Cyclolepis genistoides D. Don

César A. N. Catalán

Cyclolepis genistoides. (Photos by the author).

Abstract The aerial parts of *Cyclolepis genistoides*, commonly called "palo azul" or "matorro negro", are widely used in folk medicine in Paraguay, Northern and central Argentina, as a diuretic and for the treatment of kidney diseases, urinary tract irritation, kidney pain, bone pain (analgesic). It is also used as an antipyretic, as a blood purifier, against liver diseases and as a hypotensive. The main metabolites identified in the chloroform extract of aerial parts are oleanolic, ursolic and betulinic acids and other closely related triterpenes along with the sesquiterpene lactones deacylcynaropicrin and its 11,13-dihydroderivative. Most of the uses of this plant could be justified by the known biological effects of above metabolites. Very little is known about the water-soluble metabolites of "palo azul", and as such, research on the content of polyphenols, flavonoid glycosides, chlorogenic acid, dicaffeoylquinic acids and phenyletanoids are welcome.

C. A. N. Catalán (✉)
Instituto de Química Orgánica, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán, San Miguel de Tucumán, Argentina
e-mail: ccatalan@fbqf.unt.edu.ar; cancatalan@gmail.com

Á. Máthé, A. Bandoni (eds.), *Medicinal and Aromatic Plants of South America Vol. 2*, Medicinal and Aromatic Plants of the World 7,
https://doi.org/10.1007/978-3-030-62818-5_13

Keywords "Palo azul" · Triterpenes · Sesquiterpene lactones · Anti-inflammatory activity · Diuretic effect

1 Introduction

Cyclolepis genistoides (Asteraceae) is a shrub known as "palo Azul" ("blue stick"). The name refers to the observations according to which when its stems are submerged in water the solution acquires color or blue fluorescence. The decoction of its aerial parts is used in traditional medicine for kidney problems, elimination of uric acid, as a diuretic, antiarthritic, hypoglycemic and antitussive. Oleanolic acid, ursolic acid, betulinic acid and other closely related triterpenes, together with the sesquiterpene lactones deacylcynaropicrin, zaluzanin C, their corresponding 11,13-dihydroderivatives and isolippidiol, are the main metabolites identified in the chloroform extract of aerial parts. The reported pharmacological properties of compounds identified in this species agree with the use in folk medicine. No adverse effects or toxic effects have been reported from the use of this plant.

2 Taxonomic Characteristics

Cyclolepis genistoides D. Don is a medicinal plant belonging to the Asteraceae family, subfamily Mutisioideae, tribe Mutisieae (Katinas et al. 2008). Shrubs that grow up to a height of 2.5 m, are densely branched, with short branches modified in thorns. Its habitats are in the sandy soils of saline margins and salty rivers from the Paraguayan Chaco, northern and central Argentina to Northern Patagonia. In Northern Argentine, *C. genistoides* blooms in early spring.

The species was first described by the Scottish botanist David Don, in 1832 (Don 1832). It is known by the vernacular names "palo azul" or "matorro negro" (Zuloaga and Morrone 1996, 1999). It has a synonym**:** *Gochnatia genistoides* (D. Don) Hook. & Arn.

3 Crude Drug Used

Cyclolepis genistoides is widely used in folk medicine as a diuretic, antirheumatic and antispasmodic agent. A decoction of aerial parts (tender branches and leaves) is used (Filipov 1994; Giberti 1983; Scarpa 2004; Alonso and Desmachelier 2006; Barboza et al. 2009).

A decoction prepared with three 20 cm long branches in 5 liters of water is recommended to treat bone pain; use as a warm bath until symptoms decrease

(Scarpa 2004). For other uses (diuretic, urinary tract irritation, kidney pain) the following preparations are reported: (i) a decoction is made with a handful of leaves in 2 liters of water. Let cool and keep in the refrigerator. Drink once a day for three consecutive days (Scarpa 2004); (ii) a decoction is prepared with five apical parts of branches in 2 liters of water. After decanting or filtering, the liquid is taken "like water" (Scarpa 2004); (iii) prepare a decoction (5 min) with 25 g of tender branches in one liter of water. Filter or decant and drink 2–3 cups per day (Alonso and Desmachelier 2006).

