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Calotropis procera: A Phytochemical and Pharmacological Review

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Review Article

Calotropis procera: A phytochemical and pharmacological review

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ABSTRACT

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

INTRODUCTION

Calotropis procera (Arka) is an important drug in the monograph of Ayurveda, and it is known in India from the earliest time (Figure 1). It was mentioned by Hindu writers and the ancient sacrificial rites many years ago. There are two common species of *Calotropis* reported in the literature, viz., *C. procera* (Ait.) R.Br. and *Calotropis gigantea* (Linn.) R.Br. mentioned by the ancient writers. Both the species consists of similar types of phytoconstituents discovered till now and may be used as substitutes for one another might have similar effects. Three varieties of Arka are mentioned in the Hindu literature of Dhanvantari Nigantu as Suklarkah, Rajarkah, and Sveta mandarah. It is widely used in the Indian traditional medicinal system as well as in the other available treatments such as Arabic, Unani, and Sudanese and for the various diseases. *C. procera* is also used by various tribes of the world as a curative agent for ailments such as skin disease, elephantiasis, toothache, asthma, leprosy, and rheumatism [1]. Different parts such as leaves, roots and bark, flower, fruits, stem, and latex of the plant have been reported to possess various phytochemicals which might possess various pharmacological activities. The coarse shrub possesses acaricidal, schizonticidal, antimicrobial, anthelmintic, insecticidal, anti-inflammatory, antidiarrheal, anticancerous, and larvicidal activities with other beneficial properties [2]. The plant is described as a golden gift for humankind containing cardiotonic agents such as calotropin, calotropagenin, calotoxin, calactin, uscharin, amyrin, amyrin esters, uscharidin, coroglaucigenin, frugoside, corotoxigenin, calotropagenin, and voruscharine used in the therapeutic treatment [2].

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

DESCRIPTION

Habitat

C. procera favors open habitat with little competition. The plant of this species grows in dry habitat where rainfall is limited to 150 to 1000 mm and also found in the area of excessive drained soil as much as 2000 mm of annual precipitation. It is also found in the common habitat of road-side, beachfront dunes, and widely disturbed in the urban areas. *C. procera* is also found at the elevated areas up to 1,000 m. Because the plant is easy to propagate and manages and can grow under the xerophytic condition, sometimes it is also grown as an ornamental plant in dry or coastal areas [2,3].

Geographical Distribution

C. procera is inborn to Southern Asia and Indo-China to Malaysia, Macaronesia, West Africa North and East Africa, Madagascar, and Arabian Peninsula. The plant is naturalized in Australia, Central America, North, South America, and West Indies. The species is now accepted and culture in many countries such as Mexico, Central and South America, Pacific islands, Australia, and the Caribbean [2,4].

Scientific Classification

Taxonomy *Calotropis procera* (Ait.) Ait.f. Kingdom: Plantae – Plants; Subkingdom: Tracheobionta – Vascular plants; Superdivision: Spermatophyta – Seed plants; Division: Magnoliophyta – Flowering plants; Class: Magnoliopsida – Dicotyledons; Subclass: Asteridae; Order: Gentianales; Family: Asclepiadaceae; Genus: *Calotropis* R.Br. – *Calotropis*; Species: *C. procera* (Ait.) Ait.f. [1].

Synonyms/Other Latin Names

Asclepias procera Aiton, common vernacular names (Sanskrit) Arka, (Hindi) Aaka. Giant Indian Milkweed. Sodom Apple, Small Crown Flower, Rooster tree, French Cotton in English. Remiga (Malaysia), Dok Hak (Laos), Kapal-kapal (Philippines), Nam t[it] b[at] (Vietnam), Pomme de Sodome (French), Rubik (Indonesia), Mudarpflanzer (German), Algodon Extranjero (Spanish), Ipekag (Turkish), Oshar (Arabic), Calotropo (Italian), Po Thuean, Paan Thuean (northern), and Rak (central) in Thailand [1,2,5].

Botanical Description

The plant is an evergreen, soft-wooded, perennial shrub; small tree attains a maximum height up to 2.5 m (maximum 6 m). A copious amount of white sap generates whenever any part of the plant is cut. The bark is corky, furrowed, and light gray. The root is simple, branched, and woody at base and covered with a fissured, corky bark, branches has very deep stout root with few branches. The leaves are opposite-decussate, simple, subsessile, and exstipulate; the leaves are slightly leathery and having a fine coat of soft hairs that sometimes sting too. Flowers are shallow bell-shaped, like a campanula, bracteate, complete, bisexual, actinomorphic, pentamerous, hypogynous, pedicellate, multiflowered, umbellate, peduncled cymes with axillary or terminal inflorescence. Five sepals, 5 lobed shortly united that are 4-5 mm long. Five-lobed petals (Corolla), gamopetalous, twisted aestivation. Androecium has five stamens, gynandrous, anther dithecous, coherent. Gynoecium is bicarpellary, apocarpus, and styles are united at their apex, peltate stigma with five lateral stigmatic surfaces. Anthers are adnate to the stigma forming a gynostegium. Fruit is simple, fleshy, inflated, and subglobose to obliquely ovoid follicle. Seeds are present in large amount, small, flat, obovate, compressed with silky white pappusat the one end, 3 cm or more long [1,2,5,6].

Ethnomedical (Traditional) Uses

The leaves were reported to use in sun worship from the Vedic times. Secretions from the root bark were used by Hindu physicians to treat skin diseases, cough, intestinal worms, ascites, and anasarca and also in enlargements of abdominal viscera, etc. The milky juice was considered as a drastic purgative and caustic. Flowers were considered to improve digestion, catarrh, and increase appetite. The root bark was also used to treat elephantiasis. *Calotropis* latex is used and applied intact in the preparations for toothache. The flowering tops were also used to treat asthma. The plant was also used in the treatment of leprosy, hepatic, and splenic enlargements. The leaves were boiled, and oily preparations were made and used in the treatment of paralysis. Leaf powder was considered as a substitute for ipecacuanha and also possesses the properties of Gutta-persica also used in wound healing. The juice was used for the purpose of infanticide and was sometimes given to women to induce abortion. Tanners used the milky juice to remove hair from hides [2,7].

