

Ethnomedicinal, pharmaceutical and pesticidal uses of *Calotropis procera* (Aiton) (Family: Asclepiadaceae)

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Calotropis procera is a multipurpose plant that is extensively used by traditional folk healers and local people for preparation of different drugs and ailments of choice to treat different diseases and disorders. Plant contains diverse phyto-chemicals which show various pharmaceutical and ethno-medicinal properties. Two related species are of Asclepiadaceae, *Calotropis procera* and *Calotropis gigantea*, and both possess enormous disease curing potential against various infectious agents such as bacteria, viruses, fungi, protozoans and worms; and are widely used for treatment of different diseases and physiological disorders. Active components of *Calotropis procera* displayed cytostatic, cytotoxic, wound healing, procogulant, analgesic, anticonvulsant, anti-arthritic, antidiabetic, hepatoprotective, anti-fertility, antipyretic, anti-coccidial, anticancer, antitumor and anti-inflammatory properties. Natural *Calotropis* latex in preserved and concentrated forms finds many pharmaceutical applications and may be more useful in interventional therapies, complementary and alternative medicine to cure different types of cancers. Latex can be used for preparation of various herbal drugs and drug templates which might be non-steroidal and show wider cancer suppressing efficacy in patients. Plant can become a future source of therapeutic drugs, pesticides and industrial products. It can be used for phyto-extraction of toxic chemicals and reclamation of polluted derelict lands.

Key words: *Calotropis gigantea*, *Calotropis procera*, ethnomedicines, pesticides, pharmaceuticals, plant latex

INTRODUCTION

Calotropis procera (Aiton) is a spreading shrub or medium-sized tree of 2.5 to 6 m of height after attaining age of 3-5 years. It is a multipurpose tree commonly known as Madar in Hindi [Figure 1]. Plant forms a deep taproot system up to 3-4 m in depth, and form secondary root system when injured severely. It forms woody lateral roots that may rapidly regenerate adventitious shoots. The stems are crooked and covered with a fissured corky bark and yield a fiber useful for making ropes, bags, nets and paper.^[1] Plant possesses gray green sessile leaves of 15-30-cm long and 2.5-10-cm broad having succulent and waxy appearance.^[2] The flowers are non-scented, small, cream or greenish white at the base and purple violet at the extremity of the lobes and pentamerous. Follicles are recurved with 2 or 1 follicles, second more often suppressed, 3-4" long. The fruit is green, fleshy and inflated, up to 10 cm or more

in diameter and arranged laterally one after one.^[1] The seeds contain a white silky floss^[3] which help to spread seeds by wind, livestock, wild animals and flood water and transported on long distances.^[4] That helps to find new locations for its floral establishment. Young pods, senescing leaves and flowers of *C. procera* are used as source of fodder for cattle in semi-arid region, but latex bearing aerial plant parts of *C. procera* are highly toxic and harmful to livestock. Plant is a potential source of renewable energy^[4] and its dry stem is a good source of fuel, fire wood and timber for local people.^[1] It also yields ash which is used for making gun powder. The bark yields white silky strong and durable fiber which is used for making, cordage, ropes, carpets, fishing nets and lines, bow strings and twines, and sewing thread. Floss, obtained from seeds, is used for stuffing purposes. *C. procera* is toxic and its latex from the stem was used to empoison the hunting arrows during war in ancient time. Plant shows great ethno-medicinal value and is extensively used by local tribes in India. Its two closely similar species, *Calotropis procera* and *Calotropis gigantea*, possess very high pharmaceutical and ethnomedicinal importance.

DISTRIBUTION

Calotropis procera belongs to the family Asclepiadaceae with 180 genera and 2200 species distributed mainly

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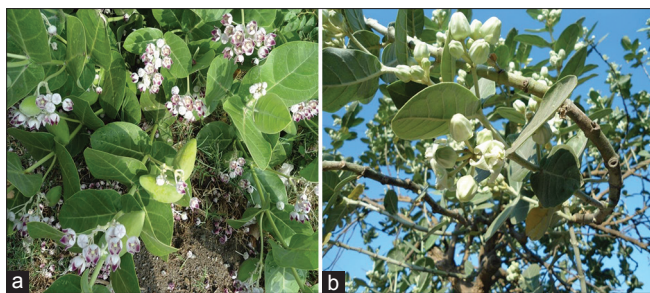