4 Major Chemical Constituents and Bioactive Compounds

A chemical investigation reported several triterpenoids with ursolic acid and oleanolic acid in a 3:2 ratio as main components, accompanied by lesser amounts of betulin, betulinic acid, methyl betulinate, β-amyrin, dihydro-β-amyrin, oleanonic acid, taraxasterol, 12α,13α-epoxyoleanolic acid, 30-hydroxylupeol and 3β,28-dihydroxylup-20(29)-en-30-al; also, significant amounts of the sesquiterpene lactones deacylcynaropicrin, 11(13)-dihydrodeacylcynaropicrin and isolippidiol were present (De Heluani et al. 1997). In addition, recently we have also identified zaluzanin C and 11(13)-dihydrozaluzanin C in the sesquiterpene lactones mixture of this plant (Catalán et al. 2020). Oleanolic acid, ursolic acid and their derivatives are pentacyclic tritepenoids with confirmed pharmacological properties (Liu 1995; Wójciak-Kosior 2013; Mlala et al. 2019). The pharmacological effect of decoctions of "palo azul" was attributed to these triterpenic acids (Alonso and Desmachelier 2006; Sosa et al. 2011). Reviews on the pharmacology of the main components of the lipophilic extract of "palo azul", *i.e.*, oleanolic acid (Liu 1995; Wójciak-Kosior 2013) and ursolic acid (Liu 1995; Wójciak-Kosior 2013; Mlala et al. 2019), are available. Oleanolic and ursolic acids displayed hepatoprotective effect (Ma et al. 1982, 1986; Shukla et al. 1992; Liu 1995; Liu et al. 1995; Sosa et al. 2011) and anti-inflammatory activity in carrageenan (Singh et al. 1992) and dextran-induced edema in rats (Sosa et al. 2011). Oleanolic acid elicited marked anti-arthritic action in adjuvant-induced polyarthritis in rats and mice and in formaldehyde-induced arthritis in rats (Liu 1995; Mlala et al. 2019 and references cited therein) and exerts an antidiabetic effect in rats (Wang et al. 2011). On the other hand, it has been reported that deacylcynaropicrin -the main sesquiterpene lactone of "palo azul"- inhibits RANKL-induced osteoclastogenesis by inhibiting NF-κB and MAPK and promoting M2 polarization of macrophages (Li et al. 2019) while 11,13-dihydrozaluzanin C showed anti-inflammatory activity in mice (Piornedo et al. 2011). The reported bioactivities of components isolated from "palo azul" seem to validate the folk uses of this plant.

5 Morphological Description

A gynodioecius shrub up to 2.5 m high, densely branched, rigid branches almost perpendicular to the stems with the short branches modified in thorns. Alternate leaves, briefly petiolated, deciduous, oblong-lanceolate, acute at the apex and contracted at the base, 6–20 mm long by 2.5–6 mm wide; pubescent on both surfaces. Capitula subsessile, homogamous, densely bracteolate; receptacle epaleate; involucre three- to six-seriate. Florets isomorphic in bisexual capitula, corolla actinomorphic, tubular funnelform, deeply five-lobed, lobes coiled; anther apical appendages apiculate, tails slightly papillose; style bifid, branches dorsally smooth; female capitula with florets without staminodes, corolla tubular-filiform, shallowly five-lobed, tube long, up to 2/3 of corolla length, lobes straight. Cypselae villose; pappus of scabrid bristles. Cylindrical achenes, densely sericeous-pubescent, 3 mm long (Cabrera 1978).

6 Geographical Distribution

This species has a wide distribution in saline areas throughout Paraguay, Northern and central Argentina to Northern Patagonia. Possibly it also grows in the bordering areas to the southeast of Bolivia.

7 Ecological Requirements

It grows on the banks of salt flats and salty rivers. This species is threatened by habitat loss. No studies on the domestication of this species have been made.

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

Aerial parts: branches, leaves and (rarely) flowers (photo). *Cyclolepis genistoides* is commonly known as “palo azul” (blue stick) or “matorro negro” (black bush) in Argentina; and “jupoty”, “ñuati hu” (Guarani language) and “matorro negro” in Paraguay (Giberti 1983; Alonso and Desmachelier 2006). Infusions and decoctions of aerial parts are widely used in traditional medicine as a diuretic, analgesic, antispasmodic, antiarthritic, antirheumatic and to treat renal ailments and liver diseases (Filipov 1994; Giberti 1983; Scarpa 2004; Alonso and Desmachelier 2006; Barboza et al. 2009). Orally ingested decoction has also been reported to suppress cough and to relieve waist pain (Filipov 1994; Alonso and Desmachelier 2006).

