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Review

An inside preview of Ethnopharmacology of *Cissampelos pareira* Linn.

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Abstract

Cissampelos pareira is significant medicinal plant of herbal materia medica. It is used in the treatment of wide range of diseases in Traditional Chinese Medicine, Ayurevda and western herbalism. The plant abounds in isoquinoline alkaloids; the chemicals that received a great deal of attention and research in the late 1960. Antitumour potential of cissampareine and neuromuscular blocking effects of hayatine are of special interest. The review summarizes ethno pharmacological investigations carried out on the plant with special reference to isoquinoline alkaloids.

Keywords: *Cissampelos pareira; isoquinoline alkaloids; pelosine; cissampareine; hayatine; pharmacology*

Introduction

Cissampelos pareira Linn. is significant plant of family Menispermaceae. There are 37 plant species summarized under this botanical name. Their taxonomic position is not clear. In most cases, *C. pareira* or Pareira is used and the single species are called subspecies. It is found in subtropical parts of India, Asia, East Africa and America (Singh,2005).

The plant is a climbing shrub, 2 - 5m high with a thickened root. Leaves have an orbicular shape 7-14 cm in diameter. They are membranous or leathery, veined, glabrous to densely pilose. Flowers are green, male ones in short umbels, 10 - 12cm long, females in pendulous spikes, 7 - 10cm long, with a little round leaflet at the base of every flower (Prasad *et al*.,1962; Smitin and Larsen,1991).

Traditional medicinal use

Brazil*: C. pariera* is widely employed in herbal medicine today as a diuretic and as a tonic, as well as to reduce fever and relieve pain. It is often employed for menstrual cramps, difficult menstruation, excessive bleeding and uterine hemorrhages, fibroid tumors, pre- and postnatal pain, colic, constipation, poor digestion, and dyspepsia (Mukerji and Bhandari,1959; Feng *et al*.,1962).

French Guyana*:* The roots are used in the treatment of dysuria and renal calculi. The Wayãpi Indians use a decoction of the leaf and stem as an oral analgesic (Gogte,2000).

India: In Ayurvedic system of medicine, the leaves are used in the treatment of indolent ulcers (Kirtikar and Basu,2001) and diarrhea (Amresh *et al*.,2003). The plant is considered to be antiseptic and on account of this property, it is used in the treatment of urinary tract infection (Dandiya and Chopra,1970). Expressed juice of *C. pareira* is given in migraine (Singh,2005).

Mexico: *C. pariera* has a long history of use for muscle inflammation, snakebite, rheumatism, diarrhea, dysentery, and menstrual problems (Mokkhasmit,1971).

South America*: C. pariera* is commonly referred to as the midwives' herb throughout South America. It ha been used for all types of women's ailments. The root is used in tropical countries to prevent a threatened miscarriage and to stop uterine hemorrhages after childbirth. Midwives in the Amazon still carry abuta with them for menstrual cramps and pre- and postnatal pain, excessive menstrual bleeding, and uterine hemorrhaging (Floriani,1936).

Thailand: The extract from its leaves can be used to make gel. The dark green gel is used as medicine for treating fever in local people. Local people use this plant as a diuretic and for the treatment of a variety of ailments, including

asthma and for traumas (Mokkhasmit *et al*.,1971).

Phytochemistry: An amorphous, white alkaloid, *pelosine* (Figure 1) was studied in association with an indifferent body, *deyamittin*. Cissampelosine was reported from *C. pariera* which was later on shortened as pelosine (Wiggers, 1838).

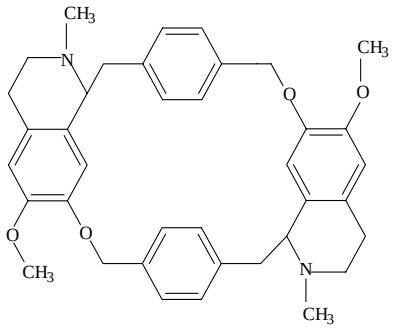


Fig.1: Structure of Pelosine

Eleven years later, studies on pelosine and bebeerine were undertaken and both the alkaloids were proved to be different (Bodeker,1849). However a study proved similarity with the alkaloids *bebeerine* and *buxine* (Flückiger,1869). A comparative analysis of *C. pareira* demonstrated presence of starch, gum, tannin, phlobaphene, and an alkaloid (Ringer and Brooke, 1982).

