Plantas Provechosas

MEDICINAL PLANTS FROM THE DON ROBERTO FOREST[1]

Xalapa, Veracruz, Mexico

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Index

Presentation

On a global scale, the available evidence points to a direction of increasing relevance of Traditional Ethnobotanical Knowledge (TEK) as an invaluable, underutilized and underdocumented body of knowledge.

In 1992, the Convention on Biological Diversity (CBD) was the first to develop measures for the use and protection of traditional knowledge related to the conservation and sustainable use of biodiversity. Member countries were expected to promote the use of indigenous knowledge (IK) systems in natural resource management (NRM), to adopt and expand the use of such knowledge, and to promote equity and the sharing of benefits arising from the use of indigenous knowledge systems.

Chapter 26 of Agenda 21 reiterates the "participation of indigenous peoples and their communities at national and local levels in resource management and conservation strategies to support and review sustainable development strategies."

The United Nations Organization of Scientific Conferences (UNESCO) and the International Council for Science Union (ICSU) in their model documents appreciate the role played by IK and advocate its application in all forms of humanity's commitments[5]. In defining TEK, several authors focus on the attributes of perception, management and utilization of plant resources by local communities. In specific terms, TEK research focuses on "how people classify, identify and relate to plant resources, examining the interactions of plants and people, the taxonomic identification of selected plants, and the biological and chemical analysis of their ingredients".

Indigenous knowledge, defined by Masango [1990], as "the totality of all knowledge and practices established on past experiences and observations possessed and used by people", is the main reservoir of ethnobotanical research and is commonly referred to as TEK.

However, changes in lifestyle brought about by globalization have led to the negation of TEK in ongoing efforts to ensure sustainable resource management with a simultaneous loss of related knowledge. In particular, the transmission of this knowledge between the older and younger generation is no longer connected.

There is a general consensus in the NRM field that traditional ethnobotanical/ecological knowledge of indigenous communities can positively influence sustainable land management (SLM) practices. In addition, TEK can broaden the way communities conceptualize and address environmental challenges, thereby enhancing the resilience of a social-ecological system.

TEK has received much attention from various researchers, hence the plethora of definitions. Raimundo et al. defined TEK as "a subset of indigenous knowledge that includes knowledge and beliefs transmitted from generation to generation by cultural transmission and that is related to human environmental interactions".

Fernández-Giménez describes TEK as "a system of experiential knowledge obtained by continuous observation and transmitted among the members of a community". We can define it as: "a cumulative set of knowledge, practices and beliefs, which evolves through adaptive processes and is transmitted from generation to generation by cultural transmission, about the relationship of living beings (including humans) with each other and with their environment."

TEK is an important component of a number of concepts within the field of community-based natural resource management (CBNRM) and related concepts, including resilience, community participation and stakeholder collaboration. Sustainable land management often requires sufficient collection, retention and transmission of knowledge gained from years of interaction with a landscape. TEK transmission is the transfer of traditional knowledge between individuals of a particular indigenous group. The main modes of transmission are dynamic, varying by place and time, although commonly occurring through direct interaction with the environment. TEK is also often conferred during normal social interaction and by oral transmission through storytelling.

Characteristics of the forest where the project is located

Santa Rosa Las Cruces farm, managed by the Bosque don Roberto Cooperative Society, Xalapa de Enriquez, Veracruz, Mexico. Approximately 300 hectares are segmented into several polygons due to the accelerated urban growth of the city of Xalapa, which places this forest in a vulnerable situation. Xalapa in Nahuatl means "water in sand" or "spring in sand" which favors the humid temperate climate characteristic of the cloud forest ecosystem. In 1804 the naturalist Alexander Von Humboldt named it "City of Flowers" in recognition of the great biodiversity of the area.

Latitude: 19°32'24" North.

Longitude: 96°55'39" West.

The type of sloping soil is rich in organic matter and humidity all year round. It is estimated that it contains 10% of the plant species in all of Mexico (2,500 species) and 30% of them are native to the cloud forest; its capacity for regeneration is slow and due to continuous disturbance it is a fragile ecosystem, in danger of extinction and a priority for conservation.

In this forest coexist trees in different strata among which we can observe: Encino Xalapeño, Encino blanco, Gravileas, Jinicuil, Gasparito, Marangola, Sangregado, Liquidambar, Hayas, Pinos, Jonote, Huizache, Higuera, Sáuco, Chalahuite and Jacaranda. Under its shade we can find the coffee plantations of the Mexican Arabica species Garnica, Mundo Nuevo and Caturra, being cultivated under shade and without any agrochemicals it is a quality coffee that has achieved scores of 9.1 / 10. Likewise, in the coffee growing area it is common to observe Guava trees, Bananas, Izote, Chinini tree, an endemic avocado species, Sour Orange, Loquat and Pepper bushes.

Among the trees grow abundant native orchids, arborescent ferns and epiphytes, which help conserve the humidity of the forest.

Some of the endemic plants selected for their ample health care properties are: Gordolobo, Acuyo, Llantén, Saúco, Flor de Mortiño and Madroño capulín agarroso.

Regarding animal life is very varied, to mention the most visible species, you can see hares, squirrels, gray fox, cacomixtle, tlacuache, tuza, armadillo, lizards, frogs, some snakes and a wide variety of reptiles such as the Dragoncito de la Sierra Madre Oriental Sur.

The presence of water is important, there is a stream that crosses the land from north to south, it is quick response because it drains the water in the rainy season.

There is also a wetland called Los Patos with an area of 40 hectares which, despite being the best preserved of the city, is under constant threat by the anarchic urban growth.

The wetland is home to herons, Pijijé ducks, the lesser ruddy duck (Tachybaptus dominicus), which is a bird native to the Americas with a length between 21 and 27 cms, excellent swimmer and is in the category of Species Subject to Special Protection.

Los Patos Wetland retains and stores water, recharges the subsoil, provides habitat for hundreds of species of raptors and migratory birds that travel from North America to southern Mexico or South America and return in the spring to nest, among these birds can be seen eaglets, vultures, kites, peregrine falcons, cormorants, dragonflies, hummingbirds, storks and swallows that cross the region between the months of August to November each year.

According to INECOL, a federal institution dedicated to scientific research on biodiversity in Mexico, this forest and wetland provide important environmental services by regulating temperature and providing oxygen, as well as absorbing CO_2 and favoring climate regulation.

Selected plants

Gnaphalium conoideum Kunth (Asteraceae)

<u>Mex: mullein</u>, purepecha: Popu

In the State of Mexico and Michoacan, its use is indicated in respiratory diseases such as cough, flu or bronchitis, administering a decoction of the flowers and leaves, which is sweetened with honey and taken very hot, preferably at night.

In the XVI century, Francisco Hernandez reports the following uses: antirheumatic, antitussive, bronchitis, emollient, sore throat and for phlegmatic moods. In the 20th century, Maximino Martínez mentions it as antirheumatic and emollient. The Pharmaceutical Society of Mexico describes the same information provided by Martinez.

<u>Gnaphalium viscosum Kunth (=syn. Gnaphalium leptophyllum DC; Gnaphalium hirtum Kunth; Gnaphalium tenue Kunth. (Asteraceae).</u>

<u>Mex: mullein,</u> canelilla

In some states of central Mexico, mullein is used in infusion to cure coughs. The infusion of the plant prepared with oak leaves (Quercus sp), serves to relieve stomach pain. The branches and leaves are used for empacho. The leaves are applied as a poultice to heal festering grains. Its use is recommended against cancer, ulcers, relapse of ladies, headache and inflammation. It is attributed properties as an expectorant.

Querétaro: chupona

Whole plant. Infusion to take. Cough, colds

Tarahumara (Chih): rsoabori, telempakate, rasoko, wiloni (“wolf”), gasará napisoame (“ashy”), chi owira' sora' (“that cures us rotten”), Chih: manzanillo, manzanillo del rio, gordolobo.

Whole plant, infusion to take. Diarrhea, cough (Pennington 1963), scanty menses, chicken pox, smallpox, asthma, bronchitis, lung congestion, colic and colds (Bye 1972), gastrointestinal pain (Palmer 1908).

Whole and crushed plant in baths and poultices. Wounds, ulcers, skin cancer, bruises.

Pharmacological use

To evaluate the antibacterial activity of the methanol and dichloromethane extract of Gnaphalium polycephalum Michx, against three bacterial strains of clinical importance. The extracts were obtained from the leaves of the plant by solvent extraction (methanol and dichloromethane) and dried in a vacuum rotary evaporator. Antimicrobial activity was evaluated by microdilution technique (adapted from Clinical and Laboratory Standards Institute, CLSI) to determine the minimum inhibitory concentration (MIC) by testing five dilutions (1,000, 500, 250, 125 and 62.5 µg/ml). All assays were performed in duplicate and incubated for 24 hours at 37 ºC. Results: Both extracts showed inhibitory effect against

Staphylococcus aureus and Escherichia coli until the second dilution, but did not act on Pseudomonas aeruginosa (ramirez Rueda 2014).

+. There are about 110 species of this genus, most are found in temperate zones, although some develop in tropical mountains and the Subtropical regions. It comprises 1311 described species and of these, only 107 accepted.

The essential oil of G. affine was observed to possess strong radical scavenging activity against 2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonate with an IC50 of 0.32 ± 0.89 µg/mL (IC50 of ascorbic acid = 24.06 ± 0.73 µg /mL). A significant inhibitory effect of the essential oil on lipid peroxidation was demonstrated in egg yolk homogenates with an IC50 value of 0.09 ± 0.75 µg/mL (IC50 of ascorbic acid = 6.73 ± 0.87 µg/mL). The essential oil had a stronger reducing power than Vc in the reduction of Fe^{3+} to Fe^{2+} by electron donation [Rojas 2001]. The scavenging effect elicited by the ethanolic extract of G. uniflorum leaves was concentration dependent in the 2,2-diphenyl-1-picrylhydrazyl test, the amount of antioxidant required to decrease the initial concentration by 50 % (SC50) was calculated as 15.96 µg of extract. The extract showed a concentration-dependent antioxidant activity also in the LP-LUV test (IC50 = 14.86 µg of extract), determination of the accumulation of peroxidation products in mixed dipalmitoylphosphatidylcholine/linoleic acid unilamellar vesicles induced by the water-soluble peroxyl radical generator 2,2'-azobis(2-amidinopropane hydrochloride).

Antibacterial and antifungal activity

The chloroform extract of G. americanuml possessed marked antimicrobial activity against Candida albicans yeast tested at a minimum inhibitory concentration (MIC) of 5 mg/mL. Chloroform extracts of G. oxyphyllum and G. americanum were active against Gram-positive bacteria tested, including Staphylococcus aureus (MIC = 2. 5 mg/mL and 5 mg/mL), Enterococcus faecalis (MIC = 5 mg/mL and 5 mg/mL), Streptococcus pneumoniae (MIC = 2.5 mg/mL and 1.2 mg/mL) and Streptococcus pyogenes (MIC = 2.5 mg/mL and 1.2 mg/mL). The methanol extract of G. oxyphyllum and the hexane and chloroformic extracts of G. hirsutum, all of which were active against S. aureus (MIC = 5 mg/mL, 2.5 mg/mL and 5 mg/mL), S. pneumoniae (MIC = 1.2 mg/ml, 1.2 mg/ml and 2.5 mg/ml) and S. pyogenes (MIC = 2.5 mg/ml, 2.5 mg/ml and 2.5 mg/ml). Methanolic extracts of G. americanum and G. hirsutum were active against S. pneumonia (MIC = 2.5 mg/mL and 2.5 mg/mL) and S. pyogenes (MIC = 2.5 mg/mL and 2.5 mg/mL), hexane extract of G. oxyphylum was active against S. pneumoniae (MIC = 2.5 mg/mL) and S. aureus (MIC = 2.5 mg/mL) [Rojas 2001]. Hexane extracts of either flowers or leaves of G. oxyphyllum, G. liebmannii, and G. viscosum showed inhibition against S. aureus and Bacillus cereus, except the leaf extract of G. viscosum, which only inhibited B. cereus. The hexane extract of G. oxyphyllum flowers inhibited both E. coli and Salmonella typhimurium, and the hexane extract of leaves showed activity against S. typhimurium [13]. The essential oil of G. affine exhibited potent inhibitory effect against bacteria (E. coli, S. aureus, Bacillus subtilis, B. cereus, Bacillus laterosporus laubach and Salmonella typhimurium with MIC values of 1.56 ± 0.41 µg/mL, 0.39 ± 0.12 µg/mL, 0.78 ± 0.30 µg/mL, 0.78 ± 0.11 µg/mL, 0.78 ± 0.13 µg/mL and 0.78 ± 0.19 µg/mL, respectively), yeast (Saccharomyces cerevisiae with MIC value of 0, 20 ± 0.21 µg /mL), and fungi (Aspergillus niger, Pencicillium citrinum, Rhizopus oryzae and Aspergillus flavus with MIC values of 0.20 ± 0.18 µg/mL, 0.20 ± 0.15 µg/mL, 0.20 ± 0.19 µg/mL and 0.20 ± 0.20 µg/ml, respectively) [Zeng 2011]. The methanolic extract of aerial parts of G. gaudichaudianum showed activity against two subcutaneous fungi Fonsecaea pedrosoi at MIC 12.5 μg/mL and Sporothrix schenckii at MIC 50 μg/mL in agar dilution assay.

Anti-complementary activity

Several chromatographic procedures on the ethyl acetate fraction of G. affine using silica gel, Sephadex LH-20, ODS and MCI gel led to the isolation of 27 flavonoids. The anti-complement activity of all compounds was evaluated in the classical pathway of the complement system in vitro, and some isolated flavonoids, including the positive control heparin, inhibited complement activation in a dose-dependent manner. Three caffeoyl flavone glycosides, apigenin 4'-O-β-d-(6''-E-caffeoyl)-glucopyranoside , apigenin 7-O-β-d-(6''-E-caffeoyl)-glucopyranoside and luteolin 4'-O-β-d-(6''-E-caffeoyl)-glucopyranoside , and caffeoyl flavonol glycosides, quercetin 4'-O-β-d-(6'' -E-caffeoyl)-glucopyranoside , with the flavonoid-sugar-caffeoyl configuration showed strong activity with IC50 values of 0.134 ± 0.016 mg/mL, 0.119 ± 0.013 mg/mL, 0.045 ± 0.005 mg/mL and 0.147 ± 0.014 mg/mL, respectively. The anticomplementary activities of apigenin , luteolin , quercetin , quercetin 7-O-β-d-glucuronide , quercetagetin 7-O-β-d-glucopyranoside and isorhamnetin were moderate, and that of 6-hydroxyluteolin 7-O-β-d-glucopyranoside was weak. The other compounds, luteolin 4'-O-β-d-glucopyranoside , acacetin 7-O-ruthinoside , quercetin 4'-O-β-d-glucopyranoside , 5-hydroxy-3, 6,7,8, 4'-pentamethoxyflavone , 5,7-dihydroxy-3,8,4'-trimethoxyflavone and 5,7-dihydroxy-3,8,3',4'-tetramethoxyflavone , showed no anti-complementary activity. A comparison of the chemical structures showed that the flavonoid-sugar-aromatic side chain configuration may play an important role in the structure-activity relationships, in which flavonoid types are less important. In addition, there were no active compounds with a substituent at the 4' position of the B-ring in the oxygenated derivatives. It appears that the hydroxy group at the 4' position of the flavonoid is essential for the anti-complementary activity, but the activity is lost when substituted by a methoxy or sugar group. However, the anti-complementary activity was also related to the number of hydroxy groups.

Antitussive and Expectorant Activity

For thousands of years, in China G. affine was cooked to treat respiratory diseases. The herbs of G. affine were extracted twice by the decoction method in water for 1 h each time, and evaporation of the solvent gave a viscous material. The aqueous extract (equivalent to 18 g/kg, 12 g/kg and 6 g/kg of plant material) was administered orally to ammonium hydroxide-induced coughing mice and acytric acid-induced coughing guinea pigs and phenol. red injected mice, respectively, to evaluate its potential expectorant and antitussive activity. The extract significantly prolonged tussive delitescence and decreased the frequency of cough caused by ammonium hydroxide and acytric acid, as well as mucus secretion from the tracheas of mice obviously increased by measuring the tracheal production of phenol red [Yu 2006]. Campos-Bedolla et al. investigated the effect of methanol extract of G. conoideum on contractile agonist responses in guinea pig tracheae and the possible role of l-type Ca2+ channels in isolated tracheal guinea pig myocytes. Cumulative concentration-response curves to carbachol or histamine as well as contractile responses to KCl with or without 30-min preincubation with 20 or 100 μg/mL methanol extract were evaluated, and intracellular Ca2+ concentrations were measured by microfluorometric method in tracheal myocytes isolated with or without preincubation with 0.1 μg/mL, 0.31 μg/mL, and 1 μg/mL methanol extract. The results showed that the extract significantly decreased the contractile responses to histamine, but not to carbachol or KCl, and significantly reduced the intracellular Ca2+ increase induced by 60 mM KCl in isolated myocytes. Because histamine contractile responses are highly dependent on extracellular Ca2+ and KCl responses are mediated mainly through l-type Ca2+ channels, the results suggested that the methanol extract of G. conoideum might be acting as a partial blocker of these Ca2+ channels. The hexane extract of G. liebmannii was the most active relaxant extract (IC30 = 54.23 ± 19.47 µg/mL with 99.5 ± 3.2 % relaxation) than dichloromethane extract (IC30 = 120.22 ± 5.27 µg/mL with 76.44 ± 2.3 % relaxation) and methanol extract (IC30 = 190.25 ± 30.02 µg/mL with 45.94 ± 10.3 % relaxation) in guinea pig tracheal smooth muscle. The hexane extract produced a parallel rightward shift of the carbachol concentration-response curve (IC50 = 0.04 ± 0.0013 µM) competitively at concentrations of 177 µg/mL (IC50 = 0, 20 ± 0.0089 µM) and 316 µg/mL (IC50 = 0.19 ± 0.001 µM), but did not modify the concentration-response curves for histamine (IC50 = 4.4 ± 0.36 µM) at concentrations of 100 µg/mL, 177 µg/mL and 316 µg/mL. The relaxant effect of hexane extract (100 µg/mL, 133 µg/mL, 177 µg/mL, 237 µg/mL and 316 µg/mL for ATP-sensitive potassium channel blockade or 31 µg/mL, 100 µg/mL, 177 µg/mL and 316 µg/mL for β-adrenergic receptors) of G. liebmannii was not affected by the presence of propranolol or glibenclamide. However, hexane extract (87 µg/mL, 130 µg/mL and 316 µg/mL) produced a leftward shift of the forskolin, nitroprusside, isoproterenol and aminophylline concentration-response curves, suggesting that G. liebmannii induced tracheal muscle relaxation, probably through phosphodiesterase inhibition [Sanchez Mendoza 2007]. By employing a bioassay-guided fractionation of the active hexane extract of G. liebmannii, using the isolated guinea pig trachea model, gnaphaliin A and gnaphaliin B were identified as the active relaxant compounds. Gnaphaliin A (EC50 = 195.97 ± 36.07 µM) and gnaphaliin B (EC50 = 134.04 ± 6.41 µM) showed more potent relaxant properties than aminophylline (EC50 = 534.50 ± 27.88 µM), a well-known relaxant drug that can be used to treat bronchial asthma , chronic asthmatic bronchitis and chronic obstructive pulmonary disease [Rodriguez Ramos 2009].