9 Modern Medicine Based on Its Traditional Medicine Uses

It has been shown that two of its major components, namely, oleanolic acid and desacylcynaropicrin, displayed significant anti-inflammatory activity in the carrageenan-induced inflammation test (Sosa et al. 2011). As previously mentioned, reviews on the pharmacology of oleanolic acid (Liu 1995; Liu et al. 1995; Wójciak-Kosior 2013) and ursolic acid (Liu 1995; Wójciak-Kosior 2013; Mlala et al. 2019) are available. However, it should be noted that these triterpenic acids and the other triterpenoid components of *Cyclolepis genistoides* are present only in small amounts in the decoction due to the water insolubility of these compounds (Catalán et al. 2020). The hydro-alcoholic extract of "palo azul" exhibited a weak depressant effect on CNS and low acute toxicity in mice (Montalbetti Moreno et al. 2018). The diuretic effect of 10% infusions of *Cyclolepis genistoides* on Wistar rats was moderate but significant in relation to the control (Sosa et al. 2007) whilst the ethanol extract promotes differentiation of adipocytes and regulates adipokine expression in 3 T3-L1 adipocytes by modulation of peroxisome proliferator–activated receptor (PPAR) (Sato et al. 2013) and induces the formation of myotubes by differentiating C2C12 myoblast cells (Sato et al. 2016). It is worth noting that the amount (concentration) of oleanolic acid, ursolic acid and other triterpenes in the ethanol extract is much higher than in the aqueous decoction due to the greater solubility of these triterpenic acids in alcohol. On the other hand, sesquiterpene lactones are well-known bioactive compounds (Sülsen and Martino 2018) with antitrypanosomal, antileishmanial, antifungal, antibacterial, antiviral, cytotoxic and anti-inflammatory activity.

The anti-inflammatory activity of 11,13-didhydrozaluzanin C in mice has been demonstrated (Piornedo et al. 2011) whilst desacylcynaropicrin, the main sesquiterpene lactone of "palo azul", in addition to its anti-inflammatory properties (Sosa et al. 2011) showed to be effective to suppress RANKL-induced inflammation and osteoclastogenesis and therefore it can be used as a potential treatment for osteoporosis and arthritis (Li et al. 2019). There is a Japanese patent registering the use of *Cyclolepis genistoides* ("palo azul") as an alpha-glucosidase inhibitor (Hasegawa 2005).

10 Conclusions

Little is known about the water-soluble components of "palo azul". Additional research on the presence of other bioactive metabolites such as polyphenols, flavonoids (aglycones and glycosides), chlorogenic acid, caffeoylquinic acids, phenyletanoids, etc., is needed for a better evaluation of this plant.

A recent study to determine the acute toxicity of *Cyclolepis genistoides,* as well as its influence on the general behavior and barbiturate-induced sleeping time in mice, has revealed that the use of hydroalcoholic extract is safe, well tolerated and

exhibits significant hypnotic properties (Montalbetti Moreno et al. 2018). Based on the well-known uses of this plant in traditional medicine and the successful isolation / identification of its lipophilic bioactive metabolites (triterpenic acids, sesquiterpene lactones), *C. genistoides* seems to have an excellent potential as a phytotherapeutic.

Acknowledgments The author thanks Consejo de Investigaciones de la UNT (CIUNT) for financial support.

Rerences

Alonso J, Desmachelier C (2006) Plantas medicinales autóctonas de la Argentina. Ed. Fitociencia, Buenos Aires, Argentina, pp 383–385

Barboza GE, Cantero JJ, Núñez C, Pacciaroni A, Ariza Espinar L (2009) Medicinal plants: a general review and a phytochemical and ethnopharmacological screening of the native argentine Flora. Kurtziana 34(1–2):7–365

Cabrera AL (1978) Flora de la provincia de Jujuy. República Argentina. Parte X. Compositae. Ed. Colección Científica del INTA, Buenos Aires, Argentina, p 592

Catalán CAN, Sánchez V, Díaz F (2020) In preparation

De Heluani CS, De Boggiato MV, Catalán CAN, Díaz JG, Gedris TE, Herz W (1997) Triterpenes and sesquiterpenes lactones from *Cyclolepis genistoides*. Phytochemistry 45:801–805

Don D (1832) Mag. Ann. Chem. 11:392. In: The Plant list. http://www.theplantlist.org/tpl1.1/record/gcc-126919. (Last access, March 2020)

Filipov A (1994) Medicinal plants of the Pilagá of Central Chaco. J Ethnopharmacol 44(3):181–193

Giberti GC (1983) Herbal folk medicine in northwestern Argentina: Compositae. J Ethnopharmacol 7(3):321–341

Hasegawa H (2005) Alpha glucosidase inhibitor comprising Palo Azul as active ingredient. Patent of Japan: JP2005263629 (A)-2005-09-29

Katinas L, Pruski J, Sancho G, Tellería MC (2008) The subfamily Mutisioideae (Asteraceae). Bot Rev 74:469–716