Figure 1: Showing *Calotropis procera* and *Calotropis gigantea*

in the tropical and subtropical regions of the world. Plant shows its indigenous presence in Afro-Asian monsoonal regions from where it has spread to northwestern Africa (Mauritania, Senegal), through Arabian Peninsula, commonly grow most abundantly in Bangladesh, India, Burma, Pakistan and in the sub-Himalayan tract.^[5] It also shows floral presence in subtropical America, Mascarene Islands and drier parts of Australia. Its natural plantation occurs from sea level up to 1300 m in semi-arid conditions where annual rainfall noted between 150 and 1000 mm. Plant grows in sandy and excessively drained soils, derelict lands and can withstand a wide range of soil texture and eco-climatic changes. It is a good tolerant of soil salinity, draught, heat and of beachfront salt spray. It is a highly adapting plant, which can withstand 2000-mm annual precipitation and established very fast in open habitat with little competition. It shows excellent adaptability to biological structures and grows along degraded roadsides, lagoon edges and in overgrazed native pastures and rangelands.^[1] When damaged, it readily develops suckers from the roots that rapidly regenerate and form adventitious shoots.^[5] The plant is also known by other common names such as Akund, apple of sodom, auricula tree, giant milkweed, madar, mudar, roostertree, rubber bush, rubberbush, small crownflower, sodom's milkweed, sodom apple, swallowwort, arbre à soie, aak, akada, rui, algodão de seda, flor-de-seda, thora thora. *Calotropis procera* Linn., also known as *Alarka*, *Surya*, *Suuryaahvya*, *Vikirna*, *Vasuka*, *Tapana*, *Tuulaphala*, *Kshirparna*, *Arkaparna*, *Aasphota Aakh*, *Madaar* or *Ashar* in India.^[6] Plant secrete milky sap (latex) which is a large source of ethnomedicines.^[3,7]

ETHNOMEDICINAL USES

C. procera is mentioned in *Ved Sushruta* (about 800-900 AD), as "*Arkaputra*" or "*Arka prana*" due to presence of its shining leaves. In India, plant has great aesthetic and cultural value as leaves of *Arka prana* were used for Sun and Shiva worship in Vedic times. Plant is under use since ancient time in Indian traditional system of medicine mainly for treatment of leprosy, ulcers, tumors, piles and diseases of spleen, liver and abdomen.^[6] The traditional folk healers use the milky sap or latex of *C. procera* for preparation of different

drugs and ailments mainly for treatment of boils, infected wounds and rushed skin.^[6] In Nigeria traditional medicine, *C. procera* latex is either used alone or with other herbs to treat common diseases such as fever, leprosy, dropsy rheumatism, indigestion, cold, eczema and diarrhoea.^[7] *C. procera* processed latex is used in treating vertigo, baldness, hair fall, tooth aches, intermittent fevers, rheumatoid/joints swellings and paralysis.^[8] Its leaf latex is applied on fresh cuts to stop bleeding immediately and is also used to treat boils,^[9] and to remove thorn from body.^[10] The dried aerial parts and roots are consumed as expectorant,^[11] purgative, improve digestion^[12] and are also used to prepare an effective laxative. Dry root powder is used to good tonic to cure bronchitis, asthma, leprosy, eczema and elephantiasis, hepatic and splenic enlargement.^[11] Its leafy slimy latex/extract is topically used to relax the muscles of uterus or to increase uterine contractility in mothers to facilitate safe childbirth or to induce abortion in women.^[13] Root extracts of *C. procera* enhance human myometrial smooth muscle cell contractility and is used as stimulant to heart.^[14]

Plant also shows great ethnopharmacology use^[15] and its root bark powder is traditionally used by Gwari communities to kill intestinal mainly nematodes^[16-18] and filarial worms.^[19] The root bark also promotes secretion, is useful in treating skin diseases, enlargement of abdominal viscera, ascites, anasarca, and is a cholagogure diaphoretic, emetic, alternative, diuretic, febrifuge, anthelmintic, depurative, expectorant, laxative, and is used for treatment of skin disease, cough, ascites, asthma, bronchitis, dyspepsia, paralysis, swellings, intermittent fevers, anorexia, dyspepsia, inflammations, tumors, elephantiasis and rheumatism.^[20] Root extract is used to treat headache, severe body pain, malarial fever and convulsion,^[21] eczema, leprosy, elephantiasis, asthma and cough.^[22,23] Root extract is orally used by the tribal ladies in dysmenorrheal, protracted labor^[23] and dysentery.^[24] It is also used as a coagulation agent for cheese making in West Africa.^[25] Root charcoal bland with oil is applied over skin to treat syphilis and leprosy and is also used to treat skin diseases, enlargements of abdominal viscera, flatulence, anorexia and indigestion.^[17] Root bark increase contractility in diverse muscles and generate a *Digitalis*-like effect on the heart, the dried root bark is a substitute for ipecacuanha and have relief from joint pain.^[26]