C. pareira contain a group of plant chemicals called isoquinoline alkaloids (Roy *et al*.,1959). Since the late 1960s, these chemicals have received a great deal of attention and research (Boissier *et al*.,1965). Cissampareine (Figure 2) was reported from *C. pareira* growing in Peru (Kupchan,1964). Cissampareine was found to show significant and reproducible inhibitory activity against human carcinoma of the nasopharynx carried in cell culture (KB). Cissampareine is isomeric with methylwarifteine found in dried rhizomes of *C. ovalifolia* DC.

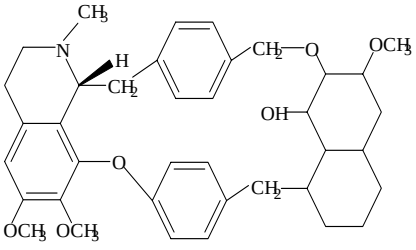


Fig. 2: Structure of Cissampareine

(++)-4^{II}-*O*-methylcurine (Fig. 3), a new alkaloid was isolated from *C. pareira* (Haynes *et al*.,1966). *l*-curine (Fig.4), *d*-iso-chondrodendrine (Fig.5), and hayatine (Fig.6) were isolated from the roots and vines of *C. pareira* from Madras (Kupchan *et al*.,1966). Preliminary pharmacological study of the methanol-extractable alkaloids, of the methiodide prepared from the latter mixture, and of the quaternary alkaloids, showed that all had curare-like activity (Mukerji and Bhandari,1959).

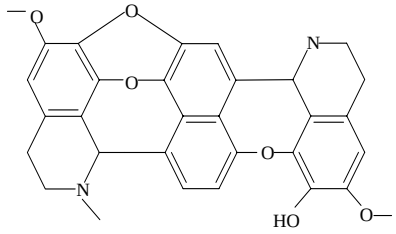


Fig. 3: Structure of (++)-4”-O-Methylcurine

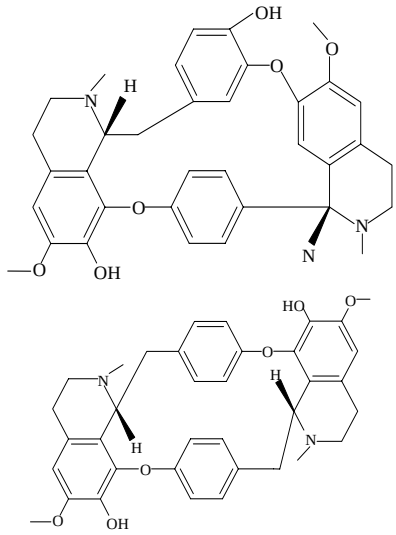


Fig 4: Structure of *l*-curine
Fig .5: Structure of *d*-iso-chondrodendrine

A study reported stereochemistry and pharmacology of hayatine (Fig.6) (Sur, and Pradhan,1963). Chemical investigation on the roots from Kashmir, reported 0.33 % of alkaloids, mainly hayatine and bebeerines (Kirtikar and Basu,2001), 0.2 % essential oils, 3.4 % fixed oils and a sterol (Bhattacharji, 1952). In the same year, stereochemistry of hayatidine (Fig.8) and hayatinine (Fig.12) was reported (Bhatnagar *et al*.,1967; Bhatnagar and Popli,1967).

