chuchuaso"	Malagón *et al.* 2016, Yesid *et al.* 2011
"chuchuguasa"	Carreño Hidalgo 2016, Iannicelli *et al.* 2018
"chuchuhuazo"	Asanza *et al.* 2018, Iannicelli *et al.* 2018
"chuchuguaza"	Bussmann *et al.* 2018
"chuchuguasi capinuri"	Iannicelli *et al.* 2018
"chuchuguaso"	Lituma Páez 2019, Mestanza *et al.* 2019

Hydroethanolic extracts of *M. laevis* are mainly used in diseases such as arthritis, rheumatism, skin cancer and sexual impotence (Asanza *et al.* 2018, Bussmann *et al.* 2016, Bussmann *et al.* 2018, Carreño Hidalgo 2016, González *et al.* 2000c, Montealegre Pinzón 2011, Reyes *et al.* 2006, Romero Duque & Velásquez Pinzón 2009). However, some reports indicate the usefulness of aqueous and hydroethanolic extracts for other diseases such as anemia, breast conditions, bronchitis, prostate cancer, colds, tuberculosis; in symptoms such as weakness, cramps, hemorrhoids, diarrhea, vaginal wounds; in sprains and as a contraceptive, immunostimulant and menstrual regulator (Bussmann *et al.* 2016, Bussmann *et al.* 2018, Camacho Martínez 2013, Carreño Hidalgo 2016, Ceuterick *et al.* 2011, Gyllenhaal *et al.* 1986, Lagos 2015, Iannicelli *et al.* 2018, Nwodo *et al.* 2015).

This plant species is highly required by the communities. In rural and urban markets, products are found in the form of syrups or tablets based on the bark and/or stem, or in mixtures with other species; It is also consumed and exported to Europe and the United States of America as a liquor (Bravo Gallardo 2010, Yesid *et al.* 2011).

Chemical constituents

Qualitative identification studies of *Maytenus laevis* report alkaloids, triterpenes, tannins, flavonoids, quinones, phenolic compounds and saponins in leaves, roots, stems and bark (Lucero & Dehesa 2011, Moya & Olarte 1977, Salazar Llumiluiza 2013, Siccha Sánchez 2018) (Table 2). This information makes it possible to highlight the relationship with its different ethnotherapeutic uses and pharmacological effects.

Although the chemical constituents are found throughout the morphology of the species, chemical elucidation studies have been developed from methanolic extracts of the stem, bark, and root. Chromatography, spectroscopy, and Nuclear Magnetic Resonance (NMR) techniques have made it possible to identify some molecules of the chemical content of this plant species (Dinda 2019, Dinda *et al.* 2007, Niero *et al.* 2011, Razzaq Mouad 2016).

Dihydro-β-agarofuran sesquiterpene pyridine alkaloids

Pyridine-derived alkaloids have been identified in methanolic extracts from the stem of *M. laevis* (Figures 2,3). These molecules are sesquiterpenoid dihydro-*β*-agarofuran, with a macrolactone structure, formed by a sesquiterpene polyester and pyridine dicarboxylic acids (Gao *et al.* 2007). Evoninate-type alkaloids have been reported in this plant species, such as 7-(acetyloxy)-O^{11}-benzoyl-$O^{2,11}$-deacetyl-7-deoxoevonine, Ebenifoline E-I, Ebenifoline E-II, Ebenifoline E-III, Laevisine A, Euonymine and Mayteine; and Wilfordate-type alkaloids such as Laevisine B, Euojaponine F, Euojaponine I, Euonine and Wilforine (Nakagawa *et al.* 2004, Piacente *et al.* 1999).

These types of chemical structures are frequently detected in the Celastraceae family; mostly in the genera *Maytenus*, *Tripterygium*, *Celastrus*, *Euonymus* and *Orthosphenia*. They are classified as chemical markers due to their usefulness at the time of their chemotaxonomic identification (Callies *et al.* 2017, Gao *et al.* 2007, Lin *et al.* 2020).

Triterpenes and sterols

Triterpenoids are characteristic molecules of the Genus *Maytenus*, friedelane-, lupane- and oleane-type have been identified (Huang *et al.* 2021). The investigations carried out on *M. laevis* report these metabolites in alcoholic extracts of the stem and roots (Figures 4-6). Some detected molecules of the friedelane-type were Pristimarin, Tingenone and 22*β*-hydroxytingenone; of the lupane-type was Maytenfolic Acid; and of the oleane-type were 22*β*-hydroxy-3-oxoolean-12-en-28-oic acid, 3-oxoolean-12-en-28-oic acid, 3*α*,22*β*-dihydroxyolean-12-en-29-oic acid and 3*β*,22*β*-dihydroxyolean-12-en-29-oic acid, among others (Gonzalez *et al.* 1982, Nakagawa *et al.* 2004, Piacente *et al.* 1999). Also, in this group is *β*-sitosterol, a molecule of biological importance for showing anxiolytic, analgesic, immunomodulatory, antimicrobial, anticancer, anti-inflammatory, lipid-lowering and hepatoprotective activity (Babu & Jayaraman 2020).

