

Review Article

CALOTROPIS PROCERA: AN OVERVIEW OF ITS PHYTOCHEMISTRY AND PHARMACOLOGY

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<p>* For Correspondence:</p> <p>Pharmacy Wing, Lachoo Memorial College of Science and Technology, Shastri Nagar, Jodhpur, Rajasthan. (INDIA).</p> <p>Email: shoaib.quazi2@gmail.com</p>	<p>ABSTRACT</p> <p>Herbal medicines have been used from the earliest times to the present day. The ethno pharmacology is as old as man himself. Herbal medicines exhibit a remarkable therapeutic diversity. Calotropis procera Linn. is an Ayurvedic plant which is used in several traditional medicines to treat a variety of diseases. The extracts from different parts of the plant have significant therapeutic value. The whole plant when dried exhibits good tonic, antihelmintic and expectorant activities. The roots also have similar activities and also act as an effective laxative. Traditionally, the powdered root is used to treat bronchitis, asthma, leprosy, eczema, elephantiasis while the latex is used to treat vertigo, baldness, hair loss, toothache, intermittent fevers, rheumatoid/joint swellings, and paralysis. The leaves are used to treat joint pain, and reduce swelling. Besides its Ayurvedic use, Calotropis procera Linn. is also used as a homeopathic medicine. In ancient Ayurvedic medicine the plant Calotropis procera Linn. was known as "Rakta arka". The pungent latex extracted from the leaves and flowers of Calotropis procera is processed and used in the commercial preparation of eye tonics.</p> <p>KEY WORDS: Ayurveda; pharmacological action; phytochemistry; <i>Calotropis procera</i> Linn</p>
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INTRODUCTION

Calotropis procera Linn. Family Asclepiadaecae is an Ayurvedic plant with important medicinal properties. It is known by various vernacular names like Swallow wort in English, madar in Hindi and Alarka in Sanskrit. It is found in most parts of the world with a warm climate in dry, sandy and alkaline soils. Calotropis is primarily harvested because of its distinctive medicinal

properties. It is commonly referred to as ark, swallow-wart or milkweed and it occurs frequently in Indonesia, Malaysia, China, and the Indian subcontinent as wasteland weed. The ark plant with white flowers is a superior variety and is referred to as Calotropis procera. In India, it is found from the Punjab and Rajasthan to Assam and Kanyakumari up to an altitude of 1050 m. It grows abundantly in Rajasthan. It is found in waste lands and grows

as a weed in cultivated areas. It also grows well on rubbish heaps, waste and fallow land, by the roadside and in sand dunes. The inner bark of *Calotropis* is used to make strong fibers called *madar* which are used in the manufacture of weave carpets, ropes, sewing thread and fishing nets. *Calotropis procera* Linn is an erect, tall, large, highly branched and perennial shrub or small tree that grows to a height of 5.4 m, with milky latex throughout (<http://www.asianjtm.com>).

MORPHOLOGY OF PLANT

Flower : Flowers consist of 5 small triangular dirty white sepals, 5 thick ovate petals (1cm x 1cm) which are white at the base and purple at the tips and 5 purple tipped stamens, which surround a white 5 lobed stigma.

Fruit: Fruits consist of green, spongy ovoid fruits (follicles), up to 15 cm long by 10 cm wide. They split open to release plumed, papery light brown seeds with a pappus of white filaments up to 6 cm long on one side.

Root: The root occurs in the entire condition. The bark is separated from the wood 0.5-2.0 cm. in diameter bearing rootlets with diameter varying from 0.2 to 0.5 cm. externally whitish grey in colour, wrinkled in the fresh condition, plenty of whitish latex exudes from cuts or wounds in the bark. Fracture is incomplete.

Leaf: Simple, opposite, sub-sessile, slightly thick, fleshy, coriaceous, 10-15 cm. long and 4.5 to 6.5 cm. broad, broadly cuneate, obovate or obovate oblong, slightly cordate and auricled at base with tuft of short simple hairs on the upper side near place of the attachment to the petiole.

