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Revisión / Review

Solidago chilensis Meyen (Asteraceae), a medicinal plant from South America. A comprehensive review: ethnomedicinal uses, phytochemistry and bioactivity

[*Solidago chilensis* Meyen (Asteraceae), una planta medicinal de Ameica del Sur. Una revisión integral: usos etnomedicinales, fitoquímica y bioactividad]

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Abstract: *Solidago chilensis* Meyen (Asteraceae) is a medicinal and aromatic herb widely distributed in South America. From 2000 to the present numerous articles on this species have been published, mainly in the last decade where the pharmacological studies and articles on its secondary metabolites have risen sharply. *S. chilensis* has potential beneficial effects on human health, particularly as an anti-inflammatory because of its high flavonoid content. This work describes the research carried out on this species with emphasis on biological and phytochemical studies..

Keywords: *Solidago chilensis*, *Solidago microglosa*, antioxidant activity, anti-inflammatory activity, solidagenone, quercetin, quercetrin.

Resumen: Solidago chilensis Meyen (Asteraceae) es una hierba aromática y medicinal, ampliamente difundida en Sudamérica. A partir del año 2000 se publicaron numerosos estudios sobre esta planta, particularmente en la última década donde se incrementó sensiblemente el estudio de sus propiedades farmacológicas y de la química de sus metabolitos secundarios. Es una planta con propiedades potencialmente beneficiosas para la salud humana, destacándose particularmente por su actividad antiinflamatoria que puede ser atribuida al elevado contenido en flavonoides. En este trabajo revisamos exhaustivamente los antecedentes de esta planta desde un enfoque cronológico, con énfasis en los estudios biológicos y fitoquímicos.

Palabras clave: *Solidago chilensis*, *Solidago microglosa*, actividad antioxidante, actividad antiinflamatoria, solidagenona, quercetina, quercetrina..

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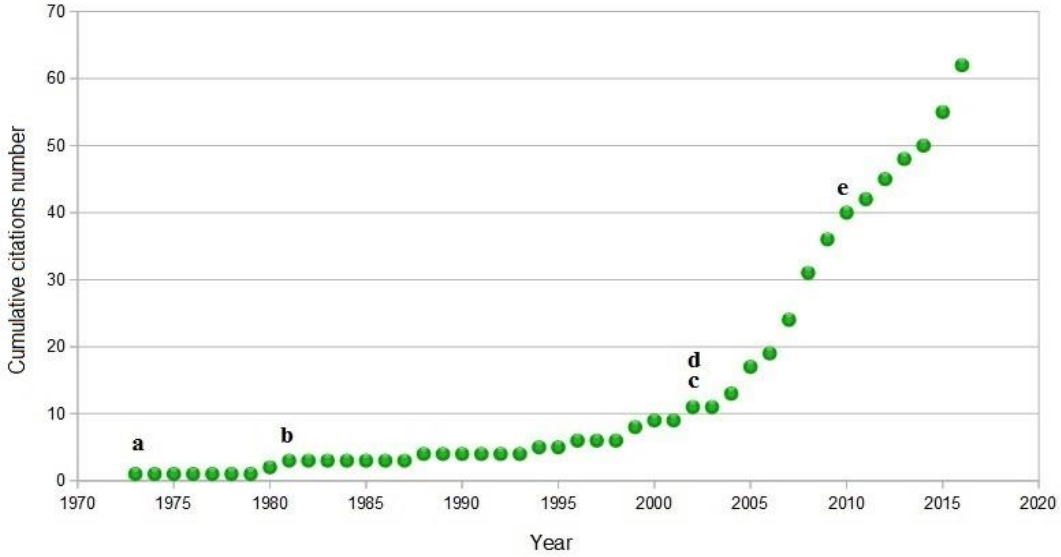
INTRODUCTION

Initials considerations

An exhaustive chronological review on *Solidago chilensis* Meyen (Asteraceae) with emphasis on the biological studies and its secondary metabolites chemistry is presented.

Interest on this species is booming. Figure 1 shows the cumulative number of publications for *S. chilensis* in the period 1970-2017. The number of publications has skyrocketed in the last decade (2007-2017).

Figure 1
Cumulative number of citations on *S. chilensis*. The first report on a relevant topic is marked with a letter: a) Distribution in South American Ecosystems in 1973 b) Phytochemical, flavonoids identification in 1981 c) Antimicrobial bioassay in 2002 d) Pharmacological study with an animal model in 2002 e) Clinical trial in 2010.



S. chilensis is a very promising species. Due to its wide range of distribution covering different ecosystems of South America, comparative phytochemical and biological studies on plants collected at different sites are needed to detect intraspecific variations (chemotypes). Studies are also needed to know seasonal variations and changes associated with the growth phase of the plant.