Traditionally, warmed leaves of *Calotropis procera* impregnated with castor oil are applied externally and tied around body organ to reduce backache and joint pains,^[27] stomach ache, swellings and paralysis.^[9] A poultice of the leaves is applied to cure rheumatism, filariasis, wounds, glandular swellings, arthralgia, intermittent fevers, eczema, pigmentation and other skin inflammations. The flowers are bitter and its extract is used as digestive tonic, astringent,

stomachic, anthelmintic, anticancer^[11] and are also used for treating blood impurity, whooping cough, asthma and cold, catarrh and appetite^[12] and cure migraine.^[24] *C. procera* flowers are used in ethno-medicines to increase uterine contractility to facilitate easy childbirth in Sudan Savanna region of Nigeria^[13] The pungent latex extracted from the leaf and flowers of *C. procera* is processed and used in the commercial preparation of eye tonic.^[9] Either dry leaves are smoked or the smoke from the burning leaves is inhaled for the cure of asthma or cough and to cure headache. The leaf juice is applied to skin diseases while its decoction is used for extracting guinea-worms, dropsy and enlargement of the abdominal viscera.

THERAPEUTIC USES

In Ayurveda, *C. procera* is described as Aak and is used in preparation of many traditional medicines to cure the patients.^[28] Owing to its unique properties, Aurvedic practitioners recommends the use of the root and leaf of *C. procera* in asthma and shortness of breath, stem bark in liver and spleen diseases.^[29] Plant is also effective in treating skin, digestive, respiratory, circulatory and neurological, disorders and is used to treat fevers, elephantiasis, nausea, vomiting and diarrhea.^[30] The aqueous suspension of milky juice of *Calotropis procera* effectively work against the arthritis,^[31] cancer^[32] and act as good antidote for snake bite.^[33] Self-medication by using *C. procera* latex is not recommended as plant possesses several poisonous substances that are much harmful for man and his livestock. The milky exudation contains cardiac glycosides a corrosive poison which is harmful for man and livestock. It generates mercury-like effects on the human body, and is referred as *vegetable mercury*. It is also used in place of mercury in aphrodisiacs. Another poisonous compound calotropin from this plant is more toxic than strychnine and is similar in structure to two cardiac glycosides which are responsible for the cytotoxicity of *Apocynum cannabinum*. Calotropin isolated from latex is used as a remedy of painful tooth cavities and applied to various skin complaints.^[34] Crystallised proteins show wound-healing property and can better cure cancer and tumors. They possess enormous wound-healing property.

Plant also shows anti-mycoplasmal^[35] and antifungal activity.^[29] Plant induce neuromuscular blocking activity and show electrophysiological effects on cardiac, smooth and skeletal muscle contraction.^[14] Chemical constituents could directly affect the cell membrane probably through receptors coupling to G proteins and regulate the ion channel physiology as in the myocardium.^[14] *Calotropis* is also a reputed Homoeopathic drug.^[29] Its Arka or latex acts as a purgative and an emetic and is used in treating

ascites of kapha type and hepatosplenomegaly ascites. The latex is used in treating enlarged spleen and liver, vertigo, baldness, hair fall, toothaches, intermittent fevers, rheumatism and paralysis. The whole plant alcoholic extract induces spermicidal and anti-microbial activities, simulates estrogens in the reproductive tract, and acts as anti-fertility agent. Natural *Calotropis* latex in preserved and concentrated forms finds many commercial applications. It possesses various proteolytic enzymes which can be used for industrial purposes as well as in leather and tanning industry remove hair from the hides.^[36] Salted fermented latex of *Calotropis* is used to remove the hair from goatskins for preparation of "nari leather" that is used in book-binding.^[36] Extracts of different plant parts of *Calotropis* show allelopathic effects to replace *Chenopodium album*, *Melilotus alba*, *Melilotus indica*, *Sphaeranthus indicus*, and *Phalaris minor*.^[37]

PHYTOCHEMISTRY

Till the date so many bioactive compounds/active principles have been identified and characterised from *Calotropis procera*^[38] and *Calotropis gigantea*^[39] [Figure 2]. These are mentioned in Table 1 with their wider biological activity explored so far by different researchers. Plant synthesises and contains several primary metabolites such as pentacyclic^[40] and ursane triterpenes,^[41,42] cardinolides,^[43] phytosterols^[44]

