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Therapeutic Potential of *Calotropis procera*: A giant milkweed

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ABSTRACT: *Medicinal plants are the local heritage with global importance playing a vital role in world health care system of developing countries. Calotropis procera (Asclepiadaceae), a giant milk weed, is known for its pharmacological importance for centuries. The coarse shrub is a very promising source of anticancerous, ascaricidal, schizonticidal, anti-microbial, anthelmintic, insecticidal, anti-inflammatory, anti-diarrhoeal, larvicidal with many other beneficial properties. Plant is described as a golden gift for human kind containing calotropin, calotropagenin, calotoxin, calactin, uscharin, amyrin, amyrin esters, uscharidin, coroglaucigenin, frugoside, corotoxigenin, calotropagenin and voruscharine used in many therapeutic applications. Different compounds like norditerpenic esters, organic carbonates, the cysteine protease procerain, alkaloids, flavonoids, sterols and numerous cardenolides made this plant of scientific attraction for centuries. Plant is not only a great source of natural hydrocarbons but also contains several metabolites used as folk medicine for the treatment of leprosy, elephantiasis, fever, menorrhagia, malaria and snake bite. The review discusses the potential of Calotropis procera in health care management*.

Keywords: *anticancer, antimicrobial, biosorbent, Calotropin, ethnomedicine*

I. Introduction

The human race started using plants/and or plant products successfully as a mean of treatment of diseases and injuries as effective therapeutic tools from the early days of civilization to modern age [1, 2]. *Calotropis procera* Linn. (Asclepiadaceae) locally known as "*aak*" in India and is commonly known as "*Sodom apple*" or "*Usher"* (Swallow wort in English and Akundia in Hindi) is well known for its high medicinal properties. It is a xerophytic, erect shrub about 6m high, growing widely throughout the tropic of Africa and Asia [3]. It is grown abundantly in arid and semi-arid regions without irrigation, chemical fertilizers, pesticides or other agronomic practices. Plant is a useful bio-indicator to monitor pollution in varying concentrations of Br, Mn, Se, Cr and Zn between urban and suburban samples [4]. For centuries, the coarse shrub of *C. procera* is known as a very promising source of ascaricidal [5], schizonticidal, nematocidal [6,7], anti-microbial [8], antihelmintic, molluscicidal [9], insecticidal, anti-inflammatory, anti-diarrhoeal, larvicidal [10-13], anticancer [14, 15], cytotoxic chemicals and many other beneficial properties make this plant as a golden gift for human kind [16].

The leaf biomass of the plant is potentially a good adsorbent for the removal of crystal violet (a cationic dye) from aqueous solution and is being used in textile industry [17]. The giant milk weed is an important source for plant hydrocarbons [18] used for testing various drugs against anti-inflammatory and antinociceptive activity [19-23]. Present review discusses the biopharmaceutical prospective future potential of *Calotropis procera* Linn.

II. Phytochemical Constituents And Principle Active Compounds

Pharmacologically substances such as calotropon [**Fig. 1 (I)**], calotropin [**Fig. 1 (II)**], uscharine [**Fig. 2 (III)**], calotoxin [**Fig. 2 (IV)**], calctin [**Fig. 2 (V)**], uscharidin [**Fig. 3 (VI)**] and calotropagenin [**Fig. 4 (X)**] etc. are some important chemicals obtained from the leaves and latex of *C. procera* plant [24] **[Table-1]**. The phytochemical studies on the aerial parts of the plant showed the presence of alkaloids, cardiac glycosides, tannins, flavonoids, sterols and/or triterpenes [25]. Earlier pentacyclic triterpenes [26-29], alkaloids, cardenolides [30], phytosterols [31], and triterpenoids saponins have been isolated from the roots of *C. procera.* Fatty acid composition in the extract of *C. procera* was analyzed which has 7 saturated and 11 unsaturated fatty

acids [32]. The essential elements Al, As, Cu, Ca, Cr, Cd, Fe, K, Mn, Na, Pb, and Zn have been reported from this medicinal plant in variable range with 27-32% total protein.

Calotropin, uscharin, calotoxin, calctin, amyrin, amyrin esters, uscharidin, calotoxin were isolated from the leaves and stalks of *C. procera* and *C. gigantae* [33-35]. The chemical constituents of the seeds of *C. procera* were investigated and reported the occurrence of coroglaucigenin [**Fig. 3 (VII)**], frugoside, corotoxigenin [**Fig. 3 (VIII)**], and calotropin [36]. Besides uscharine another cardenolide namely voruscharine [**Fig. 4 (IX)**] was identified in the latex of *C. procera* [37]. The constitution of calotropagenin [**Fig. 4 (X)**] and voruscharine were determined and reported [37-39]. Pyrocatechuic acid [**Fig. 4 (XI)**] α- amyrin, ß-amyrin, taraxasterol, ψ-taraxastrol, ß-sitosterol, taraxasteryl acetate, taraxasteryl bebzoate, α- amyrin benzoate, ß-amyrin benzoate, ß-amyrin acetate, acetic acid and isovaleric acid, taraxasterol isovalerate , benzoyllineolone [**Fig. 5 (XII)**] and benzoylisolineolane [**Fig.5 (XIII)**] were isolated from the root bark, leaf and latex of *C. procera* [40, 41]. Uzarigenin [**Fig. 6 (XIV)**], syrigenin [**Fig. 6 (XV)**] and proceroside [**Fig. 6(XVI)**] were also isolated from the latex of *C. procera* [43]. The presence of D-glucose, D-arabinose, D-glucosamine and α-rhamnose in the aqueous extract of the leaves of *C. procera* were reported [44] while α- and ß-amyrin and ß-sitosterol were identified in the unsaponifiable matter of the petroleum ether extract of same species [45]. Calotropin, calotoxin, uscharine, uscharidin and choline [**Fig. 7 (XVII)**] were also isolated from the latex of *C. procera*.

Calotropenyl acetate [**Fig. 7 (XVIII)**] and procesterol [**Fig. 7 (XIX)**] were isolated from the flowers of *C. procera* [29, 31]. The presence of lupeol, ß- amyrin, α- and ß- calotropeol and 3 -epimoretenol were reported in the latex of *C. procera* [46] while in the following year multiflorenol, [**Fig. 8 (XX)**] cyclosadol, [**Fig. 8 (XXI)**] cyloart-23-ene-3ß, 25-diol, ß-sitostenone, [**Fig. 8 (XXII)**] α- and ß-amyrin, stigmasterol and ß-sitosterol, procerain were identified in the flowers, latex and leaves of the same species [47, 48].Alkaloids, flavonoids, tannins, steroids, triterpenoids, saponins and saponin glycosides were detected in the leaves and root extract fractions [49], with only flavonoids, triterpenoids and saponins in the stem bark extracts. The results obtained lend scientific credence for the use of the plant against fungal diseases. Two flavonol glycosides were isolated and identified from the leaves of *C. procera* [50, 51]. There is hardly any doubt that *C. procera* is a recommended natural source of phytochemicals having a good sign for future biopharmaceutical prospect.