Iridoids

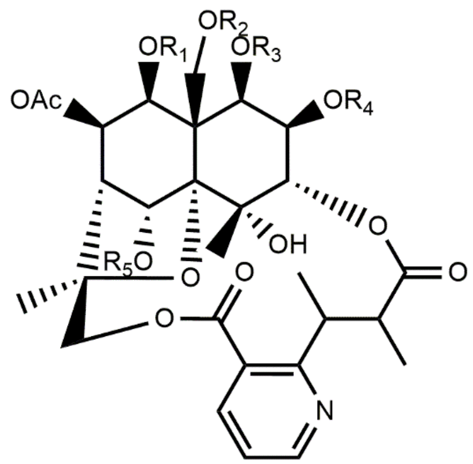
The iridoids of *M. laevis* were found in the alcoholic extracts of the stems and are derived from ajugol (Fig. 7) (Nakagawa *et al.* 2004). Ajugol is a type of glycosylated iridoid relevant for its anti-inflammatory and antioxidant activity (Kupeli *et al.* 2007, Zhang *et al.* 2021). In addition, it has been reported that this molecule has hepatic metabolism, and its elimination is via the kidneys (Xue *et al.* 2015); therefore, when consuming their chemical derivatives, they would have the same pharmacokinetic behavior.

Table 2. Chemical compounds of *Maytenus laevis*

Compound name	Part	Country of origin	Technique	Reference
Alkaloids				
7-(acetyloxy)-*O*[11]-benzoyl-*O*[2,11]-deacetyl-7-deoxoevonine	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Ebenifoline E-I	Stem	Ecuador	NMR	Piacente *et al.* 1999
Ebenifoline E-II (6-benzoyl-6-deacetylmayteine)	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Ebenifoline E-III	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Euojaponine F	Stem	Ecuador	NMR	Piacente *et al.* 1999
Euojaponine I	Stem	Ecuador	NMR	Piacente *et al.* 1999
Euonine	Stem	Ecuador	NMR	Piacente *et al.* 1999
Euonymine	Stem	Ecuador	NMR	Piacente *et al.* 1999
Laevisine A	Stem	Ecuador	NMR	Piacente *et al.* 1999
Laevisine B	Stem	Ecuador	NMR	Piacente *et al.* 1999
Mayteine	Stem	Ecuador/ Colombia	HPLC, NMR	Piacente *et al.* 1999, Nakagawa *et al.* 2004
Wilforine	Stem	Ecuador	NMR	Piacente *et al.* 1999
Triterpenoids and sterols				
Maytenfolic acid	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Triptocallic acid D	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Triptocallic acid A	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Epikatonic acid	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Abruslactone A	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
3-epiabruslactone A	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
28-hydroxy-12-ursene-3*β*-yl-caffeate (3-(*E*)-caffeoyluvaol)	Stem	Colombia/ Ecuador	HPLC, NMR	Nakagawa *et al.* 2004, Piacente *et al.* 2006
Wilforlide B	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Canophyllol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Salaspermic acid	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Tingenone	Root	Colombia	UV, IR, NMR	González *et al.* 1982
22*β*-hydroxytingenone	Root	Colombia	UV, IR, NMR	González *et al.* 1982
β-sitosterol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
22*β*-hydroxy-3-oxoolean-12-en-28-oic acid (22-*epi*-triptotriterpenonic acid A)	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
3-oxoolean-12-en-28-oic acid	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
3*α*,22*β*-dihydroxyolean-12-en-29-oic acid	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004

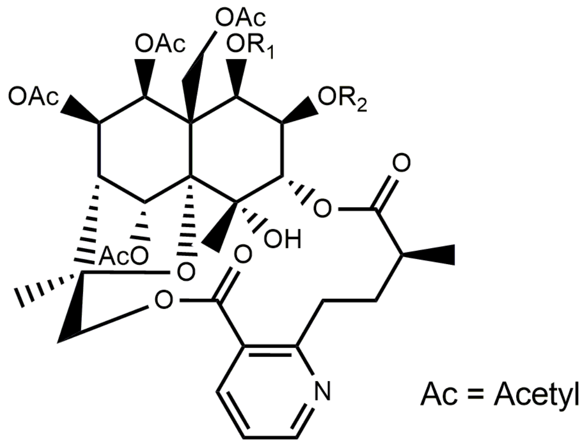
3β,22β-dihydroxyolean-12-en-29-oic acid (22-*epi*-maytenfolic acid)	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Pristimerin	Stem	Colombia	HPLC, NMR	Nakagawa et al. 2004
Iridoids				
Ajugol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
6-*O*-(3′,4′,5′-trimethoxybenzoyl)ajugol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
6-*O*-(3′,4′-dimethoxybenzoyl)ajugol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
6-*O*-(*p*-hydroxybenzoyl)ajugol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
6-*O*-(4′-hydroxy-3′-methoxybenzoyl)ajugol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Phenolics				
(-)-4′-*O*-methylepigallocatechin (Ourateacatechin)	Stem	Colombia	HPLC, NMR, UV, IR	Nakagawa *et al.* 2004, González *et al.* 1982
(2*R*,3*S*)-4′-*O*-methyl-2,3-dihydromyricetin	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
3′,4′-di-*O*-methyl-(-)-epicatechin	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Mearnsetin	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 200
Ourateaproanthocyanidin A	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Ourateaproanthocyanidin B	Root	Colombia	UV, IR, NMR	González *et al.* 1982
p-hydroxybenzoic acid	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Other compounds				
Lambertic acid	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Ent-isolariciresinol	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
(-)-secoisolariciresinol-4-*O*-β-D-(6-*O*-veratroyl)glucopyranoside	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004
Isoverbascoside	Stem	Colombia	HPLC, NMR	Nakagawa *et al.* 2004