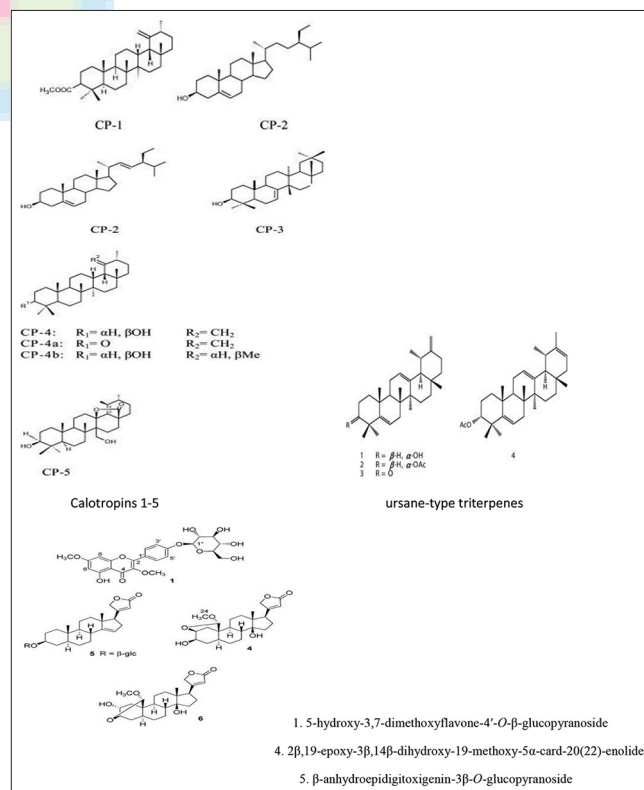


Figure 2: Major constituents isolated from *Calotropis procera* latex and various plant parts

Table 1: Biological activities of chemical constituents isolated from *Calotropis procera* and its other associating species

Species/plant parts	Compounds isolated	Biological activity	
<i>Calotropis procera</i>			
Root	Digitoxigenin, digitoxin, digoxigenin	Antimicrobial, toxic	
	Calotropinol	Cytotoxic and repellent	
	Proceragenin, calotoxin, hydroxyketone	Procoagulant and toxic, insecticidal	
	Proceragenin, calotoxin, hydroxyketone	Cytotoxic, anti-helmintic	
	Procesterol, multiflorenol, cyclosadol, β -sitostenone	Cytotoxic, anti-helmintic	
	β -sitosterol and stigmaterol	Nutritive	
	Multiflorenol, calonyl acetate	Anti-microbial and anti-parasitic	
	2-oxovoruscharin	Antitumor and anticancer	
	Urs-19 (29)-en-3- β -ol and 3 β	Antitumor and anticancer	
	Urs-19 (29)-en-3-yl acetate	Antitumor and anticancer	
	3 β , 27-dihydroxy-urs-18-en-13,28-olide	Anti-angiogenetic, antiproliferative	
	Lupeol	Anti-inflammatory, anti-arthritis	
	Latex	Osmotin	Antifungal, plant defense
Calotropin		Cytotoxic, cytostatic, anticovulsant, phytomodulatory, antitumor, hepatoprotective, pain-soothing, pro-coagulant, regulator of signaling pathway	
Procerin		Antimicrobial, insecticidal, proteolytic	
Cysteine protease and endopeptidase		Insecticidal, defensive	
Lectin		Insecticidal	
Acetogenins		Insecticidal	
Protein fraction		Wound healing, pro-coagulant	
Flavonoid glycosides		Antimicrobial, anti-parasitic, anti-arthritis	
Cardiac glycosides		Muscle activator, disease curing potency	
Flavanols		Anti-oxidant and cytotoxic, anti-convulsant	
Methomyl and cardenolides		Pesticidal, acaricidal	
(24S)-24-ethyl stigmast-4-en-6 α -ol-3-oneC-6		Toxic, anti-parasitic, anti-tumor	
C-24 diepimer of stigmast-4-en-6 β -ol-3-one		Insecticidal, anticancer	
5-hydroxy-3,7-dimethoxyflavone-4'-O- β -glucopyranoside		Cytotoxic, anti-tumor	
2 β ,19-epoxy-3 β ,14 β -dihydroxy-19-methoxy-5 α -card-20 (22)-enolide		Cytotoxic, anti-tumor	
2 β ,19-epoxy-3 β ,14 β -dihydroxy-19-methoxy-5 α -card-20 (22)-enolide		Cytotoxic, anti-tumor	
β -anhydroepidigitoxigenin-3 β -O-glucopyranoside		Cytotoxic, anti-tumor	
2-tridecanone		Insecticidal and anti-worm	
Uzariogenine, β -anhydroepidigitoxigenin		Cytotoxic and antimicrobial	
Triterpenoid saponins		Toxic, pesticidal	
(24S)-24-ethyl stigmast-4-en-6 α -ol-3-oneC-6 C-24		Cytotoxic, anti-tumor	
Diepimer of stigmast-4-en-6 β -ol-3-one		Cytotoxic, anti-tumor	
Akundaric acid, akundrol, madarlbun, mudrol		Anti-arthritis, anti-pyretic	
Ursane triterpenes		Cytotoxic, anti-tumor	
Oleanene triterpenes		Cytotoxic, anti-tumor	
Norditerpinic ester		Anti-cancer and insecticidal	
Pentacyclic triterpenoids		Cytotoxic and antimicrobial	
Quercetin-3-rutinoside		Toxic, poisonous	
<i>Calotropis gigantea</i>			
Extract			Cytotoxic
Latex	19-Nor-and 18,20-Epoxy-cardenolides	Pro-coagulant Fibrinolytic, wound healing	
	Flower		
Flower	Di-(2-ethylhexyl) phthalate	Cytotoxic, ant-proliferative	
	Glyceryl-1,2-dicapriate-3-phosphate	Cytotoxic, ant-proliferative	
	Glyceryl mono-oleoyl-2-phosphate	Cytotoxic, ant-proliferative	
	Proceranol 2	Cytotoxic, antimicrobial, anti-oxidant	
	Procerursenyl acetate 1	Toxic, pesticidal	
	Methyl myrisate	Cytotoxic and antimicrobial	
Dried latex	Power	Protective to oxidative stress and renal damage, allergic, larvicidal, anti-helmintic, ascaricidal, insecticidal, schizonticidal, anticancer, insecticidal, proteolytic activity, anti-mycoplasmal, anti-bacterial, anti-fungal, insecticidal, anti-oxidant	