Valverde *et al.* (2012) emphasize the importance of this medicinal plant in Brazil where it is being widely used by people and companies (private and public). In 2010 the Brazilian Ministry of Health considered *S. chilensis* as a plant with potential to generate products of pharmaceutical interest for the Brazilian Unified Health System. Currently this species is under cultivation in the Agroecological Platform of Phytomedicines (PAF) at Campus Fiocruz Atlantic Forest (CFMA)-Río de Janeiro.

General description and distribution

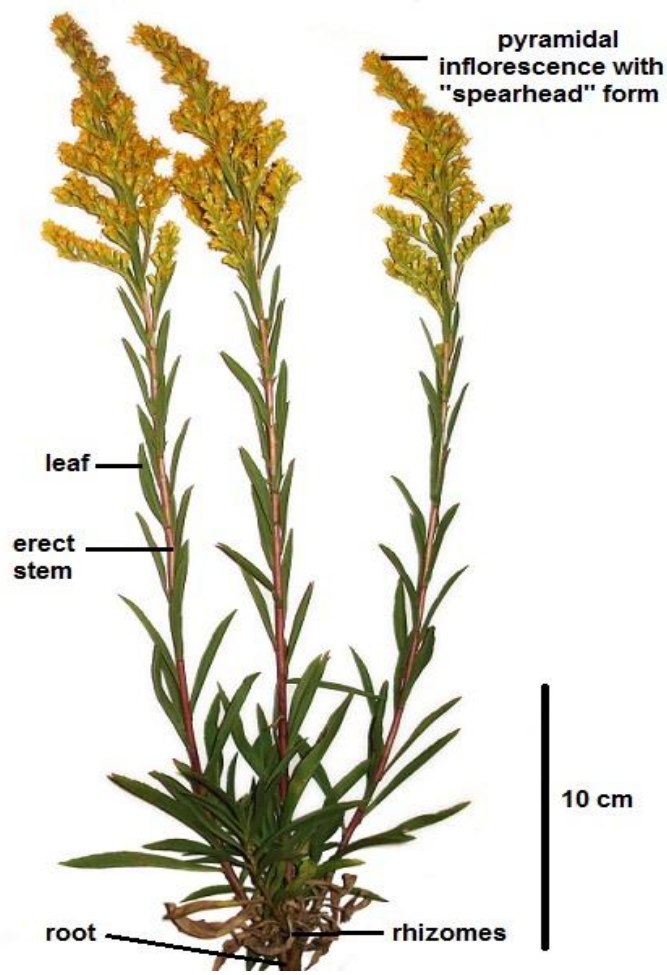
Solidago chilensis Meyen (Asteraceae) is a native species to South America that grows between 0 and 2500 meters above sea level. It is an herbaceous plant with abundant rhizomes that can reach up to 1.4 meters in height. It has an erect and leafy stem, the flowers arrangement is a typical dense pyramidal inflorescence. Figure 2 shows a representative picture of this plant. The first report and description of this plant was made by F. Meyen (1834) and in Argentina by Spegazzini (1897) under the synonymy *S. linearifolia* var. *brachypoda*.

A recent anatomical study was done by Hernandez *et al.* (2013) who noted epidermal characteristics of a xerophile species; also identified essential oils reservoirs in different organs of the plant. The chromosome composition for *S. chilensis* is 2n = 2x = 18 (Dematteis *et al.*, 2007; Laphitz & Semple, 2015; Semple, 2016).

According to Catalog of vascular plants of South Cone (http://www.darwin.edu.ar) and Correa (1971), in Argentina this plant occurs in Buenos Aires, Catamarca, Chaco, Chubut, Cordoba, Corrientes, Entre Ríos, Formosa, Jujuy, La Pampa, La Rioja and Mendoza provinces. In Brazil it is mainly found in the states of Rio Grande Do Sul and Santa Catarina. In Chile it grows in Region I, Region III, Region IV, Region V, Region VI, Region VII, Region VIII, Region IX, Region X, Region XI, Juan Fernández archipelago and Metropolitan Santiago Region. In Paraguay it is found in Alto Paraguay and Cordillera. In Uruguay its presence has been reported in Montevideo, Paysandú and Soriano.

Laphitz & Semple (2015) made up a map of the current distribution of *S. chilensis*, although we consider the actual distribution is wider, since the species is found also in Brazil (Valverde *et al.*, 2012). In Figure 3 we propose an updated map of *S. chilensis* distribution in South America. In addition Silva *et al.* (2008) recorded *S. chilensis* in the Madeira Islands of Portugal, where it could have arrived by sea.

Figure 2
***S. chilensis* photography**



Synonyms and common names

Synonyms

According to Catalog of vascular plants of South Cone (http://www.darwin.edu.ar) and The Plan List (http://www.theplantlist.org), the main accepted synonyms are: *Solidago linearifolia* DC., *Solidago microglossa* DC. Other synonyms registered in

these databases are: *Aster sagei* Phil., *Solidago coquimbana* Phil., *Solidago floribunda* Phil., *Solidago laxiflora* Phil., *Solidago parviflora* Phil., *Solidago recta* Phil., *Solidago valdiviana* Phil. In addition Russo & Garbarino (2008) quotes the following: *Solidago polyglossa* DC., *Solidago marginella* DC., *Solidago odor*a Hook., *Solidado vulneraria* Mart., *Solidago nitidula* Mart.