III. Ethanomedicinal Aspects

Medicinal plants have remained the major source of both orthodox and traditional medicine worldwide. Accordingly, attention of scientists and researchers have been attracted towards developing new antibiotics that will curtail the increasing drug resistance among microorganisms [52]. An infusion of bark powder of *C. procera* (Giant milkweed) is used to treat leprosy and elephantiasis [53]. The tissues, especially the root bark, are used to treat a variety of illness including leprosy, fever, menorrhagia, malaria, and snake bite [54]. Extracts, chopped leaves, and latex have shown great promise as nematicides, i*n vitro* and *in vivo* [55, 56]. Local administration of the latex has been reported to elicit an inflammatory response that is mediated through histamine and prostaglandins [21, 22, 57, 58]. It has been reported that the latex exhibit potent anti-inflammatory, antidiarrheal, analgesic, antipyretic and schizonticidal activities [59-63]. Plants used for traditional medicine generally contain a number of compounds which may be a potential natural antimicrobial combination and which may serve as an alternative, effective, cheap and safe antimicrobial agents for treatment of common microbial infections.

C. procera showed adversely affects early and late pregnancy in rats [64]. A recent survey of different regions of the Kingdom of Saudi Arabia showed that roots and aerial parts of the giant milk weed are commonly used in traditional medicine for the treatment of variety of diseases including constipation, fever, joint pain and muscular spasm. Latex proteins from the plant are partially digested upon *in vitro* enzymatic action and are not immunologically detected in fecal material as found in Wistar rats [65]. It was reported that *C. procera* used in traditional medicine as a purgative, anthelmintic, anticoagulant, anticancer as well as antipyretic, analgesic, antimicrobial and antiseptic for skin infection [66, 67]. The root of the giant milk weed is used as a carminative in the treatment of dyspepsia and also used by various tribes of central India as a curative agent for jaundice [68, 69].

IV. PHARMACOLOGICAL ASPECT

Medicinal plants and their values play an important role in health care system of developing countries. There is always an increase emphasis on primary health care: basic health care which is not only effective, but affordable by under-equipped and under-financed countries and by poor communities within those countries. It is expected that this plant could benefit the upcoming needs of the population looking to various pharmacological aspects, in future. The different pharmacological properties of *C. procera* are shown in **[Fig.-9].**

V. ANTI-CANCEROUS ACTIVITY

The incidence of cancer is increasing worldwide and it is the single most common cause of deaths in both developed and developing countries [70, 71]. However, in view of the side effects of drugs used in the chemotherapy of different cancers, traditional herbal medicine and complementary and alternative medicine (CAM) are increasingly becoming popular among cancer patients in the developed countries [72, 73]. The root extract of *C. procera* has been found to produce a strong cytotoxic effect on COLO 320 tumor cells. The anticancer property of the dried latex (DL) of *C. procera* was evaluated in the X15-myc transgenic mouse model of hepatocellular carcinoma and elucidated its mechanism of action in cell culture. DL treatment of mice showed a complete protection against hepatocarcinogenesis. The serum VEGF (Vascular endothelial growth factor) level was significantly lowered in the treated mice as compared to control animals. Cell culture studies revealed that the methanolic extract of DL as well as its fraction 8 induced extensive cell death in both Huh-7 (hepatoma cells) and COS-1 (non-hepatoma cells) while AML12 (non transformed hepatocytes 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 [14, 15].

The protein fraction of the latex (LP) was evaluated to determine its potential cytotoxic activity against human cancer cell line MCF-7. The cell line MCF-7 (breast) was treated with increasing concentrations of LP for 24h and analyzed by the MTT assay. A decrease of cell growth was detected in the presence of LP and values of IC_{50} obtained after 24h of exposure for LP was 88.33µg/ml. It has been suggested in the literature that the cytotoxic activity of LP is due, partly, the inhibition of the synthesis of DNA. The *in vitro* cytotoxic activity of laticifer proteins (LP) recovered from the latex of *C. procera* was evaluated [74]. The LP displayed considerable cytotoxicity with IC_{50} values ranging from 0.42 to 1.36 µg/ml to SF295 and MDA-MB-435 cell lines, respectively. The result suggested that LP is a target for DNA topoisomerase-I triggering apoptosis in cancer cell lines. The cytotoxic and anti-mitotic potential of latex of *C. procera* by standard assay method was evaluated using *Allium cepa* root meristem model, the effect was compared with standard anticancer drug cyclophosphamide and non-cytotoxic drugs cyproheptadine and aspirin. DL (dried latex) significantly inhibited the growth of roots and mitotic activity in a dose-dependent manner [75, 76].

Anti-tumor studies with extracts of *C. procera* root employing Hep2 cancer cells and their possible mechanism of action was observed, results indicated that the root extracts of the plant inhibited the proliferation of Hep2 cancer cells via apoptotic and cell cycle disruption based mechanisms [77]. Recently the cardiotonic steroid UNBS1450 (derived from 2-oxovoruscharin) from *C. procera* was shown to additionally exert an anti-cancer activity. UNBS1450 has been proven to be a potent sodium pump inhibitor, showing anti-proliferative and cell death-inducing activities. This anti-cancer potential of UNBS1450 is achieved by disorganization of the actin cytoskeleton after binding to the sodium pump at the cellular membrane, by inducing autophagy-related cell death, by repressing NF-KB activation as well as by down-regulating c-Myc in cancer cells [77].

VI. Anti-Inflammatory Activity

The latex of the plant *C. procera* has been reported to exhibit potent anti-inflammatory activity against carrageenin and formalin that are known to release various mediators. The efficacy of extracts prepared from the latex of *C procera* against inflammation induced by histamine, serotonin, compound 48/80, bradykinin (BK), and prostaglandin E2 (PGE2) in the rat paw oedema model was evaluated [78]. The anti-inflammatory effect of aqueous and methanolic extracts of DL was more pronounced than phenylbutazone (PBZ) against carrageenin while it was comparable to chlorpheniramine and PBZ against histamine and PGE2, respectively. Both extracts produced about 80%, 40%, and 30% inhibition of inflammation induced by BK, compound 48/80, and serotonin. The histological analysis revealed that the extracts were more potent than PBZ in inhibiting cellular infiltration and subcutaneous oedema induced by carrageenin. The extracts of DL exert their anti-inflammatory effects mainly by inhibiting histamine and BK and partly by inhibiting PGE2.

The anti-inflammatory property of the latex of *C. procera* was studied on carrageenan- and formalin-induced rat paw oedema model [60]. A single dose of the aqueous suspension of the dried latex was effective to a significant level against the acute inflammatory response. The crude dry latex of *C. procera* possesses a potent anti-inflammatory activity [79]. The anti-inflammatory activity of petroleum ether, acetone, methanol and aqueous extracts of dry latex of the plant were tested in the carrageenan induced rat paw oedema model. All the fractions exhibited anti-inflammatory activity but inhibition of oedema was found to be greatest with the acetone and aqueous extracts.

The latex is as potent as standard anti-inflammatory drug phenylbutazone (PBZ) in inhibiting inflammatory response induced by various inflammagens in acute and chronic models of inflammation [80], oral administration of DL significantly inhibited oedema formation induced by carrageenan and Freund's adjuvant. It also inhibited granuloma formation induced by cotton pellet and carrageenan. DL significantly inhibited fluid exudation, possibly due to its effect on vascular permeability. Besides, it also delayed the onset and intensity of UV induced erythema. In all these models, the anti-inflammatory activity of DL was comparable to standard anti-inflammatory drugs. Interleukin-1β (IL-1β), a pro-inflammatory cytokine, has been reported to exhibit anti-

inflammatory properties in the carrageenan-induced paw oedema model. For the protection against inflammation and oxidative stress taking methanolic extract of dried latex (MeDL) on the levels of prostaglandins (PGE_2), tumor necrosis factor (TNF-α), nitric oxide (NO), myeloperoxidase (MPO), oxidative stress parameters, and joint histology in Freund's Complete Adjuvant (FCA)-induced monoarthritis in rats was evaluated [81]. The effect of MeDL was compared with rofecoxib, a selective COX-2 (cyclooxygenase-2) inhibitor, and phenylbutazone (PBZ) a nonselective COX inhibitor. The result obtained was satisfactory because MeDL of *C. procera* markedly reduces cell influx, release of mediators, and oxidative stress associated with arthritic condition, and therefore has the potential to be used as an anti-arthritic agent.