Pear-shaped fruit and latex have medicinal properties. The raw latex is often considered poisonous, but reports of its toxicity may be exaggerated. A safe, effective dose could be obtained by scooping out the seeds and pulp from a halved ripe fruit and drinking sheep, goat, or camel milk from the remaining green skin “cup.” Poultices made from the leaves used to heal rheumatism. Levey identifies the Sodom apple with Ladanum asclepiad, which Al-Kindi used in a dentifrice, for lengthening the hair, and in a formula for exterminating worms and purifying the air during an epidemic [8].

The powder of the root mixed with milk of goat is used in epilepsy; route of application is in the nostrils. The tribes of the Varanasi use latex to remove worms from teeth and in the preparations of toothache. Traditionally, *C. procera* bark is used to treat cholera, extracting Guinea worms, and digestion. The drug is well known to enhance bile secretion and has a sedative effect on intestinal muscles. The tender leaves are also used to cure migraine. An ethnomedicinal profile of different plant parts of *C. procera* was compiled by Verma *et al*., 2010 [9].

PHYTOCHEMICAL REPORTS

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

total dry weight. The important cardenolides found in the plant are voruscharin, uscharidin, uzarigenin, calotroposide, calactin, calotoxin, uscharin, ascleposide, calotropagenin, coroglaucigenin, calotropin, proceroside, proceragenin, and syriogenin. Many of these compounds formed in the mechanism of extraction when hydrolyzed in a chemical reaction. Latex differs in the quantities of cardenolides from the other plant parts stem, fruit, leaves, and root bark. The main cardenolides in the various parts of the plant are uscharin and calotropagenin in the latex; calotropin and calotropagenin in the leaves; uscharidin, calotropin, proceroside, and calactin in the stem; calotoxin and calactin in the root bark; coroglaucigenin and uzarigenin in the fruit pericarp. The seeds contain 0.23-0.47% cardenolides, mainly coroglaucigenin or frugoside [10].

Besides the cardenolides, other phytochemicals are also reported from the plant such as sterols, flavonoids, coumarins, alkaloids, triterpenes, saponins, tannins, and hydrocarbons were isolated from the plant. The major flavonoid is rutin (quercetin-3-rutinoside): Roots contain 1.7%, stem 4.8%, leaves 5.0%, flowers 7.6%, and latex 9.7%. The plant is also reported to contain resins, fatty acids, proteases, hydrocarbons, amino acids, and many minerals. The polyphenol content in different plant parts varies from 3.3% (leaf) to 4.9% (stem) [11].

The flowers mainly contain α-and β-amyrins, an alkaline phosphate, cyaindin-3-rhamnoglucoside, cycloart-23-en-3β, 25-diol, cyclosadol, multiflorenol, procestrol, quercetin-3-rutinoside, β-sitosterol, β-sitost-4en-3one, and stigmasterol. Cyanidin-3-rhamnoglucose and the triterpene calotropenyl acetate are found in the flowers [12].

The leaves contain ascorbic acid, calactin, calotoxin, calatropagenin, calotropin, polysaccharide containing D-arabinose, D-glucose, D-glucosamine and L-rhamnose, calotropagenin, and 3-proteinase. The latex contains calotropin, α-calotropeol, 3-epimoretenol, gigantin, giganteol, isogiganteol, α-lactuceryl acetate, α-lactuceryl isovalerate, lupeol, proceroside, proceragenin, syriogenin, taraxast-20α-(30)-en-(4-methyl-3-pentenoate), 3'-thiazoline cardenolide uscharidin, uzarigenin, voruscharin and β-sitosterol, powerful bacteriolytic enzyme in latex [13]. The latex contains 11-23% rubber, the triterpenoids α- and β-amyrin, lupeol, taraxasteryl acetate, α-and β-calotropeol, 3-epimoretenol, multiflorenol, cyclosadol, several triterpene esters, the sterols β-sitosterol and stigmasterol, the non-toxic cysteine proteases calotropin, procerain and procerain-B and the alkaloid choline [13].

The root-bark contains benzolisoleneolone, benzollineolone, long-chain fatty acids, and C (18) isoursane. The plant also reported to contain calactinic acid, choline and O-pyrocatechuic acid, β-sitosterol, taraxasterol, its ϕ-isomer: taraxasteryl isovalerate and taraxasteryl acetate [14]. The Presence of four new ursane-type triterpenes: Vrsa-13(18), 19(29)-diene-3α-yl-acetate, 18αH-urs-19(29)-en-3-one, 18αH-ursa-12, 20(30)-diene-3 α -yi-acetate and 18αH-urs-12-en-3α-ol, were reported from the root bark [15]. Mudarine as principal cardioactive constituent present in the leaves is reported by Chaudhari [16]. Carruthers isolated and characterized isorahamnetin-3-O-rutinoside, isorahamnetin-3-O-glucopyranoside and taraxasteryl acetate, flavonoids from *Calotropis* [12]. A yellow resinous substance from root bark was also found by Sharma [17]. From the root bark, several digitanol glycosides were isolated, which lack cardiac activity.

Four new ursane-type triterpenes calotroprocerol A, calotroproceryl acetate A, calotroprocerone A, and calotroproceryl acetate B from the root bark of *C. procera* were isolated and structure elucidated in addition to five known compounds [18]. Two labdane-type di terpenic galactosides have been isolated for the first time from the roots of *C. procera*, and structures are established as Labdan-18-ol-β-D-galactofuranoside and Labdan-3 β-ol-11, 15-olide-18,20-dioic acid-3 β-D-galactofuranoside [19]. In a study, phytoconstituent of leaves hexane extract of *C. procera* was investigated qualitatively and quantitatively by GC-MS. 12 major phytocompounds were identified and estimated. The highest peak area was obtained by Ergost-5-en-3-ol ($C_{28}H_{48}O$), and the lowest peak area was obtained by 9 octadecenoic acid 9-Octadecenoic acid (Z)-($C_{18}H_{34}O_2$) [20].

