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CALOTROPIS PROCERA: A ETHNOBOTANY, PHYTOCHEMICAL AND PHARMACOLOGICAL REVIEW

Kamini Verma*[1], Dr. Avinash Kumar Lall[1], Jhakeshwar Prasad[2], Trilochan Satapathy[3], Divya Sahu[2], Vandana Dewangan[4]

[1]Department of Botany, Atal Bihari Vajpayee Govt. College, Pandatarai, Kawardha - 491559, Chhattisgarh, India.
[2]RITEE, College of Pharmacy, Chhatauna, Mandir Hasaud, Raipur – 492101, Chhattisgarh.
[3]University College of Pharmacy, Pt. Deendayal Upadhyay Memorial Health Sciences and Ayush University, Raipur-493 661, Chhattisgarh, India.
[4]Columbia Institute of Pharmacy, Tekari, Raipur – 493111, Chhattisgarh.

***Corresponding Author: Kamini Verma**

Department of Botany, Atal Bihari Vajpayee Govt. College, Pandatarai, Kawardha - 491559, Chhattisgarh, India.

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ABSTRACT

Medicinal plants are used from the ancient time as the major sources of drugs. The fact is that we can obtain many of the presently available drugs, either directly in the extract form or in the modified synthetic form. Naturally, plants have the ability to synthesize products beneficial for us namely as phytoconstituents that are used to perform biological functions, which also protect us against predators such as virus fungi and other microorganisms. The phytoconstituents obtained from the natural products are one of the most successful strategies for the discovery of new drugs. *Calotropis procera* is a plant which is used in several traditional medicine and folklore systems to cure various ailments as reported in the Hindu literature. It is widely used in the Indian traditional medicinal system as well as in Arabic, Unani, and Sudanese systems. *C. procera* is also used by various tribes of the world as a curative agent for ailments such as skin disease and elephantiasis. Different parts of the plant have been reported to possess various phytochemicals containing cardiotonic agents such as calotropin, calotropagenin, calotoxin, calotropagenin and voruscharine, steroids, di and triterpenes such as stigmasterol, β-sitosterol, flavonoids, polyphenolic compounds, and various newer reported hydrocarbons and proteins. This shrub is known to possess a wide range of pharmacological activities such as anticancer, acaricidal, schizonticidal, antimicrobial, anthelmintic, insecticidal, anti-inflammatory, antidiarrheal, anticancerous, and larvicidal activities with other beneficial properties. *C. procera* is small, erect shrub, which is used in several herbal and empirical medicines to cure simple and deadly diseases and disorders. It is also reported widely in various folklore preparations and ethnomedicines. This review is a profound attempt to stack the information concerning pharmacognostical, phytochemical, and pharmacological features of *C. procera* shrubs.

KEYWORDS: *Calotropis Procera;* Phytoconstituents; Plant pharmacology; Traditional medicine

INTRODUCTION

Calotropis procera (Arka) is an important drug in the monograph of Ayurveda, and it is known in India from the earliest time (Figure 1). It was mentioned by Hindu writers and the ancient sacrificial rites many years ago. There are two common species of *Calotropis* reported in the literature, viz., *C. procera* (Ait.) R.Br. and *Calotropis gigantea* (Linn.) R.Br. mentioned by the ancient writers. Both the species consists of similar types of phytoconstituents discovered till now and may be used as substitutes for one another might have similar effects. Three varieties of Arka are mentioned in the Hindu literature of Dhanvantari Nigantu as Suklarkah, Rajarkah, and Sveta mandarah. It is widely used in the Indian traditional medicinal system as well as in the other available treatments such as Arabic, Unani, and Sudanese and for the various diseases. *C. procera* is also used by various tribes of the world as a curative agent for ailments such as skin disease, elephantiasis, toothache, asthma, leprosy, and rheumatism.[1]

Different parts such as leaves, roots and bark, flower, fruits, stem, and latex of the plant have been reported to possess various phytochemicals which might possess various pharmacological activities. The coarse shrub possesses acaricidal, schizonticidal, antimicrobial, anthelmintic, insecticidal, anti-inflammatory, antidiarrheal, anticancerous, and larvicidal activities with other beneficial properties. The plant is described as a golden gift for humankind containing cardiotonic agents such as calotropin, calotropagenin, calotoxin, calactin, uscharin, amyrin, amyrin esters, uscharidin, coroglaucigenin, frugoside, corotoxigenin, calotropagenin, and voruscharine used in the therapeutic

treatment.[2] Different compounds such as norditerpenic esters, organic carbonates, the cysteine protease procerain, alkaloids, flavonoids, sterols, and numerous cardenolides made this plant of scientific attraction for centuries. Hence, in this review, an account of reported pharmacological actions of the plant with reported active chemical constituents were discussed in this study.