PHYTOCHEMISTRY

The plants contain the cardenolide, *proceragenin*, while the root bark contains *benzoylinesolone* and *benzoylisolinellone*. The leaves and stalk contain *calotropin*, and *calotropagenin* while the flower contains *calotropenyl acetate*, and *multiflavenol* and the latex contains *uzarigenin*, and *terpenol*

ester. Chemical investigation of this plant has shown the presence of triterpenoids, *calotropursenyl acetate* and *calopfriedelenyl*, a norditerpenyl ester, *caloptropternyl ester* oleanene triterpenes like *calotropoleanyl ester*, *procerleanol A* and *B* and cardiac glycosides *calotropogenin*, *calotropin*, *uscharin*, *calotoxin* and *calactin* The plant also has been investigated for the presence of cardenolides and anthocyanins. Phytochemical investigation of the roots of *Calotropis procera* Linn yields two new phytoconstituents, *procerursenyl acetate* and *proceranol*, together with the known compounds *N-dotriacont-6-ene*, *glyceryl mono-oleoyl-2-phosphate*, *methyl myristate*, *methyl behenate* and *glyceryl-1, 2-dicapriate-3-phosphate*. The structures of the new compounds have been identified as *urs-18 alpha-II-12, 20 (30)-diene-3 beta-yl acetate* and *n-triacontan-10 beta-ol* on the basis of spectral data analysis and chemical reactions. The root bark has also been found to possess α -*amyrin*, β -*amyrin*, *lupeol*, β -*sitosterol* [9] and flavanols like *quercetin-3-rutinoside*. In the leaves, *mudarine* is the principal active constituent as well as a bitter yellow acid, resin and 3 toxic glycosides *calotropin*, *uscharin* and *calotoxin*. The latex contains a powerful bacteriolytic enzyme, a very toxic glycoside *calactin* (the concentration of which is increased following insect or grasshopper attack as a defense mechanism), *calotropin D I*, *calotropin D II*, *calotropin-F I*, *calotropin F II* and a non-toxic proteolytic enzyme *calotropin* (2 %-3 %). This *calotropin* is more proteolytic than *papain*, and *bromelain* coagulates milk, digests meat, gelatin and casein. The whole plant contains α and β -*amyrin*, *beta-amyrin*, *teraxasterol*, *gigantin*, *giganteol*, *isogiganteol*, *beta-sitosterol* and a wax (Perwez and Mohammad, 2009).

PHARMACOLOGICAL ACTIVITIES

The plant has attracted much attention due to following biological activities: The previous

pharmacological studies include reports of anticancer, antifungal and insecticidal activity of *C. procera* (Ahmed et al., 2006). The flowers of the plant exhibit hepatoprotective activity, anti-inflammatory, antipyretic, analgesic, and antimicrobial effects and larvicidal activity. The latex of the plant is reported to possess analgesic and wound healing activity as well as anti-inflammatory and antimicrobial activity while the roots are reported to have anti-fertility and anti-ulcer effects (Yoganarasimhan, 2011).

Analgesic Activity

A single oral dose of dry latex ranging from 165 to 830 mg/kg produces a significant dose-dependent analgesic effect against acetic acid-induced writhing. The effect of dry latex at a dose of 415 mg/kg is more pronounced than a 100 mg/kg oral dose of aspirin. In addition, dry latex (830 mg/kg) produces marginal analgesia in a tail-flick model which is similar to that of aspirin. The analgesic effect of dry latex is delayed 1 h by naloxone at a dose of 0.5 mg/kg, which completely blocks the analgesic effect of morphine (10 mg/kg). However, the effect of aspirin was not blocked by naloxone. An 830 mg/kg oral dose of dry latex did not produce any toxic effects in mice and the LD50 was found to be 3000 mg/kg (Ahmed et al., 2005). Antinociceptive effect of proteins from *Calotropis procera* (Asclepiadaceae) latex using three different experimental models of nociception in mice. The latex protein fraction administered intraperitoneally to male mice at doses of 12.5, 25 and 50 mg/kg showed a dose-dependent antinociceptive effect compared with the respective controls in all assays. Inhibition of the acetic acid induced abdominal constrictions was observed at doses of 12.5 (67.9 %), 25 (85 %) and 50 (99.5 %) mg/kg compared with controls. Latex protein at doses of 25 (39.8 %; 42 %) and 50 mg/kg (66.6 %; 99.3 %) reduced the nociception produced by formalin in the 1st and 2nd phases, respectively, and this effect was not reversed by pretreatment with naloxone (1

mg/kg). In the hot plate test, an increase in the reaction time was observed only at 60 min after treatment with latex at doses of 25 (79.5 %) and 50 (76.9 %) mg/kg, compared with controls and naloxone was unable to reverse this effect. It was concluded that the protein fraction derived from the whole latex of *Calotropis procera* possesses antinociceptive activity, which is independent of the opioid system (Saber et al., 1969).