The ethyl acetate fraction of the methanolic extract of the root barks of *C. procera* (Asclepiadaceae) resulted in the identification of a new cardenolide glycoside named proceraside A [21]. Three new cardenolides, along with eight known ones, were isolated from the latex of *C. procera* [22]. Two new cardenolides, named ischarin and ischaridin, were isolated from *C. procera* Ait. (Asclepiadaceae) [23]. The n-BuOH fraction of the root bark of *C. procera* (Ait) R.Br. Seven new oxypregnane oligoglycosides: Calotroposides H-N (1-7) were isolated and identified [24].

Beside this, various parts of the plant possess various phytochemicals reported till date. Various newer phytochemicals reported till now; Table 1 shows the chemical structures of phytoconstituents present in *C. procera*.

PHARMACOLOGICAL ACTIVITIES

The literature of the plant revealed us that various parts of the plant such as root bark, stem bark, leaf, flower, and latex and their extracts, fraction, and isolated compound showed significant anticoagulant, antidiarrheal, anti-inflammatory, antioxidant, antiulcer, analgesic, cough-suppressing, hepatoprotective, smooth muscle-contracting, neuromuscular blocking, spermicidal, and wound healing activity. Various pharmacological activities of the plant parts reported on *Calotropis procera* are shown in Table 2.

Analgesic and Antinociceptive Activity

In this study, analgesic activity of dry latex (DL) of *C. procera* has evaluated. The effect of DL at a dose of 415 mg/kg against acetic acid-induced writhing was more pronounced as compared to an oral dose of aspirin (100 mg/kg). DL (830 mg/kg) produced marginal analgesia in tail-flick model which was comparable to aspirin [25,26].

Antinociceptive effect of proteins from the *C. procera* latex using three different experimental models of nociception - acetic acid, formalin-induced abdominal constrictions, and hot plate test in mice - was evaluated. The latex protein fraction at the doses of 12.5, 25, and 50 mg/kg showed the antinociceptive effect in a dose-dependent manner, which is independent of the opioid system [27,28].

Table 1: Secondary metabolites of *Calotropis procera* (R.Br.)

Compound names	Plant part	References
Steroid		
Procesterol (24S)-24-ethyl-stigmast-4-en-6a-ol-3-one	Flower	[10]
Ergost-5-en-3-ol	Leaves	[41]
ß-Amyrin	Root bark	[26]
α-Amyrin	Root bark	[26]
Calotropin 12β-*O*-benzoyl-3β,14β,17β-trihydroxypregnane 20-one	Roots	[42]

(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Taraxasterol	Root bark Leaves	[42]
α-amyrin acetate Urs-12 -en-3 -olyl acetate	Roots	[26]
ß-Amyrin acetate	Root bark	[26]
Proceraursenolide 18 a H - urs - 1 2 en - 3 , 25 - olide	Roots	[43]
Calotroprocerone-A ursa-5,12,20(30)-trien-18aH-3-one	Root bark	[44]

(Contd...)

Table 1: *(Continued)*

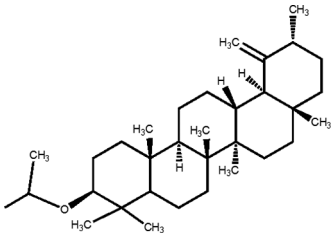
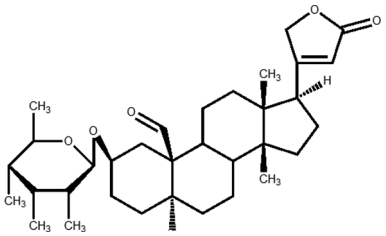
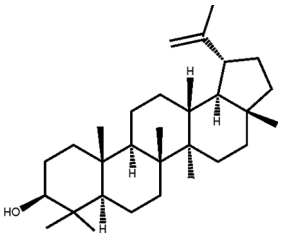
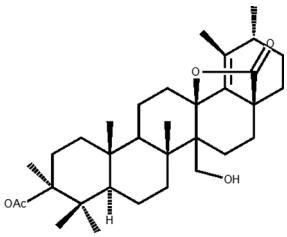
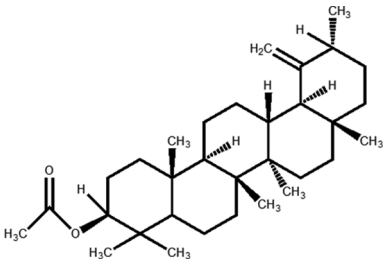
Compound names	Plant part	References
DI and triterpenes		
Calotropenyl acetate Urs-19(29)-en-3-ol, acetate, (3beta)	Root bark	[44]
		
Gofruside Corotoxigenin 3-O-β-D-allomethyloside)	Roots	[42]
		
Lupeol	Root bark	[43]
		
3b,27-dihydroxy-urs-18-en-13,28-olide	Latex	[45]
		
urs-19(29)-en-3-yl acetate	Latex	[45]
		