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Table 1: Contd...

Species/plant parts	Compounds isolated	Biological activity
Root bark	Milky sap Extract	Purgative, anti-syphilis, anti-worm, insecticidal, anti-oxidant Anticoccidial, anti-diarrhea, antipyretic, contraceptive, analgesic, anti-tumor, anti-metastatic, anticancer
Leaves	Extract	Analgesic, antiplasmodial, antiproliferative, anti-inflammatory myocardium, stimulatory effect on smooth muscle motility
Flower	Extract	Analgesic, anti-convulsant, anti-arthritis, sedative, antipyretic

triterpenoid saponins.^[45] It also contains few secondary metabolites such as 5-hydroxy-3,7-dimethoxyflavone-4'-O- β -glucopyranoside, 2 β ,19-epoxy-3 β ,14 β -dihydroxy-19-methoxy-5 α -card-20 (22)-enolide, β - anhydroepidigitoxigenin-3 β -O-glucopyranoside, along with two known compounds, uzarigenine and β -anhydroepidigitoxigenin^[46] [Figure 1]. From *Calotropis procera* A steroid procersterol; and hydroxyketone; (24S)-24-ethyl stigmast-4-en-6 α -ol-3-one C-6 C-24 diepimer of stigmast-4-en-6 β -ol-3-one. Lupeol a triterpenoid is isolated from *Calotropis gigantea* latex showed anti-inflammatory, anti-arthritic activity and wound-healing activity.^[47] Besides this, different types of proteins such as Calotropin DI^[48] and DII,^[49] Osmotin.^[50] Procerain B and enzymes such as cysteine proteases^[51] have been isolated from *C. procera*. Few other plant products such as Akundaric acid, akundrol, madarlbium, pekilocerin, mudrol, Cardenolides (Proceragenin) were isolated from leaves and latex of *Calotropis procera*.^[52] From root bark of *Calotropis procera* Oleanene triterpenes, norditerpinic ester and pentacyclic triterpenoids^[53] and triterpenoids.^[54] Similarly, few important plant sterols such as stigmastrol and β -sitosterol were isolated from methnolic extract of root bark of *Calotropis gigantea*^[55] 19-Nor-and 18,20-Epoxy-cardenolides from the leaves of *Calotropis gigantea*.^[56] Furthermore, few other principal active constituents such as flavonol glycosides^[57] and cardiac glycosides^[58] have been identified which show very high disease-curing potency [Figure 1].

PHARMACEUTICAL ACTIVITIES

Proteolytic and Pro-coagulant Activity

Calotropis procera secretes milky sap or latex that contain various enzymes such as proteases peptidases which shows proteolytic activity^[59] that causes tenderness of meat.^[60] Plant latex also contains different types of proteins such as Calotropin DI^[48] Calotropin DII.^[49] Procerain B, cysteine proteases that exhibit procogulant activity and also effect activity of angiotensin-converting enzymes (ACE).^[61] Latex proteases hydrolyzed the subunits of fully cross-linked fibrin efficiently and show thrombin and plasmin-like activity.^[62] These proteins also exhibit similar action^[63] on fibrinogen and fibrin^[64] and found to be involved in homeostasis, blood clot inducing and dissolving properties.^[65] Similarly a UNBS1450 protein isolated from *Calotropis procera* acts as a regulator of signaling pathways involved in proliferation and cell death.^[66] *Calotropis procera* latex proteins also show

in vitro enzyme activity^[67] and are widely concerned to plant defense.^[68]

