

**EVALUATION OF THE TOXICITY, MEDICINAL USE AND PHARMACOLOGICAL
ACTIONS OF *CALOTROPIS PROCERA******Innocent O. Imosemi**

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Article Received on 22/06/2016

Article Revised on 13/07/2016

Article Accepted on 02/08/2016

ABSTRACT

The African continent is one of the continents endowed with the richest biodiversity in the world, with an avalanche of many food plants used as herbs, health foods and for therapeutic purposes. Higher plants as sources of medicinal compounds continue to play a dominant role in maintenance of human health since antiquities. *Calotropis procera* (*C. procera*) also known as the giant milk weed is one of the flowering plants commonly found in the tropics world over. It is known as sodom apple, calotrope, French cotton, small crown flower (English) and algodón de seda, bomba (Spanish). The plant is used as arrow poison and the latex is toxic to the skin and poisonous to the eyes, which can lead to blindness. Inspite of the toxicity of *C. procera*, it has been used in traditional medicine as a purgative, antihelmintic as well as in the treatment of leucoderma, ulcer, rheumatoid arthritis and diseases of the spleen, liver and stomach. *C. procera* possesses anti-inflammatory, antibacterial, antipyretic, antidiabetic, anticancer and antioxidant properties. This review, consisting of literature search of journals and chapters in books aims at evaluating the toxic effects, medicinal use and pharmacological actions of *C. procera*.

KEYWORDS: herbs, *Calotropis procera*, traditional medicine, anti-oxidant, anti-inflammatory.**BACKGROUND**

Plants are the most researched and have been the major source of drugs that are used in modern medicine today and will continue to provide cure for man.^[1,2] Natural products also play an important role in drug development programme of the pharmaceutical industry.^[3] In developing countries, especially in rural contexts, people usually turn to traditional healers when in diseased conditions and plants of ethnobotanical origin are often presented for use.^[4] Over 5,000 different species of plant substances have been recognized to occur in these areas and many of them have been found to be useful in traditional medicine, for prophylaxis and cure of diseases.^[5] The growing awareness of the harmful side-effects of chemotherapy has made people to explore the time tested remedies from traditional alternative medicine. The anti-inflammatory, antibacterial, antipyretic and antioxidant activities of some medicinal plants such as *Vernonia amygdalina*, *Calotropis procera* and *Garcinia kola* (*Kolaviron*) have been well documented.^[6,7]

Calotropis procera is found in almost all parts of Nigeria but more abundant in the Northern part of the country.^[8] *Calotropis procera* is a perennial grayish green, woody shrub with broad ovate fleshy leaves that grows wild in the tropics and warm temperate regions.^[9,10] It derived its common name, giant milk weed, from the thick white

sap which oozes from a cut stem or from the stem when a leaf is plucked off. Hence, the family to which the plant belongs is referred to as milkweed family.^[11] Giant milkweed roots were found to have few branches and reach depths of 1.7 to 3.0 m in Indian sandy desert soils.^[12] The opposite leaves are oblongobovate to nearly orbicular, short-pointed to blunt at the apex and have very short petioles below a nearly clasping, heart-shaped base.

The leaf blades are light to dark green with nearly white veins. They are 7 to 18 cm long and 5 to 13 cm broad, slightly leathery, and have a fine coat of soft hairs that rub off. The flower clusters are umbelliform cymes that grow at or near the ends of twigs. The flowers are shallowly campanulate with five sepals that are 4 to 5 mm long, fleshy and variable in color from white to pink, often spotted or tinged with purple. The fruits are inflated, obliquely ovoid follicles that split and invert when mature to release flat, brown seeds with a tuft of white hairs at one end.^[13,14]