Table 1: *(Continued)*

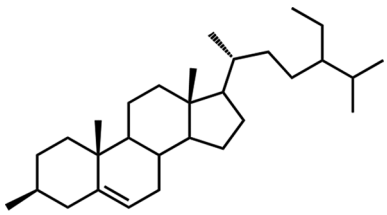
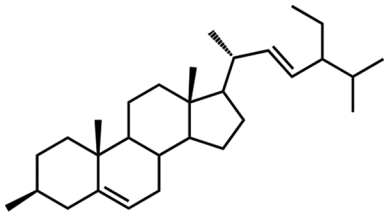
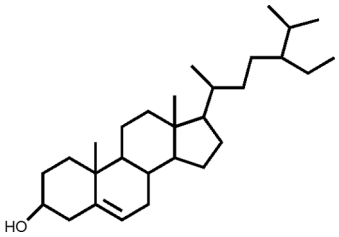
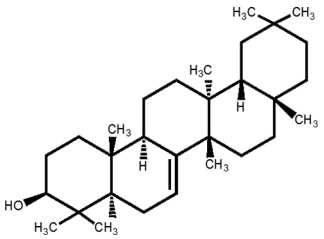
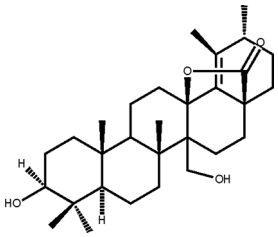
Compound names	Plant part	References
β-Sitosterol	Latex	[45]
		
Stigmasterol	Latex	[45]
		
Stigmasta-5,22-dien-3-ol	Leaves	[20]
		
Multiflorenol urs-19(29)-en-3-b-ol	Latex	[45]
		
3b,27-dihydroxy-urs-18 -en-13,28-olide	Latex	[45]
		

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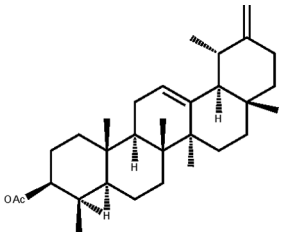
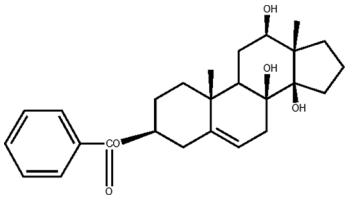
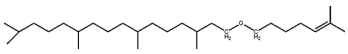
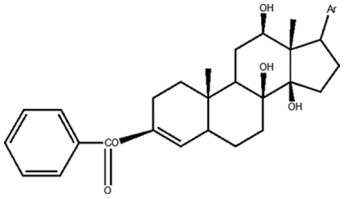
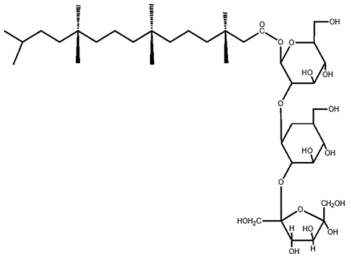
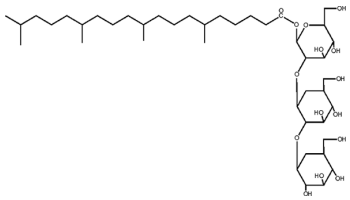
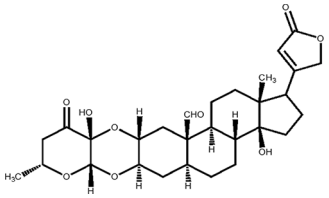
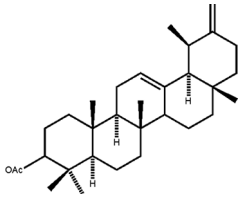
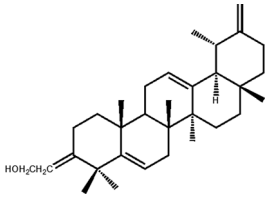
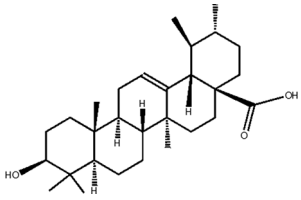
Table 1: *(Continued)*

Compound names	Plant part	References
Procerursenyl acetate urs-18a-H-12, 20 (30)-diene-3ß-yl acetate	Roots	[26]
		
Benzoyllineolone	Root bark	[26]
		
Diterpene 3,7,11,15 tetramethyl hexadecanyl 6′-methyl hept-5′-enyl ether (phytyl isooctyl ether)	Roots	[46]
		
Benzoylisolineolone	Root bark	[26]
		
Diterpene 3,7,11,15 tetramethylhexadecanoyl -β-D-glucopyranosyl -(2→1)-β-D-glucopyranosyl-(2→1)-β-D-glucopyranosyl(2→1)-β-D-glucofuranoside (dihydrophytoyl tetraglycoside)	Roots	[46]
		

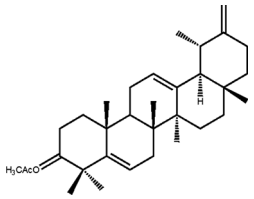
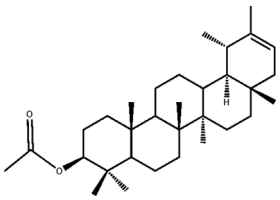
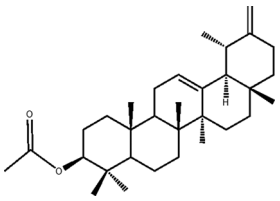
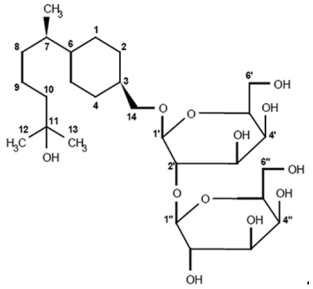
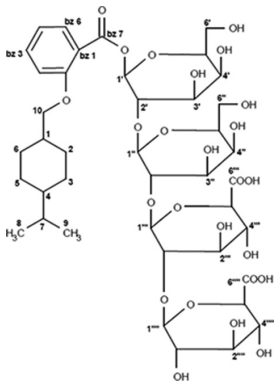
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Procerasesterterpenoyl triglucosideDiterpene 2,6,10,14,18-pentamethylnonadecanoyl-β-D glucopyranosyl-(2→1)-β-D-glucopyranosyl -(2→1)-β-D-glucopyranoside	Roots	[46]
		
Uscharidin	Latex	[26]
		