Geographical Source

C. procera is inborn to Southern Asia and Indo-China to Malaysia, Macaronesia, West Africa North and East Africa, Madagascar, and Arabian Peninsula. The plant is naturalized in Australia, Central America, North, South America, and West Indies. The species is now accepted and culture in many countries such as Mexico, Central and South America, Pacific islands, Australia, and the Caribbean.[3]

Scientific and Vernacular Name

Taxonomy *Calotropis procera* (Ait.) Ait.f. Kingdom: Plantae – Plants; Subkingdom: Tracheobionta – Vascular plants; Superdivision: Spermatophyta – Seed plants; Division: Magnoliophyta – Flowering plants; Class: Magnoliopsida – Dicotyledons; Subclass: Asteridae; Order: Gentianales; Family: Asclepiadaceae; Genus: *Calotropis* R.Br. – *Calotropis*; Species: *C. procera* (Ait.).

Synonyms/Other Latin Names

Asclepias procera Aiton, common vernacular names (Sanskrit) Arka, (Hindi) Aaka. Giant Indian Milkweed. Sodom Apple, Small Crown Flower, Rooster tree, French Cotton in English. Remiga (Malaysia), Kapal-kapal (Philippines), Mudarpflanzer (German), Calotropo (Italian) and Rak (central) in Thailand.[4]

Fig. 1: Flower, leaves and fruits of *Calotropis procera* plant.

Botanical Description

The plant is an evergreen, soft-wooded, perennial shrub; small tree attains a maximum height up to 2.5 m (maximum 6 m). A copious amount of white sap generates whenever any part of the plant is cut. The bark is corky, furrowed, and light gray. The root is simple, branched, and woody at base and covered with a fissured, corky bark, branches has very deep stout root with few branches. The leaves are opposite-decussate, simple, subsessile, and exstipulate; the leaves are slightly leathery and having a fine coat of soft hairs that sometimes sting too. Flowers are shallow bell-shaped, like a campanula, bracteate, complete, bisexual, actinomorphic, pentamerous, hypogynous, pedicellate, multiflowered, umbellate, peduncled cymes with axillary or terminal inflorescence. Five sepals, 5 lobed shortly united that are 4-5 mm long. Five-lobed petals (Corolla), gamopetalous, twisted aestivation. Androecium has five stamens, gynandrous, anther dithecous, coherent. Gynoecium is bicarpellary, apocarpus, and styles are united at their apex, peltate stigma with five lateral stigmatic surfaces. Anthers are adnate to the stigma forming a gynostegium. Fruit is simple, fleshy, inflated, and subglobose to obliquely ovoid follicle. Seeds are present in large amount, small, flat, obovate, compressed with silky white pappusat the one end, 3 cm or more long.[5]