Anti-Protozoan Activity

Ethanol extracts of *C. procera* leaves, stems, roots, flowers and buds showed *in vitro* schizonticidal activity against chloroquine (CQ)-sensitive and CQ-resistant *Plasmodium falciparum* strains.^[69] Similarly, n-hexane soluble portion of the chloroform extract of root bark of *C. gigantea* shows *in vitro* anti-amoebic activity against the HK-9 strain of *Entamoeba histolytica*.^[70] Compounds isolated from dry leaves of *C. procera* found to be active against the malaria parasite^[71] while *Calotropis gigantea* non-polar fractions were found active against amastigotes of *Leishmania major*.^[72] Similarly, acetogenins isolated from *C. procera* latex also showed anti-plasmodial activity and display inhibitory effect on *P. falciparum*.^[73] *Leishmania* and *Trypanosoma* species.^[74] Similarly solvent extracts of aerial parts of *C. procera* showed antimalarial,^[75] antiproliferative and antiplasmodial activities.^[76] Its herbal concoction showed anticoccidial activity in broiler chickens challenged with *Eimeria tenella*.^[77]

Anthelmintic and Anticoccidial Activity

Aqueous extract of *C. procera* flowers showed a good anthelmintic activity against nematodes in sheep.^[78] A single oral dose of 0.01 ml or 0.02 ml/kg body weight reduced and obstruct nematode egg production.^[79] It also shows anticoccidial activity in sheep (single oral doses of 0.02 ml/kg body weight) mainly in lambs.^[80] The latex of *C. procera* also display ascaricidal effect *in vitro*^[81] and also actively work against intestinal worms in children.^[82]

Analgesic, Anticonvulsant, Anti-arthritis and Sedative Properties

The alcoholic root and flower and leaf extracts of *C. procera* show analgesic^[83,84] and anticonvulsant properties.^[85] Similarly, *Calotropis procera* latex shows anti-pyretic effects,^[86] while root extract showed significant analgesic potential.^[87] The leaf extracts of *C. gigantea* Linn. also acclaimed anti-arthritic activity in albino rats.^[88] This potent anti-arthritic activity of leaves of *C. gigantea* may be due to nature of steroids, triterpenoids and saponin glycosides and presence of different enzymatic proteins.^[88] Plant also shows hypoglycemic effect in streptozotocin-induced diabetic rats^[89] and show free radical-scavenging activity.^[90]

Antipyretic, Anti-diarrheal and Purgative

C. procera latex, and ethanol extract of root and flower reported to have antipyretic effects,^[86] against both yeast-induced and typhoid vaccine induced fever.^[91] The milky juice of *C. procera* is used as purgative, while the flowers are used as a digestive, stomachic and tonic, and in the treatment of cough, asthma, and loss of appetite and show anti-diarrhoeal activity in experimental animals.^[92] Similarly, *C. gigantea* also showed antipyretic effects^[93] while its root bark is used to treat skin diseases, enlargement of abdominal viscera, intestinal worms, ascites, and anasarca and diarrhea.

Wound Healing and Hepatoprotective

The latex of *C. procera* and *C. gigantea* latex display a good wound-healing efficacy of dermal wounds in guinea pigs.^[94] Similarly, root bark of *C. gigantea* shows wound-healing activity in rats.^[95,96] The chloroform extract of the root has shown to exhibit protective activity against carbon tetrachloride-induced liver damage.^[96,97] Protein fraction of *C. procera* latex protects against 5-fluorouracil-induced oral mucositis^[97,98] associated with down-regulation of pivotal pro-inflammatory mediators and activates murine macrophages.^[99] *Calotropis procera* extract showed antioxidant and protective effects against alloxan-induced diabetics^[100] and carbon tetrachloride induced liver and gastric injuries in rats.^[101]

Antifertility

Calotropis gigantea roots showed pregnancy interceptive^[102] and anti-fertility activity in female rats.^[103] These also showed histomorphometric and histopathological effects in male reproductive organs of wistar rats.^[104]