VI. Larvicidal Activity

Commonly mosquitoes proliferate abundantly in Africa, Latin America, North-eastern Brazil as well as in natural areas like the Amazon Region. In early 1980s a brief communication pointed out the whole latex of *C. procera* as a suitable source of active compounds exhibiting larvicidal activity [10]. They act as vector of endemic diseases such as yellow fever in the Amazon Region and dengue hemorrhagic fever in many regions of America, South East Asia, the Pacific islands area, and Africa [82]. The mosquito *Aedes aegypti* is the vehicle of transmission of theses infirmities, can be found disseminated everywhere within these areas and this contributes to aggravate the morbidity statistics. As attempts to control the drastic effects on public health the strategies include massive dissemination of expensive commercial pesticides into air and personal training visiting people in loci, which in turn is time-consuming. Thus, it would be of great relevance to search for alternatives to improve the effectiveness of combating and preventing the proliferation of *Ae. aegypti* as well as other important mosquitoes involved in disease transmission to people and animal. Many sources of natural compounds have been suggested as alternatives for conventional chemical control [83]. *C. procera* was tested against *Anopheles labranchiae* mosquito larvae and exhibited high larvicidal activity with LC_{50} (24 h) ranging from 28 to 325 ppm [84].

The giant milk weed was effective in both inhibition of feeding and causing mortality of larvae. The effect of several commercial and locally extracted biorational pesticides was showed which included *C. procera* against the Egyptian alfalfa weevil (EAW) and *Hypera brunneipennis* (Boheman) [85]. The present review had now extended the work done by various researchers and reported the effect of different rubber-free fractions of the latex upon egg hatching and larval development of the mosquito *Ae. aegypti*. Latex constituents from *C. procera* display toxicity upon egg hatching and larvae of *Ae. aegypti* [65]. The whole latex was shown to cause 100% mortality of 3rd instars within 5 min. It was fractionated into water-soluble dialyzable (DF) and non-dialyzable (NDF) rubber-free materials. It may be possible that the highly toxic effects of the whole latex from *C. procera* upon egg hatching and larvae development should be at least in part due to its protein content found in NDF. However, the toxicity seems also to involve non protein molecules present in DF.

The different water concentrations of this biocide which have brought forward very important observations on the ovipositioning behaviour of *Aedes aegypti* was evaluated [86]. At 0.7% concentration of latex, the ovipositioning was avoided by the gravid female mosquitoes and this behaviour continued till three gonotrophic cycles. However, at lower concentrations (0.2% and 0.1%) of the larvicidal latex, the refractory behaviour of ovipositioning could not be retained up to the third gonotrophic cycle. The concentration of the latex such as 0.7% and 0.2% were observed as ovicidal also and this effect continued across all the gonotrophic cycles. The behavioural observations reported may serve as significant information on choosing bio-larvicides for vector control against dengue. The latex of *C. procera* has shown larvicidal efficacy against all three important vector species *viz*, *Ae. aegypti*, *An. stephensi* and *Cx. quinqefaciatus*, vectors of dengue, malaria and Lymphatic filariasis respectively. The effects of alkaloid extracts of *C. procera* leaves at the vegetative stage on survival of fifth instar larvae and on ovarian growth of *Schistocerca gregaria* have been studied. The results revealed that a mortality rate of 100% was reached in the hoppers on the 15th day after the beginning of the treatment [87]. Insecticidal potentialities of aqueous extracts from *C. procera* against *Henosepilachna elaterii* were evaluated by two methods of extraction [88]. The shaker aqueous extract of leaf, flower and roots of the plant proved most effective in the control of *Henosepilachna elaterii* as a strong repellent and thus deterred the insects from feeding. Soxhlet extract had no anti-insect activity. The toxic effects of crude extracts (both for leaves and flowers) of *C. procera* against two species of termites i.e. *Heterotermes indicola* and *Coptotermes heimi* were studied [89]. Toxic effects of both extracts (leaves and flowers) were more profound against the *Coptotermes heimi* than *Heterotermes indicola* during feeding stage. Also the flower extracts caused more mortality than the leaves for both species suggesting the availability of high contents of toxic materials in flowers. Similarly, *C. procera* showed moderate larvicidal effects against second and fourth instar larvae of the laboratory-reared mosquito species, *Culex quinquefasciatus*, in which the major lymphatic filariasis was used [90]. *C. procera* appears to be more effective than *H. recurvum* and *A. indica* in the sense that crude extract

application on sugarcane sets and then mixing whole plants of *C. procera* into the soil did not allow the termites to forage in large number [91].

VII. Anti-Microbial Activity

It is well known that infectious diseases account for high proportion of health problems, especially in the developing countries. Microorganisms have developed resistance to many antibiotics, and this has created immense clinical problem in the treatment of infectious diseases [92]. This resistance has increased due to indiscriminate use of commercial antimicrobial drugs commonly used in the treatment of infectious diseases. This situation forced scientists to search for new antimicrobial substances from various sources, such as medicinal plants [93]. Antimicrobials of plant origin are efficient in the treatment of infectious diseases mitigating simultaneously many of the side effects that are often associated with synthetic antimicrobials. The antimicrobial activities of plant oils and extracts have formed the basis of many applications, including raw and processed food preservation, pharmaceuticals, alternative medicine and natural therapies [94]. The anti-microbial activity of the leaf extracts of *C. procera* was evaluated and the inhibitory effect of extract of latex of *C. procera* against *Candida albicans* was also observed [95, 96].

Moreover, the increasing use of plant extracts in the food, cosmetic and pharmaceutical industries suggests that in order to find active compounds, a systematic study of medicinal plants is very important [97]. The anti-bacterial activity of a new cardenolide, 7B, 14B-dihydroxy-5-card-20(22) enolide (proceragenin) of *C. procera* was evaluated [98] which has been found to be active against *Pseudomonas pseudomallei*, a causative agent of melioidosis. The antimicrobial activity of the giant milk weed was also showed [66]. The anti-fungal activity was screened (agar dilution method) using organic solvent extracts of the stem bark of *C. procera* [49], which significantly ($p<0.05$) inhibited growth of *Trichophyton rubrum* and *Microsporum gypseum*. All the leaf extract fractions completely inhibited the growth of the tested organisms. The root fractions of hexane (HX) and petroleum ether (PE) extracts showed significant ($p<0.05$) growth inhibitions of *Microsporum gypseum* and *Aspergillus niger*. All the aqueous extract fractions of the plant parts showed complete growth inhibition of all the tested organisms. The antimicrobial activity was evaluated against some of the tested microorganisms (pathogenic bacteria, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and one pathogenic fungus, *Candida albicans*) from the extracts of *Calotropis procera* [99]. The antifungal activities of aqueous extract of *Calotropis procera* was determined against *Epidermophyton flocosum* and *Tricophyton gypseum* using agar diffusion techniques [100]. The crude extract of *C. procera* showed activity on *E. flocosum* and *T. gypseum* at 4.0 mg/ml. The result of minimum inhibitory concentration (MIC) was 0.5 and 0.9 mg/ml and that of minimum fungicidal concentration (MFC) were 2.0 and 4.0 mg/ml, respectively. The result of the Ames test indicated that the crude extract is not mutagenic. The results of the study suggest that *C. procera* stem could be a potential source of chemotherapeutic drugs for the treatment of tinea associated with *E. flocosum* and *T. gypseum.* The *n*-butanol extract of *Calotropis procera* flowers proved to be the most effective against the tested bacterium [101]. The aqueous and organic solvents (hexane and petroleum ether) extracts of leaves, stem barks and roots of *C. procera* were screened for antifungal (agar dilution method) property [102], organic solvents extracts of the stem bark significantly ($p<0.05$) inhibited growth of *Trichophyton rubrum* and *Microsporum gypseum*. The root fractions of hexane (HX) and petroleum ether (PE) extracts showed significant ($p<0.05$) growth inhibition of *Microsporum gypseum* and *Aspergillus niger*.