Cytotoxic activity

The compound 5,7-dihydroxy-3,6,8-trimethoxyflavone derived from G. elegans effectively decreased the cell viability of human colon cancer Caco-2 cells (EC50 = 12.42 µM), human pancreatic cancer Panc28 cells (EC50 = 51.76 µM) and human colon cancer HCT-116 cells (EC50 = 69.99 µM) in a concentration-dependent manner. However, that did not decrease the cell viability of human pancreatic cancer MIA PaCa cells, human breast cancer MCF-7 and SK-BR3 cells, and human prostate carcinoma LNCaP and PC3 cells. Cell viability of normal CCD-112 coN colon fibroblasts was not affected after 24 h treatment with increasing concentrations of the compound between 5 and 80 mM [Thomas 2012]. The compound 5,7,3',4'-tetrahydroxy-3-methoxyflavone isolated from the Mexican plant G. indicum inhibited phorbol ester tumor promoter-enhanced phospholipid synthesis and sugar transport activity in cultured cells [Asaka 1993]. Ethanolic extracts of stems, leaves, and flowers of Gnaphalium spicatum showed no cytotoxic activity in this bioassay. Root extracts showed cytotoxicity in all tumor cell lines except M-14. They were also less cytotoxic in relation to cisplatin in the 3T3 cell line (Callacondo Rivas 2008).

Anti-inflammatory activity

Air-dried G. stramineum flowers were successively extracted with n-hexane, methanol and water. The anti-inflammatory activity of each extract was tested orally using carrageenan-induced edema in rat paws. The methanol extract (140 mg/kg) was the most active, showing 36.8% edema inhibition (5 h), while the n-hexane extract (200 mg/kg), inhibiting edema by 35.7%, was less active. The aqueous extract showed no significant anti-inflammatory activity. Bioassay-guided fractionation of the methanol extract of G. stramineum resulted in the isolation of four caffeoylquinic acid derivatives, 4-O-caffeoylquinic, 3,5-di-O-caffeoylquinic, 4,5-di-O-caffeoylquinic and 3 acids ,4,5-tri-O-caffeoylquinic and quercetin glycosides, isoquercitrin, quercetin 3-O-β-d-galactopyranoside and rutin). The caffeoylquinic acid derivatives were tested in activated human macrophages for their activities on some functions of human leukocytes related to the inflammatory mechanism, such as monocyte migration and superoxide anion production. Compounds 113 and 114 exhibited appreciable anti-inflammatory activity, whereas compound 115 was inactive. Compound 113 inhibited the chemotactic index peak at a concentration of 1 × 10-11 M, but revealed significant activity at a concentration as low as 1 × 10-13 M; compound 114 blocked chemotaxis only at a concentration of 1 × 10-7 M; compound 115 was completely at either concentration tested (1 × 10-7 M-1 × 10-17 M). Quercetin glycosides (glycoside, galactoside, and rutinoside) were able to reduce carrageenan-induced edema and granuloma-induced exudative response in cotton pellets. Comprehensive evaluation showed that the anti-inflammatory activities of G. stramineum extracts may be due to a combination of caffeoylquinic acid derivatives and flavonol glycosides [Rastrelli 1999].

Hypoglycemic activity

G. uliginosum decoction was documented to reduce experimental epinephrine and diabetic hyperglycemia, but not to elevate the decrease in blood insulin level in a model of hyperglycemia with epinephrine and alloxan diabetes in rats and mice [Jiang 2008]. In 1995, Tachibana, et al. found that ethyl acetate and methanol extracts of G. affine showed inhibitory effects on aldose reductase (IC50 = 4.3 μg/mL and 1.4 μg/mL, respectively). Bioassay-guided fractionation resulted in the isolation of luteolin , quercetin , gnaphalin and scopoletin. The aldose reductase inhibitor assay test revealed that compounds 6, 31 and 68 exhibited potent activities with IC50 values of 0.7 μM, 2.6 μM and 4.5 μM, respectively, while compound 121 was less active [Osti Castillo 2010].

Antihypouricemic Activity

The hypouricemic actions of G. affine were examined in vivo using oxonate-induced hyperuricemic mice. Aqueous extracts of G. affine at 25, 12.5 and 6.5 g/kg injected intraperitoneally were shown to possess potent hypouricemic effects [Li 2005].

Other pharmacological activities

The aqueous extract of G. affine (2.0 g/kg, 1.0 g/kg and 0.5 g/kg) exhibited the protective effect for carbon tetrachloride-induced acute liver injury [Jiang 2008]. A gel formulation containing G. uniflorum extract was shown to provide significant in vivo protection against UV-B-induced skin erythema in healthy human volunteers [Aquino 2002]. As reported by Kubo et al. the methanol extract of G. cheiranthifolium showed significant inhibitory activity (<200 μg/mL) for mushroom tyrosinase-mediated L-3,4-dihydroxyphenylalanine oxidation. The compounds luteolin 4'-O-β-d-glucopyranoside and gnaphalin exhibited significant inhibition (nearly 100 % at 100 μg/mL) of L-3,4-dihydroxyphenylalanine oxidation by tyrosinase. Its limited availability precluded further studies, so neither ID50 values nor its mode of inhibition were investigated. [Kubo 1995]. The ethyl acetate extract of G. affine promoted ADP-induced rabbit platelet aggregation, whereas its methanol extract inhibited aggregation. Compound 68 isolated from this plant showed an inhibitory effect (IC50 = 1.6

mM) on ADP-induced rabbit platelet aggregation of approximately the same potency as quercetin (IC50 = 1.7 mM) (Tachibana 1995).

Pas

Previous phytochemical investigations of the genus have led to the identification of ca. 125 chemical constituents in total, including flavonoids, sesquiterpenes, diterpenes, triterpenes, phytosterols, anthraquinones, caffeoylquinic acid derivatives, and other compounds. Biological studies have demonstrated the antioxidant, antibacterial and antifungal, anticomplementary, antitussive and expectorant, insect antifeedant, cytotoxic, anti-inflammatory, antidiabetic, antihypouricemic and other activities of the extracts and chemical constituents of Gnaphalium species.(Zhang 2013)

To date (Zhang 2013), 28 flavone derivatives,,, 37 flavonol derivatives,, one flavanone derivative, and two chalcone derivatives, , which constitute the majority of the secondary metabolites of the genus Gnaphalium Among them, 28 compounds, were isolated as O-glycosides. The most frequently found flavonoids were quercetin , present in seven species, luteolin and gnafalin A found in six species, and ganfalin , which was isolated from five species. Also relatively common were apigenin , luteolin 4'-O-β-d-glucopyranoside and isoquercitrin . The presence of gnaphaliin A (=5,7-dihydroxy-3,8-dimethoxyflavone), gnaphaliin B (=3,5-hydroxy-7,8-dimethoxyflavone) and gnalialin (=4,2', 4'-trihydroxy-6'-methoxychalcone 4'-β-d-glucopyranoside), appear to be a characteristic chemotaxonomic feature typical of the genus Gnaphalium. Five labdane-type diterpenes were isolated from G. gaudichaudianum, G. graveolens, G. pellitum and G. undulatum . Approximately 15 kaurane-type diterpenes were isolated, three, from G. rufescens , six from G. gaudichaudianum , one,from G. inornatum , five from G. undulatum , one from G. graveolens two , from G. oligandrum , two from G. pellitum , and sylviside from G. sylvaticum . Seven pimara-type diterpenes were isolated and identified from G. gaudichaudianum . Only one wedeliasecokaurenolide derivative was characterized from G. undulatum .Among the tritrpenes, α-amyrin, taraxasterol acetate, β-amyrin and betulinic acid were isolated from G. affine , and squalene was identified from G. gaudichaudianum. β-Sitosterol was isolated from G. affine, G. hypoleucum, G. inornatum, and G. pellitum , and (20R)-cholest-4-en-3-one and 3β-hydroxy-stigmast-5,22-dien-7-one were also identified from G. affine. Compound 107 belongs to stigmastane-type was obtained from G. gaudichaudianum. Two derivatives of caffeoylquinic acid, i.e., chlorogenic acid and cynarin , were identified from the aerial parts of G. uliginosum , and four derivatives of caffeoylquinic acid, i.e., 4-O-caffeoylquinic acid , 3,5-dicaffeoylquinic acid , 4,5-dicaffeoylquinic acid , and 3,4,5-tri-O-caffeoylquinic acid were isolated from the flowers of G. stramineum. A new 3-hydroxyhydroxydihydrobenzofuran glycoside, gnaphaliol 9-O-β-d-glucopyranoside , was isolated from the aerial parts of G. polycaulon together with gnaphaliol 3-O-β-d-glucopyranoside , (Z)-3-hexenyl O-β-d-glucopyranoside and adenosine.

<u>Gnaphalium chartaceum Greenm. (Syn. = Pseudognaphalium chartaceum (Greenm.) Anderb.9 (Asteraceae)</u>

<u>Mex: mullein</u>, Yoreme (Sin): talampacate

Whole plant/leaves. Decoction to be taken for coughs

Gnaphalium attenuatum DC (Asteraceae)

Mex:mullein. Purepecha: xurhateri

Its medicinal qualities are used, in Michoacán, to remove stomach pain, cough and spasm; in Oaxaca, against gastritis, and in Puebla, to relieve heartburn and bile from the kidneys. It is also used against respiratory disorders such as cough, hoarseness, and flu. The treatment involves the use of the aerial part of the plant prepared in cooking and administered orally.

<u>Gnaphalium americanum Mill. (=syn.</u> <u>Gnaphalium guatemalense Gandoger and Gnaphalium purpureum L. var. americanum Klatt) (Asteraceae)</u>

<u>Purepecha:</u> “**<u>mullein”,</u>** “xurhateri”.

Whole plant. Boiled and taken. expectorant, blows.

Pharmacological uses

Eighteen crude extracts, including six hexanic, six chloroformic and six methanolic from six different plant species used in traditional Mexican medicine for the treatment of respiratory infections, were evaluated for potential antimicrobial activity against Staphylococcus aureus, Enterococcus faecalis, Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli and Candida albicans. The minimum inhibitory concentration was determined for each extract using a double dilution assay. The results showed that 16 crude extracts (89 %) exhibited antimicrobial activity against at least one of the tested microorganisms at concentrations of 5 mg/ml or less. Extracts of Gnaphalium oxyphyllum, Gnaphalium americanum and Crescentia alata possessed strong antimicrobial activity against the tested pathogens (Rojas 2014).

<u>Piper auritum Kunth. (=Syn. Artanthe seemanniana Miq., Piper alstonii Trel., Piper auritilaminum Trel., P. heraldi Trel., P.heraldi var. amplius Trel., P.heraldii Trel., Piper heraldii var. cocleanum Trel., P. perlongipes Trel) . (Piperaceae).</u>

<u>Mex: Acoyo, acuyo, cordoncillo, cordoncillo blanco,</u> hierba anís, hoja de cáncer, hoja santa, momo, yerba santa. Oaxaca: 'ma jóo, ma 'haw, tzon tzko ntko, wo, woo; Puebla: jinan (Totonac). coyoquelite, omequelite, omequilit-dos quelite,tlanepa, xalcuahuitl; Quintana Roo: x-maculan (Mayan); San Luís Potosí: bakanil a iits' (Tenek); Veracruz: aguiyu, alahan, homequelite, totzoay. It is known as tlanepa, or clanilpa in Izucar de Matamoros, tlanepaquelite (Nahuatlisms of tlanecpahquílitl 'fragrant medicinal herb'), hoja santa (a Mexican legend says that the Virgin Mary dried the swaddling clothes of Baby Jesus on a bush of this plant, from which it gets its name).

In Oaxaca, Quintana Roo and Veracruz the most common application of hierba santa is on skin pimples. However, it is used in women's ailments such as inflammation of the vagina, infection of the womb, after childbirth (to help the newborn), as a galactogen and to accelerate childbirth, in this case, the leaves are soaked in brandy or mescal.

It is also used in disorders of the digestive system such as stomach pain or spasm, lack of appetite and constipation. The leaves are the most used part of the plant. In the case of fractures, the leaves are boiled together with the leaves of saffron and herbatoro, a cloth is dipped in this liquid to “choconearse” in the painful part. For scorpion bites, take the decoction of the leaf, sweetened with honey. To reduce fever, take a bath with the water where the leaves were boiled. For diarrhea, pain and inflammation of the stomach and ventures, the leaves are soasadas and oiled and placed on the belly. In bronchitis and cough problems, the juice of the soasadas leaves and buds is given. For espanto, it is given to the person who has it.

Its use is also indicated in diseases such as asthma, laryngitis, acecido, rheumatism, rheumatism, sores, kidneys, for eyesight, purify the blood, snake bites, inflammation, muscle aches, colic, burns, for the navel and give baths to newborns, for the pujo, festering, against intestinal worms, fright, venting, burns. In addition, some authors assign it properties as oxytocic and emmenagogue. Quality of the plant: hot.

In the twentieth century, Maximino Martinez refers its use for: local anesthesia, antiblenorrágico, asthma, bronchitis, dyspnea, stimulant, eupeptic, laryngitis and as an analgesic. Narciso Souza, attributes diaphoretic, diuretic and stimulant properties; for angina, erysipelas, fevers, gout, rheumatism and sores. Finally, the Pharmaceutical Society of Mexico reports it as: balsamic, dyspepsia, stimulant for gastralgia and analgesic.

Highlands of Chiapas

Leaves/stem, infusion to take. Hemorrhoids, weight loss.

In homeopathy the tincture of the whole plant and dilutions are used against asthma, bronchitis, acute or chronic laryngitis, dyspnea and inflammations in general.

Costarica: anisillo, Cow fool, Star leaf, juniapa, koloko.

Leaves topical use in poultices, scabies, headache, abdominal pains.

Guatemala: anisillo

Honduras: Santa Maria

Crushed leaves in topical poultices. Headache, hemostatic in wounds, external inflammations.

Leaves in decoction in rinses. Toothache

Nicaragua:

Leaves in infusion to be taken. Fevers, bruises, headaches.

Panama:

Leaves/stems (dried): infusion to take. Flu, emmenagogue

Pharmacological use

The smooth muscle relaxing activity of a decoction of this plant tested on isolated rat ileum and the absence of antimicrobial activity of this same extract have been demonstrated (Feng 1962; Martínez 1990; Misas 1979; Morón 1992).

In this work we characterized (Monzote 2010) the essential oil of Piper auritum, evaluated its cytotoxicity and determined its antileishmanial activity. The chromatogram obtained by gas chromatography revealed 60 peaks and we found that safrole was the most abundant compound, composing 87% of the oil. The oil was active against promastigotes of Leishmania major, Leishmania mexicana, Leishmania braziliensis and Leishmania donovani with a favorable selectivity index against peritoneal macrophages of BALB/c mice. Piper oil inhibited the growth of intracellular amastigotes of L. donovani with an IC50 value of 22.3 ± 1.8 µg/mL. This study demonstrates the usefulness of essential oils as a promising alternative to treat leishmaniasis.We investigated the effect of hexane, chloroform and methanol extracts of Piper auritum in cell culture system and the effect on streptozotocin-induced type 1 diabetic rats treated for 28 days on physiological, metabolic parameters and oxidative stress. Treatment with hexane extract of P. auritum (HS) significantly reduced food intake, water and body weight loss, as well as blood glucose levels, serum cholesterol, triglycerides and increased HDL-cholesterol. After 4 weeks of HS antioxidant enzyme administration such as SOD, CAT, GSH, GPx, were determined in the pancreas. These enzymes were significantly increased compared to those of control diabetic rats and normal animals. For all estimates, the results of the HS-treated groups lead to a restoration of the defense mechanism. The treatment also improves the level of pancreatic TBARS-reactive substance and serum NO and iNOS. To determine insulin-releasing activity, after extract treatment, serum and pancreas sections were processed to examine insulin-releasing activity using an immunocytochemistry kit. The results showed that administration of hexane extract (200 and 400 mg/kg) showed a significant increase of insulin in serum and pancreatic tissue. Administration of streptozotocin decreased insulin secretory activity compared to intact rats, but treatment with HS extract significantly increased beta-cell activity compared to diabetic control rats. The extract decreased serum glucose in streptozotocin-induced diabetic rats and increased insulin release from pancreatic beta cells. In cultured RIN-5F cells, we examined whether hexane extract of P. auritum would protect pancreas-derived β-cells from oxidative stress. Furthermore, HS could protect pancreatic β-cells from oxidative stress induced by advanced glycation end products. (Perez Gutierrez 2012) From these results, it is suggested that HS shows an anti-diabetic effect by stimulating insulin-dependent pancreatic β-cells and protecting them from oxidative stress induced by advanced glycation end products.

Antidiabetic effects were investigated with C-glycosylflavone against advanced glycation end product (AGE) in vitro and in vivo. Chromatographic fractionation of the MeOH extract of P. auritum led to the isolation of the known 5,3′,4′-trihydroxy-7,8-dimethoxy-6-C-[β-D-xsilopyranosyl-(1 → 2)] -β-D-glucopyranosyl flavonoside (1). The structure was established on the basis of spectroscopic methods. The effects of 1 against advanced glycation end product (AGE) were investigated in vitro and in vivo in a mouse model of streptozotocin (STZ)-induced diabetes. Flavonoids significantly reduced the formation of fluorescent (AGE, AOPP), non-fluorescent (Nε-CML) and fructosamine level in the AGE-BSA system. It also prevented the oxidation of protein products, which was demonstrated by reduction of protein carbonyl and increase of thiol group, decreased the level of β-crossover structure of amyloid and suppressed protein carbonylation in the MGO-BSA model. Oral administration of 1 produced a significant decrease in serum glucose, inhibited GlyHb formation, prevented circulating AGE level, attenuated AGE accumulation in liver and kidney and reduced lipid accumulation possibly due to improved β-cell function in diabetic mice. Findings, indicated that 1 may alleviate these parameters through various mechanisms with marked antiglycation activity. Flavonoids participate in the early and intermediate stages of glycation, leading to a reduction of AGE production in the late stage. The results indicated that 1 improves AGE formation in type 2 diabetes (Perez Gutierrez 2022).

The aim of the present work (Estrada Reyes 2013 was to evaluate the effects of organic and aqueous compounds of Piper auritum leaf extract on the Central Nervous System (CNS) in mice. For acute toxicity evaluation, the LD50 of all extracts was determined according to Locke's method the action of organic and aqueous extracts of P. auritum leaves were tested in sodium pentobarbital induced sleep, hot plate and open field tests. Anxiolytic-like effects were determined by burying behavioral models and perforated board. In this study we demonstrate for the first time that both organic and aqueous extracts of P. auritum leaves possess antinociceptive effect while at higher doses the organic extracts exert a depressant effect on the CNS in mice. The aqueous extract showed antinociceptive and anxiolytic-like effects in the tested model, without affecting the locomotor activity of experimental animals. Acute toxicity tests show that ingestion of extracts of different polarities of P. auritum does not involve health risks. The present study supports, in part, the uses of P. auritum leaves as a tranquilizer, sedative, and as a remedy for pain relief in traditional Mexican medicine.