HPLC: High Performance Liquid Chromatography, NMR: Nuclear Magnetic Resonance, UV: Ultraviolet, IR: Infrared



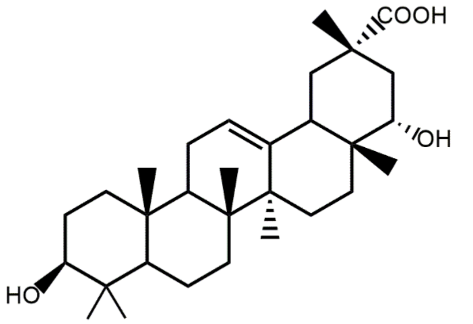
Compound	R_1	R_2	R_3	R_4	R_5
Ebenifoline E-I	Ac	Ac	Benzoyl	OH	Ac
Ebenifoline E-III	Benzoyl	Ac	Benzoyl	Ac	Ac
Ebenifoline E-II	Ac	Ac	Benzoyl	Ac	Benzoyl
Euojaponine I	Ac	Ac	Nicotinoyl	Ac	Ac
Euonymine	Ac	Ac	Ac	Ac	Ac
Laevisine A	Ac	Ac	$COC(CH_3)=CHCH_3$	Ac	Ac
Mayteine	Ac	Ac	Benzoyl	Ac	Ac
7-(acetyloxy)-O^{11}-benzoyl-$O^{2,11}$-deacetyl-7-deoxoevonine	Ac	Benzoyl	Ac	OH	Ac

Figure 2. Structures of the sesquiterpene dihydro-*β*-agarofuran pyridine alkaloids identified in *Maytenus laevis* (part 1)

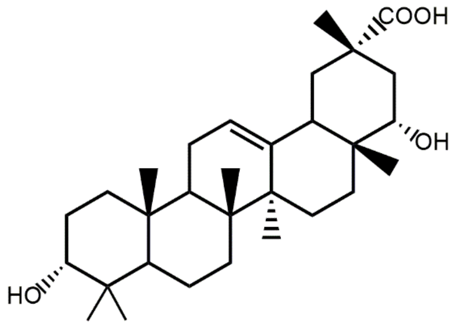


Compound	R_1	R_2
Laevisine B	Nicotinoyl	Acetyl
Euojaponine F	Benzoyl	Acetyl
Euonine	Acetyl	Acetyl
Wilforine	Acetyl	Benzoyl

Figure 3. Structures of the sesquiterpene dihydro-β-agarofuran pyridine alkaloids identified in *Maytenus laevis* (part 2)



3α,22β-dihydroxyolean-12-en-29-oic acid



3β,22β-dihydroxyolean-12-en-29-oic acid

Compound	R_1	R_2	R_3
Maytenfolic acid	Methyl	β-OH	α-OH
Triptocallic acid D	Methyl	α-OH	α-OH
Triptocallic acid A	H	α-OH	α-OH
Epikatonic acid	Methyl	β-OH	H

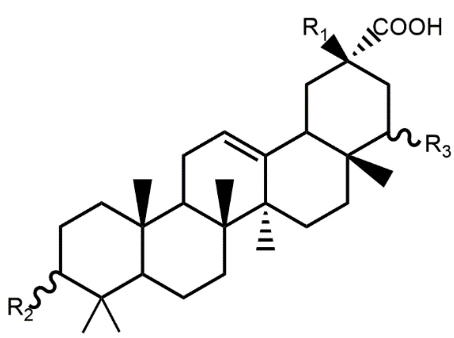


Figure 4. Structures of triterpenes identified in *Maytenus laevis* (part 1)