The antimicrobial effect of ethanol, aqueous and chloroform extracts of leaf and latex of *C. procera* were studied on five bacteria namely, *Escherichia coli, Staphylococcus aureus, Staphylococcus albus, Streptococcus pyogenes, Streptococcus pneumoniae* and three fungi: *Aspergillus niger, Aspergillus flavus, Microsporium boulardii* and one yeast *Candida albicans* using agar well diffusion and paper disk methods [103]. The results revealed that ethanol was the best extractive solvent for antimicrobial properties of leaf and latex of *C. procera* followed in order by chloroform and aqueous ($P<0.05$). The ethanolic extracts of *C. procera* latex gave the widest zone of inhibition (14.1mm) against *E.coli* using agar well diffusion while 9.0 mm was recorded for the same organism in the disc plate method. The growth of six bacterial isolates was inhibited by the three extracts except *P. aeruginosa* and *S. pyogenes* that were not inhibited by the aqueous extracts of both leaf and latex of *C.procera*. Similarly, the growth of four test fungi were inhibited by ethanol and chloroform extracts while the aqueous extract was the least effective on the test fungi. The best antifungal activity was recorded in ethanol extract of *C.procera* latex against *Candida albicans*. The minimum inhibitory concentration (MIC) for the ethanol extract was between 5.0 and 20.0 mg/ml for fungi. The study revealed that the *C. procera* latex demonstrated strong inhibitory effect on the test organisms than its leaf. The results therefore established a good support for the use of this plant in traditional medicine. All the research mentioned definitely shed the light on the antimicrobial ability of extracts from *C. procera*, which lend scientific credence for the use as a natural antimicrobial agents in pharmaceutical and food preservation systems in future.

VIII. Anti-Diarrhoeal Activity

The dry latex (DL) of *C. procera* was evaluated for the anti-diarrhoeal activity [61]. Like atropine and phenylbutazone (PBZ), a single oral dose of DL (500 mg/kg) produced a significant decrease in frequency of defecation, severity of diarrhoea and afforded protection from diarrhoea in 80% rats treated with castor oil. DL produced a decrease in intestinal transit (27–37%) as compared to both normal and castor oil treated animals. Unlike atropine, DL significantly inhibited castor oil induced enteropooling. However, it did not alter the electrolyte concentration in the intestinal fluid as compared to castor oil treated rats.

IX. Anthelmintic Activity

The antihelmintic activity using adult earthworms from the crude latex of *C. procera* was evaluated [57]. Both fresh as well as aqueous extracts of dried latex exhibited a dose-dependent inhibition of spontaneous motility (paralysis) and evoked responses to pin-prick. With higher doses (100mg/ml of aqueous extract of dry latex and 100% fresh latex), the effects were comparable with 3% piperazine. However, there was no final recovery in the case of worms treated with latex in contrast to piperazine with which the paralysis was reversible and the worms recovered completely within six hours. The results showed that latex possesses wormicidal activity and thus, may be useful as an anthelmintic. The anthelmintic activity of *C. procera* latex in sheep was investigated [104] that had been infected with single oral doses of 12000 infective *Haemonchus contortus* larvae. Inappetence, dullness, erosive abomasitis, decreased haemoglobin concentration and increased eosinophils were the main features of haemonchosis in the sheep. In the sheep treated with single oral doses of 0.01 ml or 0.02 ml/kg body weight of *C. procera* latex, egg production was significantly reduced, but not completely suppressed, and fewer adult *Haemonchus* worms were found in the abomasum. Although the appetite improved, the haemoglobin concentration and serum copper, iron and zinc levels were still reduced after therapy with *Calotropis* latex. *Calotropis* latex showed a concentration-dependent larvicidal activity *in vitro* within 20 min of application.

The anthelmintic activity of *C. procera* flowers in comparison with levamisole was evaluated through *in vitro* and *in vivo* studies [105]. *In vitro* studies revealed anthelmintic effects (P<0.05) of crude aqueous (CAE) and crude methanolic extracts (CME) of *C. procera* flowers on live *Haemonchus contortus* as evident from their mortality or temporary paralysis. For *in vivo* studies, its flowers were administered as crude powder (CP), CAE and CME to sheep naturally infected with mixed species of gastrointestinal nematodes. Egg count percent reduction (ECR) was recorded as 88.4 and 77.8% in sheep treated with CAE and CP at 3 g kg^{-1} body weight on day 7 and 10 post-treatment (PT), respectively. CME was least effective resulting in 20.9% reduction in ECR on day 7 PT. It was found that *C. procera* flowers possess good anthelmintic activity against nematodes, yet it was lower than that exhibited by levamisole (97.8–100%). It is suggested that further research on large scale should be carried out involving a large number of animals, doses higher than those used in the current study, identification of active principles, and standardization of dose and toxicity studies for drug development.

X. Spasmolytic Activity

Spasmolytic is referred as a muscle relaxant, is a drug which affects skeletal muscle function and decreases the muscle tone. It may be used to alleviate symptoms such as muscle spasms, pain, and hyperreflexia. The aqueous extract of *C. procera* was evaluated for its spasmolytic effect using *in vitro* trachea smooth muscle chain of Guinea-pig. The extract (50, 100 and 200 µg/ml) showed a dose-dependent relaxant activity probably exhibited through the direct relaxant action on the smooth muscle [106].

XI. Immunomodulatory Activity

The ability of *C. procera* to activate macrophages-effector cells in inflammatory and immune responses was investigated [107]. Intraperitoneal injection of *C. procera* extract (CPE) in mice (2 mg/mouse) induced migration of macrophages to the intraperitoneal cavity, confirming the pro-inflammatory effects of water-soluble CPE. The direct effects of CPE on macrophages were then assessed by measuring the production of nitric oxide (NO) as an indicator for macrophage activation. Addition of CPE (1-10 µg/ml) to the culture medium of the murine monocyte/macrophage cell line RAW264.7 caused an increase in NO production in a time- and dose-dependent manner. CPE-elicited NO production was blocked by application of an inhibitor of inducible nitric oxide synthase (iNOS). Expression of iNOS mRNA was induced by treatment of cultured macrophages with CPE. Injection of CPE in mice also resulted in an increase in plasma NO level. The results thus suggested that CPE activates macrophages and facilitates NO production via up-regulation of iNOS gene expression.