Antifertility activity

The effect of an ethanolic extract of the roots of *Calotropis procera* has been studied in albino rats to explore its antifertility and hormonal activities. Strong anti-implantation (inhibition 100 %) and uterotropic activity was observed at a dose of 250 mg/kg (1/4 of LD50). No antiestrogenic activity was detected (Saxena and Saxena, 1979).

Anti-tumor studies

The anti-tumor potential of the root extracts of *Calotropis procera* Linn., was investigated using the methanolic (CM), hexane (CH), aqueous (CW) and ethyl acetate extract (CE) and its possible mechanism against Hep2 cancer cells was studied. Cellular proliferation activities were assayed by tetrazolium bromide (MTT) colorimetry. Morphological changes in cancer cells were observed under an inverted microscope and the cell cycle parameters were determined by flow cytometry following propidium iodide staining. Treatment with the extracts at different doses of 1, 5, 10 and 25 µg/ml revealed that CM, CH and CE possessed cytotoxicity, whereas CW had no cytotoxic effect. CE (10 µg/ml) showed strongest cytotoxic effect (96.3 %) on Hep2 at 48 hr following treatment, whereas CM and CH exhibited cytotoxicity of 72.7 and 60.5 %, respectively. The extract-treated cells exhibited typical morphological changes of apoptosis. The results of flow cytometric analysis clearly demonstrated that the root extracts produced apoptosis of Hep2 cells through cell cycle arrest at the S phase, thus preventing cells from entering the G2/M

phase. The results of this study indicate that the root extracts of *C. procera* inhibit the proliferation of Hep2 cells via mechanisms based on apoptosis and cell cycle disruption (Rajani and Gupta, 2009; Lal et al., 1985).

Anthelmintic activity

The anthelmintic activity of *Calotropis procera* Linn. Flowers, in comparison with levamisole, was evaluated in a series of in vitro and in vivo studies. The in vitro studies demonstrated the anthelmintic effects ($P < 0.05$) of crude aqueous (CAE) and crude methanolic extracts (CME) of *Calotropis procera* flowers on live *Haemonchus* (*H.*) *contortus* as shown by mortality or temporary paralysis. For the in vivo studies, *Calotropis procera* flowers were administered as a crude powder (CP), CAE and CME to sheep naturally infected with a mixed sample of gastrointestinal nematodes. The percentage reduction in egg count (ECR) was recorded as 88.4 and 77.8 % in sheep treated with CAE and CP at 3000 mg/kg body weight on day 7 and 10 post-treatment (PT), respectively. CME was the least effective producing only a 20.9 % reduction in ECR on day 7 PT. It was found that *Calotropis procera* flowers possess good anthelmintic activity against nematodes, although this was less than that exhibited by levamisole (97.8 %–100 %). It is suggested that further research be carried out on a larger scale involving a greater number of animals, doses higher than those used in the current study, together with identification of active principles, and standardization of the dose and toxicity studies for drug development (Larhsini et al., 1997).

Anti-hyperglycemic effect

The dry latex (DL) of *Calotropis procera* possessing potent anti-inflammatory activity was evaluated for its antioxidant and antihyperglycemic effects in rats with alloxan-induced diabetes. Daily oral administration of dry latex at 100 and 400 mg/kg produced a dose-dependent decrease in blood glucose and an increase in hepatic glycogen. Dry latex also

prevented the body weight loss in diabetic rats and reduced the daily water consumption to values comparable with those of normal rats. Dry latex also produced an increase in the hepatic levels of endogenous antioxidants, namely superoxide dismutase (SOD), catalase and glutathione, while it reduced the levels of thiobarbituric acid-reactive substances (TBARS) in alloxan-induced diabetic rats. The efficacy of dry latex as an antioxidant and as an anti-diabetic agent was comparable with that of the standard antidiabetic drug, glibenclamide (Silvania, 2005).