Anti-inflammatory

The milky white latex obtained from the plant exhibits potent anti-inflammatory activity in various animal models that is comparable to standard anti-inflammatory drugs.^[105] It shows protective effect against inflammatory hyperalgesia and reduces oxidative stress in Freund's complete adjuvant-induced mono-arthritis in rats.^[106] *C. procera* ethanolic extract of the flowers is reported to have anti-inflammatory activity while latex administration in animal models induce peritonitis, paw edema, hemorrhagic cystitis,^[107] immunological and allergic responses which are controlled by administration of different anti-inflammatory drugs.^[108] Similar activity was also reported after administration of aspirin, ibuprofen and other non-steroidal anti-inflammatory drugs which also help in cancer prevention.^[109] Protein fraction of *C. procera* latex inhibit growth of sarcoma, a type of cancer.^[110] However, latex from *C. procera* shows anti-inflammatory activity in experimental murine models^[87] and reduced the activity of different mediators of inflammation.^[111] Similarly *C. gigantea*

leaves^[112] show anti-inflammatory activity in various biological systems.^[113]

Anticancer Activity

C. procera latex showed great medicinal and pharmacological potential.^[114] It is used for preparation of herbal drugs but that reported cytotoxic^[115] and apoptotic potential in cell lines and animal models.^[116] *C. procera* possesses a novel compound cardenolide that displays potent *in vitro* anti-tumor activities and *in vivo* high tolerance.^[117] Similarly, di-(2-ethylhexyl) phthalate (DEHP) isolated from *C. procera* showed anti-tumor activity,^[118] while Copper nanoparticles synthesised by using aqueous extract of *C. procera* latex showed cytotoxic^[115] and cytostatic activity against tumor cells and cell lines.^[119] Similarly, latex proteins from *C. procera* showed *in vitro* cytotoxicity^[120] to human cancer cell lines and show *in vivo* growth inhibition of sarcoma 180.^[121] It also showed anticancer and cytotoxic properties against hepatocellular carcinoma in a transgenic mouse model. Similarly, UNBS1450 from *C. procera* regulate cell proliferation and cell death.^[95] While, cardenolides,^[122] pregnanone,^[123] 19-nor- and 18,20-epoxy-cardenolides isolated from the leaves of *C. gigantea* showed potent cytotoxic activity against cancerous cells^[56] and block VEGF-induced angiogenesis in animal models.^[124] However, a novel protein that can suppress tumor growth in breast cancer through the suppression of NF- κ B pathway has been identified in *C. procera*.^[125] It also shows protective efficacy against acute and chronic liver injury generated by carbon tetrachloride^[126] and display cytotoxic effects against KB cell lines^[54] and human epidermal carcinoma of the nasopharynx tissue.^[127] Similarly, root bark of *C. gigantea* show anti-tumor activity against Ehrlich ascites carcinoma in Swiss albino mice,^[118] while aqueous extract of the latex has been shown to inhibit cellular infiltration and afford protection against development of neoplastic changes in the transgenic mouse model of hepatocellular carcinoma.^[120] *C. procera* active components show anti-cancerous activity.^[44] It also displayed much higher anti-metastatic activity against different cancerous cells and cell lines than any conventional drug and can be used for interventional therapies used in complementary and alternative medicine to cure different types of cancers.^[128] Plant is a good source of various future herbal drugs and drug templates which might be non-steroidal and anti-inflammatory in nature and show wider cancer suppressing efficacy in cancer patients.^[129]

Antimicrobial Activity

C. procera latex shows antimicrobial^[130-133] and anti-parasitic activities.^[132] Proteins from latex of *C. procera* prevent septic shock due to lethal infection by *Salmonella enterica serovar Typhimurium*.^[134] and show very high antimicrobial potential against *Helicobacter pylori*.^[135] Various extracts of plant parts of *C. procera* such as leaves,^[135] flower and root^[136] possess

high pharmacological potential^[137] against bacteria and parasites.^[132] The n-butanol extract of *C. procera* leaves proved to be the most effective against the bacteria *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus pyogenes*, *Streptococcus pneumonia* and three fungi: *Aspergillus niger*, *Aspergillus flavus*, *Microsporium boulardii* and one yeast *Candida albicans*. Its ethanol extract shows a minimum inhibitory concentration (MIC) between 5.0 and 20.0 mg/ml for fungi.^[138] Similar antimicrobial effects of *C. procera* were also noted in active principles against aquatic microbial pathogens isolated from shrimp and fishes.^[139] Leaf extracts of *C. gigantea* shows antibacterial activity against Gram-negative and Gram-positive bacteria.^[139] This antimicrobial activity in *C. procera* is due to presence of four flavonoid glycosides and -O-rutinosides of quercetin, kaempferol and isorhamnetin, and flavonoid 5-hydroxy-3,7-dimethoxyflavone-4'-O- β -glucopyranoside.^[140] Similarly, *C. procera* latex and aerial plant parts showed antibacterial^[141] and antifungal^[142] activities against several pathogenic bacteria.^[143,144]