Li Z, Xiaodong Z, Xu R, Wang Y, Hu R, Xu W (2019) Deacylcynaropicrin inhibits RANKL-induced Osteoclastogenesis by inhibiting NF-κB and MAPK and promoting M2 polarization of macrophages. Front Pharmacol 10:article 599

Liu J (1995) Pharmacology of oleanolic acid and ursolic acid. J Ethnopharmacol 49:57–68

Liu J, Liu YP, Klaassen CD (1995) The effect of oleanolic acid on chemical-induced liver injury in mice. Acta Pharmacol Sin 15:16–23

Ma XH, Zhao YC, Yin L, Han DW, Ji CX (1982) Studies on the effect of oleanolic acid on experimental liver injury. Acta Pharm Sin 17:93–97

Ma XH, Zhao YC, Yin L, Han DW, Wang MS (1986) Studies on the preventive and therapeutic effects of ursolic acid on acute hepatic injury in rats. Acta Pharm Sin 21:332–335

Mlala S, Oyedeji AO, Gondwe M, Oyedeji OO (2019) Ursolic acid and its derivatives as bioactive agents. Molecules 24:2751

Montalbetti Moreno Y, Ibarrola DA, Heinichen O, Alvarenga N, Dolz Vargas JH, Hellion-Ibarrola MC (2018) Acute toxicity and potentiation of barbiturate-induced sleep in mice orally treated with hydro-alcoholic extract of *Cyclolepis genistoides* D. Don (Asteraceae). J Appl Pharm Sci 8(11):42–47

Piornedo RR, de Souza P, Alves Stefanello ME, Strapasson RLB, Zampronio AR, Leite Kassuya CA (2011) Anti-inflammatory activity of extracts and 11,13-dihydrozaluzanin C from *Gochnatia polymorpha* ssp. *floccosa* trunk bark in mice. J Ethnopharmacol 133:1077–1084

Sato H, Ishikawa M, Funaki A, Kimura Y, Yoshida H, Fukata H, Hasegawa H, Ueno K (2013) *Cyclolepis genistoides* D. Don (palo azul) promotes differentiation of adipocytes and regulates adipokine expression. Nutr Res 33(11):922–931

Sato H, Funaki A, Kimura Y, Sumitomo M, Yoshida H, Fukata H, Ueno K (2016) Ethanol extract of *Cyclolepis genistoides* D. Don (palo azul) induces formation of myotubes, which involves differentiation of C2C12 myoblast cells. Nutr Res 36(7):731–741

Scarpa GF (2004) Medicinal plants used by the Criollos of Argentine Chaco. J Ethnopharmacol 91:115–135

Shukla B, Viser S, Patnaik GK, Tripathi SC, Srimal RC, Day S, Dobhal PC (1992) Hepatoprotective activity in the rat of ursolic acid isolated from *Eucalyptus* hybrid. Phytother Res 6:74–19

Singh GB, Singh S, Bani S, Gupta D, Banerjee SK (1992) Antiinflammatory activity of oleanolic acid in rats and mice. J Pharm Pharmacol 44:456–458

Sosa A, Fusco MR, Petenatti ME, Juárez A, Del Vitto LA, Petenatti E (2007). Estudios farmacognósticos y farmacológicos comparativos sobre tres especies diuréticas de amplio uso popular en el centro-oeste argentino. Bol Latinoam Caribe Plant Med Aromát (BLACPMA) 6(6):386–387

Sosa A, Fusco MR, Rossomando P, Juárez A, Robles S, Petenatti E, Pelzer L (2011) Anti-inflammatory properties from isolated compounds of *Cyclolepis genistoides*. Pharm Biol 49(7):675–678

Sülsen VP, Martino VS (eds) (2018) Sesquiterpene lactones. Advances in their chemistry and biological aspects. Ed. Springer International Publishing AG, Switzerland. Chapters 8, 9 and 10, and references cited therein. 175–240

Wang X, Li YL, Wu H, Liu JZ, Hu JX, Liao N, Peng J, Cao PP, Lian X (2011) Antidiabetic effect of oleanolic acid: a promising use of a traditional pharmacological agent. Phytother Res 25(7):1031–1040

Wójciak-Kosior M (2013) Effect of different extraction techniques on quantification of oleanolic and ursolic acid in *Lamii albi flos*. Ind Crop Prod 44:373–377

Zuloaga FO, Morrone O (eds) (1996/1999) Catálogo de las plantas vasculares de la República Argentina. I. Pteridophyta, Gymnospermae y Angiospermae (Monocotyledonae), II. Dicotyledonae. Monogr Syst Bot Missouri Bot Gard 60:74