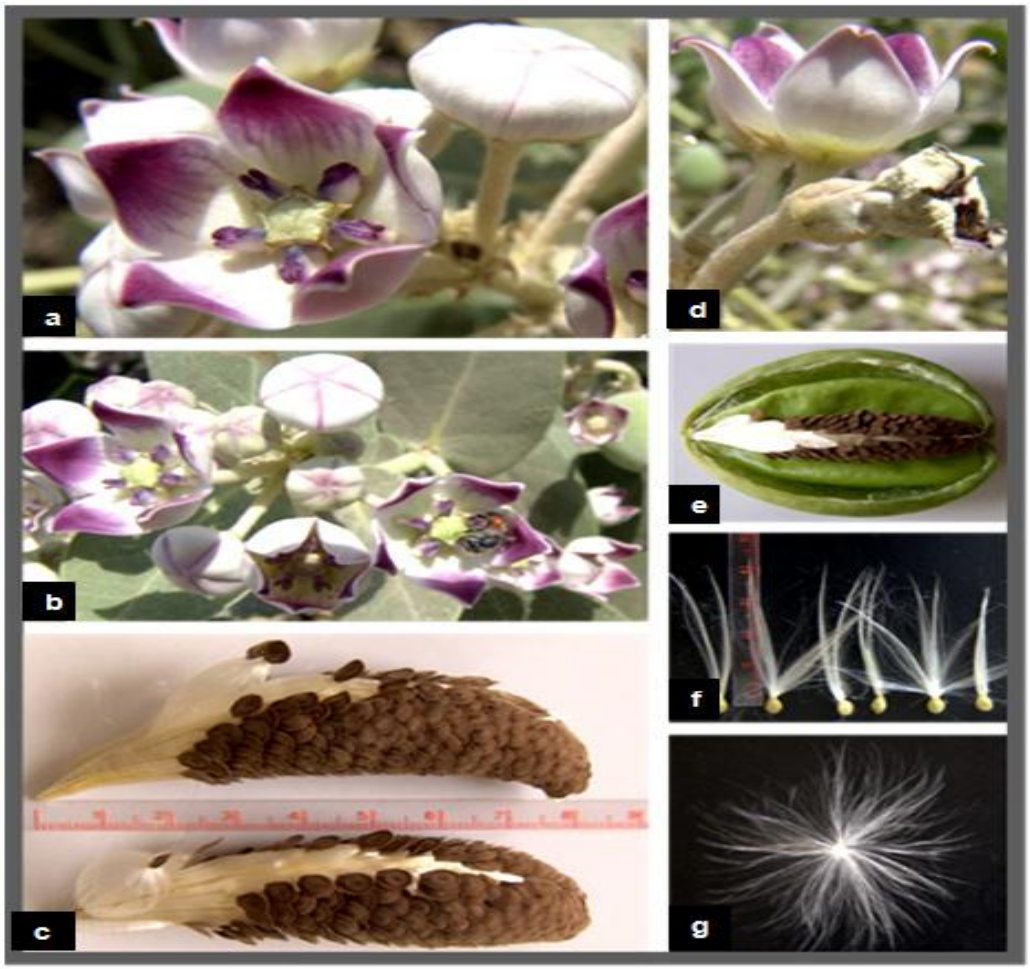

Fig. 2: Flower and fiber development stages of *Calotropis procera*.
(a) Blossomed flower. (b) Insect as a source of cross pollination. (c) The cone bearing the seeds and fibers. The cone is about 8.5 cm in length. The end with fibers without seeds indicate attachment region on the stem and has shortest fibers (2.5-3.0 cm). The fibers on the other end are largest (4-4.5 cm). (d) Withering of the petals and initiation of fruit development. (e) Mature opened fruit indicating the outer integument, spongy layer, inner integument and the cone bearing the fibers. (f) The fiber length at the distal end region of the cone. (g) Seed carrying the tuft of fibers and ready for seed dispersal.

Ethnomedicinal (Traditional) Uses

The leaves were reported to use in sun worship from the Vedic times. Secretions from the root bark were used by Hindu physicians to treat skin diseases, cough, intestinal worms, ascites, and anasarca and also in enlargements of abdominal viscera, etc. The milky juice was considered as a drastic purgative and caustic. Flowers were considered to improve digestion, catarrh, and increase appetite. The root bark was also used to treat elephantiasis. *Calotropis* latex is used and applied intact in the preparations for toothache. The flowering tops were also used to treat asthma. The plant was also used in the treatment of leprosy, hepatic, and splenic enlargements. The leaves were boiled, and oily preparations were made and used in the treatment of paralysis. Leaf powder was considered as a substitute for ipecacuanha and also possesses the properties of Gutta-persica also used in wound healing. The juice was used for the purpose of infanticide and was sometimes given to women to induce abortion. Tanners used the milky juice to remove hair from hides.[6] The powder of the root mixed with milk of goat is used in epilepsy; route of application is in the nostrils. The tribes of the Varanasi use latex to remove worms from teeth and in the preparations of toothache. Traditionally, *C. procera* bark is used to treat cholera, extracting Guinea worms, and digestion. The drug is well known to enhance bile secretion and has a sedative effect on intestinal muscles. The tender leaves are also used to cure migraine.