18 H-urs-12, 2 0(30)-dien-3-yl acetate	Roots	[43]
		
Calotroprocerol–A ursa-5,12,20(30)-trien-18aH-3b-ol	Root bark	[44]
		
Urosolic acid	Leaves	[25]
		

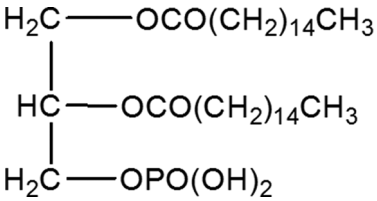
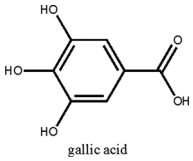
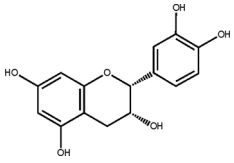
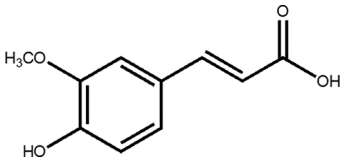
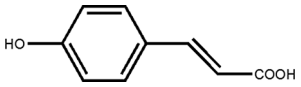
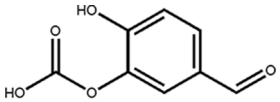
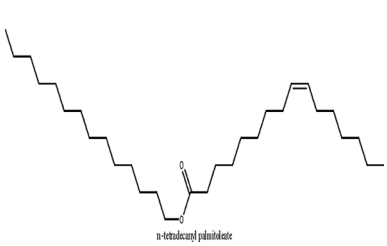
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Calotroproceryl acetate A ursa-5,12,20(30)-trien-18aH-3b-yl acetate 	Root bark	[44]
Pseudo-taraxasterol acetate 	Root bark	[44]
Calotropursenyl acetate-B 	Root bark	[44]
Terpenoid glycosides bisabolan-11,14-diol-14-b-D -glucopyranosyl-(1→2) -b-Dglucopyranoside 	Roots	[43]
2-limonenyloxybenzoyl-1β-D-glucopyranosyl -(1→2)-β-D-glucopyranosyl-(1→2) -β-D-glucuronopyranosyl-(1→2)-β-D -glucuronopyranoside 	Roots	[43]

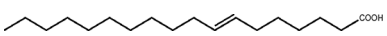
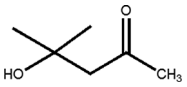
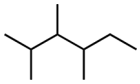
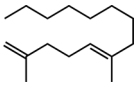
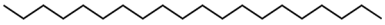
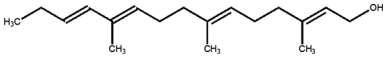
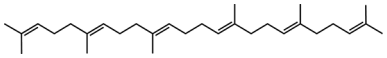
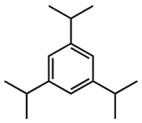
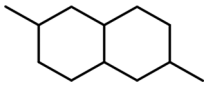
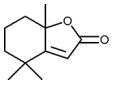
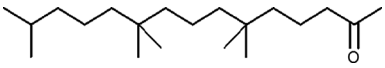
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
1,2-dihexadecanoyl -3-phosphatyl glycerol 	Roots	[43]
Polyphenolic compounds		
Gallic acid  gallic acid	Whole plant	[47]
(−) Epicatechin 	Whole plant	[47]
Ferulic acid 	Whole plant	[47]
p-coumaric acid 	Whole plant	[47]
Vanillic acid  vanillinic acid	Whole plant	[47]
n-tetradecanyl n-hexadec-9-enoate (n -tetradecanyl palmitoleate)  n-tetradecanyl palmitoleate	Roots	[43]

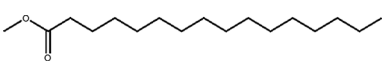
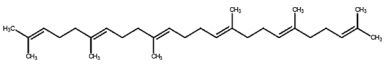
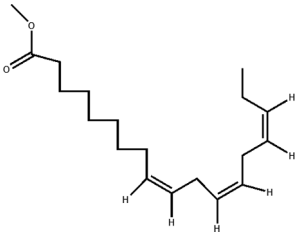
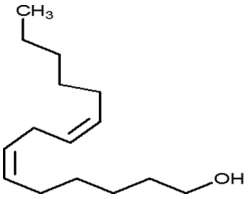
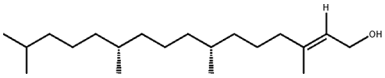
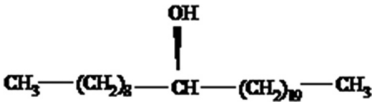
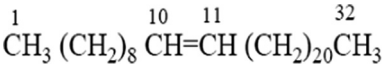
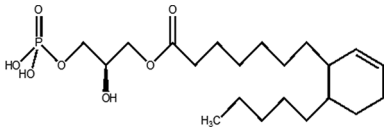
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Hydrocarbons		
(E)-Octadec-7-enoic acid 	Root bark	[44]
4-hydroxy-4-methylpentan-2-one 	Latex	[48]
2,3,4-trimethylhexane 	Latex	[48]
Decane 	Latex	[48]
n-Pentadecane 	Latex	[48]
2,6 dimethyl tetra-1,5-decaene 	Latex	[48]
n-Eicosane 	Latex	[48]
3,7,11-Trimethyl-2,6,10,12 -pentadecatrien-1-ol 	Latex	[48]
2,6,10,15,19,23-Hexamethyl -2,6,10,14,18,22-tetracosahexaene 	Latex	[48]
1,3,5-Triisopropylbenzene 	Latex	[48]
Napthalene decahydro2,6 dimethyl 	Leaves	[20]
2-H Benzofuranone 5,6,7, 7A tetrahydro 4,4,7A trimethyl 	Leaves	[20]
6,10,14-trimethyl, Pentadecanone -2 	Leaves	[20]