Giant milkweed favours open habitat with little competition. This condition is most completely met in overgrazed pastures and rangeland. Other common habitats are beachfront dunes, roadsides, and disturbed urban lots. The species grows in dry habitat (150 to 1000 mm precipitation) and sometimes in excessively drained

soils in areas with as much as 2000 mm of annual precipitation. Giant milkweed may be found in areas up to 1,000 m in elevation in India.^[15] It roots very deeply and rarely grows in soils that are shallow over unfractured rock. Soils of all textures and derived from most parent materials are tolerated, as well as soils with high sodium saturation. Beachfront salt spray is not detrimental. Competition with tall weeds, brush, and especially grass weakens existing plants, and being overtopped and shaded by trees soon eliminates them. During droughts in Puerto Rico, giant milkweed is attacked by the orange aphid, *Aphis nerii* Boyer de Fonscolombe, which causes defoliation, death of branches, and aborted fruits.^[16]

Flowering and fruiting takes place throughout the year.^[16] Hundreds to thousands of seeds may be produced per plant each year. Eighty-nine percent germination takes place in potting mix between 7 and 64 days after sowing. Half the seed weight was found in the wing (silk). The seeds are dispersed by wind and may fly for several hundred yards in gentle breezes. Seedlings may arise in abundance after rainy periods, but only a few survive the first season. Using the reserves in its large taproot, giant milkweed can re-sprout year after year when burned or cut.^[16]

Giant milkweed usually reaches heights of about 2 m, but may occasionally reach 5 m in height and stem diameters of 25 cm.^[16] Growth is about 1 m the first year after sprouting in Puerto Rico. Senescence of individual stems takes place in about 5 years, but plants often re-sprout afterwards. Giant milkweed does not form dense stands, normally occurring as scattered individuals. It can be a serious weed in pastures, overgrazed rangelands, and poorly managed hay fields. Some form of chemical control would seem to be the only practical option for eliminating existing stands but no specific guidelines are available. Establishing giant milkweed has been advocated for environmental protection and as a nurse crop for more valuable species.^[17] This can be done

easily by planting containerized seedlings or rooted cuttings.

In India, *C. procera* known locally as “aak” holds a pride of place largely because of its uses and economic values. The fibres extracted from the bark of the stem is white, silky, strong, flexible and durable and is used in making ropes for cots, gunny bags, fishing nets, and bow strings. The wood is used as cheap fuel and latex is used in tanning industries. The latex is used as wound healing agent by different traditional healers. It is also used as an abortifacient in folk medicines.^[18] Giant milkweed tissues, especially the root bark, are used to treat a variety of illness including leprosy, fever, menorrhagia, malaria, and snake bite.^[15] It is recommended as a host plant for butterflies.^[19] In the past, the silky hairs were used to stuff pillows.^[16]

Sheep, goats, and camels will eat the leaves of giant milkweed during droughts, but consumption is low. If the leaves are chopped and mixed with other feed, consumption greatly increases with no ill effects.^[20,21] Shade-dried giant milkweed leaves contained 94.6 percent dry matter, 20.9 percent ash, 19.6 percent crude protein, 2.2 percent fat, 43.6 percent acid detergent fiber, and 19.5 percent neutral detergent fiber.^[21] Although it is lightweight, the wood is used in impoverished desert areas for a cooking fuel.^[22]

Taxonomy of *Calotropis Procera*

The taxonomic position of the genus, *Calotropis* among the flowering plants is as follows.^[23]

Phylum	-	Angiospermae
Class	-	Dicotyledonae
Subclass	-	Sympetalae
Order	-	Gentianales
Family	-	Asclepiadaceae
Subfamily	-	Cyanchoideae
Genus	-	<i>Calotropis</i>
Species	-	<i>Calotropis procera</i>



Figure 1: The plant, *Calotropis procera* (Asclepiadaceae)



Figure 2: The stem, leaf and flower of *Calotropis procera*

TOXICITY OF *CALOTROPIS PROCERA*

Calotropis procera produces milky white latex that is to various animal models.^[24] When injured, leaves or the nearest other green parts exude the latex secretion which has a clingy effect capable of immobilizing insects. Local administration of the latex of *C. procera* induces intense inflammatory response.^[25] Accidental exposure to the latex produces contact dermatitis, keratitis, and toxic iridocyclitis.^[26-28] The acute inflammation induced by latex involves edema formation and cellular infiltration that has been attributed to the presence of histamine in the latex and the release of mast cell histamine.^[29,25] The milky exudation from the plant is a corrosive poison. *Calotropis* species are poisonous plants; calotropin, a compound in the latex, is more toxic than strychnine.^[30]