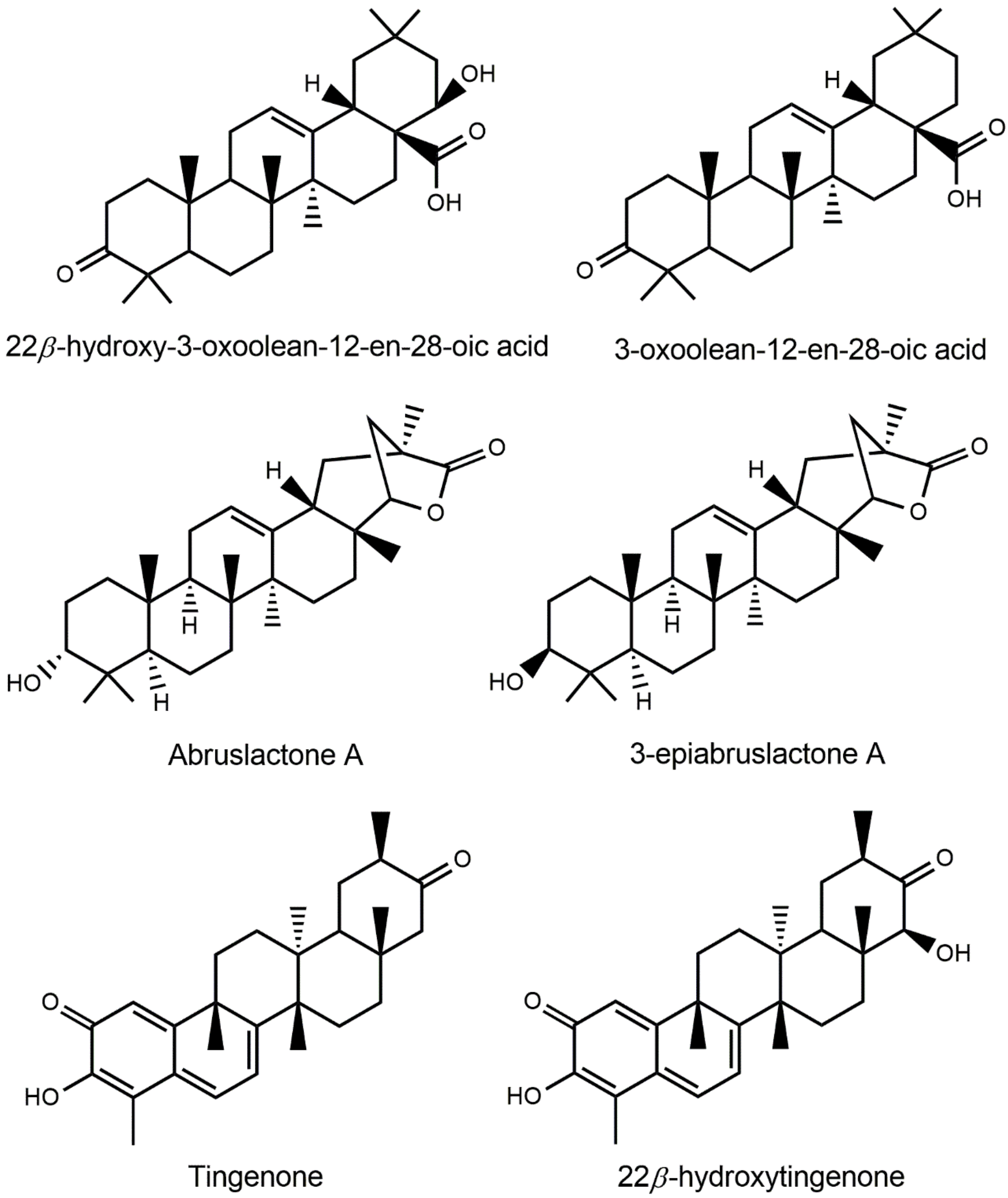


Figure 5. Structures of triterpenes identified in *Maytenus laevis* (part 2)

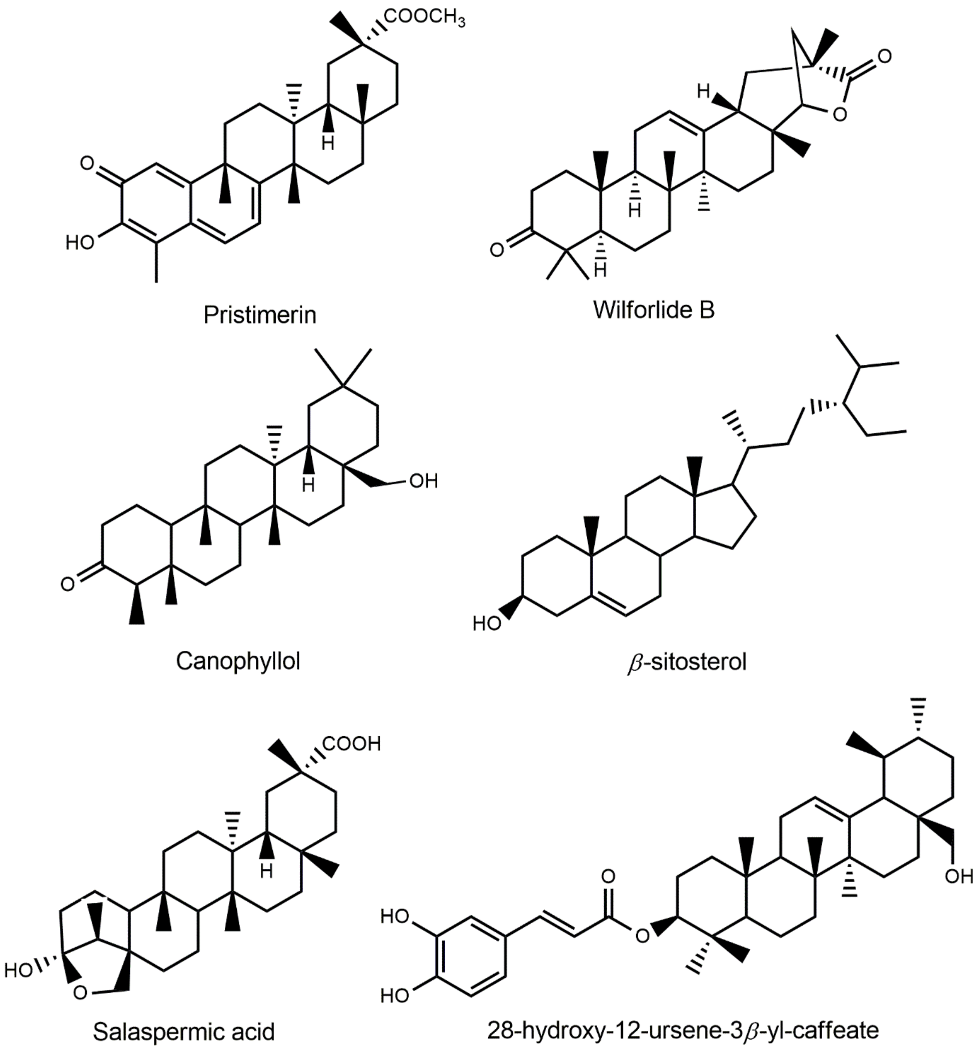
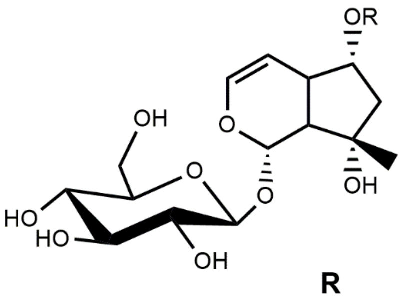