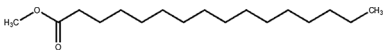
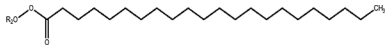
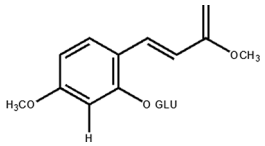
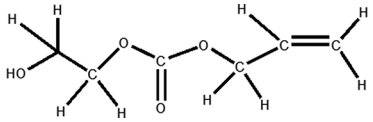
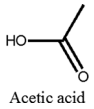
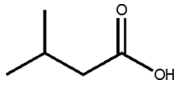
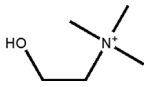
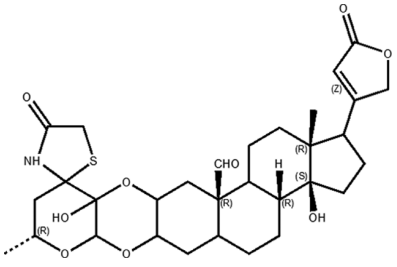
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Hexadaconic acid, methyl esters 	Leaves	[20]
9-Octadecenoic Acid (Z)- 	Leaves	[20]
9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z)-2-Hexadecen-1-ol, 3,7,11,15-tetramethyl-, [R-[R*, R*-(E)]]- 	Leaves	[20]
(6Z), (9 Z) Pentadecadien 1-ol 	Leaves	[20]
Farnesol isomer 	Leaves	[20]
Tetratetracontane 	Leaves	[20]
Proceranol n-triacontan -10ß-ol 	Roots	[29]
N-dotriacont-6-ene 	Roots	[29]
Glyceryl mono-oleolyl-2-phosphate 	Roots	[29]

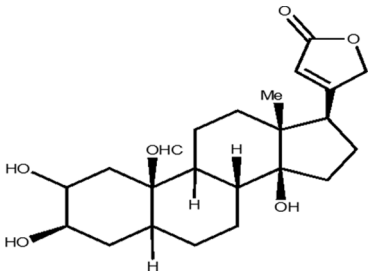
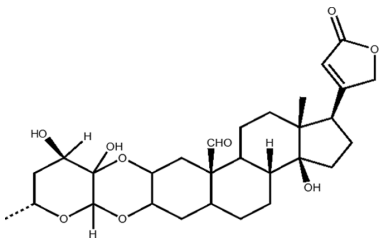
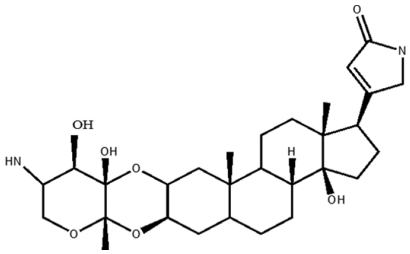
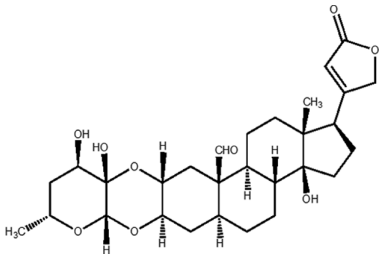
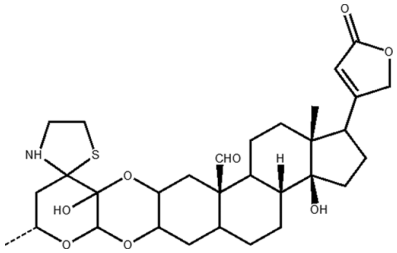
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Methyl myrisate, 	Roots	[29]
Methyl behenate 	Roots	[29]
(E)-3-(4-methoxyphenyl-2-O-beta -D-4C1-glucopyranoside)-methyl propenoate 	Leaves	[49]
Ž2-propenyl-2-hydroxyethyl carbonate 	Latex	[50]
Acetic acid  Acetic acid	Root bark	[26]
Isovaleric acid 	Root bark	[26]
Choline 	Latex	[26]
Cardenolides		
Cardenolide 2”-oxovoruscharin 	Root barks	[41]

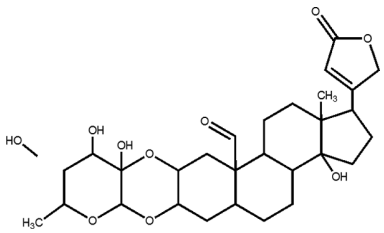
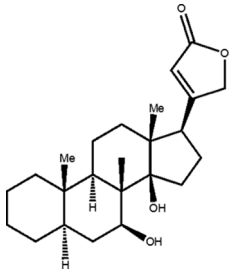
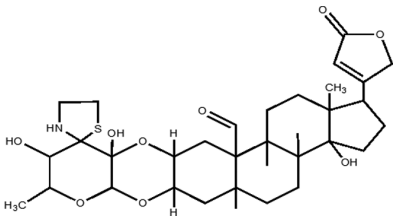
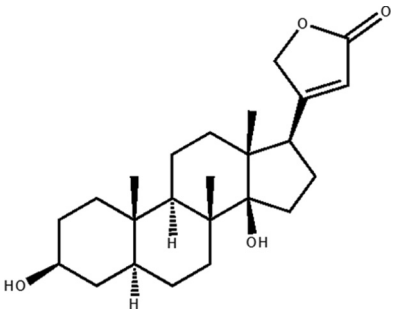
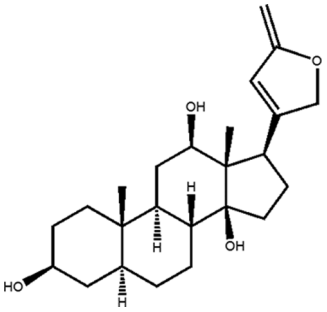
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Calotropagenin 	Leaves	[25]
Calotropin 	Latex	[25]
Calotoxin 	Latex	[25]
Calactin 	Latex	[25]
Voruscharin 	Latex	[25]