Calotropin is similar in structure to two cardiac glycosides which are responsible for the cytotoxicity of *Apocynum cannabinum*. Extracts from the flowers and latex of *Calotropis procera* have shown strong cytotoxic activity.^[31] Cattle often stay away from the plants because of their unpleasant taste and their content of cardiac glycosides. *Calotropin* isolated from latex and roots of *C. procera* inhibit spermatogenesis in male and induce abortion in female rats and rabbits. *C. procera* has been reported to have abortifacient effect as it has uterine stimulating effect.^[32,33]

The latex of *Calotropis procera* contains several alkaloids (such as *Calotropin*, *Catotoxin*, *Calcilin*, *Gigantin*) which are caustic and considered poisonous in nature.^[34] Previous reports showed that accidental contact of *Calotropis* latex into the eye caused violent kerato-conjunctivitis with associated corneal edema and gross dimness of vision but without any pain.^[35,26,36]

Calotropis procera have been reported to stimulate several smooth muscles including that of the uterus,^[37,38] hence ^[39] and ^[28] described the plant as abortifacient. Dada et al.^[40] reported that diarrhoea is one of the toxic signs of the latex of *C. procera* in animals.

Studies have shown that the treatment with 50 or 100 mg/kg of latex proteins from *C. procera* decreased locomotor activity in animal model and may have depressant effects on the central nervous system when assayed at higher doses, but do not present any anxiolytic effect.^[41]

The latex from *C. procera* has been used as arrow poison for hunting in most part of Africa and ^[10] reported that it is highly toxic to the land snail. They concluded that the presence of the compound Uscharine, found in the latex of *C. procera* is responsible for the molluscicidal activity.

MEDICINAL USE OF *CALOTROPIS PROCERA*

In spite of the toxicity of the latex of *C. procera*, the plant has been reported to be of high medicinal value. The medicinal effect of *C. procera* has been observed in India, using root bark extract to treat leprosy as well as using the latex to treat leprosy in human adult.^[42] The juice from the leaves of the plant has been used for headache, catarrh, conjunctivitis, skin diseases and wound dressing, while the root extract has been used for the treatment of venereal diseases like syphilis and gonorrhoea.^[43]

The latex, flowers and root bark of this plant are used in Indian folk medicine mainly for digestive system disorders but also for the treatment of asthma, cough, catarrhal inflammation of the upper respiratory tract and skin diseases.^[44]

The use of *C. procera* as a chewing stick enhances amylase activity, and also supports the use of its root as digestive agent.^[45] Traditionally, *C. procera* bark is used to treat cholera, extracting guinea worms and indigestion. The drug is well known to enhance bile secretion and has sedative effect on the intestinal muscles. Ethanol extract of *C. procera* when applied to skin ulcers, showed 60% cell regression. The tender leaves of *C. procera* are also used to cure migraine.^[45] It is also used as a remedy for black scars of face, boils, cold, cough, asthma, ear-ache, eczema, skin eruptions, inflammatory lesions, pains, rheumatism, syphilis, leprosy and oedema.^[45] It has also been used as an antiseptic for skin infection,^[46] laxative,^[42] eardrops^[47] and antifertility agent.^[48]

The root of *C. procera* Linn has been used as a carminative in the treatment of dyspepsia.^[49] The root bark and leaves of *C. procera* have been used by various tribes of central India as a curative agent for jaundice.^[50] In the traditional Indian medicinal system, *C. procera* has been used for a variety of disease conditions that include the treatment of leprosy, ulcers, piles and tumors.^[49]

In Japan, Khuarana^[51] reported that the latex of *C. procera* used on cell culture has antiviral activity on tobacco mosaic virus. Also the dried latex of the plant has been shown to have antihelmintic activity against *ascaris lumbricoides*. The calotropin, an enzyme in the latex of the plant was said to have greater antihelmintic activity than phenothiazine.^[42]