Figure 6. Structures of triterpenes identified in *Maytenus laevis* (part 3)

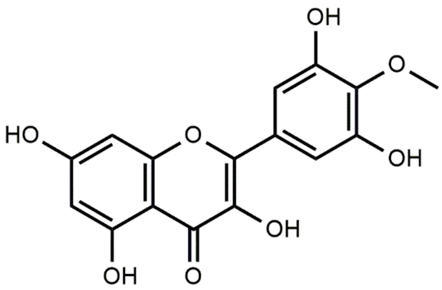


Compound	R
Ajugol	H
6-*O*-(3',4',5'-trimethoxybenzoyl)ajugol	3',4',5'-trimethoxybenzoyl
6-*O*-(3',4'-dimethoxybenzoyl)ajugol	3',4'-dimethoxybenzoyl
6-*O*-(*p*-hydroxybenzoyl)ajugol	*p*-hydroxybenzoyl
6-*O*-(4'-hydroxy-3'-methoxybenzoyl)ajugol	4'-hydroxy-3'-methoxybenzoyl

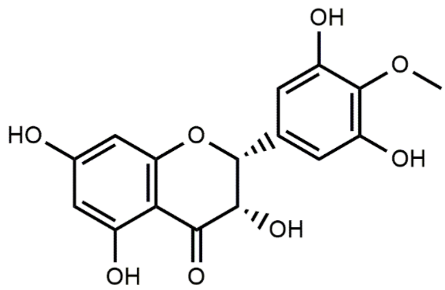
Figure 7. Structures of iridoids identified in *Maytenus laevis*

Phenolic compounds

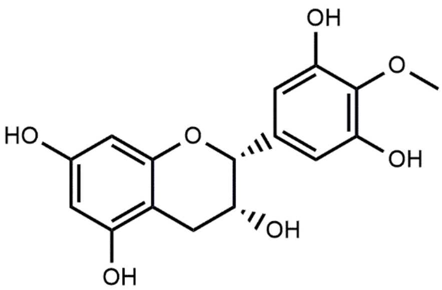
The phenolic compounds (Fig. 8) identified in this genus have a methoxyl group in the 4' position of the C6-C3-C6 nucleus of the flavonoids (Rodrigues *et al.* 2017). The alcoholic extracts of the stem and root of *M. laevis* contain catechin derivatives (Gonzalez *et al.* 1982, Nakagawa *et al.* 2004) that are potentially therapeutic agents for gastric diseases (Baggio *et al.* 2007) and antiparasitic (Olivaro *et al.* 2021).



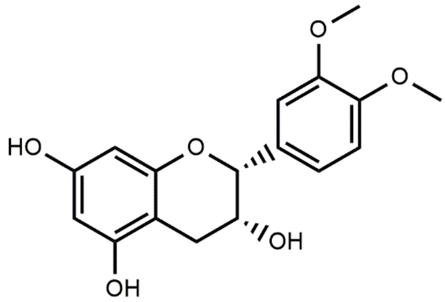
Mearnsetin



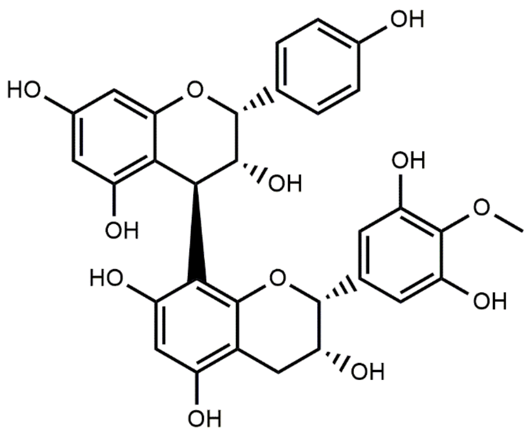
(2*R*,3*S*)-4'-*O*-Methyl-2,3-dihydromyricetin



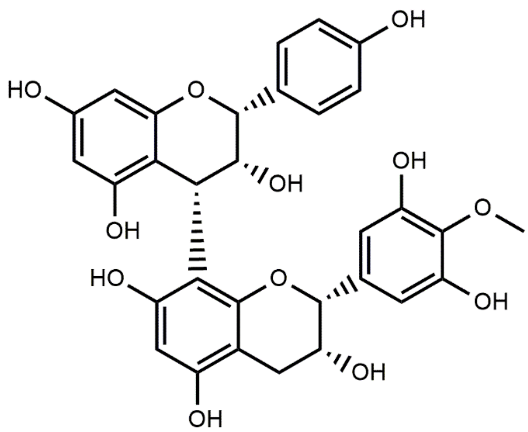
(-)-4'-*O*-methylepigallocatechin



3',4'-di-*O*-methyl-(-)-epicatechin



Ourateaproanthocyanidin A



Ourateaproanthocyanidin B

Figure 8. Structures of phenolic compounds identified in *Maytenus laevis*

Other bioactive compounds identified are Lambetic Acid, Ent-isolariciresinol, among others (Fig. 9). The quantification of each molecule, as well as the analysis of chemical and physical stability of the chemical structures and interactions with other substances, could support their potential as therapeutic agents and their physicochemical behavior in a phytopharmaceutical.