The main objective of this work was to characterize the toxicity of the venom by determining the Minimum Edema Dose (MED), Minimum Coagulant-Plasma Dose (MCD-P), Minimum Hemorrhagic Dose (MHD) and to determine the neutralizing power of Total Ethanolic Extract (TEE) of PA leaves on the localized and systemic effects caused by the venom of the snake Bothrops rhombeatus. To begin with, the minimum dose that causes edematous, coagulant and hemorrhagic activities was determined. The protocols investigated included coagulant and edematous activities elicited by Bothrops rhombeatus venom that were neutralized by PA TEE. The MCD-P was found to be 0.206 ± 0.026 µg, the MED was the same 0.768 ± 0.065 µg and the MHD was 3.553 ± 0.292 µg, which are different from the reports for Bothrops asper and Bothrops ayerbei. Next, a phytochemical screening was performed to TTE where mainly triterpenes, steroids, coumarins, saponins and lignans were identified. Also present were 43.733±2106mg AG/g ES of phenols, which are secondary metabolites probably responsible for the neutralization of coagulant and edematous activity at 2363.870µL and 1787.708µL of extract/mg of venom, respectively. As a comparative parameter, the effective dose of the NHI antivenom was used as a comparative parameter. In addition, we determined the toxicity of PA ETE on Artemia salina, being moderately toxic at 6 and 24h, while PA essential oil at the same hours of observation is in the extremely toxic range. The results reflect that P. auritum extract has an anti-inflammatory effect similar to that of NIH serum. It could be used as a complement to NIH antivenom, using them together so that it contributes to effectively reduce inflammation and the socioeconomic impact generated by the permanence of a snakebite victim patient in health centers. (Muñoz Gomez 2019)

The objective of our work was to determine the chemical composition and evaluate the antifungal activity of the essential oil of the aerial part of P. auritum obtained by hydrodistillation on Fusarium oxysporum and Fusarium equiseti isolated from Capsicum chinense. The antifungal activity was evaluated by direct contact and poisoned food tests, and the minimum inhibitory concentration (MIC50) and maximum radial growth inhibition (MGI) were determined. Identification of the oil metabolites was performed by direct analysis in real-time mass spectrometry (DART-MS). By direct contact, the essential oil achieved more than 40% inhibition on Fusarium spp. The concentration of 8.4 mg/mL showed the highest inhibition on F. oxysporum (40-60 %) and F. equiseti (>50 %). The MIC50 was 6 mg/mL for F. oxysporum FCHA-T7 and 9 mg/mL for F. oxysporum FCHJ-T6 and F. equiseti FCHE-T8. DART-MS chemical analysis of the essential oil showed [2M-H]- and [M-H]- adducts of high relative intensity that were mainly attributed to eugenol and thymol/p-cymen-8-ol. The findings found in this study show a fungistatic effect of P. auritum essential oil on Fusarium spp. (Chacon 2021).

In the analysis of antifungal activity, chemical compounds such as safrole and dillapiol obtained from the essential oil of P. auritum and P. holtonii, respectively, have been reported to have a direct fungitoxic effect in vitro against Botryodiplodia theobromae and Colletotrichum acutatum, and it was found that the highest values of inhibition of mycelial growth of both fungi were obtained for dillapiol, compared to safrole [Vizcaino Paez 2016. There are reports testing different phytoextracts obtained from P. auritum on different phytopathogenic fungi, including the genus Fusarium. The essential oil of P. auritum has been tested against Alternaria solani, inhibiting mycelial growth at seven and fourteen days [Daurte 2013]. In another study, total inhibition (fungicidal effect) of mycelial growth of Curvularia lunata, Sarocladium oryzae and Bipolaris oryzae was reported at 96 h [Daurte 2014]. In a previous report, it was observed that the essential oil of P. auritum leaves had an inhibitory effect on the growth of F. oxysporum f. sp. comiteca (75.32%), F. oxysporum f. sp. tequilana (86.57%) and F. solani f. sp. comiteca (63.36%), indicating a fungistatic effect [Drate 2013]. While in another report, the essential oil of P. auritum caused a total inhibition of the growth of F. solani (isolates F2 and F5) and F. redolens (isolates F3) [Chacon 2020].

The antioxidant and antimicrobial effects of ethanolic extracts (HSEE) of Hierba Santa (Piper auritum Kunth) from plant powder of particle size 425 µm (EPA) and 850 µm (EPB) were evaluated on raw and uncooked beef patties stored for 9 days at 4 °C, as well as raw-frozen and raw-frozen-cooked beef patties stored for 90 days at -20 °C. Four treatments were prepared, including control (no extract), sodium ascorbate solution (NaASC at 500 mg/kg), MEPA (meat with EPA HSEE at 750 mg/kg) and MEPB (meat with EPB HSEE at 750 mg/kg). kg). The in vitro antioxidant and antimicrobial activities, as well as the total phenol, chlorophyll and carotenoid contents of HSEE were studied. The chemical composition in the beef used for the patties was evaluated. Beef patties were evaluated for thiobarbituric acid reactive substances (TBARS), pH, color, metamyoglobin content, and microbial load. The results indicated that HSEE showed in vitro antioxidant activity and its incorporation in beef patties inhibited lipid oxidation compared to NaASC, while pH was below the maximum permissible limit. However, neither EPB nor EPA was effective in reducing the total bacterial count (TBC) in raw beef patties. Therefore, HSEE could be recommended as a natural antioxidant in beef patties. (Trujillo Santiago 2021).

Toxicity

A low acute toxicity of an aqueous extract of the plant was observed in mice, administered orally (at a dose of 9g/kg no deaths occurred) and administered intraperitonially a mean lethal dose of 2g/kg was obtained. The extract obtained from the leaves did not show genotoxicity against the Aspergillus nidulans strain.

A low acute toxicity in mice was detected in the leaves, so it is necessary to avoid the frequent use of this plant especially when it is indicated when taken, since it has been proved that safrole, a component present in the essential oil obtained from the leaves, presents a carcinogenic action (Martínez 1991; Torre déla 1991).

Food use

It is frequently used in Mexican cuisine, especially in tamales in certain areas of southern Mexico, where fish or meat is wrapped in its fragrant leaves to cook delicious dishes, such as tapixtle and pilte in southern Veracruz and Tabasco. In Guatemala it is used in the Mayan-q'eqchi' region to prepare pachay, which is basically fish with chili and achiote, wrapped in Santa Maria leaves, to give it another wrap in banana leaves, maxan leaves can also be used, it is buried and a bonfire is made on top of which a fish soup is cooked. When the soup is ready, the fish is dug up and the pachay is steamed, this is an authentic pre-Hispanic recipe. In addition to being used as a condiment, the leaves are used as a stomachic, analgesic and stimulant in traditional medicine. The particular flavor of acuyo has been compared to eucalyptus,licorice, sassafras, anise, nutmeg, mint, tarragon and black pepper.(Katzer 2012, Davidson 1999) It is the essential ingredient in mole verde, a green sauce native to the Oaxaca region of Mexico.It is also used to flavor eggs and soups such as pozole. In central Mexico, it is used to flavor chocolate drinks. In southeastern Mexico, a green liquor called verdín is made from hoja santa. In some regions of Mexico, goat cheese is wrapped in hoja santa leaves and infused with its flavor.

Pas

The leaves contain an essential oil in which the monoterpenes borneol, its acetate, delta-cadinene, camphene, camphor, car-3-ene, 1-8 cineol, para-cimen-8-ol, para-cymene, limonene, linalool, myrcene, alpha- and beta-phellandrene, alpha- and beta-pinene, sibinene, alpha- and gamma-terpinene, terpinolene and alpha-thujene have been identified; the sesquiterpenes acadin-1-4-diene, beta-bisabolene, beta-bourbonene, batacaryophyllene oxide, alpha-copaene, alpha-cubenene, delta-elemene, humulene, murolene, spatulene; and the phenyl compounds elimicin, eugenol and safrole. Other components detected in the leaf are the flavonoid 3'-hydroxy-4'-7-dimethoxy-flavone, the sterol beta-sitosterol and the diterpene trans-phitol. In the root, the isoquinilone alkaloids cepharadiones A and B and the phenyl compounds 1-allyl- 2,3 -(methylenedioxy,-5- methoxy-benzene and its propenyl derivative, dilapiol and safrole have been identified (Ampofo 1987; Gupta 1985; Hansel 1975; Nair 1989; Osear 1983.).

Piper auritum leaf oil contains a relatively high concentration of safrole, about 70%. Some of the other 40 constituents found in lower amounts were α-tujene, α-pinene, camphene, β-pinene, myrcene, and limonene (Gupta 1985). Aporphine alkaloids, such as 1,2,3-trimethoxy-4,5-dioxo-6a,7-dehydroaporphine(Hansel and Leuschse, 1975; Pérez-Gutiérrez et al.,2013), flavonoids such as 5,3'-dihydroxy7,4'dimethoxyflavone and phenylpropenoids have been isolated, in addition to eugenol (Nair et al., 1989;Ampofo et al., 1987; Gupta and Arias, 1985).

<u>Plantago major L. (=syn. Plantago asiatica L.; Plantago erosa Wall; Plantago lanceolatum Link; Plantago loureiri Roemer & Schultes; Plantago mexicana Link.) (Plantaginaceae).</u>

Generic name derived from plantago = very principally, name of several species of the genus Plantago L. (Plantaginaceae) -related to the Latin word planta, -ae f. = "plant of the foot"; from the shape of the leaves, so they say-. Thus, Ambrosini (1666) tells us: "It is called Plantago by the Latin authors, a word they take from the plant of the foot (because of the width of its leaves, which resemble the plant of the foot; and also because the leaves have lines as if made with a plow, similar to those we see in the plant of the foot)".

Mex: **<u>llantén, cinconervios,</u>** Anten, antenna, cancerina, chile de pato, dianten, diasten, hierba del manzo, hojas de lantes, lanté, lantén, lanter, lantey, lengua de vaca, lenteja, lentem, liante, liantel, mucilago, planten, sábila, valeriana, yantén. Chiapas: yok tje; Michoacán: yurés xukuri (Purhépecha); Puebla: snoktail (Totonaco); Yucatán: xiw kin.

At the national level, most of the uses reported for plantain correspond to digestive ailments, however, two groups of properties can be distinguished in a general way that are explicitly attributed to it: in the first one it has an anti-inflammatory action and in the second one as an analgesic; in the rest of the ailments, one or both functions are suggested, but they are not specified. As a disinflammatory it is used in diverse ailments, mainly in inflammation of the stomach or abdomen in Chiapas, Distrito Federal, Puebla, Tabasco, Tlaxcala and Veracruz. In this case the infusion of the leaves is drunk, varying the schedule and quantity, it can be as time water, three times a day and on an empty stomach or at night. In Chiapas the infusion is used "fogueando" locally. In addition, it is used to relieve mumps in Chiapas and Veracruz; festering sores, bumps, wounds and eye inflammation in Michoacán and Morelos; and swellings or inflammations (unspecified) are mentioned in Morelos, Puebla and Veracruz. The treatment used for inflammations or apparent lesions, in general is the external and local application of the decoction of the leaves by means of compresses, fomentations, poultices, washes or directly of the crushed leaf, alone, smeared with some oil or ointment or rubbed directly with alcohol. In Chiapas, it is used as an anti-inflammatory for bruises, wounds, festering sores and mumps, the decoction of the leaves is applied in poultices or fomentations in the affected area and, for abscesses, a poultice is applied with the crushed leaves. In Durango, for pimples and sores with pus, the leaf is applied directly alone or with ointment to extract the accumulated pus. In Michoacán for wounds and sores, after washing them, they apply cold compresses with the infusion of the leaves. In Puebla, they smear the macerated herb with oil on the grains; to reduce bruises they rub the plant directly with alcohol; they wash the feet with the decoction of the plant when there are chilblains; and for inflammations in general (it is not specified what type), they drink the decoction of the leaf with chamomile (Matricaria recutita) and barquilla (Rhoeo spathacea) as a water of time.

It is used as an analgesic in various ailments. It is administered orally for stomach pain in Durango, Tabasco and Veracruz, for kidney pain in Morelos and Puebla, for headache in Michoacán and Veracruz. Locally, the fresh leaf is applied to relieve toothache in Durango and Veracruz; and to treat foot ailments, baths are given with the decoction of the plant in Guanajuato. In Chiapas, the Tzotziles apply it locally for bone pains, rheumatic pains and arthritis.

As for other ailments related to the digestive system, it is widely used in many parts of the country for the treatment of dysentery, amoebic dysentery or amoebas, as well as for diarrhea and yellow diarrhea. In these cases, it is customary to drink the decoction of the plant, whole or only the leaves or flower, sometimes combined with another plant or substance, on an empty stomach or as time water, sometimes for a week. In Durango, they drink a preparation of the inflorescence ground and boiled in milk, alone or with guava leaves, grains of raw rice and mint. In the Federal District and Puebla, they add lemon juice (Citrus aurantifolia) to the decoction when it comes to cure dysentery. In the Balsas basin, between Michoacán and Guerrero, they prepare a syrup by soaking in wine: unto, ground raw leaves and cooked leaves of the plantain. In some regions the whole plant is boiled and used as a drink to relieve constipation (V. constipation of the belly). In Durango, Distrito Federal and Veracruz, it is used in some parasitosis, for stomach inflammation caused by worms or intestinal parasites, Ascaris lumbricoides, that is, as an anthelmintic. It is also used for bile and biliary disorders in Sonora and Veracruz, for mouth ulcers (aphthae) in Morelos and Sonora and against caries, gastritis, ulcer and vomiting.

Among Mixes, Zapotecs and Totonacs, they drink it in tea to treat dysentery either alone or mixed with myrtle, guava, chamomile, peppermint, cinnamon and rosemary or combined with patent medicines such as terramycin, enterobioform, sulfadiazine or with lime, coca cola or alka seltzer. In addition, they use it to treat fear. The Tzotzil people know it as yole the' and use it in tea as time water, for diarrhea and stomach illnesses; in acute cases as an adjuvant for internal healing, the leaves are usually heated in a comal and applied to the stomach and belly area.

It is also frequently used externally, in various skin conditions such as sores in Michoacán and Veracruz; sores with pus, pimples, pimples with pus or infected pimples in Puebla, Durango and Zacatecas. In skin abscesses, chilblains and suppurations in the skin, itching in the anus, chafing and in general for skin diseases or infections, in Michoacán and Veracruz. Other types of injuries in which it is used are for bruises or contusions in Morelos and Sonora, wounds, burns and scorpion stings. Plantain is used in some respiratory conditions such as angina in Chiapas and Veracruz; cough in Tabasco and Veracruz; as well as asthma, bronchitis and catarrh. It is also used in urinary problems, in addition to the kidney pain mentioned above, and in ocular ailments such as carnosities (V. clouds), lagañas, watery eyes and eye inflammation, mainly in Michoacán, Puebla and Tlaxcala. It is also used to stop external or internal hemorrhages in Guanajuato, Michoacán and Tlaxcala. It is useful to reduce fever in Morelos, Puebla and Tlaxcala and to treat cancer in Puebla and Veracruz. It is used in the treatment of vaginal infections by washing, in Chiapas and Veracruz, and as an anti-abortive. It is also used in cases of diabetes in Morelos and Veracruz, and for growth problems in children. Finally, in Quintana Roo it is used for cleansing and to treat the evil eye.

In the XVI century, the Florentine Codex mentions that it "cures mumps and throat inflammations". In the same century, Francisco Hernandez reports it only as edible. Gregorio Lopez, in the XVII century notes: "useful to sores, stop blood, carbuncles, and scabs. Against dog bites, against inflammations, burns, diviesos and lamparones. For dysentery, asthma and coral gout. The drink simenta is against the blood of the chest, some bring the root tied to the neck against lamparones. Put on the forehead and temples it restores the blood of the nostrils. John of Esteyneffer, in the early eighteenth century describes its uses as "antidysenteric, vulnerary, for burns, bruises and mouth ulcers. The infusion with rose water is useful in eye inflammations. Also for cholera morbus, in loanda disease, liver distemper, worms". Later, in the last decade of the same century Vicente Cervantes mentions that it is astringent and vulnerary and is used in burns, bruises and mouth ulcers. At the end of the XIX century, Francisco Flores comments that it was believed to be a sedative for pains of the whole body, and in the second decade of the XX century, Alfonso Herrera points out that it is used as an astringent and is used in vulgar medicine as a febrifuge and against snake bites. Later, Maximino Martínez describes it for aphthous ulcers, as an antidysenteric, and caustic, in bruises, for eye diseases and vulnerary. Finally, the Pharmaceutical Society of Mexico describes it as antidysenteric and emollient.

Tarahumara(Chih): rorogochare, rejogochachi, rorogochi

Whole plant in infusion to be taken. Constipation, heartburn, canker sores, blood and bladder cleanser, eye infections, expectorant, diarrhea.

In Western Europe, it was used in ancient times against inflammations such as hemorrhoids and diseases of the respiratory system [1758], or administered to anemic young people. The flower head of the inflorescence is much richer in mucilage and has laxative properties.

Dominican Republic, Caribs: llantén, miye'.

Leaves in decoction in eye drops for conjunctivitis, temporary blindness.

Trinidad and Tobago: miye', plantain, Dominican Republic: plantain.

Leaves in infusion and/or maceration in eye baths for conjunctivitis.

Plantago major is called “Lesan-ol-haml” or “Barhang” in traditional Persian medicine (TPM). Researchers believed that Plantago major has existed for almost 4000 years, especially in Europe, America and Asia. The reality of temperament existed in traditional medicines such as TPM, Greek, European, Arabic, Indian and Chinese. According to TPM, Plantago major has a cold, dry temper and has been used to decrease inflammation and bleeding.

TPM practitioners believed that the temperament of Plantago major is cold and dry. Basically, the cold temperament is due to the water and soil elements, and the soil component leads to its dry and astringent temperament. According to traditional medicine experts, temperament means the dominant quality of the compound object, and it is made of the interaction of four basic qualities (hot, cold, wet and dry). From this point of view, both individuals and plants have certain temperament. Temperament plays an important role in maintaining the ideal healthy state of an individual. To determine the temperament of plants, you should check the effect of the plant after entering the human body. After the consumption of plants, if the human body is warmer, colder, drier or wetter than before, the temperament of the plant is warm, cold, dry or wet, respectively. After the use of P. major, the body temperament had a cold and dry quality. The dryness and astringency in the seed and root is greater than in the leaf. As a result, the seed of Plantago major is more useful in stopping bleeding, especially if roasted. In traditional medicine, the mucilage is one of the important parts of this plant and in addition to the use of medicines, it is used as a binder in the preparation of some pharmaceutical forms such as “habb” or tablets.

The use of Plantago to treat various diseases dates back thousands of years. The oldest known account of Plantago is found in the “Materia Medica” or “Hashayesh” in Arabic, which was written by “Pedanius Dioscorides” (40-90 AD), a Greek botanist. There is a picture of

Dioscorides and Plantago major in Materia Medica that was painted by Dioscorides. After the advent of Islam, distinguished experts and scientists such as Rhazes, Avicenna and al-Biruni appeared in Islamic medical schools. They presented herbs and discussed the properties of each herb such as P. major, including: its temperament, habitat, indications, contraindications, duration of action, effectiveness, toxicity, dosage, types of preparations, and side effects.

Neurological uses This plant has been used to cure epilepsy alone, either exclusively, or with other herbs such as lentils cooked with plantain leaves, which in traditional Persian medicine is called "Adasiyyat". It also helps to improve nervous pains such as earache by using mucilage drops or massages, or nasal inhalation.

Ophthalmic effects Plantago major is effective in the treatment of many eye diseases, including diseases of the choroid, day blindness, conjunctivitis and eye ulcers. The leaf juice has been used as drops with other herbs or independently in addition to the oral form. (Ashili 2000, Razi 2002, Arzani 2007).

ENT effects Plantago major is advised for toothache, earache, halitosis, oral lesions, mouth sores, epistaxis, hemoptysis, loose teeth, gingivitis and tonsillitis by gargling with the juice of the leaves or its decoction, or throwing it in the ear and applying semi hot dry leaves in the location (Ashili 2000, Razi 2002, Arzani 2007).