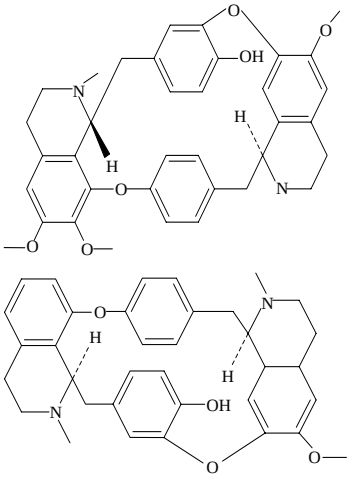


Fig. 6: Structure of Hayatine
Fig .7: Structure of Bebeerine

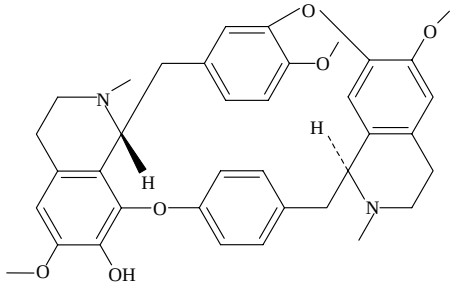


Fig .8: Structure of Hayatidine

Cissamine (Fig.9) and cycleanine (Fig.10) have been reported from the roots (Anwer et al.,1968; Bhattacharji, *et al*.,1952). Root is reported to contain *l*-curine. Root bark is reported to contain menismine, pareirine (Fig.11) and hayatinine (Combes *et al*.,1965; Dwuma-Badu *et al*.,1975).

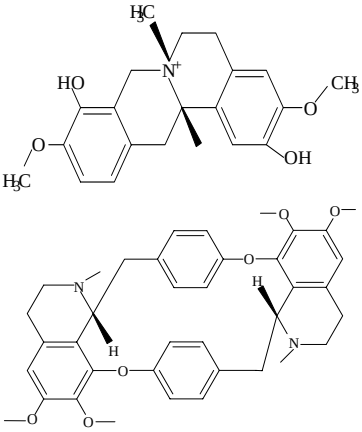


Fig.9: Structure of Cissamine
Fig. 10: Structure of Cycleanine

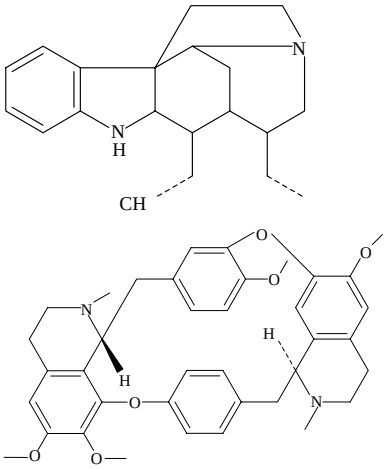


Fig. 11: Structure of Pareirine
Fig .12: Structure of Hayatinine

Tetrandrine (Fig.13) has been reported from the roots of *C. pareira* growing in Thailand (Rojanasonthorn,1970). Dicentrine (Fig.14), dihydrodicentrine, cycleanine, insularine (Fig.15) and isochondrodendrine have been reported from roots of the plant growing in Ghana (30). Isolation of pareirubrine A (Fig.16) and B (Fig. 17), novel tropoloisoquinoline alkaloids with antileukemic activity has been reported (Morita *et al*.,1993).

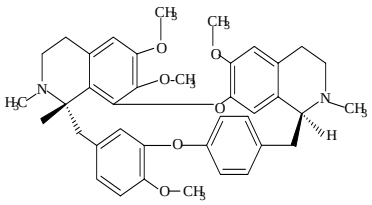


Fig. 13: Structure of Tetrandrine

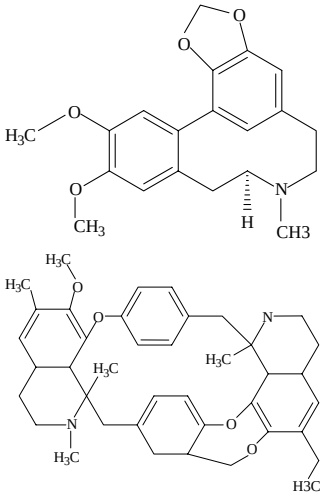


Fig 14. Structure of Dicentrine
Fig 15. Structure of Insularine

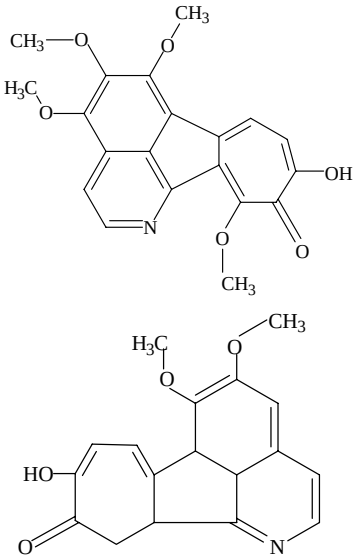


Fig. 16: Structure of Pareirubrine A
Fig. 17: Structure of Pareirubrine B

Tropoloisoquinoline alkaloid pareitropone (Fig. 18) has been reported (Morita *et al*.,1993). A novel azafluoranthene alkaloid, norimeluteine (Fig.19), has been isolated as a cytotoxic substance from *C. pareira* together with an alkaloid having the same skeleton, norruffscine (Morita *et al*.,2002).