PHYTOCHEMICAL CONSTITUENTS

A vast number of research and review articles are published on the phytochemical and screening properties of *C. procera*. All parts of the plant have toxic potential, due to the presence of cardenolides (cardiac glycosides). The latex was found to be richest in cardenolides, which is already mentioned in the literature. According to research, the leaf of the plant consists of cardenolides 162 mg/g at dry weight and 2 mg/g total dry weight. The important cardenolides found in the plant are voruscharin, uscharidin, uzarigenin, calotroposide, calactin, calotoxin, uscharin, ascleposide, calotropagenin,

coroglaucigenin, calotropin, proceroside, proceragenin, and syriogenin. Many of these compounds formed in the mechanism of extraction when hydrolyzed in a chemical reaction. Latex differs in the quantities of cardenolides from the other plant parts stem, fruit, leaves, and root bark. The main cardenolides in the various parts of the plant are uscharin and calotropagenin in the latex; calotropin and calotropagenin in the leaves; uscharidin, calotropin, proceroside, and calactin in the stem; calotoxin and calactin in the root bark; coroglaucigenin and uzarigenin in the fruit pericarp.

The seeds contain 0.23-0.47% cardenolides, mainly coroglaucigenin or frugoside.[7] Besides the cardenolides, other phytochemicals are also reported from the plant such as sterols, flavonoids, coumarins, alkaloids, triterpenes, saponins, tannins, and hydrocarbons were isolated from the plant. The major flavonoid is rutin (quercetin-3-rutinoside): Roots contain 1.7%, stem 4.8%, leaves 5.0%, flowers 7.6%, and latex 9.7%. The plant is also reported to contain resins, fatty acids, proteases, hydrocarbons, amino acids, and many minerals. The leaves contain ascorbic acid, calactin, calotoxin, calatropagenin, calotropin, polysaccharide containing D-arabinose, D-glucose, D-glucosamine and L-rhamnose, calotropagenin, and 3-proteinase.