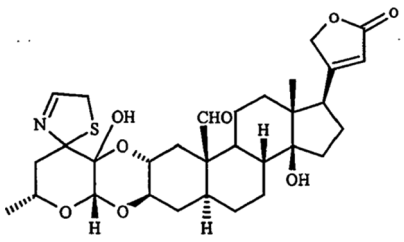
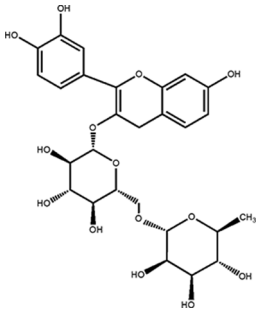
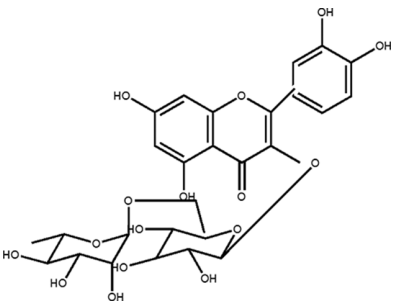
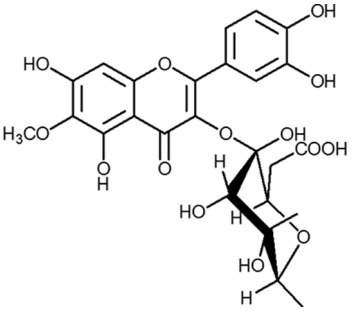
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Proceroside	Flower	[25]
		
Proceragenin	Flower	[25]
		
Voruscharin a-calotropeol	Flower	[25]
		
Uzarigenin	Latex	[26]
		
Syriogenin	Latex	[26]
		

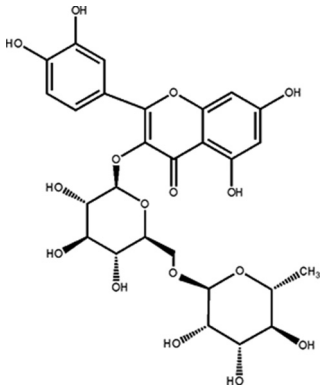
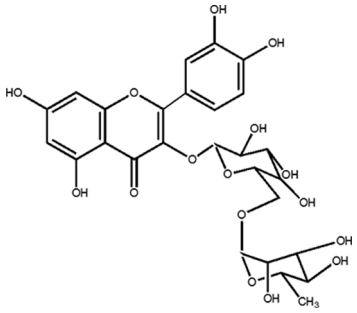
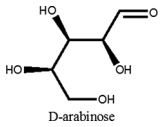
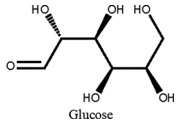
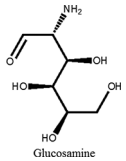
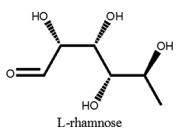
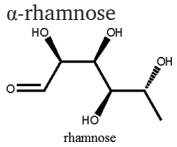
(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Uscharin	Latex	[26]
		
Flavonoids		
Quercetin-3 rutinoside	Latex	[26]
		
Quercetin 3-O-rutinoside	Stem, leaves and flower	[51]
		
Quercetagetin-6-methyl ether 3-O-beta-D-4C1-galacturonopyranoside	Leaves	[49]
		

(Contd...)

Table 1: *(Continued)*

Compound names	Plant part	References
Isorhamnetin-3-O-rutinoside 	Leaves	[26]
Isorhamnetin-3-O-robinobioside 	Leaves	[26]
Carbohydrates		
D-arabinose 	Flower	[26]
Glucose 	Flower	[25]
Glucosamine 	Flower	[25]
L-rhamnose 	Flower	[25]
α-rhamnose 	Leaves	[26]

Anticonvulsant Effects

The anticonvulsant activity by maximal electroshock seizures (MES), pentylenetetrazol (PTZ), lithium-pilocarpine, and electrical kindling seizures of *C. procera* root aqueous and chloroform extracts in rats was performed [29]. In the MES test and the PTZ test, the chloroform extract showed a highly significant effect. Both the extracts also inhibited convulsions induced by lithium-pilocarpine and electrical kindling [26].

Antimalarial Activity

The ethanolic extracts of the different parts of *C. procera* showed IC_{50} values ranging from 0.11 to 0.47 mg/ml against *Plasmodium falciparum* MRC20 CQ-sensitive strain and from 0.52 to 1.22 mg/ml against MRC 76 CQ-resistant strain, flower, and bud extracts being the most effective. Although 220, 440 times less effective than CQ, these extracts deserve further studies aimed at the identification of the active constituents [25].

Anthelmintic Activity

The anthelmintic activity of *C. procera* flowers in comparison with levamisole was evaluated through *in vitro* and *in vivo* studies on live *Haemonchus contortus*. In the *in vitro* study crude aqueous (CAE) and crude methanolic (CME) extracts, and for in vivo study, CAE, CME extracts and crude powder (CP), of flowers were used. Egg count percent reduction was recorded as 88.4% and 77.8% in sheep treated with CAE and CP at 3 g/kg^{-1}; CME was found least effective in (20.9%) reduction in ECR. All the extracts exhibited lower activity than that exhibited by levamisole (97.8-100%). Cavalcante *et al*. evaluated the chemical composition and *in vitro* activity of latex on *H. contortus* [26,28,30].

Antioxidant and Antidiabetic Activity

The antioxidant activity of dried latex (DL) of *C. procera* and antidiabetic effect against alloxan-induced diabetes rats was evaluated. The oral dose of DL at 100 and 400 mg/kg was administered. The result revealed us that there is decrease in blood glucose and increase in the hepatic glycogen content. Tsala *et al*. evaluated the antioxidant activity of the ethanol extract of *C. procera* bark against surgical wounds [25,28,31,32].