PHARMACOLOGICAL ACTIONS OF *CALOTROPIS PROCERA*

Edman,^[52] Mossa *et al.*^[53] Al-Robai *et al.*^[54] and Hussein *et al.*^[10] reported the presence of alkaloids, flavonoids, cardiac glycosides, tannins, triterpenes steroids and uscharin in the entire part of *C. procera*, and the safety evaluation studies revealed that the use of the extract in a single high doses (up to 3 g/kg) does not produce any visible toxic symptoms or mortality.^[53]

A new norditerpenyl ester, named Calotropterpenyl ester, and two unknown pentacyclic triterpenoids, namely calotropursenyl acetate and calotropfriedelenyl acetate have been isolated from the root bark of *C. procera*. Their structures have been established as 6,10,14-trimethylpentadec-6-enyl-2',4',8',12',16'-pentamethyl nonadecane ester, urs-12,19(29)-diene-3 beta-yl acetate and friedelin-1-ene-3 beta-yl acetate, respectively, on the basis of spectral data analysis and chemical reactions.^[55] A powerful bacteriolytic agent capable of lysing *Micrococcus lysodekticus* had been found to be present in latex of *C. procera*. The enzyme had a maximum activity at pH 5-5.4 at 45°C.^[56]

The laticifer fluid of *C. procera* is rich in proteins and there is evidence that they are involved in the pharmacological properties of the latex. In a study by Freitas *et al.*^[57] laticifer proteins of *C. procera* were pooled and examined by 1D and 2D electrophoresis, masses spectrometry (MALDI-TOF) and characterized in respect of proteolytic activity and oxidative enzymes. Strong antioxidative activity of superoxide dismutase and proteolytic activities of laticifer proteins from *C. procera* were shown to be shared by at least four distinct cysteine proteinases that were isolated by gel filtration chromatography. The presence of these enzymatic activities in latex from *C. procera* may confirm their involvement in resistance to phytopathogens and insects, mainly in its leaves where the latex circulates abundantly.

Srivastava *et al.*^[58] reported fibrinolytic and anticoagulant activities of *C. procera*, while Tariq *et al.*^[59] demonstrated the neuromuscular blocking activity of the plant in mouse. Extracts from *C. procera* caused marked contraction in isolated preparation of rabbit's duodenum, rat's ileum, and uterine horn from rat.^[60]

Effect of ethanolic and aqueous extracts of *C. procera* roots have been studied on oestrous cycle and oestrogenic functionality in rats. Both extracts have been shown to interrupt the normal oestrous cycle by 60 and 80%, respectively, of rats treated^[61] and a strong antiimplantation (inhibition 100%) and uterotrophic activity was observed at the dose level of 250 mg/kg suggesting that the extract could be used as a potent contraceptive.^[62]

The alcoholic extracts of the root and leaves of *C. procera* were found to have anticancer activity against human epidermal carcinoma of the nasopharynx tissue culture.^[63] The antitumor activity of the ethanolic extract of *C. procera* evaluated by Arul *et al.*^[64] against Dalton's ascetic lymphoma in Swiss albino mice, and reported a significant enhancement of mean survival time of tumor bearing mice, inhibition of tumor cell growth and reversal of the changes in haematological parameters, protein and pack cell volume consequent to tumor inoculation.

The aqueous extract of the latex of *C. procera* has been shown to inhibit cellular infiltration and afford protection against development of neoplastic changes in the transgenic mouse model of hepatocellular carcinoma.^[65] The chloroform extract of the root of *C. procera* has been shown to exhibit protective activity against carbon tetrachloride-induced liver damage.^[66] Padhy *et al.*^[67] evaluated the antioxidant and anti-inflammatory properties of the latex of *C. procera* for its hepatoprotective effect against carbon tetrachloride-induced hepatotoxicity in rats. In the experiment, carbon tetrachloride administration twice a week produced a marked elevation in the serum levels of ALT, AST and tumor necrosis factor- α (TNF- α), while histological analysis of the liver of the treated rats revealed marked necro inflammatory changes associated with increased LPO, prostaglandin E2 (PGE2), CAT and decreased levels of GSH, SOD and GPX. Padhy *et al.*^[67] then reported that daily oral administration of dried latex of *C. procera* produced a dose-dependent reduction in the serum levels of the liver enzymes and inflammatory mediators, and attenuated the necro inflammatory changes in the liver. They suggested that the dried latex of *C. procera* could be used as a hepatoprotective agent.