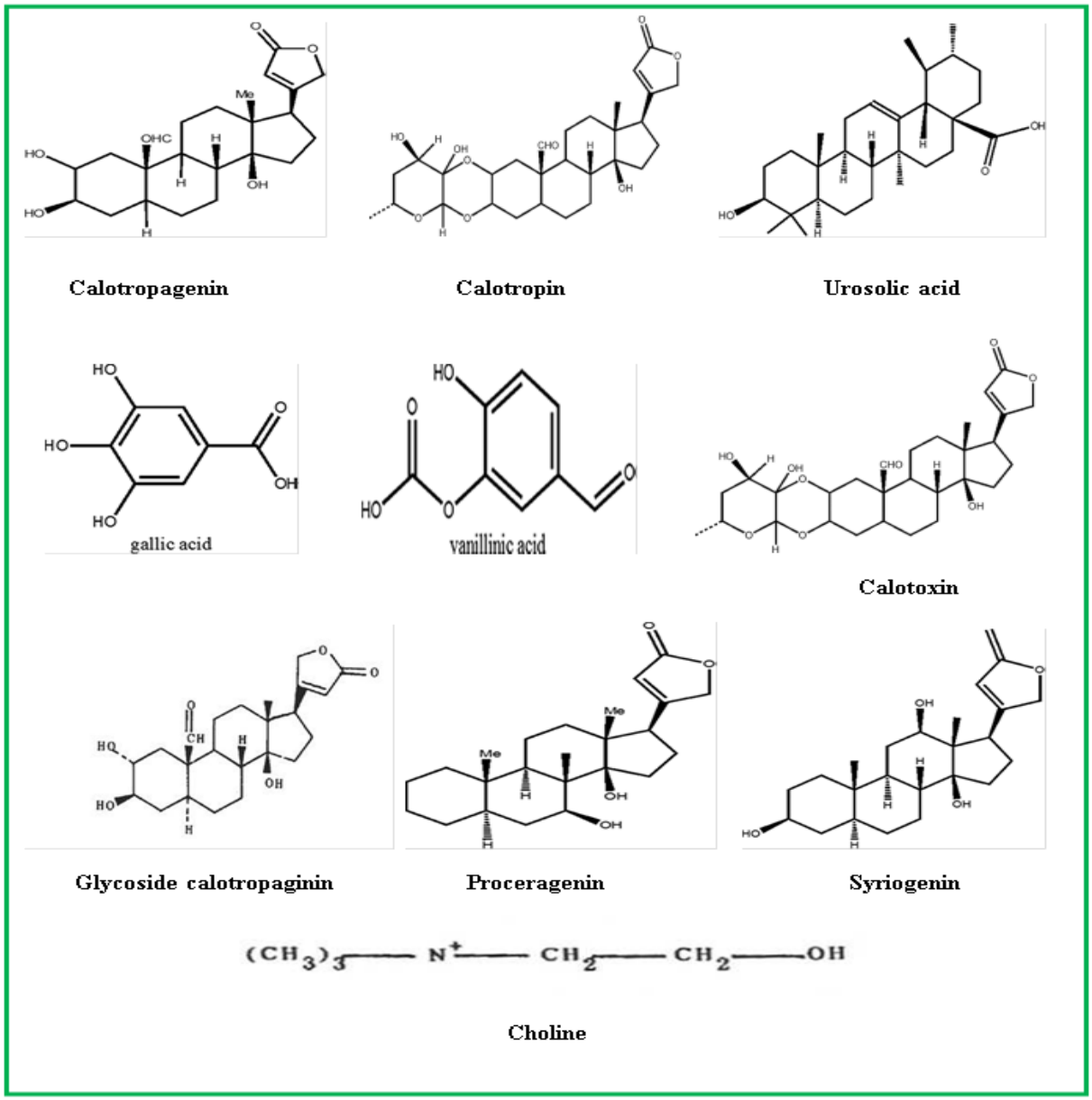

Fig. 3: Secondary metabolites of *Calotropis procera*.

Mechanism of Action of Cardenolides for their ATPase Activity

Cardiac glycosides are allosteric inhibitors of Na+⁄K+-ATPase.[8] The inhibition of Na+⁄K+- ATPase by cardiac glycosides is highly specific which implies that Na+⁄K+-ATPase is the receptor for cardiac glycosides. The catalytic site of the enzyme faces the intracellular matrix while the regulator site (cardiac glycoside binding site) is

towards extracellular matrix. Sodium and potassium activates the enzyme at intracellular and extracellular site, respectively. During catalysis, the enzyme undergoes several conformational changes involving phosphorylation (activated by sodium) and dephosphorylation (activated by potassium). These steps lead to transport of ions (Na^+, K^+) across the membrane.[9] Inhibition of Na^+/K^+-ATPase results in high intracellular sodium concentration which in turn inhibits NCX exchanger (responsible for pumping calcium ions out of the cell and sodium ions in (3Na/Ca) as a result calcium ions build up inside the cell, as well. Increased cytoplasmic calcium concentrations cause increased calcium uptake into the sarcoplasmic reticulum via the SERCA2 transporter. Raised calcium stores in the SR allow for greater calcium release on stimulation, so the myocyte can accomplish faster and more potent contraction by cross-bridge cycling (Fig. 4). This affects the electrical physiology of the heart, blocking atrioventricular (AV) conduction and reducing the heart rate by enhancing vagal nerve activity (negative chronotropy). Thus, cardiac glycosides not only act on cardiac fibers but also on cardiac nerves, pulmonary circulations, and on autonomic reflex activity.[10,11] The vagomimetic action (decreased conduction velocity through the AV node), baroreceptor sensitization (resulting in anti-sympathetic activity) and renin-angiotensin system (neurohormonal deactivating effect), results in slowing heart rate so tht it can pump more blood per beat through the body. The diastolic phase lasts longer, thus decreasing the heart rate. Raised extracellular potassium decreases binding of cardiac glycoside to Na^+/K^+-ATPase. As a consequence, increased toxicity of these drugs is observed in the presence of hypokalemia. Cardiac glycosides are prescribed in conditions of atrial flutter, atrial fibrillation, paroxysmal tachycardia, congestive heart failure that cannot be controlled by other medication.[12] Recently, Na^+/K^+-ATPase has emerged as a flexible signal transducer which can activate several downstream signaling pathways and thus may have role in regulating several other disease conditions.[13]