It should be noted that Laphiz (2009) and Laphiz & Semple (2015) consider that *S. chilensis* and *S. microglossa* are different species with different anatomical characteristics (stem hair length). However, in South America both species have the same popular use and a similar phytochemical profile. The morphological differences of *S. microglossa* could be attributed to a morphotype adapted to the environmental conditions of the northern populations. It would be very useful to perform chemotaxonomic and molecular analysis to confirm whether we are dealing with a single species or not, as well as if there exist variations in the phytochemical profile among populations of different habitats.

At this point it should be noted that *S. microglossa* is the only synonym that remains in use in current literature. So, and according to Mercandeli *et al.* (2012), in pharmacognosy and related areas it could be considered as a species with two accepted names: *S. chilensis* and *S. microglossa*.

Figure 3
Distribution for *S. chilensis* in South America

Common names

"Golden rod" is the most used common name of this plant and for members of genus Solidago in general. Other common names in Argentina and Chile are "vara amarilla" (yellow stick), "lanceta" (lancet), "punta de lanza" (spearhead), "romerillo amarillo" (yellow romerillo), (Alonso & Desmachelier, 2005). Mapuche names in Argentina and Chile: pfelel, felel (González & Molares, 2004). Brazilian common names: arnica, arnica-brasileira, arnicahorta, arnica-de-terreiro, arnica-brasil, arnica-silvestre, erva-federal, erva-lanceta,

espiga-ouro, federal, flecha, lanceta, macela-miu´da, rabo-de-foguete, rabo-de-roja˜o, sape´-macho (Alonso & Desmachelier, 2005; Russo & Garbarino, 2008). Guaraní names in Paraguay: mbuí, mbuí saiyu, mberí ivotí, mbuychi, mbuí guazú and cohete ruguai. (Marzocca, 1997; Alonso & Desmachelier, 2005; Russo & Garbarino, 2008).

ETHNOMEDICINAL USES

S. chilensis has variety of uses in the countries where it is present. According to Ferrari *et al.* (2014) and Mercandeli *et al.* (2012), the plant is used for numerous purposes and conditions. Ethnopharmacological uses are mostly related to inflammatory conditions and can be explained by the high contents of flavonoids in the plant.

Argentina

Argentinean literature cites it has been used as vulnerary, anti-gonorrhea and because of its revulsive properties. The root has been used as a sedative and for headaches, in addition to being used as baths for children with nervous problems. (Toursarkissian, 1980; Marzocca, 1997; Nuñez & Cantero, 2000).

Alonso & Desmachelier (2005) state *S. chilensis* has similar uses to *S. virgaurea*, a species widely known in Europe and Japan. The most common use is as infusion or decoction of aerial parts or roots. These authors report its use as sedative, diuretic, anti-inflammatory and for wound healing. Forcone (2004) also mentions it is used as a therapeutic agent for renal and urinary inflammations.

Brazil

In Brazilian popular medicine, it is recommended as a diuretic, analgesic and anti-inflammatory to treat burns and rheumatic disease, among others (Goulard *et al.*, 2007; Liz *et al.*, 2008). It is observed that most common use in folk medicine is related to inflammatory conditions, being used in the reduction of pain and edema, characteristic symptoms of inflammation (Valverde *et al.*, 2012). Mercandeli *et al.* (2012) indicated that this plant have antiseptic, analgesic, and healing properties. Other uses include treating rheumatic and lumbar pain, contusions, wounds, and inflammations caused by insect bites. Also it is used as a gastrointestinal stimulant, healing and antiseptic.

Chile

The plant is used to treat symptomatology related to inflammation (Schmeda-Hirschmann *et al.*, 2002).

Paraguay

Degen *et al.* (2005) indicate the plant has been used for kidney diseases.

Uruguay

The infusion of *S. chilensis* has been reported as antilithic, since it is used preventively and as a therapeutic agent for renal and urinary inflammations (Güntner *et al.*, 1999). The study of the RI index (Relative Importance) made by Ferrari *et al.* (2014) in an ethnobotanic survey, reported a RI = 100% for *S. chilensis*, which means that the plant is used for numerous purposes and conditions.

PHYTOCHEMISTRY

The most relevant compounds isolated from *S. chilensis* are shown in Figure 4.