Ramachandra *et al.*^[68] also evaluated the hepatoprotective activity of *C. procera* flowers against paracetamol-induced hepatic injury in rats. In the experiment, paracetamol altered the levels of biochemical markers of hepatic damage like ALT, AST, ALP, high density lipoprotein (HDL) and tissue GSH. Treatment with hydro-ethanolic (70%) extract of *C. procera* flowers at 200 mg/kg and 400 mg/kg brought back the altered levels of the biochemical markers induced by paracetamol to the near normal levels in a dose-dependent manner.

The anti-inflammatory property of the latex of *C. procera* was studied on carrageenan- and formalin-induced rat paw oedema model. A single dose of the aqueous suspension of the dried latex was effective to a significant level against the acute inflammatory response.^[69] A chloroform-soluble fraction from *C. procera* roots showed significant dose-related anti-inflammatory activity in rats using the pharmacologic models of carrageenan-induced paw oedema, cotton pellet granuloma and formaldehyde-induced arthritis. In addition, significant analgesic potential was demonstrated using acetic acid-induced writhing in mice.^[70] Dewan *et al.*^[71] evaluated the analgesic activity of dry latex (DL) of *C. procera*. A single oral dose of DL ranging from 165 to 830 mg/kg produced a significant dose-dependent analgesic effect against acetic acid-induced writhing's in mice.

Daily treatment of rats with 50 mg/kg and 500 mg/kg methanolic extract of dried latex of *C. procera* has been reported to afford protection against inflammation and oxidative stress in Freund's complete adjuvant-induced monoarthritis, by bringing to normal the reduced levels

of GSH, CAT, SOD and GPx, and an increased LPO as well as produced a significant attenuation in the inflammatory response and ameliorated the arthritic changes in the joint, thereby improving locomotor functions in experimentally induced monoarthritis in rats.^[72] The antioxidant and anti-inflammatory activities of the *C. procera* extract were comparable to standard anti-inflammatory drug rofecoxib.

An ethanolic extract of the flowers of *C. procera* was investigated for anti-inflammatory, anti-pyretic, analgesic and anti-microbial activities. The plant extract reduced the paw swelling induced by carrageenan by 37%, fever in rats by 40% and showed some weak effect in rats on the writhing induced by acetic acid. The growth of both gram-positive and gram-negative bacteria was significantly inhibited. A dose-dependent effect on prostaglandin release was also observed.^[73] Mossa *et al.*^[53] investigated the ethanolic extract of the *C. procera* for its anti-pyretic, analgesic, anti-inflammatory, anti-bacterial, purgative and muscle relaxant activities. The results of the study showed a significant anti-pyretic, analgesic and neuromuscular blocking activity. Pharmacological studies on aerial parts of *C. procera* revealed that the smooth muscle of guinea pig ileum fed with the extract, produced contractions which was blocked by atropine, supporting the use of the plant in constipation.^[53]

The aqueous extract of *C. procera* was evaluated by Iwalewa *et al.*^[74] for its spasmolytic effect using in vitro trachea smooth muscle chain in guinea pigs and reported that the extract administered at a dose of 50, 100 and 200 microgram/ml, showed a dose-dependent relaxant activity probably exhibited through direct relaxant action on the smooth muscle.

Sen *et al.*^[75] demonstrated the anti-ulcer activity of *C. procera* against aspirin, indomethacin, ethanol, indomethacin and ethanol, or stress-induced ulcerations by investigating the role of *C. procera* root extract on different experimental ulcer model in rats. They reported that *C. procera procera* extract significantly inhibited gastric secretory volume and total acidity in the pylorus ligated rats and arachidonic acid metabolism induced by soyabean lipoxygenase, and suggested that the anti-ulcer activity of *C. procera* extract might be attributed to the inhibition of 5-lipoxygenase (5-LO), thereby protecting the gastric mucosa.