XII. Anti-Pyretic Activity

Antipyretic effect from aerial parts of *C. procera* was reported [25]. Similarly, the ethanolic extract of *C. procera* latex to possess antipyretic effect against yeast induced fever in rats was also reported [108], four hours after administration of yeast, either dose of DL (250 or 500 mg/kg), aspirin (200 mg/kg) or saline were administered orally in 1 ml volume. Body temperature (ºF) was measured at 0, 3, 4 and 6 hours through rectal route using a digital thermometer. Administration of yeast produced an increase in rectal temperature from 97.32±0.19ºF which reached to its maximum in 4 h (100.0±20.27ºF). There was no further rise in temperature at 6 h in the control group and the mean temperature remained at 99.74±0.15ºF. Administration of DL-250 mg/kg and 500 mg/kg at 4 h produced a significant ($P<0.05$) decline in rectal temperature to 98.50±0.29ºF and 98.45±0.60ºF respectively. The antipyretic effect was compared with that of aspirin, which was found to be more potent and brought down the temperature to 96.9±0.38ºF ($P<0.001$). This study suggests that DL of *C. procera* has actions similar to aspirin. The antipyretic activity of *C. procera* in experimental rats was also investigated [109]. The antipyretic effect retained the test and was comparable to that of acetylsalicylic acid used as the standard drug.

XIII. Anti-Oxidant Activity

Scientific evidence suggests that under oxidative stress conditions, oxygen radicals such as superoxide anion ($O2^{-}$), hydroxyl radical (-OH) and peroxyl radicals (H_2O_2) are produced in biological systems. These oxygen radicals are called Reactive Oxygen Species (ROS) and they can lead to oxidative damage to cellular components such as proteins, lipids and DNA. These oxygen radicals play important roles in degenerative processes such as ageing [110], cardiovascular diseases, cancer, Alzheimer's disease and other neurodegenerative diseases, [111-113]. Antioxidants are reported to boost the function of immune cells against homeostatic disturbance and their free radical scavenging activity has been substantially investigated [114]. Similarly, the antioxidant potential of the methanolic extract was determined on the basis of their scavenging activity of the stable 1, 1-diphenyl-2-picryl hydrazyl (DPPH) free radical. IC_{50} of the methanol extract of *C. procera* was 110.25 µg/ml indicating the strong antioxidant activity of the plant. However, the aqueous extract showed mild antioxidant activity [102].

The antioxidant potential of the root, leaf extracts and latex of field grown as well as tissue cultured *C. procera* plants were analyzed [115]. Free radical scavenging activity was determined by DPPH. The highest antioxidant capacity was exhibited by extracts of lyophilized latex (IC_{50} = 0.060 mg/ml) and the lowest (IC_{50} = 0.27mg/ml) was in root extracts of field grown plants. The obtained results thus provided a support for the use of *C. procera* in traditional medicine and suggest its further advance investigation. Antioxidant effect of latex of *C. procera* against alloxan-induced diabetic rats was evaluated [116]. DL produced an increase in the hepatic levels of the endogenous antioxidants, namely superoxide dismutase (SOD), catalase and glutathione, while it brought down the levels of thiobarbituric acid-reactive substances (TBARS) in alloxan-induced diabetic rats. The efficacy of DL as an antioxidant agent was comparable to the standard drug, glibenclamide.

XIV. Wound Healing Activity

Based on its traditional use, *C. procera* was selected for evaluation of its wound healing potential in guinea pigs [117], for this purpose four full thickness excision wounds of 8.0 mm diameter were inflicted on the back of guinea pigs. Topical application of 20 µl of 1.0% sterile solution of the latex of the plant, twice daily was followed for 7 days. The latex significantly augmented the healing process by markedly increasing collagen, DNA and protein synthesis and epithelisation leading to reduction in wound area. Thus the result provided a scientific rationale for the traditional use of this plant in the management of wound healing.

XV. Protective Activity

Hydro-ethanolic extract (70%) of *C. procera* flowers was prepared and tested for its hepatoprotective effect against paracetamol-induced hepatitis in rats [118]. Alteration in the levels of biochemical markers of hepatic damage like SGPT, SGOT, ALP, bilirubin, cholesterol, HDL and tissue GSH were tested in both treated and untreated groups. Paracetamol (2 g/kg) has enhanced the SGPT, SGOT, ALP, bilirubin and cholesterol levels and reduced the serum levels of HDL and tissue level of GSH. Treatment with hydro-ethanolic extract of *C. procera* flowers (200 mg/kg and 400 mg/kg) has brought back the altered levels of biochemical markers to the near normal levels in the dose dependent manner.

The alcoholic extract of the latex obtained from *C. procera* was evaluated for protection against isoproterenol (20 mg/100g body wt., s.c.) induced myocardial infarction in albino rats [119]. The heart damage induced by isoproterenol was indicated by elevated levels of the marker enzymes such as Creatine Kinase-isoenzyme (CK-MB), Lactate dehydrogenase (LDH), Serum Glutamate Oxaloacetic Transaminase (SGOT) and Serum Glutamate Pyruvate Transaminase (SGPT) in serum with increased lipid peroxide and reduced glutathione content in heart homogenates. Microscopical examination (histopathology) was also performed on

the myocardial tissue. Pretreatment with an ethanolic latex extract of *C. procera* at a dose of 300 mg/kg body wt., administered orally thrice a day for 30 days, reduced significantly ($p<0.01$) the elevated marker enzyme levels in serum and heart homogenates in isoproterenol-induced myocardial infarction. Histopathological observation revealed a marked protection by the extract in myocardial necrotic damage.

The protective effects of latex of *C. procera* in Freund's Complete Adjuvant (FCA) induced monoarticular arthritis in rats were observed [120]. Daily oral administration of dried latex (DL) and its methanol extract (MeDL) produced a significant reduction in joint inflammation (about 50% and 80% inhibition) and associated hyperalgesia. The anti-hyperalgesia effect of MeDL was comparable to that of rofecoxib. Both DL and MeDL produced a marked improvement in the motility and stair climbing ability of the rats. The histological analysis of the arthritic joint also revealed significant reduction in oedema and cellular infiltration by MeDL that was comparable to that of rofecoxib. Thus, the result suggests that the latex of *C. procera* has the potential to be used as an anti-arthritic agent and hence concluded as an efficient protective agent.

XVI. Analgesic Activity

An analgesic (also known as a painkiller) is any member of the diverse group of drugs used to relieve pain (achieve *analgesia*). The word *analgesic* derives from Greek *an-* ("without") and *algos* ("pain"). Analgesic drugs act in various ways on the peripheral and central nervous systems; they include paracetamol (acetaminophen), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol, and various others.

Henceforth, the analgesic activity of dry latex (DL) of *C. procera* was evaluated [59]. A single oral dose of DL ranged from 165 to 830 mg/kg produced a significant dose dependent analgesic effect against acetic acid induced writhings. The effect of DL at a dose of 415 mg/kg was more pronounced as compared to a 100 mg/kg oral dose of aspirin. On the other hand DL (830 mg/kg) produced marginal analgesia in a tail-flick model which was comparable to aspirin. The analgesic effect of DL was delayed by 1 h by naloxone at a dose of 0.5 mg/kg, i.p., which completely blocked the analgesic effect of morphine (10 mg/kg, i.p.). However, the effect of aspirin was not blocked by naloxone. The 830 mg/kg oral dose of DL did not produce toxic effects in mice and the LD_{50} was found to be 3 g/kg. A significant analgesic property by the hot plate method was showed [25] which were described previously against mice [121]. It is clearly concluded that *C. procera* shows tremendous analgesic activity which is a boom for medicinal world.