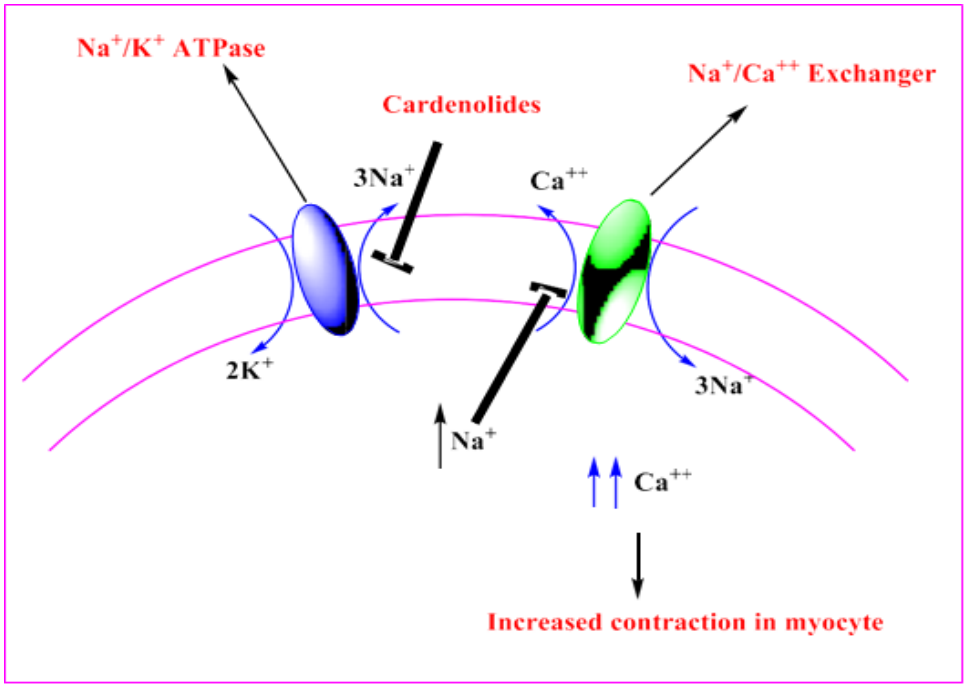

Fig. 4: Mechanism of action of Cardenolides (Calotropin).

PHARMACOLOGICAL ACTIVITY

Anti-malarial Activity

The ethanolic extracts of the different parts of *C. procera* showed IC50 values ranging from 0.11 to 0.47 mg/ml against *Plasmodium falciparum* MRC20 CQ-sensitive strain and from 0.52 to 1.22 mg/ml against MRC 76 CQ-resistant strain, flower, and bud extracts being the most effective. Although 220, 440 times less effective than CQ, these extracts deserve further studies aimed at the identification of the active constituents.[14]

Immuno-modulatory Activity

Ethanolic extract of the root bark of *C. procera* was evaluated for immunomodulatory activity using immunological tests in mice, humoral mediated antibody titer, delayed-type hypersensitivity, peritoneal macrophage count, vascular permeability, hematological profile, i.e. total red blood cell count, total leukocyte count, % neutrophils and % lymphocytes, and cyclophosphamide-induced myelosuppression at three dose levels (50, 100, and 200 mg/kg). The extract stimulates defense system by modulating several immunological parameters. Nascimento *et al.*, 2016 discover immunomodulatory properties of latex protein extracts from *C. procera* which protect against experimental infections with Listeria monocytogenes.[15,16]

Wound Healing Activity

Based on its traditional use, *C. procera* was selected for evaluation of its wound healing potential in Guinea pigs. 20 µl of 1.0% sterile solution of the latex of the plant in the animals was applied topically. The latex significantly augmented the healing process by markedly increasing collagen, DNA and protein synthesis and epithelization. Tsala *et al*. evaluated the antioxidant activity and the healing action of the ethanol extract of *C. procera* bark against surgical wounds.[17,18]

Anti-ulcer Activity:

The antiulcer activity of *C. procera* using different *in vivo* ulcer models was performed. The results of the study revealed that it significantly inhibited aspirin, reserpine, absolute alcohol, and serotonin-induced gastric ulcerations in rats and also protecting the gastric mucosa from aspirin-induced ulceration in pyloric-ligated rats, and significant protection was observed in histamine-induced duodenal ulcers in Guinea pigs.[19]

Anti-fertility Activity

The effect of an ethanolic extract of the roots of *C. procera* was studied in albino rats to explore its antifertility and hormonal activities. Strong anti-implantation (inhibition 100%) and heterotrophic activity was observed at a dose of 250 mg/kg (1⁄4 of LD50). No anti-estrogenic activity was detected.