Phenolic compounds and antioxidant activity

In 1981 appeard in Buenos Aires-Argentina the first report on phenolic compounds from aerial parts of *S. chilensis* where several flavonoids were isolated and identified: isorhamnetin, quercetin 3-O-rhamnoside, quercetin 3-O-galactoside, and rutin. (Gutierrez *et al.*, 1981). Günter *et al.* (1999) from plants collected at Montevideo-Uruguay, reported that the inflorescences are a source of free and glycosidic flavonoids derived from kaempferol, quercetin and others. In the same work, the antioxidant properties of different flower extracts and fractions containing flavonoids were studied. The total antioxidant capacity of the extracts was monitored spectrophotometrically measuring the color loss of solutions of □-carotene in presence of 0.1% hydrogen peroxide. The most effective fraction was composed of 50% quercetin which has more effective antioxidant activity than butylated hydroxytoluene (BHT), a food industry synthetic antioxidant. Russo and Garbarino (2008) indicated that *S. chilensis* showed antioxidant activity similar to other *Solidago* species.

Tamura *et al.* (2009) investigated the main components of a hydroalcoholic extract (93% ethanol) from aerial parts of plants collected in São Paulo-Brazil. The extract was analyzed using high pressure liquid chromatography coupled to a diode detector and a mass spectrometer (HPLC–DAD–MS). The major components of the extract were

rutin and two caffeoylquinic acid derivatives.

From an ethanol extract Sabir *et al.* (2012) in Santa María-Brazil reported the following values in terms of milligrams of compound per gram of freeze-dried extract (mg/g): total phenolics (226 mg/g), total flavonoids (115.2 mg/g), quercetrin (quercetin-3-O-α-L-rhamnoside) (51.9 mg/g), gallic acid (24.1 mg/g), rutin (3.82 mg/g), quercetin (2.57 mg/g). The extract showed high antioxidant activity. In a similar approach, from an aqueous extract of leaves, Löbler *et al.* (2013) also in Santa María-Brazil, identified and quantified: quercetin (441.4 mg/g), chlorogenic acid (95.7 mg/ g) and rutin (46.9 mg/g).

Roman *et al.* (2015) from Chapecó-Brazil, using HPLC with the internal standard method, identified quercetrin as the main flavonoid in hydroalcoholic extracts. The amount of quercetrin was 0.2916 g of quercetrin/g of total extract, so they concluded that aerial parts of *S. chilensis* contain 6.5% of quercetrin. In similar works, Schneider *et al.* (2015) and Vechia *et al.* (2016) found, respectively, 2.4% and 5.29% of quercetrin in the aerial parts, and the amount of quercetrin is proposed as a quality control marker of the plant drug. Barros *et al.* (2016) also reported quercitrin for a Santa Catarina-Brazil collection, where the flavonoid azeliny was also identified.

Gastaldi *et al.* (2016a) in Esquel-Argentina with a dietary approach found the following values for one infusion cup (250 ml) prepared from 5.0 g of air dried aerial parts (flowers, leaves and stems): antioxidant capacity equivalent to 192 mg of ascorbic acid (Vitamin C); a total phenol content equivalent to 93 mg of gallic acid and a total flavonoid content equivalent to 69 mg of quercetin.

Terpenes

The first report on terpenoids was in 1980 that showed dihydroxycarotenoids as the main carotenoids of *S. chilensis* (Caffini *et al.*, 1980).

From the roots of populations from Buenos Aires-Argentina, two well-known furan diterpenes were isolated by Gutierrez *et al.* (1981): junceic acid and solidagenone. Solidagenone, a highly bioactive molecule, was also isolated from plants collected in Asunción-Paraguay (Schmeda-Hirschmann, 1988) and tested in mice.

Composition of the essential oil from aerial parts has been analyzed by gas chromatography-flame ionization detector-mass spectrometry (GC-FID-MS) in two Argentina populations: one from Santa Fe province (Vila *et al.*, 2002) and the other from Chubut province (Gonzalez *et al.*, 2013; Gastaldi *et al.*, 2016b). In the essential oil from the Santa Fe collection, pumiloxide, an unusual labdane diterpene, was found to be one of the major components, up to 15.3%; other important components were limonene 15,4%, caryophyllene oxide 3,5%, β-elemene 3,4%, γ-cadinene 8,2%, and germacrene D 3,1%. The composition of the essential oil of the population from Chubut was analyzed during four years; the main identified components being myrcene 8,2%, alfa-phellandrene 13,1 %, limonene 46,6 % and germacrene D 43%. A high content of limonene and germacrene D was found in both populations from Argentina.

Other compounds

Gutierrez *et al.* (1981) reported the presence of hydrocarbons in flowers and leaves. The flowers have hydrocarbons of 22 to 35 carbons, mostly C_{29} 10,46%, C_{31} 52,19%, C_{32} 5,50%, C_{33} 18,74% and C_{35} 4,17%. The leaves have hydrocarbons of 17 to 37 carbons, mostly C_{31} 69,04%, C_{32} 3,88% and C_{34} 7,31%.

Using histochemical methods Hernandez *et al.* (2013) identified inulin, lipophilic substances and starch.