XVII. Acaricidal Activity

Acaricides (or miticides) are pesticides that kill ticks and mites. Antibiotic miticides, carbamate miticides, formamidine miticides, mite growth regulators, organochlorine, permethrin and organophosphate miticides are all in this category. Similarly, the cardiac glycoside (cardenolide) extract from *C. procera* was tested for the effect against larvae and adult stages of the camel tick, *Hyalomma dromedarii* Koch (Acari: Ixodidae) [122]. The contact LC_{50} value of the material against adults was 9.63µgcm^{-2} whereas the dipping LC_{50} value of the material was 1096 mg/litre^{-1}. Contact and dipping LC_{50} values of the extract against larvae were 6.16cm^{-2} and 587.7 mg litre^{-1}. Results of the cardiac glycoside material were compared with those of several commercial acaricides and the risks and benefits associated with the use of cardiac glycoside were considered.

XVIII. Antinociceptive Activity

Nociception is defined as "the neural processes of encoding and processing noxious stimuli". It is the afferent activity produced in the peripheral and central nervous system by stimuli that have the potential to damage tissue. This activity is initiated by nociceptors (also called pain receptors), that can detect mechanical, thermal or chemical changes, above a set threshold. Once stimulated, a nociceptor transmits a signal along the spinal cord, to the brain. Nociception triggers a variety of autonomic responses and may also result in the experience of pain in sentient beings.

The antinociceptive effect of proteins from the *C. procera* latex was evaluated using three different experimental models of nociception in mice [123]. The latex protein fraction administered intraperitoneally in male mice at the doses of 12.5, 25 and 50 mg/kg showed the antinociceptive effect in a dose dependent manner compared to the respective controls in all assays. Inhibitions of the acetic acid-induced abdominal constrictions were observed at the doses of 12.5 (67.9%), 25 (85%) and 50 (99.5%) mg/kg compared to controls. Latex protein at the dose 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 of the reaction time was observed only at 60 min after the treatment with latex at the dose of 25 (79.5%) and 50 (76.9%) mg/kg, compared to control and naloxone was ineffective to reverse the effect. It was concluded that the protein fraction derived from the whole latex of the giant milk weed possesses antinociceptive activity, which is independent of the opioid system.

XIX. Antiulcer Activity

The antiulcer activity of *C. procera* using different *in vivo* ulcer models were reported [124]. 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.

XX. Anti-Fertility Activity

The effect of ethanolic extract of the roots of *C. procera* in albino rats was studied [125] to explore its anti-fertility and hormonal activities. A strong anti-implantation (inhibition 100%) and uterotropic activity was observed at the dose level of 250 mg/kg (1/4 of LD_{50}).

XXI. Anti-Coccidial Activity

Coccidiosis is the disease caused by coccidian infection. Coccidiosis is a parasitic disease of the intestinal tract of animals, caused by coccidian protozoa. The disease spreads from one animal to another by contact with infected feces or ingestion of infected tissue. Diarrhea, which may become bloody in severe cases, is the primary symptom. Most animals infected with coccidia are asymptomatic; however, young or immuno-compromised animals may suffer severe symptoms, including death.

The comparative anti-coccidial activity of *C. procera* latex and sulfadimidine was examined in experimental *Eimeria ovinoidalis* infection in Najdi lambs which had been infected with single oral doses of 150,000 infective oocysts [126]. The symptoms revealed positive for coccidiosis in Najdi lambs. They were treated with single oral doses of 0.02 ml/kg body weight of *C. procera* latex or 2 g/kg body weight of sulfadimidine, oocysts production was considerably suppressed 4 days post-treatment and feces were completely free from oocysts between 7 and 17 days after treatment with both *C. procera* latex and sulfadimidine. These findings were accompanied by a return of normal appetite and activity, regular pelleted feces and markedly reduced number of schizonts in intestinal cells. Although bouts of diarrhea were severe post-infection, the concentration of serum sodium returned to normal but that of potassium remained high after therapy with *C. procera* latex and sulfadimidine. Repetition of dosing lambs with *C. procera* latex and sulfadimidine was suggested.

XXII. Schizontocidal Activity

Schizonts are protozoan cells that divide by schizogony and *C. procera* acts an agent (schizontocide) to kill these schizonts. Good record keeping of subjective and objectively recorded cures by practitioners of traditional medicinal system will help in the establishment of the use of *C. procera* as an antimalarial plant. Researchers attempted to see the effect of crude fractions of its flower, bud and root against a chloroquine sensitive strain, MRC 20 and a chloroquine resistant strain, MRC 76 of *Plasmodium falciparum* using the Desjardins method and the effectiveness of its fractions compare better with the CQ sensitive strain than the CQ resistant strain *in vitro* [62]. Whereas, again the scientists evaluated the ethanol extracts of the plant leaves, stems, roots, flowers and buds and screened *in vitro* for schizontocidal activity against chloroquine (CQ)-sensitive and CQ-resistant *Plasmodium falciparum* strains [62].

XXIII. The Plant

Calotropis procera (Giant milkweed) is known as sodom apple, calotrope, French cotton, small crown flower (English), algodón de seda, bomba (Spanish), cotton-france, arbre de soie, and bois canon (French) [54]. This plant is a soft-wooded, evergreen, perennial shrub. It has one or a few stems, few branches, and relatively few leaves, mostly concentrated near the growing tip. The bark is corky, furrowed, and light gray. A copious white sap flows whenever stems or leaves are cut. It has a very deep, stout taproot with few or no near-surface lateral roots. Its roots were found to have few branches and reach depths of 1.7 to 3.0 m in Indian sandy desert soils [127]. 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.

The latex of the giant milk weed is well known for its toxic as well as for various medicinal properties. The latex can cause blisters and rash in sensitive persons. The plant is occasionally grown as an ornamental in dry or coastal areas because it is handsome, of a convenient size, and is easy to propagate and manage.

C. procera is classified into 10 groups i.e. Kingdom- Plantae, Subkingdom- Tracheobionta, Superdivision- Spermatophyta, Division- Magnoliophyta, Class- Magnoliopsida, Subclass- Asteridae, Order- Gentianales, Family- Asclepiadaceae, Genus- *Calotropis* and Species- *procera*. It is native to West Africa as far South as Angola, North and East Africa, Madagascar, the Arabian Peninsula, Southern Asia, and Indochina to Malaysia [128]. The species is now naturalized in Australia, many Pacific islands, Mexico, Central and South America.