Lung effects Plantago major can treat hemoptysis, asthma, tuberculosis, lung and plural lesions and was used as a decoction and incense. The leaf extract was found to be suitable for the treatment of lung and plural lesions. Taken orally with honey is the most desirable dosage form for the treatment of pulmonary disorders.

Gastrointestinal effects Plantago major is effective in upper and lower gastrointestinal bleeding, hematemesis, dysentery, hemorrhoids, stomach pain, intestinal ulcers, dyspepsia and constipation by ingesting the extract and baking the leaves with salt and vinegar or enema of the extract or its mucilage.

Hepatic and splenic effects The extract and seed or root of Plantago major has been widely applied as a liver tonic and is recommended in obstructive diseases of the liver and spleen.

Urogenital effects Plantago major is prescribed in uterine warts, uterine ulcers, menometrorrhagia and polymenorrhea in oral or vaginal form Due to the diuretic effect of Plantago major, it is also recommended for urinary retention, hematuria and bladder and kidney pain. For this purpose, it was used as a poultice or oil on the skin, locally.

Dermatological effects Plantago major is used in different types of wounds and skin diseases in TPM such as deep wounds, purulent wounds, chronic and progressive wounds, malignant wounds, fire burns, erysipelas, progressive blisters, pruritus, irritant urticaria and fistula, by sprinkling the plantar powder on the wound or its poultice with salt or separately. It is also used for skin ulcers of the head and face in the same way (Ashili 2000, Razi 2002, Arzani 2007)).

Pharmacological uses

Experimental evaluation of the cytotoxic and antitumor properties of various types of extracts of the aerial parts of the plant have yielded some positive and some negative results. Thus, an extract prepared with the leaves gave cytotoxic activity in experiments with cell cultures of CA Ehrlich-solida and Sarcoma 180 (solid), as well as an ethanolic extract (95%) prepared with the leaves and which was administered daily for five days to mice intraperitoneally (0.20mg/kg), showed antitumor activity against tumors of the Sarcoma 180 (ascites) type.

The healing accelerating effect of several chromatographic fractions obtained from the leaves has been experimentally demonstrated in rabbits. An ethanolic extract of the leaves was positive in experiments to evaluate its cholesterol-lowering effect in rabbits administered up to 500mg/kg, although this activity was classified as weak.

The aerial parts of the plant added at 40% in the diet administered to female mice, caused a weak growth retarding activity in the treated animals for 22 days. While a dichloromethane extract prepared from the whole plant showed weak antimalarial activity against Plasmodium falciparum at a dose of 49mcg/ml. Several studies report that the administration to rats of an aqueous extract of the leaves, intragastric and intravenous, caused a decrease in blood pressure in experimental animals, while the evaluation of this same aqueous extract of leaves in spiral muscle of guinea pig trachea caused a smooth muscle relaxant effect, even in the presence of serotonin, histamine or acetylcholine. On the other hand, a dose of 50 mg/kg administered subcutaneously in rats with the pylorus ligated, caused a decrease in the number of ulcers and ulceration index, and a decoction of P. major leaves, administered to rats nasogastrically at a dose of 1 g/kg, gave diuretic activity. A clinical trial conducted with human volunteers in Thailand, tested the effect of a decoction prepared from the whole plant in dissolving kidney stones. The three patients reported in this trial were treated for two to six months, twice a week with a dose of 97.5 g/day (dry weight of the plant). It has been reported that a tincture prepared from dried leaves had a positive antibiotic effect against Bacillus subtilis, Escherichia coli and Staphylococcus aureuss, isolated from patients with conjunctivitis.

Other activities evaluated in human clinical trials for which positive responses of biological activity have been obtained are: its smoking deterrent effect, tested in the form of an aerosol prepared from the whole plant; the antipruritic activity of the leaves, demonstrated in human volunteers suffering from dermatitis caused by poison ivy; as well as the antihemorrhagic activity and the estrogenic and progestagenic effects of the seeds. The laxative effect of the seeds of the cruenta variety of this species was proven in human adults treated orally with a dose of 0.5 g of seeds/person (Abraham 1983; Arroyo 1963; Cáceres A. et al. 1987 and 1987b; Dornberger K. and Lich H. 1982; Duckett S. 1980; Estévez A. and Lich H. 1982; Duckett S. 1980; Estévez A. and Lich H. 1982). 1980; Estevez A. et al. 1976; Fazal U. 1979; Fernandez M. and Nieto A. 1982; Gaw H. and Wang H. 1949; Maksyutina N. et al. 1978; Manil P. 1949; Mironov 1983; Morton J. 1981; Nemity W. 1970; Robineau L. 1991; Suganda 1983; Wasicky R. 1961; Weenen 1990; Yu L. and Xu Q. 1989).

Modern research demonstrated the cytotoxic effect of methanolic extracts of P. major on cancer cells. The human cells corresponded to renal adenocarcinoma (TK-10), breast adenocarcinoma (MCF-7), and melanoma (UACC-62). The effects are attributed to iridoids and flavonoids (Galvez 2018).

Immune-enhancing effects Methanol extracts of P. major leaves increase the creation of nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and stimulate lymphocyte proliferation, thereby producing activated macrophages in a variety of cytotoxicity such as nitric oxide, TNF-α, and lymphokines. As a result, it can prevent the development of tumors and infections (24). Plantago major shows immunomodulatory activity, increasing lymphocyte proliferation and interferon-γ secretion at low concentrations (< 50 μg/ml), but at high concentrations it can inhibit this property (< 50 μg/ml). Hot water extracts of Plantago major can help ameliorate leukemia, carcinoma, and viral infections (Chiang 2003).

Hepatoprotective effects In an animal model study, Plantago major seed extract exhibits hepatoprotective activity whereby alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels showed a reduction (Türel 2009, Atta 2006).

Gastrointestinal effects Due to the anti-inflammatory effect of Plantago major, it can be used to treat endoparasites and stomach problems in animals. The polyholozidic fraction separated from the leaves and seeds of some Plantago species (Plantago major, media, lanceolata) accounts for its gastroprotective action, and a laxative effect was obtained with higher doses of Plantago major (Gomez Estrada 2011, Hriscu 1989, Lans 2007). The seeds of the plant have a high gastroprotective effect compared to the leaves, which may be due to the high mucilage content. A water immersion stress ulcer model was used in rats to test the ability of the plant extract to inhibit ulcers. Gastric acidity and gastric fluid decreased significantly with the extract, which may be due to inhibition of gastric acid secretion and increased mucosal defensive factors (Atta 2005, Lima 2011). On the other hand, Plantago leaf extract decreased duodenal motility and also had an antidiarrheal effect on oral administration (Atta 2005). Plantago major seeds are recommended for inflammatory bowel disease (IBD). Although oral administration of leaf extract can decrease gastric ulcers, seed extract has no effect. But both seed and leaf extracts can also decrease total acidity (Atta 2005).

Lung effects Plantago major inhibits mast cell degranulation and can be used to treat asthma and allergic diseases (Ikawati 2001, Matev 1981). It protects against pneumococcal infection in mice and treatment of chronic bronchitis (Hetland 2000).

Urinary effects Plantago major has diuretic effects (Dioan 1992) and may also inhibit angiotensin converting enzyme activity (Nhiem 2011). Another study on Plantago major extract showed that it is more efficient than allopurinol and potassium citrate in inhibiting calcium oxalate crystal size in vitro and can be consumed to improve urolithiasis (Aziz 2005).

Dermatological effects Plantago major is an effective herb in the treatment of acute urticaria (Yazdian 2014). Ursolic acid, oleanolic acid, and α-linolenic acid are three major constituents of Plantago that have shown inhibitory effects on COX-2 catalyzed prostaglandin production. Luteolin (one of the flavonoids) also has the ability to suppress leukocyte migration and inhibit mast cell degranulation, which together can be considered as treatment strategies against urticaria (Yazdian 2014).

Antihypercholesterolemia, antiatherosclerosis and hypoglycemic effect Plantago major leaves can inhibit the progression of atherosclerosis and hypercholesterolemia in animals through the lecithin/cholesterol ratio (Angarskaya 1963). The seeds of Plantago major have a hypoglycemic effect in mice (Alracon Aguilar 1998). Plantagoside and its aglycone in

Plantago major seeds inhibit protein cross-linking glycation and have potential beneficial applications in the prevention of diabetic complications (Matsuura 2014).

Antinociceptive effects Methanolic extracts of leaves, seeds or aqueous extract of plants have shown anti-inflammatory and analgesic activities through inhibition of prostaglandin synthesis (Atta & El Sooud 2004).

Antioxidant and free radical scavenging effects Cold and hot water ethanolic extracts of Plantago major leaves and seeds have antioxidant activity (Mazzutti 2017, Mello 2015, 2012, Karima 2015). Plantago major contains flavonoids such as luteolin, apigenin, hispidulin and baicalein, which can induce carcinoma cell death. In addition, Plantago extracts have inhibitory and cytotoxic effects on breast adenocarcinoma and melanoma cell lines and these preliminary results could be justified by the cytotoxic activity of the flavone, luteolin-7-O-β-glucoside, the main flavonoid in Plantago species (Stenhaolm 2013).

Anti-infective, antibiotic, antifungal, antiviral, antimalarial and antigiardiasis effect Some types of Plantago major extract were effective in the treatment of fungal, bacterial and viral infections. Antimalarial and antigiardia effects of the plant have also been demonstrated (Chiang 2002, Metiner 2012, Ponce Macotela 1993, Sharma 2016). However, the aqueous extract of Plantago major had slight activity against herpes virus against caffeic acid, which exhibited the highest activity against HSV-1, HSV-2 and ADV-3. However, chlorogenic acid possessed the strongest anti-ADV-11 activity (Chiang 2002). Ethyl alcohol extract showed antibacterial activity against E. coli and Bacillus cereus and acetone extract was effective on bacterial species (Bacillus cereus, Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabilis, Salmonella enteritidis) at different concentrations (Metiner 2012). Plantago major extract also showed acceptable potency against C. albicans (ATCC 66027) comparable to synthetic antifungal agents (Sharma 2016).

Anticancer and cytotoxic activity The cytotoxic activity of Plantago major methanolic extract was evaluated against three human cancer cell lines including human renal adenocarcinoma (TK-10), human breast adenocarcinoma (MCF-7) and human melanoma (UACC-62). Flavonoids, flavone and luteolin are the main factors in cytotoxic activity (Galvez 2003). Plantago major may be partially effective in preventing carcinogenesis (Oto 2011). The cytotoxic activity of Plantago major methanol extract on human transformed cells: HCT-15 (colon carcinoma), SQC-UISO (cervical carcinoma), OVCAR (ovarian carcinoma) and KB (nasopharyngeal carcinoma) has also been evaluated in vitro (Velasco Lezama 2006). . Aqueous and methanolic extracts of Plantago major also stimulate cell proliferation in bone marrow and spleen cell cultures. Although the same number of cells was cultured in both tumor types, the cell population was significantly higher in spleen cultures than in bone marrow cultures. In fact, oleanolic acid and ursolic acid stimulated splenocyte proliferation and enhanced the recovery of the hematopoietic system (Velasco Lezama 2006).

Wound healing effects Plantago major was used to heal wounds and the leaves were used as a wound remedy. The anti-inflammatory action occurs through a complex event linked to tissue damage either by bacteria, physical trauma, chemical, heat or any other phenomenon. In addition, the inflammatory response is the critical protective reaction to this type of injury, characterized by redness, fever, edema (swelling) and pain in the affected tissue (Lima 2011). In an animal study, aqueous extract of Plantago major is recommended as a suitable substitute for silver sulfadiazine, especially when applied at a concentration of 50% in wound healing (Amini 2010). Polyphenols, especially plantamajoside, are considered the main important compounds for wound healing (Zubir 2012).

The adequate use of plantain (plantago major) favorably influences the treatment of first-degree burns in people aged 10 to 20 years - Paucartambo in Peru". The most important conclusions are the following: 1.- Out of a total of 29 (100%) people from 10 to 20 years old, by age, according to sex, the majority are male with 55.2 % (16), followed by female with 44.8 % (20). 2.- The majority of people 48.2% (14) are between 10 to 13 years old, followed by those between 14 to 17 years old, with 34.5% (10), and those between 18 to 20 years old with 17.3% (5). 3.- The majority of people between 10 and 20 years of age come from Paucartambo with 51.7% (15), followed by the annexes of Paucartambo with 31% (9) and another place with 17.3% (5). 4.- The majority of the people 86.3% (25) are single, followed by those married with 10.3% (3), and those with another condition with 3.4% (1). 5.- Of a total of 29 (100%) of the people between 10 and 20 years of age, the majority have a low economic income, with 82.8% (24), followed by medium economic income with 13.8% (4) and high economic income with 3.4% (1). 6.- According to the degree of burns, the majority presented very slight burns with 72.4 % (21), followed by slight burns with 20.7 % (6) and moderate with 6.9 % (2). 7.- The majority of the people 65.5% (19) have an appropriate level of knowledge, followed by moderately appropriate with 24.2% (7) and inappropriate knowledge with 10.3% (3). 8.- According to the treatment of first degree burns, the majority received a favorable treatment with 75.9 % (22), followed by moderately favorable treatment with 20.7 % (6) and unfavorable with 3.4 % (1). 9.- According to the use of plantain, the majority used adequately 72.5% (21), followed by moderately adequate with 24.1% (7) and inadequate with 3.4% (1). (Arzapalo 2019).

Toxicity

It has been estimated that an aqueous extract of the leaf, administered to rats by the intravenous route, presented a mean lethal dose of 175mg/kg body weight.In a study to observe the nephrotoxic activity of the aerial parts of the plant when administered for 22 days to female mice, in the diet in a proportion of 40 %, negative results were observed.(Bergeron J. and Gouler M. 1980; Robineau 1991.).

Food use

Leaves are edible as a salad green when young and tender, but quickly become tough and fibrous as they age. Older leaves can be cooked in stews.The leaves contain calcium and other minerals, and 100 grams (3.5 ounces) of plantain contain about the same amount of beta-carotene as a large carrot. The seeds are so small that it is tedious to collect them, but they can be ground into a flour substitute or extender.

Pas

Particularly the leaves and seeds of plantain, have been the most studied organs of this plant from a chemical point of view. The flavonoids, apigenin, baicalein, herbacetin galactoside, hispidulin, camferol and its ruti-noside; luteolin, myricetin, nepetin, quercetin and two glycorides of quercetin: scutellarein and syringic acid have been detected in the leaves; as well as the monoterpenes aucurbine and two glycorides and the aromatic components: cinnamic acid and various derivatives and chlorogenic and ferulic acids. The seed contains fatty acids common in edible oilseeds, gum, mucilage, a resin and tannins; the monoterpenes aucuboside, melitoside; two mono-terpene alkaloids, plantagonin and indicain; the triterpenes alpha- and beta-amyrin and the sterols beta-sitosterol, stigmasterol and campesterol. The monoterpene speruloside has been identified in the flowers (Andrzejewska E. 1984; Balbaa S. 1.1971; El-Sayed N. H. 1986; Harborne J. B. 1971; Lebedev V. 1980; Maksyutina N. P. 1971; Pailer M. 1969; Swiater L. 1980; Maksyutina N. P. 1971; Mena I. 1974).

Phytochemical studies of Plantago spp. have determined the presence of several metabolites to date; in addition, about 60 secondary metabolites of Plantago herb, including phenylethanoid glycosides, triterpenoids, polysaccharides, phenolic acids and other compounds (Wang 2010, Nemereshina 2015, Mazzutti 2017, El Gawad 2015Goncalves 2016)) such as alkaloids, caffeic acid derivatives, coumarins, fats and oils, mucilages, polysaccharides , sterols and volatile substances have been identified (Akram 2014, Fons 2008, Kuhn 2000). According to a series of studies of various leaf extracts (petroleum ether, methanol, ethyl acetate, n-butanol and aqueous), 51 components were isolated. Most of the constituents in the petroleum ether extract were phytol, benzofuranone, pentanediol and benzenopropanoic acid and in the methanol extract, the diglycerol and glycol group contained organic acids, such as fumaric acid, syringic acid, vanillic acid, p-hydroxybenzoic acid, ferulic acid, p-coumaric acid, gentisic acid, traces of salicylic acid, benzoic acid and cinnamic acid were found. In the ethyl acetate extract, glycerin, benzene and dibutyl phthalate were isolated and in the n-butanol extract, phthalic acid, benzenopropanoic acid and phenol groups were isolated. Finally, ethnophenol, diathioapentene, naphthalenone and glycerin were found in the aqueous extract. In addition, all these five extracts had phenol groups (jamilah 2012).

History

Apparently introduced to the Americas by Puritan colonists, plantain was known to some Native American peoples by the common name “white man's footprint” because it thrived in the disturbed and damaged ecosystems surrounding European colonies. The plant is native to most of Europe and northern and central Asia, but has become widely naturalized in other parts of the world.

Other uses

The mature plant contains flexible, tough fibers that can be used in survival situations to make small cords, fishing line, sutures, or braids [Tilfort 1997)].

Plantago lanceolata L. (=Syn. Plantago decumbens Bernh. ex Rchb., P. dubia L., P. eriophora Hoffm. & Link, P. glabriflora Sak) (Plantaginaceae)

Mex: Siete venas, plantén. Llantén and plantago (Bajío).

Leaves.infusion to take.mildly astringent and emollient, against pharyngeal catarrh.

In Europe, a tea from the leaves is used as a cough medicine. In traditional Austrian medicine, the leaves of Plantago lanceolata have been used internally (as syrup or tea) or externally (fresh leaves) for the treatment of disorders of the respiratory tract, skin, insect bites and infections.

In traditional French herbalism, plantain is first used against all diseases of the respiratory organs and especially in case of congestion of the lungs, fatty cough, whooping cough, pulmonary asthma, even in case of pulmonary tuberculosis to disinfect the respiratory tract. At the beginning of the 20th century, Abbot Johann Künzle (de), a popular Swiss herbalist, wrote that "llanten is used, whatever the species, with the root, the plant with the leaves, the flower and the seeds. It purifies the blood, lungs and stomach as no other plant can do and is therefore indicated for people who are anemic or of poor blood quality, weak of lungs and kidneys, pale and sickly, who have rashes, sores or who cough, who are hoarse, and remain as thin as nails even if they are force-fed like geese" (M. Treben). Treben) Plantain is used in infusion (1 heaping teaspoon of leaves with 1/4 liter of water, leave to infuse briefly), in poultice of crushed leaves or in syrup.

In Central Europe, its fresh leaves or its juice have been used to treat wounds, laryngeal and bronchial ailments and asthma.

Pas

Plantago lanceolata contains phenylethanoids such as acteoside (verbascoside), cystanoside F, lavandulifolioside, plantamajoside and isoacteoside.[Tamayama 1995] It also contains the iridoid glycosides aucubin and catalpol. [Schmitt 1995] These iridoid glycosides make the plant inedible to some herbivores, but others do not bother them, e.g., the chestnut butterfly Junonia coenia, whose larvae eat the leaves of P. lanceolata and ingest the iridoid glycosides to become unpalatable to predators.

Food use

The whole plant is edible (leaves, flowers, fruits, seeds). The young, tender, mushroom-flavored leaves are eaten raw in salads. Older, tougher leaves are eaten cooked in soup or as a vegetable.

History

This exotic plant native to Europe and Asia grows in ruderal environments in cities with temperate climates. It is also a sometimes serious weed in perennial crops, especially alfalfa. It is possibly expanding. Considered as an indicator of agriculture in pollen diagrams, P. lanceolata has been found in western Norway from the early Neolithic onwards, which is considered an indicator of grazing in that area at that time [Hjelle 2006]. This would make sense, as P. lanceolata thrives in open fields where cattle frequently disturb the soil.