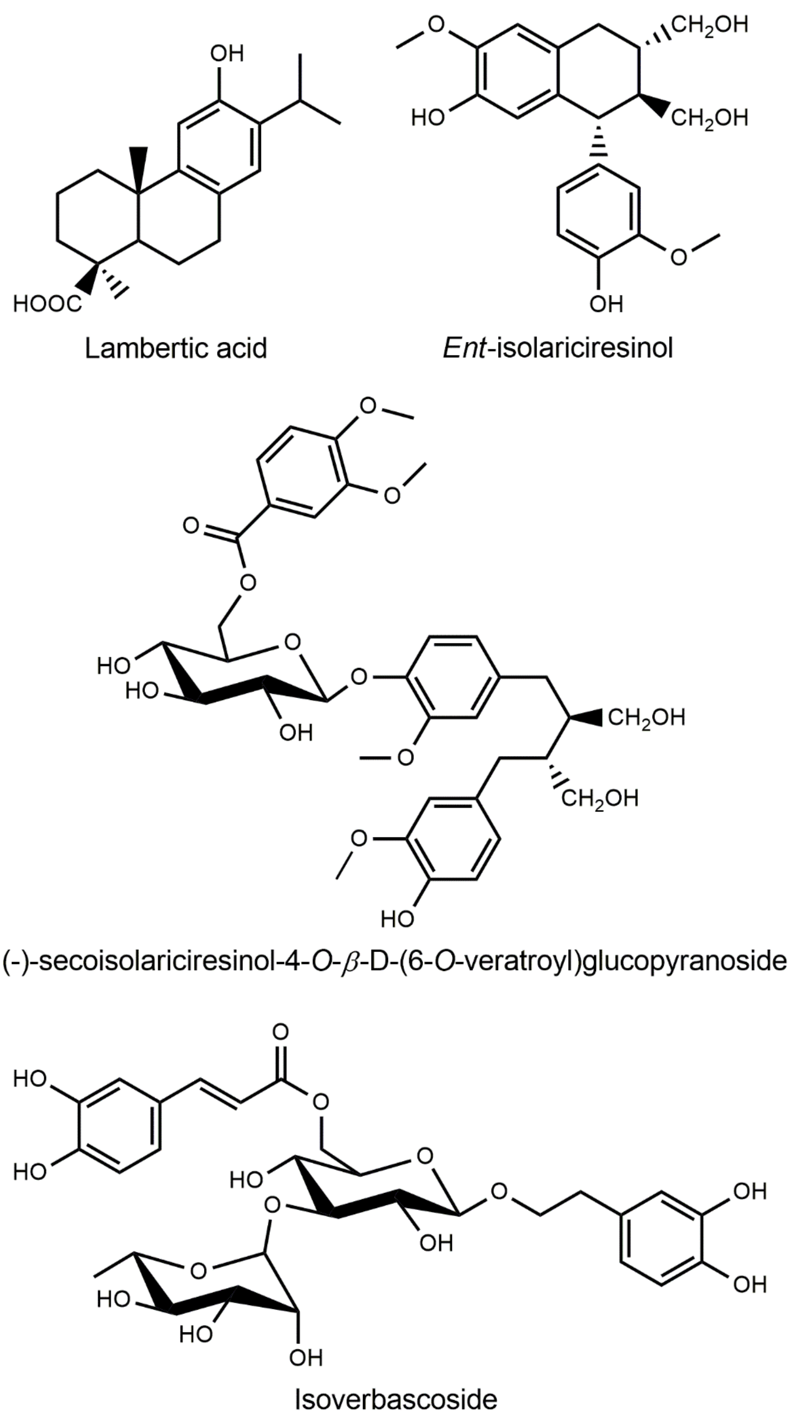


Figure 9. Other compounds identified in *Maytenus laevis*

Pharmacological activities

The pharmacological activities of *M. laevis* have been evaluated from aqueous and alcoholic extracts, from the leaves, root, and bark, in preclinical studies. Although the information focuses only on the verification of the effect, the chemical content of the extracts bases the pharmacological action according to some of its traditional utilities.

Anti-inflammatory activity

In ethnobotanical studies, the usefulness of species of the Genus *Maytenus* for the treatment of arthritis and rheumatism, diseases characterized by pain and inflammation of joints, is reported. Thus, the largest amount of pharmacological research focuses on verifying anti-inflammatory and analgesic activities. The hydroalcoholic extract and decoction of the roots and bark of *M. laevis* were shown to reduce inflammation and produce analgesia in experimental animals; where, these effects were attributed to the chemical content of fractions of semipolar solvents (Moya & Olarte 1977, Salazar Llumiluiza 2013). However, no research of the chemical-pharmacological activity relationship in this plant species are reported, although the molecules identified in *M. laevis* support the action in the face of an inflammatory process; as shown by studies in other species of the same family (Veloso *et al.* 2017).