The seasonal variation of saponins in plants collected in Beriso, Buenos Aires, Argentina was studied by Arrambarri & Hernandez (2014). The saponins content was determined by the height of the foam formed. Saponins were always present in underground organs (roots and rhizomes), but leaves collected at the end of summer and early autumn (March-April) also gave a highly positive reaction. Accordingly, March and April are the most suitable months to extract saponins from *S. chilensis* under natural conditions.

BIOACTIVITY

Cell assays

Razmilic & Schmeda (2000) studied the cytotoxicity of diterpene solidagenone and four semi-synthetic derivatives in L 1210, BHK and COS 7 cell lines that exhibited inhibitory concentrations 50 (IC_{50}) between 10-100 μg/ml. They also studied possible mechanisms of anti-inflammatory activity on glucocorticoid-mediated signal transduction and found activities between 1-25 μg/ml.

Bagatini et al. (2009) using the Allium cepa test showed that infusions of this plant have

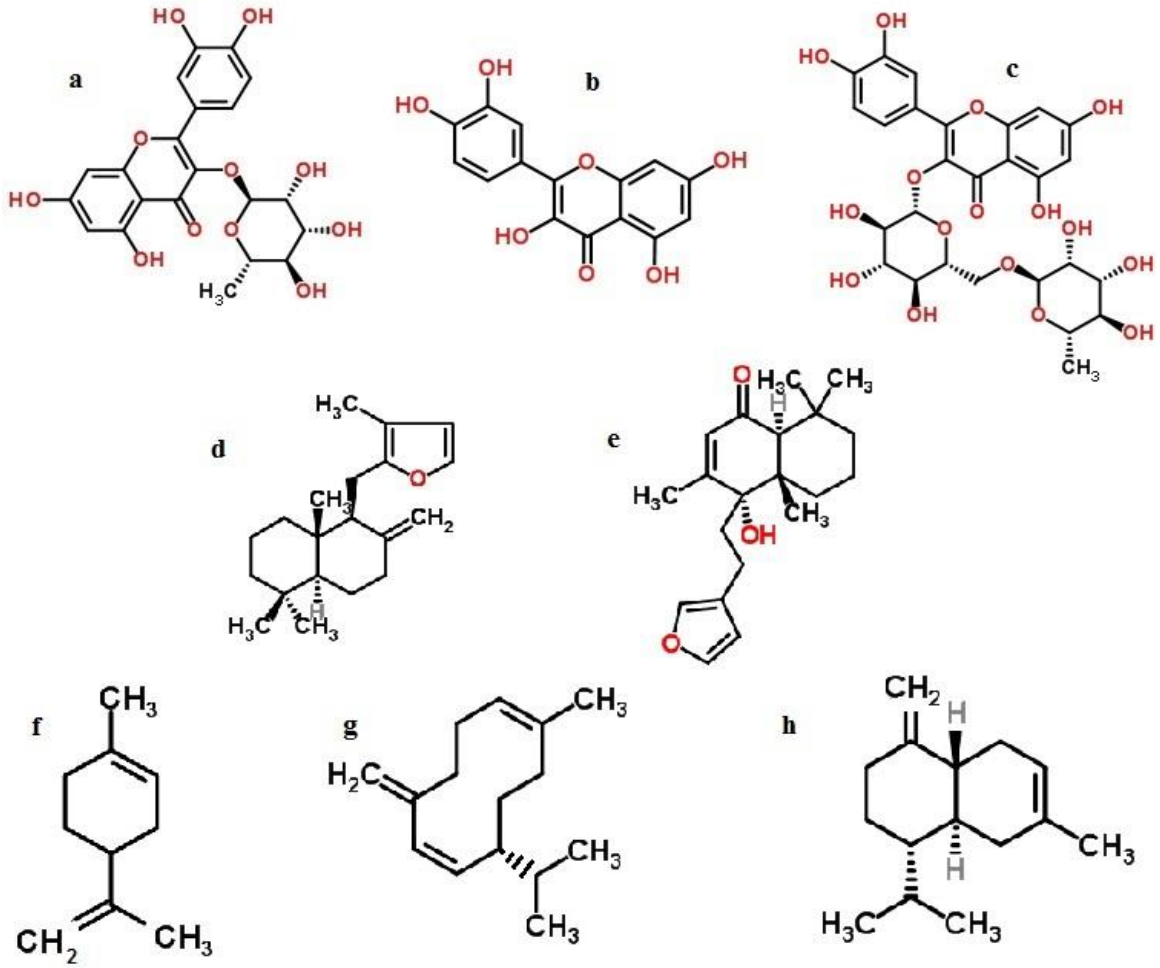
cytotoxic but not mutagenic effect. They showed the existence of antiproliferative and cytotoxic activities suggesting a possible therapeutic potential to inhibit the cell cycle in eukaryotic organisms. Accordingly, Gastaldi *et al.* (2016a) investigated the antiproliferative effect of the infusion on colon cancer cell line T84, finding an effective concentration 50 (EC_{50}) of 0.16 mg/ml; this is a promising result suggesting that this plant has potential to inhibit the proliferation of colon cancer cells.