In England, children use the plant in a game in which the flower head is “shot” from the stem end; it has been alternately called “1 o'clock gun,” “rifle,” among other names. To play, one would pluck a stem and wrap a loop from the distal end of the stem around the section of the stem closest to the flower head. One squeezes the loop so that it stops behind the flower head and pulls the stem back until the flower head pops out. The stem is slightly springy, so when the flower head separates, (the head) flies out in the direction the stem is pointing like a gun, hence the gun-related names given to it.In Edinburgh, Scotland, this game is called “The 1 o'clock Gun” after the gun that fires every day from Edinburgh Castle. Writer Sean Michael Wilson notes that, “When I was a kid in Edinburgh, we used to use it for a cute game called ‘The 1 o'clock Gun’: we would twist the stem into a sort of loop, pull it quickly (with the left hand pulling sharply back and the right hand moving forward) and then the head of the stem would shoot out.Piitttt! We used to see how far we could go, great fun.” In the West Country of England the same game is called 'cannonballs'. Another game played with the plant in Britain and Ireland is a variation of conkers; a child tries to pluck the flower head from the stem of his friendly rival using his own stem with a quick downward thrust. This pastime is vernacularly known as 'dongers' in Kent and 'Carl doddies' (along with the plant itself) in Scotland.

Sambucus nigra var.mexicana (=Syn. Sambucus mexicana C. Presl and S. canadensis L.) (Caprifoliaceae(/Adoxaceae).

There are several other closely related species, native to Asia and North America, similar to and sometimes treated as subspecies of Sambucus nigra. The blue elderberry or Mexican elder, Sambucus mexicana, is now generally recognized as one or two subspecies of Sambucus nigra subsp. canadensis and Sambucus nigra subsp. caerulea.

Mex: **Sauco**, Cundumbo, cundemba, ocoquihui; Anshiquel (tojolobal), yaga-zulaque (Zapotec), condemba, tengatsi, xomet (Purepecha), cayapa (Zoque), nttxirza and tzirza (Otomí), tsolos-ché (Maya), tokxihuá (Totonaco), xiicsh (Mixe), xómet (Nahuatl dialect), xúmetl (Nahuatl), yah-cuio (Cuicatleca), yutnucate (Mixtec), azumiatl, bixhumi, shauc, shiksh (Martínez, 1979). tengatsi, xomet; San Luis Potosí: sawko (Tenek); Veracruz: azumate, azumatl, toxiwua; Veracruz: toxio (Tepehua), s'auco (Zoque-Popoluca). Chiapas: chuté, chiki té, chijii té (Tzeltal / Tzotzil), sikil anjel (Tzotzil), anshiomel, chihilté, chijii te, cayapa, ocoquihui, shaul;

In Chihuahua, Baja California Norte, Baja California Sur, Sonora, and Nayarit is popular the use of elderberry to treat fever and cough, the latter described as a lung condition, which can occur as a result of cold catarrh, gives a dry and constant cough with difficulty breathing and dry throat". In addition, it is used in various respiratory diseases such as bronchitis: "cold that grips the chest", chest pain, fever and cough. It is also used to treat whooping cough which is defined as a whistling cough, frequent at night and spaced during the day, there is fever, chest pain ("heart") when coughing, difficulty breathing, catarrh, hot and rapid pulse, it makes you sick, there is vomiting when eating, sore throat, chills, white saliva is spit, the lung (chest) and throat feel tight. It is also prescribed in cases of hoarseness, asthma, cold or flu and tonsillitis (tonsillitis). It is recommended in the treatment of digestive disorders such as bile, gall, diarrhea, diarrhea, red dysentery (feces with blood threads, with stomach pain, seats, chills, make pure water and colic), stomach pain, liver and constipation. In skin problems such as dandruff, dissipates rash, hair loss, measles, scabies, chilblains, burns, edema and embarrassment (redness, swelling and small red pimples on the face).

It is also used in inflammatory processes of kidneys, belly, stomach, muscles, skin and gums. As well as in cultural ailments such as burned (referring to children who are impressed to see their mother give birth or some animal, dog or cat; it also refers to adults who are very disgusting and see something nauseating), evil eye, air, bad air or "bad wind", bad post, "strong air" or "scares"; in these cases baths are given with the decoction of the leaves, or the patient is rubbed with the leaves soasadas. Elderberry is also recommended as a purgative, disinfectant and diuretic and used to combat tooth decay, conjunctivitis and infection in eyes and ears, against parasites and rabies. For the heart, muscular pains, wounds, wounds, sores, breaks, rheumatism, cramps, expulsion of placenta, menorrhea, hemorrhoids, blood purification, heat in the face, cooling and alcoholism. For the treatment of these ailments, in general, the flower is the most used part in decoction orally, or in baths, washes, fomentations or rubbing; although the fruit or leaves can also be used ground or rubbed in water, applied locally and sometimes, the decoction of branches or seeds, orally. It should be noted that, in most cases referred to relieve cough, the flower is boiled in milk, sometimes accompanied by prunes, or boiled with sarsaparilla (Smilax sp.) and bougainvillea flowers (Bougainvillea spectabilis) or with five negritos (Lantana camara), Prunella vulgaris, peppermint and wild grape (spp. n/r). For whooping cough, it is used boiled with milk. Mullein (Gnaphalium spp.), eucalyptus (Eucalyptus globulus), elder (Sambucus mexicana), myrtle (Psidium sartorianum), obelisk flower (Hibiscus rosa-sinensis), bougainvillea flower, cuastecomate pulp (Crescentia alata), tejocote (Crataegus mexicana) and capulin bark (Prunus serotina subsp. capulli), is drunk before each meal to treat asthma, or a concentrated decoction is ingested with lumps of salt for alcoholism problems.

Elderberry is part of indigenous magical-religious ceremonies performed to alleviate traditional illnesses. In Amatenango del Valle, Chiapas, when a person falls and injures a bone, the Tzeltal bonesetter takes the sick person and his family to the site of the fall, there he calls out the spirit of the sick person, naming it with prayers until it returns to him. If there are muscular pains he bathes him in the temazcal, sweeping him with the leaves of ihljiteh, elder and may, he places them hot in the affected part, puts the bone in its place and splints the leg with pine board and the leaves. He speaks to the bone saying: “put bone together, heal bone, put bone in place”, repeating these phrases countless times.

The Tzeltal healers perform a ritual to cure the “espanto”, which consists of placing elder, corn, willow and fern, “where the soul has been imprisoned” (susto and ch'ulel). The place is decorated forming an arch of sedge with ferns, fragrant flowers, ears of red corn, some sticks of jul. Candles, willow branches and willow tips, eggs, one to pass in front of the sick person and the remaining ones for the sides are taken. According to the sex of the patient, a hen or a rooster, black in color, is carried. The healer sucks with the mouth the head and the heart and spits out the evil that he transfers to the hen, then throws away the animal, prays and lays the patient with the head towards the sedge arch. He bathes right there in the eye of water and is sprinkled with water pressed from cocoa, guibaj fern leaves, rose petals and grains of colored corn (V. raise the soul). Then a drink of “yerbas de espanto” is given with cider syrup water, marjoram and a sachet of fruit salt. The sick person takes a spoonful daily.

In the highlands of Chiapas, when it is a sickness of the spirit, caused by a fall or any other frightening experience, sometimes the healer goes to the place where the accident occurred and there offers a white candle and a pig tallow candle, places three feathers on the ground and sacrifices a hen to the gods of the earth. After drinking aguardiente with the sick person's family, the healer rings the tecomate to call the spirit and places it on the ground facing the patient's hut, with a handful of ahijilte (elder) branches. If the place where the spirit was lost is distant and unknown or if the illness originated in some event in the life of the animal companion (Vchanul) of the individual, the h'ilol is to call the spirit from the door of the hut in a loud voice and order it to return wherever it is to enter the body of its owner. He guides it through the door and symbolically deposits it on the patient's body, passing the branches three times over the patient's chest to form the cross, at the same time, the healer begs his animal companion to find the patient's animal and help him return to the sacred mountain. Quality of the plant: there is no agreement on this matter. Some authors consider the elder as a hot plant, but some refer to it as a cold plant.

The first reference to the medicinal use of elderberry is found in the sixteenth century, when Francisco Hernandez in his work indicates its usefulness as an antidiarrheal, antiscabies, against bile and as a cathartic. In the Relaciones Geográficas of the same century it is reported that the plant is used as a purgative. In particular, “when the disease is of blood, it is also used for women who have just given birth, it serves as an ointment and takes away the pain”. Later, at the beginning of the XVII century, Francisco Ximenes mentions “it removes the pain born of a hot cause, retains the flow of blood from the nostrils, cures fevers that repeat at intervals evacuating the cause of the damage, removes the pain born of the French disease and heals the cramps and pains of the womb of those who have recently given birth. The vaporizations are very useful for piles, to purge and heals other stomach and belly ailments”. In the same century, Gregorio Lopez mentions its use as a “special purge for hydropics, it also purges phlegm and cholera, against viper bites. It softens secret places of women and heals their indispositions, sitting on it. As a poultice mitigate inflammation fire burns and dog bites, conglutinate deep and cavernous wounds. Composed with other plants, it is used as a remedy for coral gout”.

At the beginning of the 18th century, Juan de Esteyneiffer reports its use for “tullage, itchy molars, drooping bells, dropsy, swelling of the testicles, vessel obstruction, band disease, pujos, phlegmon, chilblains, mange, scabies, tuberculosis, and dandruff”, and almost at the end of the 19th century, the Mexican Society of Natural History mentions it as a stimulant. Francisco Flores, consigns it “to combat cephalalgias, diseases of the nasal cavities and epistaxis. As sancocho it is used as a good sudorific, corrects abundant urine and as a sedative for hemicrania”. For the same years, Eleuterio Gonzáles refers that “it is of very common use as a béquicas sudorific, in colds, bronchitis, anginas, colds. Externally it is used in baths, fomentations and poultices, as emollient and resolving”. He mentions that Berhabe and Sydenham used it as an emmenocathartic in ascites. For the twentieth century, Alfonso Herrera refers that “it has slight medicinal virtues, so it is little used, in domestic home practices, as a stimulant and sodorific. “Later, Paul Stanley, in addition to recognizing it botanically, cites that it is used to relieve headaches. Maximino Martínez indicates its usefulness as an anti-inflammatory, diaphoretic antitussive, stimulant and resolvent. Luis Cabrera, refers it as cathartic, diuretic, for febrile gastric pregnancy and food poisoning. Finally, the Pharmaceutical Society of Mexico describes it as diaphoretic and stimulant.

Tzoltzil (Chps): chijilte', elderberry

Whole plant in decoction to be taken for colds.

Leaves applied hot in topical poultices. Shortness of breath, fatigue, stomach pains.

Leaves heated in fire and rubbed on the body. Total or partial swelling of the body (“Sital chamel”), body aches (“k'ush basil”), antispasmodic in legs and arms.

Leaves in topical poultices with a cloth. Bone pains and fractures.

Leaves in infusion to take. Fever with paralysis (“mu kta k'ok'”).

Maya (Guatemala): B'ajman, Tzoloj-ya'.

Flowers in infusion to take. Digestive diseases, bronchitis, cough, respiratory system diseases, diuretic, depurative, asthma, fever.

Ripe fruits eaten raw or in jam, laxative, purgative.

The black elderberry is part of the traditional pharmacopoeia, at least since ancient times and even for Ayurvedic medicine in India. In the 1st century A.D., Pliny the Elder recommended it against colds and excess mucus, as did the Greek physician Galen in the 2nd century. The native peoples of North America attributed the same properties to the white elderberry

(Sambucus canadensis, whose composition is similar to that of its European cousin). In various regions of the world, the flowers of Sambucus nigra, in herbal teas, were or still are used as a diaphoretic against colds and flu. They remain in use throughout historical times, particularly in the 17th century, the heyday of purgative medicine, and here and there, in the countryside, to the present day.

The bark, leaves, flowers and fruits have different medicinal uses, at least in part. The inner bark of the twigs contains purgative resin, tannin, traces of essential oil, valerianic acid, alkaloids (conicin, sambucin). It is diuretic, laxative, analgesic, sedative and is used to treat dropsy, ascites, anasarca, edema, nephritis, rheumatism. The leaves and young shoots, fresh, have the same uses in decoction; externally, they are vulnerary (after crushing), soothing the bites of vipers by friction and wasps by a decoction, or used as a poultice against sprains, bruises. The flowers, diuretic and laxative when fresh, are very sudorific after drying.

The flowers have antioxidant properties due to the presence of anthocyanin monomers. In everyday life in Bagnes at the beginning of the 20th century, the elderberry (whose patois names for this region were syœu, syœ, sœ or sœu) was used through its fruits (in syrup), its flowers (in infusions and inhaled against colds.) and chills); it was also considered “good for circulation”, and in particular a mixture of Elderberry and Avens was used as a compress to relieve varicose veins (Nicollier 1984).

In traditional European and North American phytotherapy and herbalism, Sambucus nigra flowers and berries are known as a traditional remedy for various types of ailments and diseases and both are commonly used in folk medicine (Kohlmünzer, 1998). They are mainly used to treat common cold-related symptoms, feverish conditions, cough, nasal congestion, mucous discharge and influenza, as well as preventively to strengthen the immune system (Elliman, 1994, Grieve, 1971, Hoffmann, 1990, The ABC Clinical Guide by Elder Berry, 2003). Due to the presence of flavonoids, elder flowers demonstrate mainly diaphoretic, antipyretic and diuretic properties. They obturate capillary walls, improve their flexibility and prevent the infiltration of red blood cells and plasma outside the vessels thanks to the content of compounds (rutin) that have the properties of vitamin P. In addition, elder flowers show anti-inflammatory and antibacterial properties, so they are used as a gargle to treat sore throat or as a compress to treat conjunctivitis. They are most often used as infusions of dried flowers for internal or external application. The fruit of Sambucus nigra, like the flowers, exhibits diaphoretic, antipyretic and diuretic properties, but also acts as a laxative and detoxifier, so elderberries are often a component of herbal mixtures used as a remedy for constipation or to aid in weight loss. In addition, elderberry fruit demonstrates a moderate analgesic effect and can be used as an adjuvant analgesic against migraine, sciatica and neuralgic pain (Beaux et al., 1999, Bown, 1995, Grieve, 1984, Ożarowski and Jaroniewski, 1987, Schmersahl, 1964.)). Not only elder flowers and berries are beneficial to health, but also the bark, root, stem and leaves of Sambucus nigra have been used especially by rural people as medicine or food. For example, elderberry bark is known for its diuretic and slimming properties, while elderberry leaves can help strengthen resistance to infectious diseases (Baytop, 1984, Wójcik, 2002). Today, remedies against cold, flu and other infectious diseases are being developed using fruits or flowers of Sambucus nigra. They are used as components of dietary supplements in the form of syrups, drops, tablets, capsules, lozenges, aerosols, emulsions or suspensions. Frequently reported in the literature is the antiviral activity of Sambucus nigra fruit. A very popular supplement with such properties sold as a prophylactic agent in many countries is the Sambucol preparation, patented in Israel by Dr.

Madeleine Mumcuoglu (Kinoshita et al., 2012, Martens, 2008, Wierzbicki, 2002, Zakay-Rones et al., 2004).

Pharmacological uses.

The presence of antispasmodic activity has been reported in experiments using isolated guinea pig organs (ileum, trachea and aorta). For this purpose, an infusion of the plant prepared with dried flowers was used, measuring then its relaxing capacity on different types of smooth muscle of the animal. It has also been reported, under the same experimental conditions, a positive effect on the stimulation of the isolated guinea pig uterus. The diuretic activity of a decoction prepared with the dried stem of this plant has also been evaluated in rats, but the evaluated action could not be proved. However, uricosuric activity was observed. The antibacterial activity of a tincture prepared from leaves was evaluated, but the results against Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus were negative, as well as against the yeast Candida albicans. The studies carried out with an infusion of flowers, administered intravenously to dogs, did not prove the presence of hypoglycemic and hypotensive activities (Aguilar A. and Zolla C. 1982; Cáceres A. et al. 1987a, 1987b; Meckes. M. and Campos V. 1986; Morton J. 1981.)

In 1986, Commission E, a German government agency, approved the medicinal use of elderflowers for the treatment of colds. In 1999, the World Health Organization recognized elderflower's traditional uses as a diaphoretic (sweat-inducing) and expectorant. In 1995, a double-blind, placebo-controlled clinical trial conducted in an Israeli kibbutz during a flu epidemic concluded that an elderberry extract was significantly superior to placebo in relieving flu symptoms: within two days, 93.3% of elderberry-treated subjects were already seeing significant relief of their symptoms, while 91.7% of those taking placebo took six days to experience similar improvement. In 2002, a pharmacovigilance study focused on 762 pregnant women who during their pregnancy took a preparation containing, among other plants, elderflower. No teratogenic or embryotoxic effects were observed.

Antioxidant activity

Elderberry fruit is characterized by a high antioxidant activity, ranging from 82.08 to 89.25% inhibition in relation to the DPPH radical. The antioxidant properties of elderberries are mainly attributed to the presence of phenolic compounds and are highly dependent on the chemical structure of the molecules and the composition of the individual berries (Pliszka et al., 2005, Rice-Evans et al., 1996, Zheng and Wang, 2003.)). Anthocyanins significantly influence the antioxidant activity of elderberries. With increasing anthocyanin concentration, antioxidant activity also increases, but only up to a certain level above which this parameter starts to fall (Pliszka et al., 2005).

According to Duymuş et al. elderberry extracts show antiradical activity (towards DPPH), but not as strong as ascorbic acid used as a standard. The IC50 value (concentration required to scavenge 50 % of free radicals) was 117 µg/ml for the 70 % acetone extract and 123 µg/ml for the aqueous elderberry extract, while for ascorbic acid it was 8 µg/ml. As for TEAC (ABTS radical scavenging activity) values, they ranged from 0.89 (acidified methanol extract) to 1.96 mmol Trolox equiv./l (70% acetone extract) and the highest value was almost the same as that of ascorbic acid (1.97 mM) . In addition, the TEAC value for the cyanidin-3-glucoside standard was almost the same as that for the aqueous extract (1.87 and 1.85 mM, respectively). Elderberries can also inhibit the oxidation of linoleic acid. The highest inhibition rate (58 %) was observed for the 70 % ethanol extract; however, none of the tested elderberry extracts were as active as the BHT control (Duymuş et al., 2014). A commercial elderberry fruit concentrate showed a lower radical scavenging capacity against DPPH compared to other studied sources of anthocyanins (fresh aronia extracts, blackthorn fruits and strawberries) and natural and synthetic antioxidants (α-tocopherol, BHT and BHA) (Espin et al., 2000). The antioxidant potential of elderberry was also investigated in human colonic mucosal cells cultured in vitro. An elderberry extract at a concentration of 1 mg freeze-dried elderberry powder/ml reduced excessive intracellular reactive oxygen species production by 22 % and oxidative DNA damage by 46 % in colonic cells. In addition, inhibition of oxidant-induced mutagenicity was observed by 26% in Salmonella typhimurium strain. These results indicate that elderberry fruit is able to protect colon cells against the harmful effects of oxidative stress (Olejnik et al., 2016).