Hepatoprotective activity

The plant is a rich source of phytoconstituents but there is no scientific basis or reports in recent literature regarding the usefulness of the root bark as a hepatoprotective agent and this prompted us to evaluate the root bark of the plant for possible hepatoprotective activity. An aqueous ethanolic extract (70 %) of *Calotropis procera* flowers was prepared and tested for its hepatoprotective effect against paracetamol-induced hepatitis in rats. Changes in the levels of biochemical markers of hepatic damage, like SGPT, SGOT, ALP, bilirubin, cholesterol, HDL and tissue GSH, were investigated in both treated and untreated groups. Paracetamol (2000 mg/kg) has been reported to enhance SGPT, SGOT, ALP, bilirubin and cholesterol levels and reduce serum levels of HDL and the tissue level of GSH while treatment with an aqueous ethanolic extract of *C. procera* flowers (200 mg/kg and 400 mg/kg) restored the altered levels of biochemical markers to almost normal levels in a dose-dependent manner (Ranab et al., 2002).

Inflammatory activity

Latex of *Calotropis procera* was studied for its inflammatory reactions using pedal oedema and air pouch models of inflammation in rats. Subcutaneous injection of aqueous solution (0.1 ml of 1%) of dry latex (DL) into the plantar surface of paw produced significant inflammation. Maximum inflammatory response was obtained 1 h after the injection

and was maintained for a further 1 h. The inflammatory response was accompanied by an increase in vascular permeability that reached its maximum within 15 min. Inflammation was also induced in the 6-day-old rat air pouch by injecting a 2.5 % solution of DL. The latter model was characterized for the exudates volume and its protein concentration, and wet and dry weights of granuloma. A time-course study indicated that both the exudates volume and the weight of granuloma were at maximum on day 5 after DL injection while the protein concentration peaked on the third day. Further, the two models were also studied for the anti-inflammatory effect of various drugs. It was observed that in the pedal oedema model, phenylbutazone was more effective than prednisolone while almost complete inhibition was produced by mepyramine and cyproheptadine. On the other hand, in the air pouch model, prednisolone was more effective than phenylbutazone in inhibiting the inflammation. Thus, the DL-induced inflammation in different models could be used to evaluate anti-inflammatory drugs (Zafar et al., 2005).

Anti-diarrhoeal activity

The dry latex (DL) of *Calotropis procera*, a potent anti-inflammatory agent, was evaluated for its anti-diarrhoeal activity. Like atropine and phenylbutazone (PBZ), a single oral dose of DL (500 mg/kg) produced a significant decrease in the frequency of defecation and the severity of diarrhea as well as protecting from diarrhoea in 80 % rats treated with castor oil. To understand the mechanism of its anti-diarrhoeal activity, we evaluated its effect on intestinal transit, castor oil-induced intestinal fluid accumulation (enteropooling) and electrolyte concentration in intestinal fluid. Dry latex produced a decrease in intestinal transit (27 %–37 %) compared with both normal and castor oil-treated animals. Unlike atropine, dry latex significantly inhibited castor oil induced enteropooling. However, it did not

alter the electrolyte concentration in the intestinal fluid compared with castor oil-treated rats.

Anti-convulsant effects

The anticonvulsant activity of different root extracts of *Calotropis procera* was studied in rats in order to evaluate the traditional use of this plant. The anticonvulsant activity of different extracts of *Calotropis procera* roots was studied using seizures induced by maximal electroshock seizures (MES), pentylenetetrazol (PTZ), lithium-pilocarpine and electrical kindling seizures. In the MES test, the chloroform extract of *Calotropis procera* roots showed the most significant ($P<0.01$) anticonvulsant effect by decreasing the duration of hind limb extension (extensor phase), clonus and also the duration of the stupor phase, compared with the controls. In the PTZ test, the chloroform extract exhibited a highly significant ($P<0.001$) effect, and the aqueous extract had the most significant ($P<0.01$) effect compared with the controls by delaying the onset of convulsions. The extracts also inhibited convulsions induced by lithium-pilocarpine and electrical kindling. The results of this study indicate that the chloroform extract and aqueous extract of *Calotropis procera* roots may be beneficial in absence (petit mal) and tonic clonic (grand mal) types of seizures.