Insecticidal Activity

C. procera latex and its chemical constituents showed larvicidal activity against third instar larvae of *Anopheles stephensi*, *Culex quinquefasciatus*,^[145] *Aedes aegypti*^[146] and *Musca domestica*, at a very low topical application of latex.^[147] In addition, its sub-lethal dose also imposed significant effects on survival of larvae and pupae, inhibit growth, cause reduction in body weight of larvae, and obstruct molting in larval stadia of *Spodoptera litura*.^[148] Further, *C. procera* latex generated toxicity significantly decreased the % pupation, pupal weight, survival and prolonged the pupal duration in treatments in comparison to the corresponding control.^[149] Latex components toxins,^[68] acetogenins,^[150] flavonoids,^[151] triterpenes,^[152] lectins^[153] and proteins act at the cellular level and make organogenesis defaulted, which lead to formation of abnormal pupae with weak texture, weight loss and structural deformities in various organs. All these effects were irreversible and growth and development inhibitory in nature. Furthermore, laticifer fluid from *C. procera* contains endogenous soluble proteins and different proteases,^[154] which seems to be associated with insecticidal activity.^[155] These proteins also play defensive role against herbivorous insects^[156,157] and operate through molecular interactions or responses between plants insects (herbivore) and its natural host similar to lectin molecules.^[157] In addition, some enzyme inhibitors such as α -amylase^[158] and chitinases inhibitors^[159] and proteases obstruct feeding in caterpillars by disrupting peritrophic matrix.^[160] Similarly, N-acetyl- β -d-glucosaminase^[161] occur in *Hevea brasiliensis* also impose similar deleterious effects in insects also play defensive role against herbivorous insects.^[161]

Besides poisoning of insects, *C. procera* latex also show high antifeedant activity at low doses.^[162] It signifies presence

of some distasteful components such as monoterpenes, phenolic glycosides,^[163] 2-tridecanone,^[162] alkaloids, resins, tannins, saponins, enzymatic proteins and allergens in natural latex that show diverse biological activities.^[164] These components make the food distasteful/unpalatable or highly allergic to insects^[165] that deter crop pests from feeding on plants.^[165] However, no volatile has been isolated from plant latex so far and major toxicants from latex are either proteins or enzymes which lack deterrent activity and act as non-restraint molecules. Thus, deterrent activity may be a consequence of feeding deterrent cum repellent effect, which is possibly operated by some volatile substance from latexes and play multi-defensive role in plants. *C. procera* latex also affected egg hatching and embryonic development in *S. litura*. It shows very high oviposition deterrence in female adults of *S. litura* exposed with sub-lethal dose (20, 40 and 60% of 24 hr LD₅₀ of latex).^[166] Latex treatment inhibited oviposition, caused reduction in % eggs laid per female insect. Its leaf extract inhibit oviposition and obstruct gonadotrophic cycles in *Aedes aegypti* female insects and refractory behavior. It also display toxic and inhibitory effects on egg hatching and larval development and increase the postembryonic development period of larvae and pupae, delayed the formation of adults and reduced the F1 emergence.

CONCLUSIONS

Calotropis procera is an important weed plant, which is largely used for preparation of many traditional medicines to cure various diseases and disorders by the local people. In the past as well as in present time, traditional folk healers use the milky sap of this plant due its unique disease-curing properties. Ayurvedic practitioners use this plant for preparation of herbal drugs/formulations, various ailments, syrup, ash and tonic to cure infectious diseases caused by various pathogens. Plant shows cytotoxic, cytostatic, hepatoprotective, wound healing, antihelmintic, anti-inflammatory, antitumor and anticancer properties. Plant is a good source of various future herbal drugs and drug templates, which might be non-steroidal and anti-inflammatory in nature and show wider cancer suppressing efficacy in cancer patients. Various extracts of plant parts of *C. procera* such as leaves flower and root possess high pharmacological potential against bacteria and parasites. Its natural latex also works as a good pesticide and kill lot of insect pests of agriculture, household and medical importance. It shows larvicidal, growth inhibitory and ovicidal activity in insects, causes sharp decrease in emergence of F1 individuals, obstructs its development, and generates non-reproductive males and females. Latex components also display spermicidal activity in male insects, which could finally control the male-female interactions and reproductive behavior. It seems to be

good control point for lepidopteran insect pests that can also applied in control of other pests. *Calotropis* species are usually found in abandoned farmlands, do phyto-extraction of toxic chemicals, and can be used for reclamation of polluted lands through bioremediation process.^[167] Digested biomass of green leaves used as manure in the crop field reduces the chances of termite attack and provides sustained yield. Natural latex of *C. procera* can be used as a raw material for production of cheaper pharmaceuticals, pesticides and many more important commercialised products of public use.

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