Sambucus nigra flowers tend to have higher antioxidant activity than berries and leaves. According to Kołodziej and Drożdżal, TEC50 (time required to reduce the initial DPPH concentration by 50 %) was 23-75 s for flowers, while TEC50 for fruit was 91-133 s. In another study, elderberry flowers exhibited stronger DPPH radical inhibitory activity (91.95-94.15 %) compared to berries (50.25-67.69 %) and leaves (16.76-48.52 %). These values also depended on the alcoholic extraction temperature; in each case, extraction at a temperature of 100 °C resulted in a higher percentage rate of free radical inhibition than extraction at a lower temperature (20 °C) (Dawidowicz et al., 2006, Kołodziej and Drożdżal, 2011). The results obtained by Stoilova et al. demonstrate that elderflower extract possesses higher radical scavenging properties compared to rutin, BHT and BHA used as standards. Elderflower extract showed the highest DPPH inhibition (97.70 %) at the lowest concentration (10 μg/ml) compared to the standards (77.47; 82.40; 89.98 % and 40; 20; 20 μg/ml, respectively) and the IC50 concentration of S. nigra extract for inhibition was the lowest (0.152 μg/ml) compared to the IC50 of rutin, BHT and BHA (14.65; 4.407; 1.120 μg/ml, respectively). Moreover, this extract scavenged highly reactive hydroxyl radicals, thus preventing deoxyribose degradation, more effectively compared to rutin and quercetin (IC50=0.0122; 0.505; 4.61μg/ml, for elderflower, rutin and quercetin extracts, respectively). In addition, elderflower extract showed metal chelating properties, preventing the initiation of hydroxyl radicals, which were also stronger than rutin and quercetin standards (Stoilova, Wilker, Stoyanova, Krastanov, & Stanchev, 2007).

The healing properties of elderberry are mostly associated with the presence of phenolic compounds, which are characterized by strong antioxidant activity and therefore are able to scavenge free radicals and counteract oxidative stress, a factor causing degradation of the human organism, thus contributing to the development of a number of diseases (Gollucke, Peres, Odair, & Ribeiro, 2013). Thole et al. used mass spectrometry and liquid chromatography-mass spectrometry to demonstrate the chemopreventive potential of elderberry. It was found that elderberry fruit extract, or rather an extract fraction that in addition to phenolic compounds included, p. iridoid monoterpene glycosides, phytosterols and sesquiterpenes caused strong induction of quinone reductase and inhibition of cyclooxygenase-2. This indicates antitumor activity of Sambucus nigra fruit, especially the prevention of initiation and promotion of cancerogenesis stages (Thole et al., 2006).

Antibacterial and antiviral properties

The antibacterial activity of elderberry flowers, berries and leaves (aqueous or ethanolic extracts of freeze-dried elderberry concentrates) was studied against 13 nosocomial pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), which is known to be a clinically significant pathogen associated with skin and soft tissue infections. Despite a 100-fold dilution, ethanol extracts of both elderberry flowers and berries exhibited inhibitory activity for most of the tested bacteria, both Gram-positive, such as Staphylococcus sp. or Bacillus cereus, and Gram-negative, such as Salmonella poona or Pseudomonas aeruginosa. Elderflower extracts showed higher antimicrobial efficacy and larger zones of inhibition against a wide range of bacteria, particularly MRSA (17 mm) or Pseudomonas aeruginosa (9 mm), than other extracts. A tenfold diluted aqueous extract of elderberry leaves showed moderate activity against the growth of Bacillus cereus and Serratia marcescens (6 mm), but was not able to inhibit the growth of any crucial nosocomial pathogens (Hearst et al., 2010). Sambucus nigra fruit possesses antimicrobial activity against human pathogenic bacteria causing upper respiratory tract infections. The addition of (Rubini®), a standardized liquid extract of elderberry, at a concentration of 10%, to bacterial liquid cultures decreased the growth of Gram-positive bacterial strains of Streptococcus pyogenes and Streptococcus Group C and G, as well as Gram-negative bacteria Branhamella catarrhalis, by more than 70% compared to control samples. A 20 % concentration of elderberry extract inhibited bacterial growth by 99 % (Krawitz et al., 2011).

The antiviral activity of Rubini® was investigated against two different human pathogenic virus strains, such as influenza A (KAN-1, H5N1) and B (B/Mass), in Madin-Darby canine kidney cell culture (Fig. 1). Treatment with elderberry extract clearly reduced the spread of the size of influenza B virus foci, while the size of KAN-1 foci increased, but their number was reduced compared to the untreated control (Krawitz et al., 2011). It was found that elderberry extract at a concentration of 252 μg/ml caused a 50% inhibition (IC50) of human influenza A (H1N1) virus applied to infect Madin-Darby canine kidney NBL-2 (MDCK) cells, while a concentration of 1000 μg/ml allowed 100% inhibition of infection by this virus. In addition, phenolic compounds from elderberry extract were shown to bind to H1N1 virions, thus blocking their ability to infect host cells. Two compounds that bind H1N1 were identified: 5,7,3′,4′-tetra-O-methylquercetin and 5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl) chroman-3- yl-3,4,5-trihydroxycyclohexanecarboxylate (Fig. 1). Both compounds were synthesized and it was shown that compound 1 achieved an IC50 of 0.13 μg/ml for the inhibition of H1N1 infection, and compound 2 corresponding to dihydromyricetin gave an IC50 of 2.8 μg/ml. Considering these parameters, the effect of elderberry flavonoids related to H1N1 inhibition is comparable to that of known anti-influenza drugs such as Oseltamivir (Tamiflu®) and Amantadine (Roschek, Fink, McMichael, Li, & Alberte, 2009). In another study also using MDCK, it was observed that concentrated elderberry juice could affect H1N1 in the early stages of viral replication: IC50 was achieved at an extract concentration of 720 μg/ml when samples were administered during infections, and at an extract concentration of 3600 μg/ml when samples were applied immediately after infection. In addition, in vivo experiments showed that elderberry effectively suppressed viral replication and could stimulate the immune response. The concentrated elderberry juice was separated into three fractions (low, medium and high molecular weight) which were administered to infected mice. The most effective fraction was the high molecular weight (HM) fraction, which suppressed viral yield in bronchoalveolar lavage fluids (BALF) and lungs. Fraction II, which was isolated from HM and contained mainly acidic polysaccharides, caused an increase in the level of IFV-specific neutralizing antibodies in BALF and serum and also in the level of secretory IgA in BALF and feces. The medium molecular weight fraction, rich in polyphenols, showed lower activity (Kinoshita et al., 2012). In addition, elderberry extracts demonstrate an inhibitory effect on infectious bronchitis virus (IBV), a chicken pathogenic coronavirus, at an early stage of virus infection. Elderberry extract reduced IBV titers by several orders of magnitude, depending on the dose applied. Increasing the concentration of elderberry extract caused a decrease in virus titers and vice versa. In addition, electron microscopy of virions that were treated with elderberry extract demonstrated compromised envelopes and the presence of membrane vesicles. There are data indicating that elderberry extract pretreatment of IBV infection causes damage to the virus membrane and likely renders the virus non-infectious (Chen et al., 2014). The antiviral activity of elderberry bark was evaluated in relation to feline immunodeficiency virus (FIV), which occurs frequently in domestic cats and from the point of view of biological and pathogenic functions is very similar to human immunodeficiency virus (HIV). Elderberry bark extract was shown to have high activity against FIV because it inhibited the formation of syncytia, and the level of inhibition was dependent on the concentration of the extract. A syncytium inhibition level of 100 % was achieved when the concentration of the extract was 500 µg/ml (Uncini Manganelli, Zaccaro and Tomei, 2005).

With clinical trials in mind, a randomized, double-blind, placebo-controlled investigation of influenza A and B virus infections was conducted in Norway in the autumn/winter 1999/2000 season (Fig. 1). The study was attended by humans suffering from at least two influenza symptoms, including fever ≥38 °C and one or more respiratory influenza symptoms. The study used a standardized elderberry extract, Sambucol® syrup. Participants, who were randomly divided into two groups, received 15 ml of the elderberry syrup or placebo four times daily for five days. The effects of the treatment were monitored using a visual analog scale. It turned out that, in the group treated with elderberry syrup, symptoms decreased on average four days earlier than in the placebo group (Zakay-Rones et al., 2004). In 2009, during the spring flu season, a randomized, short-term, double-blind, placebo-controlled clinical trial was conducted with participants who showed three or more flu symptoms, such as fever, cough, headache, muscle aches, runny nose or nasal congestion, of less than 24 h (Fig. 1). Patients were randomly divided into two groups. The first group received 4 slow-dissolving tablets of a proprietary elderberry extract per day (each tablet contained 175 mg of the proprietary elderberry extract) and the second group received placebo tablets. After 48 h of treatment, patients in the elderberry extract-treated group demonstrated a significant reduction in most flu-like symptoms: 28% of patients were free of all symptoms and 60% of patients received relief of some symptoms and had one or two mild symptoms, while the placebo group demonstrated no improvement or even aggravated symptoms (Kong, 2009). The selected antiviral properties of elderberry (with respect to influenza A and B virus) are illustrated in Fig. 1.

Activities on diabetes, obesity and metabolic dysfunctions

Elderberry may be an effective traditional remedy for diabetes and, as such, could be used as a dietary supplement in the treatment of diabetes. It was found that water-soluble compounds included in elderberry flowers could directly stimulate glucose metabolism and promote insulin secretion through clonal pancreatic β-cells. An extract of elderberry flowers (1g/L) significantly increased glucose uptake, glucose oxidation and glycogenesis in vitro in abdominal muscles of mice without added insulin (Gray, Abdel-Wahab and Flatt, 2000). The fruit of Sambucus nigra positively influences the treatment of diabetic osteoporosis. A polyphenolic extract of elderberry improved bone mineral density and reduced body fat in diabetic rats. In addition, serum antioxidant capacity improved in rats treated with the polyphenolic extract as the concentration of reduced glutathione (GSH) was restored to normal. The concentration of malondialdehyde, which is an index of lipid peroxidation level, decreased in serum, resulting in improved osteoporosis status (Badescu, Badulescu, Badescu, & Ciocoiu, 2012). Salvador et al. investigated the effect of supplementation with polar and lipophilic elderberry extract on diabetes control indices in rats. Type 2 diabetic rats (streptozotocin-induced) were fed a high-fat diet and received for 4 weeks doses of 190 and 350 mg/kg bw/day of polar and lipophilic elderberry extract, respectively. The polar extract reduced fasting blood glucose, whereas the lipophilic extract decreased secretion. Both extracts reduced insulin resistance and no significant alterations were observed in hematological indices, serum lipids, and serum and tissue trace element homeostasis (Salvador et al., 2017). Farrel et al. studied the effect of anthocyanin-rich elderberry extract on metabolism in a diet-induced obese mouse model. Four types of diet were used for 16 weeks: low-fat diet (LFD), lard-based high-fat diet (HFD), HFD with 0.25% elderberry extract, and HFD with 1.25% elderberry extract. Both groups of mice receiving elderberry extract were found to be characterized by significantly lower liver weight and serum TAG concentration, and significantly lower serum inflammatory markers, insulin resistance and hepatic fatty acid synthase mRNA, compared to HFD. In addition, HFD with 1.25 % elderberry extract reduced hepatic cholesterol and PPARγ2 mRNA compared to HFD and HFD with 0.25 % elderberry extract (Farrel, Norris, Ryan et al., 2015). In addition, supplementation with 1.25% elderberry extract of hyperlipidemic mice was performed to determine the effect on atherosclerosis and HDL dysfunctions. No significant differences in serum lipids were observed between the elderberry and control group, however, aspartate transaminase and fasting glucose were reduced in the elderberry group of mice. Hepatic and intestinal mRNA changes were also reported with an improvement in HDL function and a decrease in hepatic cholesterol levels in elderberry-fed mice. In addition, this group showed significantly increased serum paraxonase-1 arylesterase activity. The results indicate the reduction of elderberry on aortic total cholesterol content and then less progression of atherosclerosis (Farrel, Norris, Lee, Chun, & Blesso, 2015).

A randomized, placebo-controlled, double-blind study was conducted to determine the impact of anthocyanins obtained from elderberry juice on lipid and antioxidant status. 34 healthy volunteers received 400 mg of atomized elderberry powder in gelatin capsules or placebo three times daily for 2 and 3 weeks. Each capsule contained 10% anthocyanins and represented the equivalent of 5 ml of elderberry juice. In addition, a further trial was conducted to study the short-term effect of elderberry anthocyanins on serum lipid concentration, in which six volunteers received a single dose of 10 capsules, which was equivalent to 50 ml of elderberry juice. In the placebo-controlled study, the elderberry group showed no statistically significant differences in changes in serum lipids, as well as in vitamin A, E and β-carotene, compared to the placebo group, and even, a decrease in the level of vitamin C. was observed in both groups. In a single-dose experiment conducted as part of the same study, an increase in serum total anthocyanins was found during the postprandial phase. Serum lipid concentration was lower in the elderberry group, but the differences were not significant (Murkovic et al., 2004). In a study in which patients took, among others, dietary supplements of fruits and flowers of Sambucus nigra, the BMI index was reduced by approx. 3%, weight was reduced by an average of 3.2 kg, systolic blood pressure decreased by an average of more than 5% and diastolic blood pressure by 2.5%. In addition, the physical and mental well-being as well as the quality of life of the patients improved significantly (Chrubasik et al., 2008). A diluted elderberry and elderflower concentrate, used among others in a hypocaloric diet in Switzerland, resulted in an average weight loss of 2.6 kg in 11 volunteers during 7 days of dieting (Walz & Chrubasik, 2008).

Activity Antidepressant potential

Mahmudi et al. (2014) evaluated the antidepressant activity of elderberry extracts by exposing mice to the forced swim test (FST) and the tail suspension test (TST). The tests demonstrated very good antidepressant properties of the tested extract: it shortened the immobility time and increased the activity of the mice administered the extract compared to the control group, depending on the immobility time and activity level of the extract dose. Furthermore, elderberry extract at a dose of 1200 mg/kg elicited much higher activity in mice in FST than imipramine (10 mg/kg), a potent and effective antidepressant drug (Mahmoudi et al., 2014).

Impact activity on urinary parameters.

Research on the impact of some proprietary elderberry concentrates on urinary electrolyte balance showed that 200 ml of concentrate made from fresh berries, flower juice and dried flower extract did not influence the pH, hydrogen ion concentration and 24-hour hydrogen excretion in urine collected from 11 Participants. Elderberry concentrate also had no impact on the solubility of stone-inducing ions, suggesting that it can be used in patients with idiopathic nephrolithiasis without any risk of harm (Walz & Chrubasik, 2008). Elderberry as a dietary supplement in the form of capsules containing flower extract had no apparent inhibitory effect on uridine diphospho-glucuronosyltransferase (UGT). The IC50 values were higher than 500 µg/ml for all five UGT enzymes studied in vitro, such as UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 (Choi, Park, Yoon, & Bae, 2014).

Toxicology

Although the cooked berries (pulp and skin) of most Sambucus species are edible, the raw berries and other plant parts of this genus are poisonous The leaves, twigs, branches, seeds, roots, flowers, and berries of Sambucus plants produce cyanogenic glycosides, which have toxic properties. [9] Ingesting a sufficient amount of cyanogenic glycosides from berry juice, flower tea, or beverages made from fresh leaves, twigs, and fruits has been shown to cause illness, such as nausea, vomiting, abdominal cramps, diarrhea, and weakness. In August 1983, a group of 25 people in Monterey County, California, became suddenly ill after ingesting elderberry juice extracted from fresh, raw Sambucus mexicana berries, leaves, and stems. The concentration of cyanogenic glycosides is higher in tea made from flowers (or leaves) than from berries.

Food uses

The ripe fruits are edible fresh (in small quantities) or processed into jams. The fruits of Sambucus nigra species of European origin are dark blue or purple berries are slightly poisonous in their raw state, but are edible after cooking. They can be used to make jam, jelly, chutney and Pontack sauce. In Scandinavia and Germany, soup made with elderberries (e.g., German Fliederbeersuppe) is a traditional meal. The berries can be made into elderberry wine. In Hungary, an elderberry brandy is made that requires 50 kilograms of fruit to produce 1 liter of brandy. In southwestern Sweden, it is traditional to make an elderflower-flavored kebab liqueur. Elderflowers are used in liqueurs such as St-Germain and in a slightly alcoholic elderflower 'champagne', although a more alcoholic homemade version can be made. In Beerse, Belgium, a variety of jenever called beer vlierke is made from the berries. The fruit macerated in alcohol can be distilled to produce brandy. The syrup can be added to white wine, sparkling wine, cider or beer. It can also be used in cooking, with pancakes, fruit salads, for a sauce, a vinaigrette or in bread or muffin recipes. In France, elderberries are used in the composition of grenadine syrup.

Commonly, the inflorescences are used in infusions, giving as a drink in northern Europe and the Balkans. These drinks are sold commercially as elderflower liqueur or elderflower press. In Europe, the flowers are made into a syrup or liqueur (Romanian: Socată, Swedish: fläder(blom)saft, Danish: hyldeblomstsaft / hyldedrik), which is diluted with water before drinking. The recent popularity of this traditional drink has encouraged some commercial soft drink producers to introduce elderflower-flavored drinks (Fanta Shokata, Freaky Fläder). The flowers can also be dipped in a light batter and then fried to make elderflower fritters.

Pas

The chemical composition of Sambucus nigra is rich and depends on different factors, such as cultivation, location, ripening stage and climatic conditions. Regarding carbohydrates, elderberries contain between 7.86 and 11.50 % total sugar and between 2.8 and 8.55 % reducing sugar. According to Veberic et al. the total sugar content in elderberries ranged from 68.53 to 104.16 g/kg FW, depending on cultivar or selection. The main sugars identified were glucose (33.33-50.23 g/kg FW) and fructose (33.99-52.25 g/kg FW), while only small amounts of sucrose were present in the fruit (0.47-1.68 g/kg FW, composing 0.33% according to Vulic et al.). Carbohydrates found in Sambucus nigra fruit also include dietary fiber, in particular, pectin, pectic acid, protopectin, Ca-pectate, and cellulose. Elderberry is a source of integral protein: its content is 2.7 to 2.9 % in the berries, 2.5 % in the flowers and 3.3 % in the leaves. This protein includes sixteen amino acids, nine of which are essential; the total content of essential amino acids is approx. 9% in flowers and 11.5% in leaves. Glutamic acid, asparagic acid and alanine were reported as the dominant amino acids. Fats accumulate mainly in elderberry seeds (fat content: 22.4%) and seed meal (fat content: 15.9%). The main fatty acids are polyunsaturated fatty acids, which constitute 75.15 % and 21.54 % of the total fatty acids in seeds and seed meal, respectively, while monounsaturated fatty acids (14.21 % and 4.21 %) and saturated fatty acids (10.64 % and 4.81 %) make up a significantly smaller share. The polyunsaturated fatty acids found in highest concentration in the seeds are α-linolenic, linoleic and oleic acid. Organic acids constitute 1.0 to 1.3% of the berry content. Veberic et al. detected four organic acids in elderberry fruit. The most abundant of these was citric acid (3.08-4.81 g/kg FW), the content of which was quite high compared to other fruits. The next was malic acid (0.97-1.31 g/kg FW) and the remaining two acids were shikimic acid (0.14-0.93 g/kg FW) and fumaric acid (0.10-0.29 g/kg FW). Minerals are found in both berries and flowers. Mineral matter content represents 0.90-1.55% of fruit mass and includes K (2953-5494mg/kg FW), P (735-1337), Ca (574-1528), Na (13-146), Mg (396-739), Fe (12.4-84.7), Zn (1.9-11.3), Mn (3.6-9.5), Cu (1.7-2.9). In addition, berries also contain heavy metals such as lead (0.016-0.098 mg/kg FW) and cadmium (0.039-0.053), as well as nitrate (V) (2.63-3.21 mg/kg FW) and nitrate (III) (0.69 -0.86) (Akbulut et al., 2009, Borowska et al., 2000, Diviš et al., 2015, Dulf et al., 2013, Fazio et al., 2013, Kislichenko and Vel'ma, 2006, Kołodziej et al. , 2012, Mratinić and Fotirić, 2007, Ognik et al., 2006, Veberic et al., 2009, Vulić et al., 2008). Elderberry fruit and flowers also include essential oils (about 0.01 % in fruit), consisting of ca. 53 compounds in berries and 58 compounds in flowers (Kaack, 2008, Kaack and Christensen, 2008).