Anti-diarrheal Activity

The DL of *C. procera* was evaluated for its anti-diarrheal activity. Like atropine and PBZ, a single oral dose of DL (500 mg/kg) was produced a significant decrease in the frequency of defecation and the severity of diarrhea as well as protecting from diarrhea in 80 % rats treated with castor oil.

Estrogenic Functionality

The effects of ethanolic and aqueous extracts of *C. procera* roots were studied on the estrous cycle and on some parameters of estrogenic functionality in rats. Both extracts were found to interrupt the normal estrous cycle in 60% and 80% of rats treated.[20]

Anti-oxidant and **Anti-diabetic activity**

(Kumar V.L. et al., 2005) author has evaluated the antioxidant activity of dried latex of CP and antidiabetic effect against alloxan-induced diabetes rats. By administrating the oral dose of dry latex at 100 and 400 mg/kg the decrease in blood glucose and increase in the hepatic glycogen content was observed.[21]

Anti-cancer and **Cytotoxic Properties**

(Choedon Tenzin et al., 2006) evaluated the anticancer and cytotoxic properties of the latex of CP in transgenic mouse model of hepatocellular carcinoma it was found that the mice which was treated with the DL of CP showed a complete protection against hepatocarcinogenesis, no adverse effect was observed in these animals. The serum vascular endothelial growth factor (SVEG) level was significantly lowered in treated mice as compared to control animal cell culture studied revealed that the methanolic extract of dried latex as well as its fraction 8 induced extensive cell death in both Huh-7 and COS-1 cells while AML12 cells were spared. This was accompanied by extensive fragmentation of DNA in Huh-7 and COS-1 cells. No change in the levels of canonical markers of apoptosis such as Bcl2 and caspase 3 was observed.[22]

Free Radicals

In cells, free radicals are generated due to redox process when oxygen is utilized to generate energy. The free radicals constitute a group of reactive oxygen species (ROS) such as hydroxyl radical, hydrogen peroxide, and super oxide anion.[23] ROS are beneficial for cellular responses and immune function at lower concentrations, while at higher levels they are harmful to the body. Oxidative stress is caused by the excess free radical generation in the body which is capable of damaging cell structure including lipids, proteins, and DNA[24] Overload of free radical plays amajor role in the development of degenerative and chronic ailments such as rheumatoid arthritis, autoimmune disorders, cataract, aging, cancer, and cardiovascular and neurodegenerative diseases.[25,26] Antioxidants being free radical scavengers minimize the damage caused by ROS and thereby enhance the immune defense and lower the risk of degenerative disorders. Antioxidants are either naturally produced *in situ* or supplied through foods and supplements.[27] Flavonoids and phenolic compounds of natural origin have been shown to act as effective antioxidant as well as antibacterial agents.[28, 29] Lipid peroxidation causes damage to unsaturated fatty acids and thereby decreases membrane fluidity which ultimately leads to many pathological events in the body.[30] Antioxidants also protect membranes from peroxidative damage through their metal ion chelating and radical scavenging capabilities.

CONCLUSION

The plant *Calotropis* is one of the widely distributed along the world geographical area. The whole summation of information about the use of *C. procera* in the entire world is matched with available literature. It is well mentioned in the Indian materia medica; there is broad categorization according to its various uses in the pharmacological as well as in traditional use. The literature showed us that it is the plant that is forgotten as the time passes. Still many scientists have worked to reveal its phytochemicals and pharmacological activity. The plants are a rich source of phytoconstituents. Searching new therapeutic agents is a big challenge for the scientist of the present modern era and plants are the biggest source of these agents. Screening of plants for their pharmacological properties with the hope of finding safe and effective agents is very essential. A large number of synthetic compounds are available but due to their environmental pollution and adverse effect on the human body there use is restricted. To find the safe,

effective, and environmental friendly agent from a plant source, *C. procera* is a plant that may present as effective one. In conclusion, the literature on *C. procera* suggests a huge biological potential of this plant. It is believed that the present manuscript may be useful to provide additional information with regard to its identification and in accordance to carry out further research on its use in the treatment of various diseases.

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