Anti-microbial activity

We studied the antimicrobial activities of chloroform and methanol extracts of seeds of *Calotropis procera* obtained from plants located in the forest area of Ghaziabad, India. The chloroform extract of *Calotropis procera* seeds exhibited better antimicrobial activity while the extracts obtained from *Calotropis procera* seeds were evaluated for their possible in vitro antibacterial activities using the paper disc method.

Oestrogenic functionality

The effects of ethanolic and aqueous extracts of *Calotropis procera* roots were studied on the oestrous cycle and on some parameters of

oestrogenic functionality in rats. Both extracts were found to interrupt the normal oestrous cycle in 60 % and 80 % of rats treated. The rats exhibited a prolonged dioestrous stage of the oestrous cycle with consequent temporary inhibition of ovulation. The contemporary administration of a commercial oestro-progestinic preparation exhibited the same effects in 100 % of rats treated. However, the extracts had no oestrogenic activity when tested in immature female bilaterally ovariectomized rats (Zafar et al., 2005).

Anti-malarial activity

The ethanolic extracts of the different parts of *Calotropis procera* showed IC50 values ranging from 0.11 to 0.47 mg/ml against *P. falciparum* MRC20-CQ-sensitive. And from 0.52 to 1.22 mg/ml against MRC76_CQ-resistant strains, flower and bud extracts being the most active. Although 220-440 times less effective than CQ, these extracts deserve further study aimed at identification of the active constituents. The results obtained support the ethnobotanical use of this plant.

TOXICITY STUDIES

The plant is toxic and is one of the few plants not eaten by grazing animals. Due to its toxicity, the latex extracted from the stem has traditionally been used to make poison arrows. The latex is highly toxic to human eyes and produces sudden painless dimness of vision with photophobia. Latex of *Calotropis procera* was studied for its inflammatory effects using pedal oedema and air pouch models of inflammation in rats. Subcutaneous injection of an aqueous solution (0.1 ml of 1 %) of dry latex (DL) into the plantar surface of the paw produced significant inflammation. It was observed that, in the pedal oedema model, phenylbutazone was more effective than prednisolone while almost complete inhibition was produced by mepyramine and cyproheptadine. On the other hand, in the air pouch model, prednisolone was more effective than phenylbutazone in inhibiting

inflammation. Thus, dry latex-induced inflammation in different models could be used to evaluate anti-inflammatory drugs (Kumar et al., 2005).

Productivity of *Calotropis procera* and its use in renewable energy

India has over 180 million of wasteland out of which 90 million ha is uncultivable. The degraded and denuded lands arise due to soil erosions as well as secondary salinizations. However *Calotropis procera* is a potential plant for bioenergy and biofuel production in semi-arid regions of the country because it is able to grow on such lands. The plant has a growth potential of 2 dry tons to 40 dry tons per ha depending on the agro climatic conditions of its growth. The plant has high level of regeneration potential and could be harvested up to 4 times a year. The plant yields valuable hydrocarbons which could be converted into diesel substitutes. The bio-diesel derived from *Calotropis procera* is free from NOx gases, SO₂ and Suspended Particulate Matter (SPM) and has high cetane value. Due to its enormous potential for growth under adverse climatic conditions *Calotropis procera* is suggested as potential plant for bio-diesel production under semi-arid and arid conditions (<http://www.science20.com>).

CONCLUSION

The World Health Organization has estimated more than 80 % of the world's population in developing countries depends primarily on herbal medicines for their basic healthcare needs. In recent years, ethno-botanical and traditional uses of natural compounds, especially those of plant origin, have received much attention as they are well known for their efficacy and are generally believed to be safe for human use. It is best to use the classical approach in the search for new molecules to manage a variety of diseases. A thorough review of the published literature on *Calotropis procera* shows that it is a popular remedy in a variety of ethnic groups, as well as

Ayurvedic and traditional practitioners for the treatment of a range of ailments. *Calotropis procera* is suggested as potential plant for bio-diesel production under semi-arid and arid conditions. Researchers are exploring the therapeutic potential of this plant as it is likely to have more therapeutic properties than are currently known.

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