Regarding the vitamins present in S. nigra, several studies mention ascorbic acid, but the quantitative findings are rather inconsistent. According to Kaack and Austed, the ascorbic acid content ranges from 6 to 25 mg/100 g of elderberry fruits and depends on the cultivar. The highest content of this vitamin was found in 'Mammoth' and the lowest in 'Sambu' and 'Haschberg' (Kaack & Austed, 1998). According to other studies, the vitamin C content in wild elderberry is 13 to 35 mg/100 g and 28 to 34 mg/100 g, depending on the location (Akbulut et al., 2009, Mratinić & Fotirić, 2007). Still others report a vitamin C concentration between 32.75 and 44.42 mg/100 g, with the highest content in the cultivar 'Samyl' and the lowest amounts in wild elderberries (Borowska et al., 2000, Vulić et al., 2008). In addition, elderberry seed meal is a source of α-tocopherol (0.49 µg/g oil), which has the highest vitamin E bioactivity, as well as γ-tocopherol (2.63 µg/g), which shows better antioxidant potential (Fazio et al. al., 2013).

All parts of elderberry contain cyanogenic glycosides, the most abundant being sambunigrin and prunasin. In addition, elderberry contains m-hydroxysubstituted glycosides, such as zierin and holocalin (DellaGreca et al., 2000, Jensen and Nielsen, 1973). These compounds are potentially toxic and potentially lethal, as they can hydrolyze and release cyanide (Bromley, Hughes, Leong and Buckley, 2005). However, they occur mainly in immature berries and are degraded during heat treatment (Williamson, Driver, and Baxter, 2009). The highest amounts of sambunigrin are present in elderberry leaves (27.68-209.61 µg/g FW), lower amounts were found in flowers (1.23-18.88 µg/g FW), while berries contain the lowest amounts of this compound (0.08-0.77 µg /g FW). It was also found that the content of sambunigrin in elderberry changes according to the altitude of growth. The highest sambunigrin content was recorded at a hilltop (1048 and 1077 m asl), which had lower temperatures and higher solar radiation compared to other altitudes studied (209-858 m asl) (Senica, Stampar, Veberic, & Mikulic-Petkovsek , 2016). Other toxic compounds present in elderberry are lectins that share high amino acid sequence homology and some of them have N-glucosidase activity, which is typical of type II ribosome inactivating proteins (RIPs). Type II RIPs occur in elderberry bark (e.g., nigrin b-SNA V, SNA I), fruits (nigrin f) and seeds (nigrin s) (Stripe, 2004, Tejero et al., 2015). In addition, elderberry contains the Sam n1 allergen, which causes type 1 allergy and some tryptic peptides of Sam n1 show high amino acid sequence with lectins and type 2 RIPs located in Sambucus (Förster-Waldl et al., 2003, Jimenez et al., 2013, Jimenez et al., 2013). However, incubation in a boiling water bath for 5 to 10 min was found to render the lectins fully sensitive to hydrolytic enzymes in vitro and thus reduced the risk of allergenicity (Jiménez et al., 2017).

The bioactive compounds found in elderberry are mainly polyphenols and anthocyanins. The fruit of Sambucus nigra is an important source of phenolic compounds; their content in elderberries is relatively high compared to other fruits (Leja, Mareczek, & Nanaszko, 2007). The main polyphenols in elderberry are chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid, quercetin, quercetin-3-ruthinoside (rutin), quercetin-3-glucoside (isoquercitrin), kaempferol-3-ruthinoside, kaempferol-3-glucoside (astragalin) , isorhamnetin-3-ruthinoside and isorhamnetin-3-glucoside. The main flavonol in this plant is rutin, while the other flavonols, isoquercitrin and astragalin are found in smaller amounts in elderberries (Dawidowicz et al., 2006, Kaack and Austed, 1998, Kaack et al., 2008, Lee and Finn, 2007, Pietta and Bruno, 1992, Veberic et al., 2009). The quercetin concentration measured in the fruit of thirteen elderberry cultivars ranged from 29 ('Gentofte') to 60 mg/100 g ('Haschberg') of fruit (Kaack & Austed, 1998). In addition, Sambucus nigra berries contain small amounts of tannins with a low degree of condensation. These are procyanidins, such as epicatechin

(88.4 % of total tannins) and catechin (11.6 % of total tannins) and their thiol derivatives (Oszmiański & Moutounet, 1995).

Phenolic compounds include anthocyanins, which are water-soluble glycosides or acylglycosides of anthocyanidins that are oxygenated derivatives of flavilium salts (Prior, 2003). They are well-known functional compounds that are used as food colorants and reduce oxidative stress by scavenging free radicals, making them potential chemopreventive agents. Therefore, as excellent food dyes with antioxidant properties, anthocyanins are a good alternative to synthetic dyes due to their safety as well as their potential nutritional and therapeutic effect (Bridle and Timberlake, 1997, Espín et al., 2000, Stintzing et al., 2002).

Elderberry is a very rich source of anthocyanins compared to other fruits. The fruit of Sambucus nigra contains anthocyanins, especially cyanidin-3-glucoside and cyanidin-3-sambubioside. Two other (minor) anthocyanins are cyanidin-3,5-diglucoside and cyanidin-3-sambubioside-5-glucoside. In addition, traces of cyanidin-3-rutinoside, pelargonidin-3-glucoside and delphinidin-3-rutinoside were identified in the fruit of certain elderberry cultivars. Their content depends on the cultivar/variety, ripening stage, growing season or type and method of extraction (Borowska et al., 2000, Duymuş et al., 2014, Fiorini, 1995, Kaack, 1997, Kaack and Austed, 1998, Kaack et al. al., 2008, Lee and Finn, 2007, Leja et al., 2007, Pliszka et al., 2005, Seabra et al., 2010, Veberic et al., 2009, Youdim et al., 2000). The cultivars most abundant in anthocyanins are 'Mammut', 'Samdal', 'Sampo' and 'Samyl', while 'Finn Sam', 'Haschberg', 'Allesoe', but also wild elderberries have the lowest amounts of these bioactive compounds. The total anthocyanin content varies almost three times depending on the cultivar, p. 'Haschberg' was found to contain 664 mg total anthocyanins/100 g, while the concentration of these compounds in 'Sampo' was 1816 mg/100 g. (Kaack, 1997, Kaack and Austed, 1998, Pliszka et al., 2005). Polyphenol content changes at different stages of fruit ripening and each compound shows its own individual pattern of change during this process. The content of anthocyanins, especially cyanidin-3-sambubioside-5-glucoside, cyanidin-3-sambubioside and cyanidin-3-glucoside, generally increases as berries ripen (Kaack et al., 2008). Polyphenol and anthocyanin content also depends on the growing season. Lee and Finn (2007) found that the total anthocyanin content of 'Korsør' fruit in 2005 was almost twice as high (343 mg cyanidin-3-glucoside/100 g) as in 2004 (176 mg cyanidin-3-glucoside)/100 g). The total phenolic content was also much higher in 2005 (510 and 582 mg gallic acid/100 g) than in 2004 (364 and 387 mg gallic acid/100 g), respectively, for 'Haschberg' and 'Korsør'. The same applies to the individual anthocyanins and almost all polyphenols investigated in berries of both cultivars. The predominant anthocyanin found in elderberry juice concentrate or must is cyanidin-3-sambubioside, whereas cyanidin-3-glucoside is the most abundant anthocyanin in elderberry wine (Bermúdez-Soto & Thomás-Barberán, 2004, Schmitzer et al., 2010) and in the fruit of thirteen elderberry cultivars except 'Allesøe' (Kaack & Austed 1998).

Alcoholic fermentation of berries causes changes in the content of phenolic compounds and anthocyanins, which also leads to color changes. The concentration of polyphenols, such as neochlorogenic acid, chlorogenic acid, quercetin-3-rutoside, quercetin-3-glucoside, kaempferol-3-rutoside, cyanidin-3-sambubioside-5-glucoside, cyanidin-3,5-diglucoside, cyanidin-3-3-glucoside or cyanidin-3-ruthinoside, was observed to be higher in wine than in must, except for cyanidin-3-sambubioside, which decreased significantly during alcoholic fermentation. Storage and aging of elderberry wine resulted in the decrease of the content of each compound analyzed, and after three years the total phenolic content was reduced by 21%, while the total anthocyanin content was lower even by 94% compared to the young wine. Due to anthocyanin degradation, the color of the elderberry wine also changed from bright red to reddish-brown tones. Antioxidant activity was also higher in the young wine than in the must and decreased after aging (Schmitzer et al., 2010). The method of juice production affects the content of bioactive compounds. For example, elderberry juices processed by enzymatic treatment (pectinolysis) showed a lower average content of most of the investigated phenolic compounds compared to juices produced without enzymatic treatment (Kaack et al., 2008). Anthocyanin content in elderberry products is affected by pH, storage time and storage temperature. It was observed that extension of storage time and increase in storage pH and temperature resulted in decreased anthocyanin content in elderberry juice concentrate (Walkowiak-Tomczak, Czapski, & Młynarczyk, 2016).

Elderberry distillation waste, although constituting 25 to 40 % of the total fruit weight, is very rich in anthocyanins: it contains 75 to 98 % of the total anthocyanins found in fresh elderberries (Brønnum-Hansen, Jacobsen, & Flink, 1985). The main anthocyanin in elderberry pomace is usually cyanidin-3-glucoside (14-78 mg/g DW) and the sum of this compound and cyanidin-3-sambubioside (15-61 mg/g DW) accounts for about 90 % of the total. anthocyanin content, which ranges from 39 to 153 mg/g dry matter, depending on the extraction method. On the other hand, the rutin content in elderberry pomace is 6 to 14 mg/g dry weight (Seabra et al., 2010).

The flowers of Sambucus nigra contain even higher amounts of phenolic compounds compared to the fruits and leaves of this species (Dawidowicz et al., 2006, Kołodziej and Drożdżal, 2011). The main group of phenolic compounds found in elderberry flowers are hydroxycinnamic acids, the most important of which is chlorogenic acid. Other hydroxycinnamic acids present in elderflowers include, among others, neochlorogenic acid, cryptochlorogenic acid, 3- and 5-feruloylquinic acid and dicaffeoylquinic acids, among which 1,5-Di-caffeoylquinic acid is the most important. The second important group of polyphenols comprises flavonols, of which several quercetin glycosides, kaempferol and isorhamnetin were detected in elderflower extracts. The main polyphenol of this group is quercetin-3-ruthinoside (rutin). This flavonol together with kaempferol-3-rutoside and isorhamnetin-3-rutoside constitute more than 90% of the total flavonoids in most of the genotypes analyzed. Other groups of phenolic compounds found in elderberry flowers are flavanols, which include catechin, epicatechin and procyanidin trimer, and flavanones, p. naringenin. Elderberry flowers contain more of certain phenolic compounds (rutin, isoquercitrin and astragalin) than berries or leaves (Christensen et al., 2008, Dawidowicz et al., 2006, Mikulic-Petkovsek et al., 2015). The content of phenolic compounds in elderberry flowers, as in elderberries, depends on the genotype, as well as on the composition of the liquid and extraction conditions. For example, the highest content of chlorogenic acid was found in the Virum genotype (20.7 mg/g PS), while the lowest in the Sambu genotype (10.1 mg/g PS). On the other hand, the Samocco genotype was shown to have the highest rutin concentration (42.3 mg/g dry weight) while the Jaegerspris genotype had the lowest concentration (11.6 mg/g dry weight) of rutin (Christensen et al., 2008). In addition, the higher flavonol content in elderberry flowers was the result of higher extraction temperature: 214.25 and 139.32 g/100 g extr. for 100°C and 20°C, respectively (Dawidowicz et al. 2006).

Other uses

Berries can provide ink that varies in color from blue to purple depending on their composition. To make ink, the berries should be ground in water, then left to macerate for a day to throw up the berries. During the maceration, add two tea bags. The tea is rich in tannin, which fixes the colors very well. Filter the macerate and reduce it by bringing it to the boil. Add powdered alum and finely ground gum arabic. Mix and continue to reduce until the right concentration is reached.

The tender heart of elder branches can be easily hollowed out, which makes this plant ideal for making simple wind instruments such as the mirliton, fife or whistle, but elder wood can also be used to make more complex traditional flutes; such as the Fujaras, Koncovkas, Moldavian Kavals, Romanian Cavals.

History

In Celtic tradition, the elder ("ruis") is the tree associated with death. Druids made flutes from its wood, which they used to converse with the souls of the dead or to protect themselves from spells. The black elder is known as the "fairy tree". Its spring foliage is at the origin of the French sayings of March 6: "At Sainte-Colette, you can see the elder leaf grow" or "At Sainte-Colette, the elder sheds its leaves.

In the mountains of the Eastern Pyrenees and Catalonia, different beliefs are linked to the black elderberry. Used in bouquets of flowers for the feast of St. John, it could also be nailed to the doors of houses to protect against bad luck. On the other hand, burning it could dry cow's milk or even mother's milk. Falling asleep under a black elder tree exposed you to erotic dreams. Finally, a necklace of nine buds could be made and placed around the neck of babies to facilitate teething, on condition that they were picked up on Corpus Christi day, when the bells rang announcing the beginning of the procession, with a bud picked up by the ringing of a bell.

Miconia albicans Steud (Melastomataceae)

Mex: mortiño flower

In Brazil it is popularly known as “canela-de-velho” meaning old man's shin (Almeida 2014). Its aqueous extract is widely used in Brazilian folk medicine to treat inflammation, infections, arthritis and joint pain, while in Mexico it is used to treat diabetes (Lima 2018; Almeida 2014; Tarawneh 2014; Rodrigues 2011; Serpeloni 2008). M. albicans leaves are readily available for purchase in the Brazilian market for medicinal purposes.

Pharmacological uses.

Cytotoxic, antimicrobial, antidiabetic, anti-inflammatory and antinociceptive properties are reported from extracts of M. albicans (Quintans-Junior et al., 2020; Serpeloni et al., 2011; Celotto et al., 2003). Ethanolic extracts of leaves also reduced the number of leukocytes in pleurisy, TNF-α and IL-1β levels in pleural lavage, IL-6 in the knee joint, as well as reduced nociceptive and hyperalgesic events. Moreover, these extracts only exhibited in their composition flavonols, some ellagic acid derivatives and few hydrolyzable tannins (Quintans-Junior et al., 2020); the latter two were not the same observed here in the infusion of M. albicans leaves. This study aimed to determine the chemical profile of the aqueous extract of Miconia albicans (MAAE), to investigate its anti-inflammatory and hyperalgesic effects, and in vivo toxicity studies (acute and repeated oral dose). Twenty-four MAAE compounds were scored by LC-DAD-MS, such as ellagitannins, ellagic acid derivatives, flavan-3-ol and O-glycosylated compounds, including flavonols, triterpenes and megastigmanes. MAAE did not induce significant toxicological effects in acute and repeated dose oral assays at lower doses and no histological changes were observed. Hematologic and biochemical results showed no significant alterations. Oral administration of MAAE 256 mg/kg inhibited the edematogenic effect and reduced leukocyte migration. In addition, MAAE decreased acetic acid-induced abdominal contortions and paw-licking time by formalin assay. MAAE showed a significant reduction in inflammatory levels and leukocyte migration, revealing antihyperalgesic properties. In addition, MAAE did not reveal acute or repeated dose toxicities (Sampaio de Oliveira 2023).

M. albicans leaves, after drying in forced air circulation chamber at ±40 °C for 48 h and grinding in blade mill, presented a moisture content below the maximum allowed for plant drugs (6.4%). The M. albicans powder was classified as moderately coarse and the total ash content was found to be 6.27 %. Preliminary phytochemical screening of DEMA (dry extract of Miconia albicans) revealed the presence of flavonoids, tannins, saponins, leucoanthocyanins and steroids. DEMA had significantly higher total phenolic (551.3 mg gallic acid equivalents/g dry extract) and flavonoid (367.19 mg catechin equivalents/g dry extract) contents. Two main compounds ($\lambda = 340$ nm) were identified in DEMA by HPLC-PDA: the flavonoids rutin and quercetin. The rutin content, selected as a chemical marker, was determined and found to be 1.16 mg/g dry extract ($r = 0.9941$). Regarding antioxidant activity, our results revealed that DEMA exhibited good antioxidant activity in different models. Treatment with M. albicans also reduced TNF-α and IL-1β levels and, consequently, inflammatory nociception and edema caused by carrageenan injection. Based on previous studies and our results, it is possible to suggest a positive correlation between rutin and quercetin flavonoids and antioxidant and anti-inflammatory capacities.Taken together, these data suggest that M. albicans has the potential for use in conditions such as arthritis or other joint pain, even needing further work to better consolidate this profile.(Lima 2020).

The anti-inflammatory effect of MAFRE (Miconia albicans fruit extract) was evaluated for the property of inhibiting edema and leukocyte recruitment to inflamed ear tissue. The croton oil model is commonly used to evaluate the anti-inflammatory response of various drugs. Its action is through the formation of a dermatitis characterized by vasodilatation, leukocyte migration and edema. The inflammatory reactions are mediated by protein kinase C which increases the activities of phospholipase A2, cyclooxygenase and lipoxygenase resulting in the release of arachidonic acid, prostaglandins and leukotrienes (Bouhlali et al., 2020, Gábor, 2000, Gar et al., 2008, Murakawa et al. ., 2006, Otuki et al., 2005). Application of CO to the ear of mice induced an evident inflammatory response at the sixth hour, with increased ear weight of animals in the inflamed control group (CO) (23.18 ± 0.59 mg) compared to the group of animals receiving vehicle alone (V) (11.25 ± 0.18 mg). Topical treatment with MAFRE significantly reduced the intensity of ear edema by 58.48% at the dose (2.5 mg/ear) (Fig. 4A). Treatment with indomethacin (1.0 mg/ear) and dexamethasone (0.1 mg/ear), the reference anti-inflammatory drugs, resulted in an intense reduction of ear edema, 91.30% and 94.34%, respectively. There was no significant difference in edema inhibition by MAFRE compared to commercial drugs ($p>0.05$).

Although MAFRE showed a high content of phenolic compounds and antioxidant capacity, in addition to a chemical profile with compounds with potential antiproliferative action, which would indicate that the extract may have antiproliferative activity, since antioxidants protect cells from oxidative damage and have been considered a first step for human. occurrence of cancer (Bonner and Arbiser, 2015), the extract did not inhibit tumor cell growth and proliferation up to the maximum concentration tested (GI50 and TGI>150 µg/mL). Doxorubicin was used as a positive control. GI50 and TGI values were interpreted through the intervals established by N'da, Smith (2014) for antiproliferative activity. A previous study showed that aerial parts of M. albicans have protective effects on doxorubicin-induced mutagenicity (Pieroni 2011). Research with species of the genus Miconia reports that their extracts have therapeutic potential, especially with anti-inflammatory and antimicrobial activity, however, there are few studies describing antitumor properties (Cunha 2019). M. albicans and other plants of the genus Miconia are rich in triterpenes with ursane and oleanane skeletons, being considered great sources for the isolation of compounds such as ursolic and oleanolic acids, which have recognized antitumor activity in vitro and in vivo. Several studies have shown that the overall activity of botanical extracts can result from mixtures of compounds that together can develop a synergistic or antagonistic effect and influence biological activities, as was observed for the antiproliferative activity of MAFRE. However, complex mixtures, such as natural product extracts, offer an important resource for drug development, as they contain substances that, if isolated, can produce a greater biological effect (Caesar and Cech, 2019; Phan 2018).