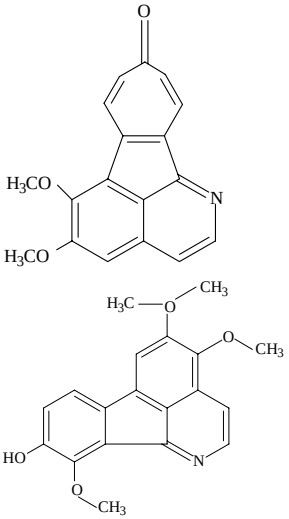


Fig.18:Structure of Pareitropone
Fig. 19. Structure of Norimeluteine

An antiprotozoal chalcone-flavone dimer, cissampeloflavone (Fig.21) has been isolated from the aerial parts of *C. pareira*. It has good activity against *Trypanosoma cruzi* and *T. brucei rhodesiense* and has a low toxicity to the human KB cell line (Carabot *et al*.,2003). D-Qurecitol (Fig.22) and grandirubrine (Fig.23) have been reported.

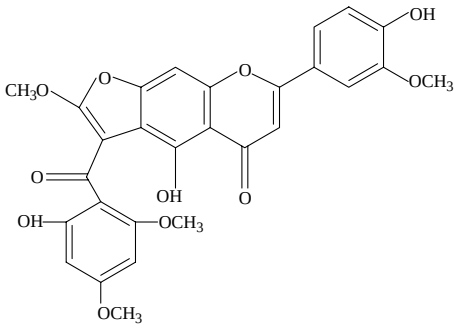
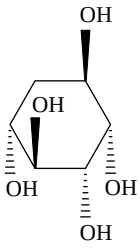


Fig. 21: Structure of Cissampeloflavone
Fig .22: Structure of D-Qurecitol



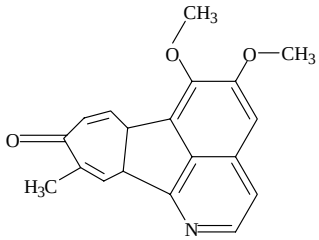


Fig. 23: Structure of grandirubrine

Pharmacology

Antinociceptive and antiarthritic activity: In the present study, 50% aqueous ethanolic extract of roots of *C. pareira* at the dose levels of 100–400 mg/kg, once daily for 3 days exhibited significant ($P < 0.001$) resistance against mechanical pain after 30 min in analgesymeter induced pain in mice. In acetic acid (0.6%; i.p.) inducing writhing, *C. pareira* significantly ($P < 0.05$) decreased the writhing episodes; the degree of percent protection at 200 and 400 mg/kg was 22.73 and 51.63. The hot plate reaction time was increased by 2.07 ($P < 0.05$) and 2.70 ($P < 0.001$) folds, respectively. Further *C. pareira* showed the dose dependent significant protective effect against complete Freund's adjuvant induced arthritis (Amresh *et al*.,2001).

Anti-inflammatory activity: Oral administration of 50% ethanolic extract of the aerial part of *C. pareira* exhibited significant and

dose dependent anti-inflammatory activity in the carrageenin test, which was based on interference with prostaglandin synthesis, as confirmed by the arachidonic acid test. In the abdominal writhing test induced by acetic acid, higher dose of the plant extract had the highest analgesic activity, whereas in the hot-plate test the best dose was 100 mg/kg ($p< 0.05$). The LD_{50} showed that *C. pareira* (2000 mg/kg) presented low toxicity (Amresh *et al*.,2007).