Freitas *et al.* (2008) analyzed the effect of aqueous extracts on the osmotic stability of human erythrocytes. In this assay the extract displayed simultaneously hemolytic and anti-hemolytic effects. The hemolytic activity may be related to the presence of saponins that form complexes with sterols, proteins and phospholipids, thereby modifying membrane permeability. The antagonistic anti-haemolytic activity may be related to flavonoids that can be incorporated into erythrocyte membranes. The presence of these antagonistic effects reflects the heterogeneous nature of the extract and indicates a need to fractionate it to characterize the components responsible for each effect.

Gastaldo *et al.* (2012) reported that a water-ethanol extract increases the release of cytokines in human cultured cells. It should be noted that this reference presents highly summarized information without in-depth analysis.

Figure 4

Some relevant compounds isolated from *S. chilensis*. Flavonoids: a) quercetrin (= quercetin-3-O-α-L-rhamnoside); b) quercetin; c) rutin. Terpenoids: d) pumiloxide; e) solidagenone; f) limonene; g) germacrene D; h) γ-cadinene.



Antimicrobial and antifungal activity

Vila *et al.* (2002) showed that the essential oil from leaves of *S. chilensis* is an efficient antifungal against the dermatophyte fungi *Microsporum gypseum* and *Trichophyton mentagrophytes*. The oil was more efficient than Amphotericin B and Nystatin whilst resulted inactive against other filamentous fungi such as *Aspergillius fumigatus*, *Fusarium oxysporum* and Penicillium *purpurogenum*. *Cryptococcus neoformans* was slightly sensitive only at the highest dose assayed (10 ul).

Duarte *et al.* (2005) reported that the essential oil displayed anti *Candida albicans* activity, whereas the ethanolic extract had no effect on this opportunistic fungus. The concentrations assayed were between 0.03 and 2 mg/ml.

Avancini *et al.* (2008) reported that a 10% decoction of aerial parts of *S. chilensis* was active against *Staphylococcus aureus* (Gram-positive) while it had no effect against *Salmonella choleraesuis* (Gram negative). A potential veterinary application is suggested due to the positive result against *S. aureus*, the main bacterium responsible for bovine mastitis.

Morel *et al.* (2006) tested the essential oil from leaves and a methanolic extract from roots against *Staphylococcus aureus* ATCC 6538p, *Staphylococcus epidermidis* (ATCC 12228), *Klebsiella pneumoniae* (ATCC 10031), *Escherichia coli* (ATCC 25792), *Salmonella setubal* (ATCC 19796), *Bacillus subtilis* (ATCC 6633), *Pseudomonas aeruginosa* ATCC 27853, *Saccharomyces cerevisiae* (ATCC 2601) and *Candida albicans* (ATCC 10231). The methanol extract showed weak activity against the tested microorganisms with a minimal inhibitory concentration (MIC) >1 mg/ml while the essential oil effectively inhibited the growth of all tested microorganisms.

Rafael *et al.* (2009) determined the antimicrobial activity of aqueous extracts of rhizomes against *Staphylococcus aureus* (ATCC 25922), *Escherichia coli* (ATCC 25923) and *Pseudomonas aeruginosa* (ATCC 27853). The extracts showed the following MIC values: *P. aeruginosa* 3.1 mg/ml, *E. coli* 6.2 mg/ml, *S. aureus* 6.2 mg/ml. The positive control using gentamicin as reference drug presented the following MIC values: *P. aeruginosa* 0.62 ug/ml, *E. coli* 1.25 ug/ml, *S. aureus* 0.62 ug/ml.

The potential use in dentistry has beentested by Freires *et al.* (2010) using the microdilution method. The tooth decay producing bacterium *Streptococcus mutans* (ATCC 25175) and *Lactobacilus casei* (ATCC 7469) were exposed to different concentrations of a commercial tincture of the plant. The MICs were 7.81 and 1.95 mg/ml respectively. These results show the potential of the tincture in dental clinic as an alternative and low cost method in the prevention of dental caries.

Animal studies

Antiulcerogenic and gastroprotective activities

Schmeda-Hirschmann *et al.* (2002) studied the antiulcerogenic effect of diterpene solidagenone and some semi-synthetic derivatives in mice. They found that a dose of 100 mg/Kg exerted a significant effect, equivalent to the control drug lansoprazole (20 mg/Kg).

In other work, Bucciarelli *et al.* (2010) analyzed the gastroprotective activity and acute toxicity of an aqueous extract in ulcerogenic models induced in female of albino mice. They studied the activity of aqueous extracts of inflorescences and compared it with the antiulcer reference drug omeprazole. The following doses of extract were tested: 125, 250, 400, 800, 1200 and 2000 mg/Kg. The extract gave promising results regarding antiulcerogenic activity which can be attributed to the flavonoid content. No toxic effects were observed. For this reason, the authors consider it as a promising plant for the development of new antiulcerogenic agents.