23.1 Endophytic Fungi from *C. procera*

Endophytic fungi are those which live inside the tissues of living plants and are under-explored group of microorganisms. These are diverse group of organisms that make symbiotic associations with higher life forms and may produce beneficial substances for host [129, 130]. Recently they have received considerable attention after they were found to protect their host against insect pests, pathogens and even domestic herbivores [129, 130, 131]. Endophytic fungi generally live peacefully with their host, while these fungi under different conditions may act as facultative pathogen. One of the important roles of endophytic fungi is to initiate the biological degradation of dead or dying host-plant, which is necessary for nutrient recycling [132]. *Calotropis procera* is a widely used medicinal plant in Indian sub-continent, was investigated for endophytic mycoflora as a possible source of bioactive secondary metabolites [133]. A total of 8 fungal species viz., *Aspergillus flavus, A. niger, Aspergillus* sp., *Penicillium sublateritium, Phoma chrysanthemicola, P. hedericola, Phoma* sp., and *Candida albicans* were isolated. Among the endophytic flora, *Phoma* was the most prominent genus. The profuse pycnidia were found on the dead plants of *C. procera* which is the characteristic of the fungus *Phoma*, the most common endophyte of this plant. The *Phoma* species are reported to produce cellulytic enzymes, necessary to degrade plant material [134]. Interestingly, no endophyte was isolated from 118 leaves samples and overall colonization frequency from surface sterilized stem was 8.86%. In their study, Deuteromycota fungi were largely prevalent. Majority of endophytic fungi belongs to Ascomycota and Deuteromycota [135]. A study of endophyte biodiversity of the two dry tropical forest of the Nilgiri Biosphere Reserve in India was conducted [136]. A monthly survey from 1989-1991 was conducted to examine the effect of seasons on the inhabited surface fungi on leaves of medicinal plant, *C. procera* [137]. A total number of 46 species of 21 genera of fungi from the plant were isolated. A high percent of fungi was obtained during May while the lowest percentage was recorded in September. Alternaria (7 species) was the most predominant genus on leaves of *C. procera*. *Alternaria alternata*, *Aspergillus flavus*, *A. niger* and *Penicilium chrysogenum* were isolated during all seasons on the leaves of the plant.

23.2 *C. procera* as a potent biosorbent

The leaf biomass of the plant is potentially a good adsorbent for the removal of crystal violet (a cationic) from aqueous solution [17]. The cation binding capacity of the adsorbent biomass can be enchanced by its treatment with alkalies like sodium hydroxide. Most plant tissue has cellulose, hemicellulose and ligin as their major constituents. These constituents contain methyl esters, which do not bind metal ions (cations) significantly. The methyl esters can be converted to carboxylate ligands by treatment of a biomass with alkalies like sodium hydroxide. The performance of the leaf biomass of the plant as biosorbent for the textiles dyes can be evaluated by comparing its uptake capacity with other biosorbents.

23.3 *C. procera* as a source of Plant hydrocarbons

C. procera was evaluated as a potential source of hydrocarbons [18]. Hexane Soxhlet extraction of oven-dried whole plants, stems, leaves and pods (≥6mo of age) yielded 4.35, 3.83, 5.13, and 9.37% (w/w) hexane extract (HE), respectively. The HE from whole plants has a density of 0.9299 g/cm^3, 0.71% total ash, 9973.4 cal/g and 78.03, 11.22 and 10.71% carbon, hydrogen and oxygen, respectively. Similar values were obtained from stems, leaves and pods when analyzed separately. Methanol Soxhlet extractions of residues previously extracted with hexane yielded 16.14, 18.50, 12.15 and 20.68% (w/w) methanol extract (ME) from whole plants, stems, leaves and pods, respectively. The ME from whole plant residues had a density of 1.2267 glcm3, 12.05% total ash, 4,647.4 callg, and 40.88, 6.86, and 30.05% carbon, hydrogen and oxygen, respectively. Similar values were obtained from stems, leaves and pods when analyzed separately.

XXIV. Conclusion

C. procera (giant milk weed) has been used as traditional folk medicine by many cultures, and it has been the subject of extensive phytochemical and bioactive investigations. It had shown significant pharmacological importance representing as a strong contender in the medical arena. It is a useful botanical monitor of pollution because of the variation found in the concentrations of Br, Mn, Se, Cr and Zn between urban and suburban samples. The plant has proved to be a good indicator for the determination of above elements when it is exposed to them from any source. Historically, the plant is being used in rural community

for pest control and as a remedial agent against various diseases. It is therefore, interesting to study the biological activity of this plant in depth to evaluate their efficacy after characterizing the bioactive principle. We believe that intensive and systemic investigation of this plant will give new insight for further pharmacological and phytochemical research.

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Abbreviations

DL- Dried latex
CAM- Complementary and alternative medicine
LP- Protein fraction of the latex

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Table-1. Phytochemicals from *Calotropis procera*

S. No.	Name of compound	Plant parts	References
1)	ß-Amyrin	Root bark	Anjaneyulu et al,
2)	α-Amyrin	Root bark	Anjaneyulu et al, [41]
3)	Taraxasterol	Root bark	Anjaneyulu et al, [41]
4)	Ψ-Taraxasterol	Root bark	Anjaneyulu et al, [41]
5)	ß-Sitosterol	Root bark	Anjaneyulu et al, [41]
6)	Taraxasteryl acetate	Root bark	Anjaneyulu et al, [41]
7)	Taraxasteryl benzoate	Root bark	Anjaneyulu et al, [41]
8)	α-Amyrin benzoate	Root bark	Anjaneyulu et al, [41]
9)	ß-Amyrin benzoate	Root bark	Anjaneyulu et al, [41]
10)	ß-Amyrin acetate	Root bark	Anjaneyulu et al, [41]
11)	Acetic acid	Root bark	Anjaneyulu et al, [41]
12)	Isovaleric acid	Root bark	Anjaneyulu et al, [41]
13)	Taraxasterol isovalerate	Leaves	Anjaneyulu et al, [41]
14)	Benzoyllineolone	Root bark	Chandler et al, [42]
15)	Benzoylisolineolone	Root bark	Chandler et al, [42]
16)	Uzarigenin	Latex	Brueschweiler et al, [43]
17)	Syriogenin	Latex	Brueschweiler et al, [43]
18)	Proceroside	Latex	Brueschweiler et al, [43]
19)	Calotropin	Leaves	Malik et al, [8]
20)	Calotropagenin	Leaves	Malik et al,[8]
21)	Calotoxin	Latex	Maharan et al, [138]

22)	Uscharin	Latex	Maharan et al, [138]
23)	Uscharidin	Latex	Maharan et al, [138]
24)	Choline	Latex	Maharan et al, [138]
25)	Procerain	Latex	Dubey and Jagannadham, [48]
26)	Isorhamnetin-3-O-rutinoside	Leaves	Gallegos-Olea et al, [50]
27)	isorhamnetin-3-O-robinobioside	Leaves	Gallegos-Olea et al, [50]
28)	Procerursenyl acetate	Roots	Alam and Ali, [51]
29)	Proceranol	Roots	Alam and Ali, [51]
30)	D-glucose	Leaves	Bhaskar and Ajay, [44]
31)	D-arabinose	Leaves	Bhaskar and Ajay, [44]
32)	D-glucosamine	Leaves	Bhaskar and Ajay, [44]
33)	α-rhamnose	Leaves	Bhaskar and Ajay, [44]