Evaluation of triterpenes and phenolic compounds in the Genus *Maytenus* have shown their anti-inflammatory properties (Zhang *et al.* 2020). Reports of its mechanism of action indicate the effect of decreasing the synthesis of proinflammatory substances. Triterpenes inhibit the effects of prostaglandin E2 (Reyes *et al.* 2006) and flavonoids block the enzymes lipoxygenase and cyclooxygenase (COX), which inhibits the production of leukotrienes and prostaglandins (Veloso *et al.* 2017). Specifically, the tingenone identified in *M. laevis* has shown antinociceptive activity by activating different peripheral pathways of L-arginine, nitric oxide, cyclic guanosine monophosphate (cGMP) and ATP-sensitive potassium channels (Veloso *et al.* 2014, Veloso *et al.* 2015).

On the other hand, the presence of ajugol-derived iridoids and pyridine-derived alkaloids provide synergistic effects in anti-inflammatory and immunosuppressive activity. Ajugol derivatives have been shown to regulate high concentrations of cytokines. In addition, its antifibrotic activity has been verified in experimental animals, demonstrating its effect against asthmatic processes (Yi *et al.* 2022). Euonine, Ebenifoline, and Wilforine molecules have an inhibitory effect on the production of cytokines (interleukins) and tumor necrosis factor alpha (TNF-α), supporting their activity as immunosuppressants (Gao *et al.* 2007, Huang *et al.* 2021).

Antibacterial and antiprotozoal activity

The antibacterial activity, in species of the Genus *Maytenus*, is related to flavonoids and triterpenes (Zhang *et al.* 2020). The evaluation of the aqueous (infusion and decoction) and alcoholic extracts of the leaves and bark of *M. laevis* have shown activity against *Staphylococcus aureus*, *Streptococcus pyrogenes*, *Enterococcus faecalis* ATCC 29212 and *Pseudomonas aeruginosa* ATCC 27853, *in vivo* and *in vitro* (Dicarlo *et al.* 1964, Graak & Flemming 2004). Research has shown that extracts of *M. laevis* induce antibacterial activity due to stimulation of the reticuloendothelial system in experimental animals (Dicarlo *et al.* 1964, Graack & Flemming 1966, Rojas *et al.* 2016).

The structure-antibacterial activity relationship is not reported in the few studies of *M. laevis*, but some chemical structures detected in the extracts show the link with said effect. Among the identified molecules are catechin derivatives (family of flavonoids) that can bind to extracellular proteins, altering the bacterial cell wall; in addition to inhibiting the functions of its cytoplasmic membrane (Tebou et al. 2017). Also, certain triterpenes such as tingenone, 22β-hydroxytingenone and pristimerine affect the cytoskeleton by inhibiting tubulin polymerization (Da Silva *et al.* 2018). These data support the potential of *M. laevis* against bacteria of interest (Huang *et al.* 2021).

On the other hand, the hexanic extract of the root of *M. laevis* has activity against *Trypanosoma cruzi* and *Giardia lamblia in vitro*. This activity is linked to pyridine-derived alkaloids and friedelane-type triterpenes; where its main effect is the inhibition of development and growth, in both microorganisms, due to its high toxicity (Bashir *et al.* 2015, Condo *et al.* 2016, Flemming 1965, Igoli *et al.* 2011).

Anticancer activity

Anticancer activity is another activity of biological importance of the species of the Genus *Maytenus* (Zhang *et al.* 2020). The ethnobotanical knowledge of *M. laevis* indicates its usefulness as a traditional treatment for skin cancer. In *M. laevis*, only the antitumor and cytotoxic activities of the aqueous and alcoholic extracts of leaves and bark have been evaluated; relating it's *in vitro* activity to sesquiterpenes, triterpenes and phenolic compounds (Hiroshi *et al.* 1986, Gonzalez *et al.* 1982). The mechanism of action of sesquiterpenes and triterpenes is based on the inhibition of protein synthesis and the incorporation of uridine into DNA; and the presence of phenolic compounds (derived from catechins and proanthocyanidins) prevent tissue damage from free radicals generated by radiation (Gonzalez *et al.* 1982).

Information on the anticancer activity of *M. laevis* is scarce and out of date; Therefore, recent studies of some of its chemical structures, isolated in other species, show its value in therapies for different types of cancer. For example, studies of the triterpenoid pristimarin explain its toxic effect on HeLa, A-549, HL60 and HepG2 cell lines, due to the action of apoptosis and activation of Caspase-3 (Huang *et al.* 2021, Yan *et al.* 2013). In addition, it is a possible therapeutic strategy in the treatment of gliomas that overexpress the epidermal growth factor receptor (EGFR);

since, they increase the generation of reactive oxygen species and the release of Cytochrome C to the cytosol (Yan-Yan *et al.* 2013).

The potential of *M. laevis* as a therapeutic agent requires further experimental action. It is necessary to evaluate the extracts of different parts of the plant species to support their use in complementary treatments. Also, it is important that the extracts of *M. laevis* be evaluated in clinical trials for the development of phytotherapies or phytopharmaceuticals; as well as research that involves explaining or substantiating its pharmacodynamics, pharmacokinetics, and toxicity.