Barros *et al.* (2016) also studied the gastroprotective activity of a methanolic extract in doses 100-300 mg/Kg. The gastroprotective effect was investigated in acute gastric ulcer models and the antisecretory activity was assessed *in vivo* and *in vitro*. They concluded that *S. chilensis* extract promotes gastroprotection and gastric healing by diversified and complementary modes of action. Flavonoids, especially quercitrin and afzelin, are related to its antioxidant and antisecretory properties in parallel to its beneficial effect on the mucus production. In agreement with Bucciarelli *et al.* (2010), this plant is considered a possible natural resource in the search for antiulcer compounds, mainly flavonoids.

Hepatotoxicity, hepatoprotection

Neto *et al.* (2004) exposed a group of rats to 16.1 mg/Kg of aqueous extract in form of daily intraperitoneal injections for 14 days. They report

the lack of significant changes in the serum levels of alanine aminotransferase and aspartate, indicating that extract was not hepatotoxic at the dose assayed. However, the lethal dose 50 (LD_{50}) and lethal dose 100 (LD_{100}) in rats were 54.7 and 86.2 mg/Kg respectively, only 3.4 and 5.4 times higher than therapeutic dose (16.1 mg/Kg), which means that the extract does not have enough safety margin to be used to prevent intoxication.

In a recent work, Sabir *et al.* (2012) reported a significant hepatoprotective effect of an ethanol extract against paracetamol induced liver injury (250 mg/Kg). The animals received oral doses of 100 or 200 mg/Kg, per day for 7 days. However, the authors suggest the need for more detailed in vivo studies to establish the safety and bioavailability of plant extract.

Hypoglycemic and hypolipidemic activities

Roman *et al.* (2015) carried out a test in order to analyze the hypolipidemic and antioxidant effects of *S. chilensis* hydroalcoholic extract (HAE) on cholesterol-fed rats. Rats treated with extract (150, 300, and 600 mg/Kg) and quercetrin showed decreased serum levels of total cholesterol and triacylglycerides similar to control drug simvastatin. Moreover, treatment with HAE and quercetrin decreased 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity (35.1% on average) and increased the amount of fecal cholesterol (38.2% on average). This study suggested that hypolipidemic effects of HAE are associated with it modulating the activity of HMG-CoA reductase and its interference in the reabsorption and/or excretion of intestinal lipids. *S. chilensis* and quercetrin, may thus be effective as cholesterol-lowering agents and in preventing atherosclerosis.

Schneider *et al.* (2015) evaluated the hypoglycemic and hypolipidemic effects of HAE from *S. chilensis* aerial parts in rats. The study showed that a glucose dose of 4 g/Kg can considerably increase serum glucose level which was mitigated by a single oral dose of HAE at 500 mg/kg for 180 min following glucose administration. Rats treated with HAE (125, 250 or 500 mg/Kg) showed decreased serum total cholesterol, more than glibenclamide drug at 10 mg/Kg. They conclude that HAE of *S. chilensis* may be effective in maintaining glucose homeostasis by reducing serum glucose levels and total cholesterol.

Anti-inflamatory activity

Goulart *et al.* (2007) made the first work of preclinical relevance to study the anti-inflammatory activity. The aim was to investigate the anti-inflammatory effect and mechanism of action of aqueous extracts obtained from rhizomes, leaves and inflorescences of *S. chilensis* in a mouse model of pleurisy induced by carrageenan. The results indicated that infusions at 25-50 mg/Kg inhibited leukocytes, neutrophils and exudation. The extracts also inhibited myeloperoxidase, adenosine-deaminase, and tumours necrosis factor alpha (TNF-α), and induced a decrease in the nitric oxide and interleukin-1 beta levels. An important anti-inflammatory effect is demonstrated, inhibiting cell infiltration and also decreasing pro-inflammatory mediators released into the site of the inflammatory process. Similar results have been obtained by Liz *et al.* (2008) and Gastaldo *et al.* (2012) using the mouse "air pouch" inflammation model.

Using Wistar rats as an experimental model, Tamura *et al.* (2009) showed the anti-inflammatory effects of alcoholic and hydroalcoholic extracts of aerial parts of *S. chilensis* on oedema and leukocyte trafficking. Their results indicated that topical (12.5 - 50 mg/kg) or intraperitoneal (25 or 50 mg/Kg) administration of the extract reduced ear oedema formation (> 25% reduction). Intraperitoneal applications of 25 mg/Kg of extract inhibited the migration of polymorphonuclear cells into the inflamed cavity (about 50%). Besides, the rolling behaviour and adherence of circulating leukocytes to postcapillary venules of the mesentery network was diminished (50%), but the mast cell degranulation in the perivascular area was not affected. In conclusion, local and systemic anti-inflammatory effects of the extract are demonstrated, and implicate the inhibition of leukocyte-endothelial interactions as an important mechanism of action.