Anti-inflammatory and analgesic activities. Species of the genus Miconia have a wide variety of uses. Some are used in Brazilian folk medicine for their analgesic and anti-inflammatory properties, increasing the need for further research on these reported effects [Gatis Carrazzoni 2019]. Spessoto et al [2003] evaluated the analgesic activity of hexane, methylene chloride and ethanol extracts of M. rubiginosa leaves, which showed central and peripheral analgesic activity in mice and rats, using acetic acid and hot plate induced contortion tests. According to these authors, this activity was probably mediated by inhibition of prostaglandin synthesis and central inhibitory mechanisms. Using a similar methodology, Vasconcelos et al. [2003] investigated the analgesic actions of extracts (hexane, methylene chloride and ethanol) of M. albicans leaves, which showed significant antinociceptive activities in the contortion test.

Vasconcelos et al. [2006] investigated the analgesic action of olenoic and ursolic acids, compounds isolated from the methylene chloride extract of M. albicans leaves; they found that these substances inhibited acetic acid-induced abdominal constriction in mice.

Gatis-Carrazzoni et al. [2019] investigated the antinociceptive and anti-inflammatory actions of the methanolic extract of M. minutiflora leaves on rat paw edema-induced edema and found a decrease in cell migration in experimental models; this was associated with inhibition of the proinflammatory cytokines TNF-α (tumor necrosis factor alpha) and IL-1β (interleukin 1β). In addition, the compound acted on inflammatory pain and as an α2-adrenergic receptor agonist. In the study by Lima et al [2020], dry extract of M. albicans leaves showed anti-inflammatory activity on carrageenan injection-induced edema in mouse paws. Oral treatment with the extract significantly decreased TNF-α and IL-1β levels, consequently reducing inflammatory nociception. This corroborated with the results of Quintans-Junior et al [2020], who reported that ethanolic extract of M. albicans significantly reduced leukocyte migration and TNF-α and IL-1β levels. The extract reduced pain in mice, without apparent liver damage, decreasing nociceptive, hyperalgesic and mechanical hyperalgesic behaviors.

According to Correa et al. [2021], the methanolic extract of M. minutiflora leaves showed anti-inflammatory effects, thus inhibiting edema and leukocyte recruitment to inflamed atrial tissue of mice. Gomez et al [2021] observed in their studies that M. albicans showed analgesic and anti-inflammatory effects in the treatment of patients with knee osteoarthritis, thus decreasing the pain of the patients, an effect comparable to the drug ibuprofen.

Antimutagenic activity. Evaluation of extracts of four Miconia species (M. albicans, M. cabucu, M. rubiginosa, and M. stenostachya) revealed antimutagenic effects of all the extracts evaluated; moreover, none of the extracts at any of the concentrations tested (5, 10, and 20 μg/mL) showed mutagenic effects [Serpeloni 2011]. Gontijo et al. [2019] demonstrated that the aqueous extract of M. latecrenata leaves showed significant antimutagenic activity against Salmonella typhimurium strains, which was observed by the Ames test; this aqueous extract showed mutagenic inhibition of approximately 70% (340.0 μg/plate) and 61% (42.5 μg/plate) against strains TA98 and TA97, respectively.

Antibacterial activity. Some Miconia species are noted for having antimicrobial activities. For example, ethyl acetate extracts of M. lepidota leaves and two isolated benzoquinones (2-methoxy-6-heptyl-1,4-benzoquinone and 2-methoxy-6-pentyl-1,4-benzoquinone (primin)), showed antimicrobial activity against Saccharomyces cerevisiae yeast strains [Gunatilaka 2001]. Ethanolic extracts of three Miconia species (M. albicans, M. rubiginosa and M. stenostachya) exhibited an antimicrobial effect against some of the eleven microorganisms tested. The extracts of M. albicans and M. rubiginosa showed antibacterial effects against three gram-positive bacteria (Staphylococcus aureus, S. saprophyticus and Streptococcus agalactiae) and two gram-negative bacteria (Shigella flexneri and Klebsiella pneumoniae). While M. stenostachya extract was only active against C. albicans [Celotto 2003].

Garcia et al. [2006) observed the antibacterial activity of methanolic extracts of M. mexicana leaves, showing an MIC of 0.5 μg/mL against S. aureus. According to Cunha et al. [2007], triterpenic acids (gypsogenic , oleanolic, sumaresinolic and ursolic acids isolated from Miconia species (M. fallax, M. albicans and M. stenostachya) showed antimicrobial effects against six different bacterial strains (Streptococcus mutans, S. mitis, S. sanguinis, S. salivarius, S. sobrinus and Enterococcus faecalis). Oleanolic and ursolic acids showed significant inhibitory effects, with MIC values ranging from 30 to 80 μg/mL. Methanolic extracts of M. rubiginosa and M. stenostachya leaves and chloroform extracts of M. cabucu leaves showed antimicrobial activity against Candida albicans and eight different species of bacteria (Bacillus subtilis, B. cereus, Staphylococcus epidermidis, S. aureus, Salmonella spp, E. faecalis, Escherichia coli and Micrococcus luteus), as analyzed by the disk diffusion method [Rodrigues 2008].In the study of Pavan et al. [2009], chloroform and methanol extracts of M. cabucu and M. rubiginosa showed inhibitory activity against strains of Mycobacterium tuberculosis bacteria. Cunha et al. [2010] demonstrated that compounds isolated from M. ligustroides have inhibitory antibacterial activities. Oleanolic acid showed inhibitory action against B. cereus and Streptococcus pneumoniae, with an MIC of 80 μg/mL for both bacteria. Ursolic acid showed antibacterial action against B. cereus, with an MIC of 20 μg/mL. Bussman et al. [2010] reported that ethanolic and aqueous extracts of aerial parts of M. salicifolia showed antimicrobial potential against gram-negative (E. coli) and positive (S. aureus) bacteria. According to Pinto et al. [2010], M. argyrophylla leaf extract showed promise in inhibiting mycelial growth and controlling the germination of Colletotrichum lindemuthianum conidia, as well as being effective in reducing disease severity, reducing it by 42 % compared to the control.

Using the broth microdilution method, Queiroz et al. [2011] demonstrated that the ethanolic extract of the aerial parts of M. rubiginosa showed antimicrobial activity against five bacterial isolates, namely E. faecalis, Kocuria rhizophila, E. coli, P. aeruginosa and Salmonella choleraesuis. The aqueous extract of M. latecrenata leaves showed antibacterial activity against Staphylococcus aureus strains, with a MIC value of 100.0 μg/mL [Gontijo 2019]. Rodriguez et al [2021] also demonstrated that the extract prepared from the leaves of M. latecrenata was promising in inhibiting bacterial growth of S. aureus and Pseudomonas aeruginosa strains; furthermore, it showed synergism with ampicillin and tetracycline, respectively. In the study by Tomé et al [2019], the antimicrobial activity of the ethanolic extract of M. albicans leaves against Listeria innocua was verified. The hexane fraction showed moderate inhibition against L. monocytogenes strains, whereas the ethyl acetate fraction showed better inhibitory activity against Listeria monocytogenes, L. innocua and Bacillus cereus. Viegas et al. [2019] revealed in their studies that the hexane fraction prepared from M. willdenowii leaves showed significant antimicrobial activity against S. aureus and Candida krusei strains, showing IC50 values of 15.6 and 62.5 μg/mL, respectively. The isolated compound primin, also showed significant activity against S. aureus (IC50 = 8.94 μM), with similar results to the reference drug chloramphenicol (IC50 = 6.19 μM). Compound 148 also showed significant antifungal activity against all Candida species. Proven. Gomez et al. (2021] found that the aqueous extract of M. chamissois showed antimicrobial activity against C. albicans and S. aureus, with an MIC of 78.1 μg/mL and 312.5 μg/mL, respectively, but showed no activity against E. coli.

Antioxidant Activity. Species of the genus Miconia have antioxidant properties evidenced in several studies, as shown by the study of Boscolo et al. [2007], where the authors found that M. cinnamomifolia had moderate activity under the influence of these antioxidant properties of Miconia. Mancini et al. [2008] confirmed the antioxidant activity of flavonoids isolated from M. alypifolia leaves using ABTS (2,2′-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid). In the study of Mosquera et al. [2009], the methanolic extract of M. lehmannii leaves showed significant antioxidant activity in DPPH (2,2-diphenyl-1-picrylhydrazyl) assays. The methanolic extract, n-butanolic fraction and flavonoids isolated from M. albicans showed a high capacity to scavenge AAPH (2,2′-azobis(2-amidinopropane) dichlorohydrazyl) and DPPH radicals [Pieroni 2011]. Methanolic extract of M. albicans fruits showed significant antioxidant activity [Pasta 2019]. Gontijo et al. [2019] confirmed the antioxidant potential of the aqueous extract of M. latecrenata leaves in DPPH, β-carotene/linoleic acid and lipid peroxidation assays, where the species showed significant potential as a source of ROS (reactive oxygen species) inhibitors. Lima et al. [2020] demonstrated the antioxidant potential of M. albicans leaf ethanolic extract through in vitro antioxidant assays, including DPPH and ABTS free radical scavenging assays, ferric reducing antioxidant assay, NO scavenging assay, metal ion (Fe^{2+}) chelating activity and antioxidant. capacity by inhibiting lipid peroxidation (TBARS). Correa et al. [2021] also found the antioxidant activity of methanolic extract of M. albicans fruits using DPPH and ABTS. Gómez et al. [2021], evaluating by DPPH and phosphomolybdenum radical reduction methods, found the antioxidant activity of aqueous extracts of M. chamissois leaves, demonstrating an IC50 close to that observed for ascorbic acid.

Cytotoxicity activity. According to Gunatilaka et al. [2001], the ethyl acetate extract of M. lepidota leaves and the isolated quinones 2-methoxy-6-heptyl-1,4-benzoquinone and 2-methoxy-6-pentyl-1,4-benzoquinone (primin) showed cytotoxic activity in murine cell lines. Calderon et al. [2003], evaluating the in vitro ability of extracts of two Miconia species to inhibit cancer cells, observed that the extract of leaves of M. impetiolaris showed low cytotoxicity, while the extract of aerial parts of M. serrulata showed significant cytotoxicity. The IC50 value was less than 12 µg/mL. Serpeloni et al. [2011] evaluated the cytotoxic activity of Miconia species on Chinese hamster lung fibroblast cells, reporting a cytotoxic effect on cells exposed to methanolic extracts of M. albicans and M. cabucu at concentrations of 40 µg/mL, as well as M. stenostachya at 60 µg/mL. At lower concentrations of the extracts (5, 10 and 20 µg/mL), no cytotoxicity was observed. M. minutiflora extract showed low cytotoxicity against tumor cell lines using the Alamar blue assay [2016]. Primin, a compound isolated from the leaves of M. willdenowii, revealed cytotoxic potential against human peripheral blood mononuclear cells (CC50 = 53.12 µg/mL) [Viegas 2017]. Studies have shown that the compound Matteucinol, isolated from M. chamissois, has cytotoxic activity on human GBM (glioblastoma) cell lines, both in vitro and in vivo, thus demonstrating high specificity [Da Silva 2019]. Cunha et al [2021] evaluated the cytotoxic activity of the extract and fractions of M. burchellii using the MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide) assay, where the ethyl acetate fraction showed potent cytotoxic action against four of the five tumor cell lines evaluated, while the ethyl ether fraction was cytotoxic only against leukemia cell lines (IC50 4.74 mg mL-1).

Rosa et al. [2000], evaluating the cytotoxicity of crude extracts of two Miconia species (M. albicans and M. chamissois), found that the species presented IC50 values below 30 µg/mL against human cervical cancer cell lines. According to Gomes et al. [2021], aqueous extracts of M. chamissois leaves showed low cytotoxicity in the cell lines evaluated, presenting IC50 values of 182.7, 414.6 and 977.0 µg/mL for human keratinocytes, mouse fibroblasts and mouse macrophages, respectively.

Other pharmacological activities. Cunha et al. [2008] demonstrated that the ethanolic extract of M. fallax and the mixture of triterpenoid acids showed inhibition of tumor growth (HeLa cells). Serpeloni et al. [2008], using the comet assay with Miconia extracts (M. albicans, M. cabucu, M. rubiginosa and M. stenostachya), found that all extracts evaluated showed low levels of genotoxicity. Pinto et al. [2016] found that the aqueous extract of M. chamissois leaves showed a phytotoxic effect on the germination and growth of Cucumis sativus (cucumber) seedlings. Santos et al. [2017], evaluating the phytotoxicity of extracts obtained from seven Miconia species (M. albicans, M. alborufescens, M. ciliata, M. ibaguensis, M. lingustruides, M. minutiflora and M. stenostachya), observed that all extracts significantly inhibited the length of Lactuca sativa radicles. In addition, the extract of M. stenostachya at 50% concentration significantly reduced the number of germinated seeds of the tested plant. The ethanolic extract of M. ferruginata leaves had an insecticidal effect on Spodoptera frugiperda caterpillars. The authors showed that caterpillars fed with the extract at a concentration of 1000 mg mL-1 had a mortality of 56.67%, compared to the control, in addition to presenting the elongations of the pupal and larval stages, causing an effect during the early stages of caterpillar development [2017].

Vagas et al [2021] demonstrated that aqueous extracts of M. albicans showed phytotoxic activity, thus reducing the length of the aerial part of lettuce seedlings, as the concentrations of the extracts increased.

Food uses

M. albicans, little explored tropical fruits, are globose, rich in carbohydrates, with small seeds and juicy consistency. Once fully ripe, it presents green color, with sweet taste similar to figs (Durigan2003; Pasta 2019). It plays an important role in biodiversity as a frugivorous food for animals, particularly in the dry season (Camargo et al., 2015; Vieira, Carvalho, 2009). Previous studies on nutritional value identified M. albicans fruits as potentially useful for human diet and a rich source of phenolic compounds with antioxidant capacity. However, in the same study, the authors found a high concentration of aluminum in the fruits, emphasizing the importance of more detailed studies on toxicological evaluation to ensure human consumption, either as food or as a medicinal plant (Li 2016; Pasta 2019). The cytotoxicity of M. albicans leaves and air was previously investigated. Bomfim et al. (2020) reported that M. albicans leaves have low toxicity (LC50 512.7 μg/ml) by Artemia salina test and Serpeloni et al. (2011) determined that aerial parts of M. albicans are non-toxic up to a concentration of 20 mg mL-1 by clonogenic assay. Efficacy and safety are important issues for the use of any plant, so it is important to perform toxicity studies, even if preliminary, to establish the safety profile, either of medicinal plants already used or of unexplored fruits and without toxicity study, as in the case of M. albicans. Commercial production of M. albicans fruits is still inexpressive, as it is still appreciated only by local populations and occasionally consumed raw or processed in jams (Pasta 2019).

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Its extracts showed several phenolic constituents, including hydrolyzable tannins, triterpenes, flavonoids, and ellagic acid and its derivatives (Quintans-Junior 2020; Lima 2018; Crevelin 2006; Vasconcelos 2006). The composition of M. albicans is affected by seasonality, where flavonols (e.g., rutin and quercetin) levels are higher in the rainy season, while triterpenes (e.g., ursolic and oleanolic acids) are lower (Gimenez, 2020).

According to Cunha (2019), the pharmacological properties reported for M. albicans are likely due to the diversity of chemicals found in the extracts. Among these chemical compounds are triterpenes with pentacyclic skeleton, ursane and oleanane skeletons stand out, with ursolic (CID64945) and oleanolic (CID10494) acids being the main representatives. Other pentacyclic triterpenes are reported from M. albicans, such as α-amyrin, β-amyrin, lupeol, epibetulinic acid, arjunolic acid, and maslinic acid. A wide variety of flavonoids, mainly glycosylated, are also found in the plant. The aglyconic units most present in these compounds are quercetin and kaempferol, and the main glycosidic units are glucose, rhamnose and arabinose. Some other complex compounds derived from gallic acid are reported, such as 1-O-(E)-caffeoyl-4,6-di-O-galloyl-β-D-glucopyranose (Lima et al., 2018). This variety of compounds also justifies the antioxidant activity of leaves and aerial parts of M. albicans as reported by Pieroni et al. (2011). Although several studies have reported on the biological activities of M. albicans in different parts, to our knowledge, no study on the chemical and pharmacological properties of fruits has investigated it in detail. Studies on the medicinal potential of M. albicans showed promising results. The ethyl acetate extract of the leaves contains flavonoids and triterpenes that act as inhibitors of protein tyrosine phosphatase 1B (PTP1B), improving insulin receptor sensitivity (Lima 2018). Hexane and methyl chloride extracts of aerial parts can reduce pain by 85% and 74%, respectively, in the contortion test (Vasconcelos 2003), and also have antibacterial activity, cytotoxicity, mutagenicity, and protective effects toward doxorubicin-induced DNA (Celotto 2003; Serpeloni 2011; Tomé 2019).

The total phenolic content in M. albicans fruit extract was 43.68 ± 0.50 mg GAE/g extract and reached a value approximately 30% higher than that published by Pasta et al. (2019) for the same dried fruits, however, it was lower compared to M. albicans leaves (70.04 mg GAE/g extract; 172.19 mg GAE/g extract) (Bomfim et al., 2020; Pieroni et al. al., 2011). However, MAFRE FC exceeds the values reported for conventional fruits, such as apple (Malus domestica - 2.73 mg GAE/g extract) (Siqueira et al., 2013) and for some Brazilian Cerrado fruits such as pitanga (Eugenia uniflora - 18.08 mg GAE/g extract) (Massarioli et al., 2013), seriguela (Spondia purpurea L- 13.5 mg GAE/g extract) and umbu (Spondia tuberosa A. - 40.4 mg GAE/g extract) (Omena et al., 2012) and also by some superfruits recognized for their exceptionally high phenolic content (Chang et al., 2019) such as pomegranate (Punica granatum L. var. Mollar de Elche - 24.41 mg GAE/g extract) and blackberry (Rubus fruticosus var.Polar - 27.02 mg GAE/g extract) (Gramza-Michałowska 2019) indicating that M. albicans fruits yield an extract that is an excellent source of phenolic compounds. The total flavonoid content was determined by the complexation reaction of aluminum with the flavonoid present in the sample. MAFRE shows 111.78 ± 3.0 mg QE/g of extract, a result five times lower than that established by Pasta et al. (2019) for M. albicans fruits, on the other hand, our result was higher than that reported for M. albicans leaves (72.69 ± 0.90 y mg QE/g) (Bomfim et al., 2020). Compared to tropical fruits, which have exceptionally high levels of antioxidant compounds and are already used as natural sources of bioactive phytochemicals, the total flavonoid content of the extarct of M. albicans was higher than pineapple extract (55.2 ± 0.2 mg QE/g extract) (Hossain, Rahman, 2011), carambola (Averrhoa carambola L) (42.70 ± 1.47 mg QE/g extract) (Khanam 2015) and pitanga (Eugenia uniflora, red type) (5.50 ± 0.68 mg QE/g extract) (Oliveira 2017).