'*Maytenus laevis*' in Peru

In Peru, more than 30 species of the Genus *Maytenus* are reported. They are distributed in the Peruvian Amazon due to their adaptation in tropical climates. Most of these species receive the denomination ''chuchuhuasi'' mainly, which generates confusion at the time of its identification by the inhabitants (Table 1). Some plant species usually receive one or more traditional or vernacular names that coincide with the name of another similar or different species; given that the community identifies the plant material according to the morphological characteristics or traditional use of the medicinal plant (Ascate-Pasos *et al.* 2020, Ramírez *et al.* 2020). Reports from the 1960s to the present have attributed the growth of *Maytenus laevis* in the Peruvian Amazon; especially in the vicinity of the Putumayo River that runs through the countries of Colombia, Peru, Ecuador, and Brazil (Camacho Martínez 2013, Cárdenas López *et al.* 2002, Carreño Hidalgo 2016). However, ethnobotanical, phytochemical, and pharmacological investigations of the species reported as *M. laevis* in Peru, do not have taxonomic validation in an accredited institution. In addition, different sources of information do not indicate their presence in Peruvian territory (Desmarchelier & Witting 2000, Lara *et al.* 2020, Siccha Sánchez 2018, Silva Santisteban Miranda 2019, Vila 2009).

On the other hand, the analysis of the Peruvian species of "chuchuhuasi" indicates its traditional use based on macerating the bark and/or stems with hydroalcoholic mixtures, and they are used for different diseases such as cancer (Graham *et al.* 2000, Odonne *et al.* 2009), anemia, rheumatism, bacterial infections, leishmaniasis and malaria. In addition, in symptoms such as abdominal pain, diarrhea, gangrene, (Odonne *et al.* 2013), hernias, in broken bones (Sanz-Biset & Cañigueral 2013) and as a ''blood purifier'' (Jauregui *et al.* 2011).

In addition, chemical elucidation investigations have been carried out through spectroscopic methods on the extracts. Friedelane-type triterpenes have been identified in species such as *M. jelsiskii*, *M. amazonica*, *M macrocarpa* and *M. retusa* (Fraga 2012, Pu *et al.* 2014), lupane-type in *M. cuzcoina* and *M. apurimacencis* (Callies *et al.* 2015, Delgado-Méndez *et al.* 2008, Nuñez *et al.* 2005, Reyes *et al.* 2006, Vazdekis *et al.* 2009), oleane- and ursane-type in the species *M. krukovi* (Shirota *et al.* 1996) and other types of triterpenes in *M. apurimanecensis* and *M. macrocarpa* (Oramas-Royo *et al.* 2010, Niero *et al.* 2006). Also, diterpene compounds in *M. cuzcoina* and *M. macrocarpa* (Vazdekis *et al.* 2009), sesquiterpenes in *M. jelsiski*, *M. cuzcoina*, *M. apurimacencis* and *M. macrocarpa* (Chávez *et al.* 1999, Delgado-Méndez *et al.* 2008, Cortés-Selva *et al.* 2004, González *et al.* 2000b, Nakamura *et al.* 1996, Perestelo *et al.* 2010, Perestelo *et al.* 2016), lignans in *M. apurimacencis* (Vazdekis *et al.* 2009), and alkaloids in *M. emerginata* (Kuo *et al.* 1990).

The evaluation of the pharmacological properties of these species indicates that the sesquiterpenes 4,15-dideoxyisoalatol and 15-deoxyisoalatol found in the root cortex of *M. apurimacensis* are molecules that generate activity against the protozoan parasite that causes leishmaniasis. In *M. cuscoina*, dihydro-β-agarofuran derivatives are potential chemoprotectors (Delgado-Méndez *et al.* 2008, González *et al.* 2000a). Some molecules have been used in bioinformatic models to generate derivatives of chemical structures with potential anti-HIV use, as in the case of lupane-type triterpenes found in *M. cuzcoina* (Callies *et al.* 2015). Tetracyclic and pentacyclic triterpenes, and sesquiterpenes dihydro-β-agarofurans from *M. macrocarpa* from the root cortex, generate antibacterial activity (Malanik *et al.* 2019).

The species of the Genus *Maytenus* that grow in Peru are important for their relationship with the ancestral knowledge about their uses in native communities; as well as its consumption in urban areas and its biotrade (Stagegaard *et al.* 2002). Despite the fact that there is an evident source of compounds of therapeutic importance, it is necessary to continue developing phytochemical and pharmacological studies; as well as chemotaxonomic identification techniques of the species, in order to avoid confusion that may influence the efficacy and safety in its use as a complementary therapy of the Peruvian health system.

Conclusions

Maytenus laevis is a tree that grows in Brazil, Ecuador, Colombia, and Venezuela. It is used in the traditional treatment for arthritis, rheumatism, and cancer; also, as a natural sexual stimulant. In this plant species, molecules of the alkaloid, triterpenoid, iridoid type and phenolic compounds have been identified, which are of great scientific interest due to their pharmacological effects. However, only *in vitro* and *in vivo* studies have been reported on the anti-inflammatory, antibacterial, antiparasitic, and anticancer activities of aqueous and hydroethanolic extracts of leaves, stem, bark, and root. Further research needs to focus on scientific verification of other traditional uses; as well as physicochemical, pharmacokinetic and pharmacodynamic studies to support its pharmacological activities within a complementary therapy.

Also, the name ''chuchuhuasi'', the botanical resemblance and its traditional use of species of the Genus *Maytenus* that grow in Peru, has generated that *M. laevis* is erroneously reported in Peruvian territory, for which it is necessary to carry out studies of its specific chemical markers that allow it to be differentiated from other species.

Declarations

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