Assini *et al.* (2013) reported the anti-inflammatory assay of formalin, based on the direct injection of formalin in the paws of mice. The aqueous extract (25, 50 and 250 mg/Kg) was administered by the oral route 30 minutes prior to behavioural test. In this test the extract produced significant analgesic and anti-inflammatory effects.

Activity on the central nervous system

In order to determinate possible antidepressant and locomotor-type activities, Assini *et al.* (2013)

performed "open field test" and "forced swimming test" on Swiss mice. Experiments were performed with doses of 25, 50 and 250 mg/Kg. Results indicate that aqueous extract from *S. chilensis* did not show antidepressant-type activity. A reduction in the locomotor activity was noted at the highest administered level (250 mg/Kg), suggesting an effect on the central nervous system, although this could also be due to a peripheral muscular relaxing effect of the extract.

Burn healing

Catarino *et al.* (2015) carried out a study to evaluate possible positive synergic effect of laser therapy and hydroalcoholic extract of *S. chilensis* as phytotherapeutic agent to heal experimental second-degree burns in Wistar rats. The application of an extract combined with 670 nm laser promoted favourable responses in tissue repair in this experimental model.

Others

Rafael *et al.* (2009) studied the in vitro antiplatelet effect using a turbidimetric method. In this assay, the platelet aggregation is induced by adenosine diphosphate (ADP). The aqueous extract (400 µg/mL) of *S. chilensis* was effective in inhibiting the platelet aggregation stimulated by ADP with a 45% of inhibition. The observed effect may have important benefits over atherothrombotic diseases, although in vivo studies should be done to corroborate this activity.

Guarda *et al.* 2016 investigated the insecticide potential of *S. chilensis* and other Brazilian plants on the mosquito *Aedes aegipty*, vector of many tropical diseases. They worked with aqueous extract at concentrations of 125, 250, 500, 750 and 1000 µg/ml. The percentage efficiency was 0% for *S. chilensis*, so this extract does not have any lethal activity on *A. aegipty* larvae.

CLINICAL TRIALS

The first clinical trial of *S. chilensis* was carried out by Silva *et al.* (2010). The authors evaluated a gel preparation based on ethanol extract in treating lumbago (low back pain). The effectiveness of *S. chilensis* used externally was examined in placebo-controlled double-blind clinical pharmacological studies. Two daily skin applications of a gel containing a 5% extract in glycol were administered for 15 days to ten volunteers in a placebo group and to an equal number in a test group. Statistical analyses of the results demonstrated a significant reduction in the perception of pain and a significant increase in flexibility of patients in the test group as compared with those receiving only the placebo.

Latter, the same group demonstrated the effectiveness of *S. chilensis* fluid extract used externally for treating tendinitis of flexor and extensor tendons of wrist and hand. Results showed a significant reduction in the perception of pain in the arms in the test group, when it was compared to those receiving only the placebo (Silva *et al.*, 2015).

DISCUSION AND CONCLUSIONS

S. chilensis is an herb widely distributed in South America that in the last years has aroused attention by its varied properties and apparent low or nil toxicity. According to the publications analyzed in this review, this herb has potential as a source of antiulcerogenic, hypoglycemic and hypolipidemic compounds and to be used in the formulation of anti-inflammatory preparations for external use. Preclinical evidence (Mercandeli *et al.*, 2012) and two clinical trials with preparations for external use (Silva *et al.*, 2010; Silva *et al.*, 2015) showed no adverse reactions or toxicity of the extracts tested.

Due to the plethora of active metabolites produced by this plant (phenolic compounds, flavonoids, saponins, diterpenes, essential oil, etc.), long-term studies on pure bioactive components or purified and standardized fractions are required to establish relationships with the observed properties as well as possible synergistic effects.

Interestingly, quercetin-3-O-α-L-rhamnoside (quercetrin) -one of the main components in the aerial parts- is widely cited in collections from northern Brazil but not reported in southern populations, probably due to existence of different chemical races. On the other hand, solidagenone, an antiulcerogenic diterpene, is a major metabolite in the rhizomes and could be used for quality control of underground parts of the plant. Studies on populations from Paraguay, Uruguay, Chile and Bolivia are scarce or nonexistent and further comparative investigations to detect possible chemotypes in terms of phenolic profile, flavonoids, diterpenes, saponins and essential oil are needed. In addition, research on variation in the type and content of active metabolites according to the stage of development of the plant will provide

extremely useful information.

Recently an experimental crop of this species was started in Rio de Janeiro, Brazil to homogenize quality and promote a sustainable harvesting for productive purposes without affecting natural populations. Initiatives of this type should be promoted and encouraged in order to protect wild genotypes of this species.

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