During evaluation for anti-diarrhoeal activity, like atropine and phenylbutazone (PBZ), a single oral dose of DL of *C. procera* (500 mg/kg) produced a significant decrease in frequency of defaecation, severity of diarrhoea and afforded protection from diarrhoea in 80% rats treated with castor oil (Kumar and Basu, 1994). Methanolic extracts of *C. procera* has been shown to possess antioxidant activity in *Trema orientalis*^[76] and *senna tora*.^[77]

Rasik *et al.*^[78] selected *C. procera* for evaluation of its wound healing potential. Topical application of 20 microlitres of 1.0% sterile solution of the latex of *C. procera* twice daily was followed for 7 days. The latex significantly augmented the healing process by markedly increasing collagen, DNA and protein synthesis and epithelization leading to reduction in wound area.

Sharma and Sharma^[79] also reported the effect of crude fractions of flower, bud and root of *C. procera* against a chloroquine sensitive strain and a chloroquine resistant strain of *Plasmodium falciparum* using the Desjardins method and the effectiveness of its fractions compared better with the chloroquine sensitive strain than the chloroquine resistant strain in vitro.

The insecticidal activity, expressed by LD₅₀ values, of acetone, ethanol, petroleum ether and water extracts of *C. procera* leaves against the flesh fly, *Sarcophaga haemorrhoidalis* Fallen was evaluated. Findings suggest that *C. procera* extracts may produce larvicidal, pupicidal and adulticidal effects, (behaving like general toxicants) against *Sarcophaga haemorrhoidalis*.^[80]

Calotropis procera latex showed antioxidant activity using 1,1-diphenyl-2-picryl hydrazyl (DPPH) free radical model^[80] and also reduced increased enzyme levels in isoproterenol-induced myocardial necrosis.^[81,82] Studies on antioxidant and protective activity of *C. procera* against alloxan-induced diabetes in rats showed that *C. procera* prevented the loss of body weight in diabetic rats, increased the hepatic levels of the endogenous antioxidants (SOD, CAT and GSH), and that its antioxidant and antidiabetic properties was comparable to standard antidiabetic drug, glibenclamide.^[83] The antihyperglycaemic activity of *C. procera* was also demonstrated by Neto *et al.*^[84] in streptozotocin-induced diabetes mellitus in rats.

Calotropis procera leaf extract has been reported to possess antioxidant activity by increasing the glutathione levels and decreasing the rate at which lipid peroxidation occurred in the developing cerebellum,^[85] preventing delayed maturation of cells of the cerebellar cortex and depletion of Purkinje cells of the developing cerebellum in phenytoin-induced oxidative stress.^[86] And that the antioxidant property of *Calotropis procera* was comparable to standard antioxidants, vitamins C and E.

Jalalpure^[87] reported the anticonvulsant activity of different root extracts of *Calotropis procera* in rats by inducing seizures with pentylenetetrazol (PTZ) and lithium-pilocarpine, and concludes that *C. procera* root extract delayed the onset of convulsion as well as inhibited convulsions induced by lithium-pilocarpine and electrical kindling.

CONCLUSION

Developing countries import a large quantity of pharmaceutical raw materials including medicinal plants

and semi-processed plant products to produce drugs and medicines. This huge foreign exchange can be saved if the indigenous medicinal plants or their semi-processed products are utilized by the manufacturers to meet their needs. *Calotropis procera* is found in almost all parts of Nigeria but more abundant in the Northern part of the country. It is also found in other parts of Africa, Asia and Central America including Mexico. As a result of the high medicinal and pharmacological values (which outweighs its toxic effects), availability and affordability of *C. procera*, further studies are required to establish the therapeutic use and safety of the plant and particularly with its active principles, so as to advise ethnomedical practitioners on the dosage and usage of the plant.

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