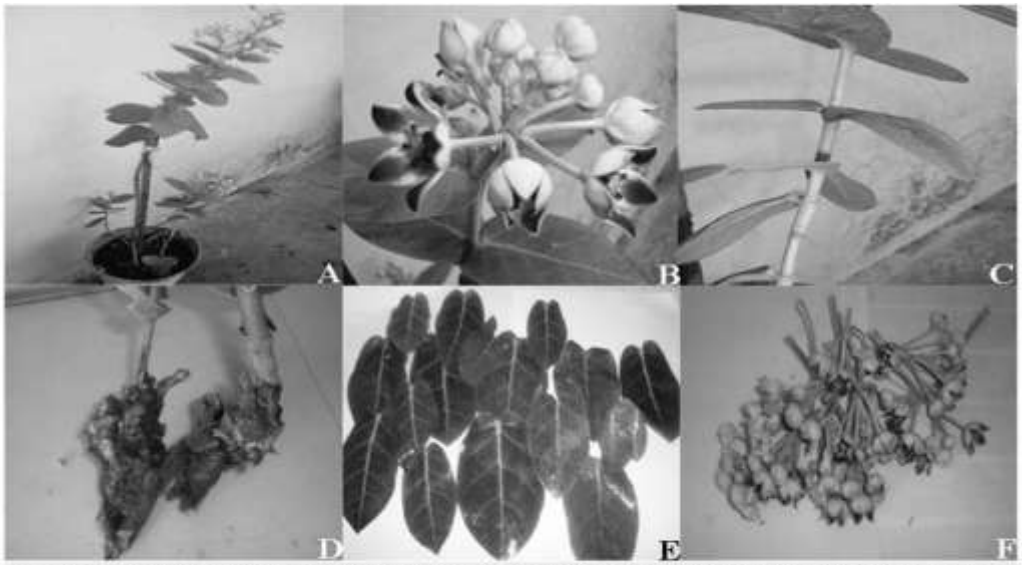

Figure 1. *Calotropis procera* (A) Plant growing in herbal garden (B) Flowers with inflorescence (C) Stem of *C. Procera* (D) Roots of *C. Procera* (E) Leaves of *C. Procera* (F) Flowers of *C. Procera*

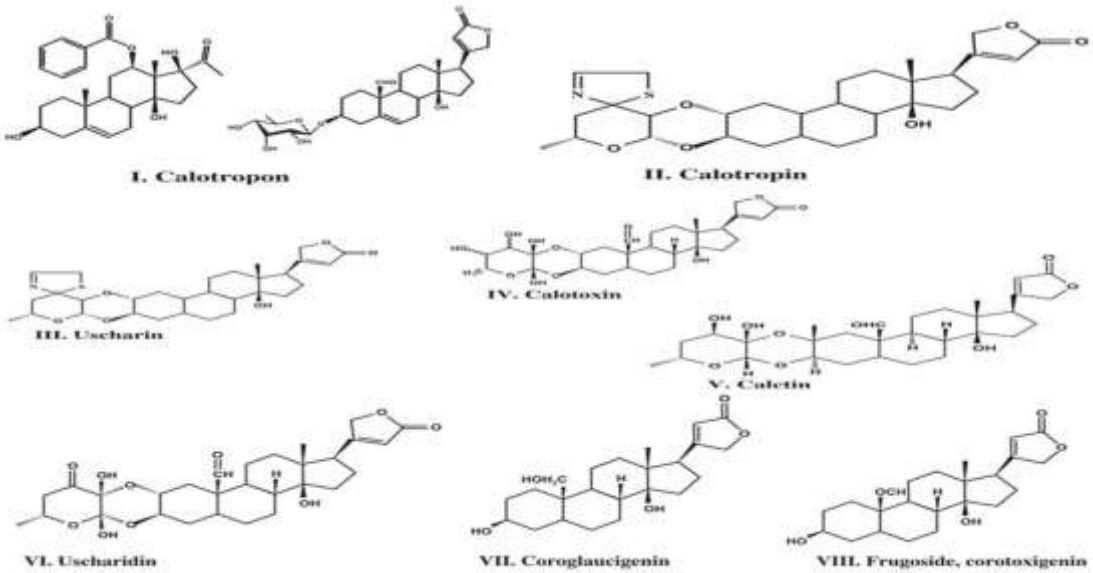

Figure 2. Phytochemical constituents of *Calotropis procera*

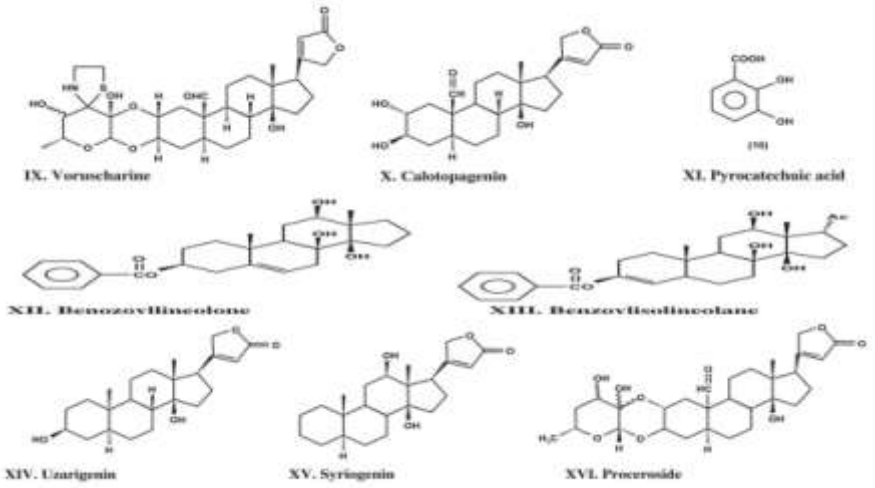

Figure 3. Phytochemical constituents of *Calotropis procera* (continue)

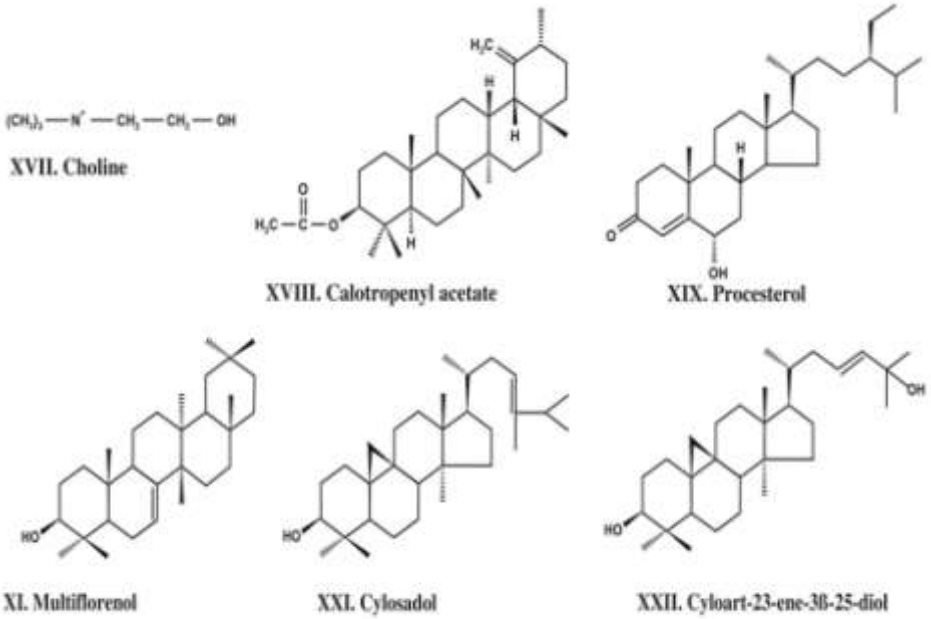

Figure 4. Phytochemical constituents of *Calotropis procera* (continue)

Figure 5. Medicinal applications of *Calotropis procera*