In yet another study, 50% ethanolic extract of *C. pareira* roots in acute, subacute and chronic models of inflammation was assessed in rats. *Per os* (p.o.) administration of *C. pareira* (200, 400 mg/kg) exhibited significant anti-inflammatory activity. In acute inflammation as produced by carrageenin 59.55% and 64.04%, by histamine 15.38% and 30.77%, by 5-hydroxytryptamine 17.78% and 31.11% and by prostaglandin E_2-induced hind paw edema 19.23% and 30.77% protection was observed. While in subacute anti-inflammatory models using formaldehyde-induced hind paw edema (after 1.5 h) 38.36% and 47.95% and in chronic anti-inflammatory model using cotton pellet granuloma 15.02% and 19.19% protection from inflammation was observed (Amresh *et al*.,2008).

Antifertility activity: *C. pareira* leaf extract, when administered orally, altered the estrous cycle pattern in female mice, prolonged the length of estrous cycle with significant increase in the duration of diestrus stage and reduced significantly the number of litters in albino mice. The analysis of the principal hormones involved in estrous cycle regulation showed that the plant extract altered gonadotropin release (LH, FSH and prolactin) and estradiol secretion. The oral LD50 of the extract was found to be 7.3 g/kg in mice. (Ganguly *et al*.,2007)

Antioxidant activity*: C. pareira* extract showed significant antioxidant activity in the 1,1 - diphenyl-2-picrylhydrazyl assay. *C. pareira* extract was found to significantly scavenge superoxide, hydrogen peroxide, hydroxyl radicals, and nitric oxide at a dose regimen of 50 to 400 µg/kg *in vitro*. *C. pareira* extract also inhibited hydroxyl radical-induced oxidation of proteins *in vitro*. *C. pareira* extract exhibit a potent protective activity in an acute oxidative tissue injury animal model: benzo (a) pyrene-induced gastric toxicity in mice *in vivo* (Amresh et al.,2007).

Chemo preventive effects*:* The protective effect of *C. pareira* extract was studied against benzo (*a*) pyrene [B(*a*)P]-induced gastric cancer in mice, and the tumor incidence was reduced and the mean number of tumors and the tumor multiplicity were reduced significantly and dose-dependently. The modulatory effect of *C. pareira* extract was also examined on carcinogen metabolizing phase I and phase II enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase, and lipid peroxidation in liver. Significant increases in the levels of acid-soluble sulfhydryl (-SH) and cytochrome P_{450} contents and in enzyme activities of cytochrome P_{450} reductase, cytochrome b_5 reductase, GST, DTD, SOD, catalase, glutathione (GSH) peroxidase, and GSH reductase but decreased malondialdehyde (MDA) were observed. (Amresh *et al*.,2007)

Anti-hemorrhagic effects*:* To establish the anti-hemorrhagic activity of aqueous extract from leaves of *C. pareira*, the skin of mice was injected with a mixture of extract and venom, and it as found that extract produced a total inhibition of this activity. On the other hand, experiments regarding the anti-proteolytic activity were conducted observing the effect on casein in a test tube or on biotinylated casein in a microplate. None of the two procedures was able to show any inhibitory activity (Badilla *et al*.,2008).

Toxicity

In the acute toxicity test, oral administration of 2 g/kg of *C. pareira* produced neither mortality nor changes in behavior or any other physiological activities in mice. In subacute toxicity studies, no mortality was observed when the two doses of 1 or 2 g/kg day of 50% aqueous ethanolic extract of *C. pareira* were administered p.o. for a period of 28 days in rats. There were no significant changes occurred in the blood chemistry analysis in both sexes of animals. Hematological analysis showed no marked differences in any of the parameters examined in either the control or treated group of both sexes. Pathologically, neither gross abnormalities nor histopathological changes were observed (Amresh *et al*.,2008).

Pharmacology of hayatine

Hayatin methiodide has been used as a muscle relaxant during surgery in 100 patients. This drug provided adequate relaxation for

endotracheal intubation and surgery. It appeared to be about one-third as potent as tubocurarine. The duration of both these drugs was of equal magnitude in equipotent doses. The neuromuscular block produced by this drug could be completely reversed by neostigmine. It was relatively free from serious side-effects and appears to be a promising muscle relaxant.

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