Myocardial Infarction

C. procera latex was evaluated for protection against isoproterenol (20 mg/100 g)-induced myocardial infarction in albino rats. The pretreatment of ethanolic latex extract at a dose of 300 mg/kg orally three times a day for 30 days, significantly reduces elevated marker enzymes (serum glutamic-pyruvic transaminase, serum glutamic oxaloacetic transaminase, and alkaline phosphatase) level in serum and heart homogenates [28].

Schizontocidal Activity

The effect of crude fractions of flower, bud, and root against a chloroquine sensitive strain, MRC 20 and a chloroquine resistant strain, MRC 76 of *P. falciparum* were evaluated. The effectiveness of its fractions was compared with the CQ-sensitive strain than the CQ-resistant strain *in vitro* [28].

Anticancer and Cytotoxic Properties

The anticancer and cytotoxic properties of the DL of *C. procera* in transgenic mouse model of hepatocellular carcinoma were performed and found complete protection against hepatocarcinogenesis. There was a significant lowering of serum vascular endothelial growth factor level and extensive cell death in both Huh-7 and COS-1 cells while AML12 cells were found live. This was accompanied by extensive fragmentation of DNA in Huh-7 and COS-1 cells. No change in the levels of Bcl_2 and caspase 3 was observed; these are the canonical markers of apoptosis. Gurung *et al*. found of the anticancer bioactive compound proceraside by molecular docking with macromolecules involved in the cell cycle and DNA replication [28,31,33,34].

Antimicrobial Activity

The antimicrobial 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 observed [25,26]. The antibacterial activity of a new cardenolide, 7B, 14B-dihydroxy-5-card-20(22) enolide (proceragenin) of *C. procera* was evaluated [26] which was found to be active against *Pseudomonas pseudomallei*, a causative agent of melioidosis. All the leaf extract fractions completely inhibited the growth of the tested organisms. The antimicrobial activity of *C. procera* was evaluated against some of the tested microorganisms (*Staphylococcus aureus* and *Pseudomonas aeruginosa*, and one pathogenic fungus, *C. albicans*) [27].

The antimicrobial effect of ethanol, aqueous, and chloroform extracts of leaf and latex of *C. procera* were studied on five bacteria, namely, *Escherichia coli*, *S. aureus*, *Staphylococcus albus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* and three fungi: *Aspergillus niger*, *Aspergillus flavus,* and *Microsporum boulardii* and one yeast *C. albicans* using agar well diffusion and paper disk methods [28]. 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. The ethanolic extracts of *C. procera* latex gave the widest zone of inhibition (14.1 mm) 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 was inhibited by ethanol and chloroform extracts while the aqueous extract was the least effective on the test fungi [26].

Anti-inflammatory Activity

The latex (DL) of the plant *C. procera* has been reported to exhibit potent anti-inflammatory activity against carrageenan and formalin that are known to release inflammatory mediators. The anti-inflammatory effect of aqueous and methanolic extracts of DL was more pronounced than phenylbutazone (PBZ) against carrageenan, whereas it was comparable to chlorpheniramine and PBZ against histamine and prostaglandin E_2, respectively. Both extracts produced about 80%, 40%, and 30% inhibition of inflammation induced by bradykinin, compound 48/80, and serotonin. The histological analysis revealed that the extracts were more potent than PBZ in inhibiting cellular infiltration and subcutaneous edema [35]. A single dose of the aqueous suspension of the DL was effective to a significant level against the acute inflammatory response. The crude DL of *C. procera* possesses a potent anti-inflammatory activity [33].

The effect of methanolic dried extract MeDL was compared with PBZ a non-selective cyclooxygenase (COX) inhibitor, rofecoxib, a selective COX-2 inhibitor. 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 antiarthritic agent. Chaudhary *et al*. reported a protective effect of high molecular weight protein sub-fraction of latex in monoarthritis rats [28,36].

Larvicidal Activity

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 [26]. The giant milkweed was effective in both inhibition of feeding and causing mortality of larvae. The different rubber-free fractions of the latex were evaluated against egg hatching, and larval development of the mosquito *Aedes aegypti* was found inhibitory effect [27].

The effects of alkaloid extracts of *C. procera* leaves at the vegetative stage on the survival of fifth instar larvae and on the ovarian growth of *Schistocerca gregaria* have been studied [28]. The toxic effects of crude extracts (both for leaves and flowers) of *C. procera* against two species of termites, i.e. *Heterotermes indicola* and *Coptoter mesheimi* were studied [26]. Similarly, *C. procera* showed moderate larvicidal effects against second and fourth instar larvae of the laboratory-reared mosquito species, *Culex quinquefasciatus* [25]. *C. procera* appears to be more effective than *Haloxylon recurvum* and *Azadiracta indica* [26].

Immunomodulatory Activity

Ethanolic extract of the root bark of *C. procera* was evaluated for immunomodulatory activity using immunological tests in mice, humoral mediated antibody titer, delayed-type hypersensitivity, peritoneal macrophage count, vascular permeability, hematological profile, i.e. total red blood cell count, total leukocyte count, % neutrophils and % lymphocytes, and cyclophosphamide-induced myelosuppression at three dose levels (50, 100, and 200 mg/kg). The extract stimulates defense system by modulating several immunological parameters. Nascimento *et al*., 2016 discover immunomodulatory properties of latex protein extracts from *C. procera* which protect against experimental infections with Listeria monocytogenes [37-39].

Wound Healing Activity

Based on its traditional use, *C. procera* was selected for evaluation of its wound healing potential in Guinea pigs. 20 μl of 1.0% sterile solution of the latex of the plant in the animals was applied topically. The latex significantly augmented the healing process by markedly increasing collagen, DNA and protein synthesis and epithelization. Tsala *et al*. evaluated

Table 2: Various pharmacological activities reported on the plant *Calotropis procera*

Part of plant	Activity	References
Root, latex flowers	Analgesic, antinociceptive, antipyretic activity	[25,27]
Latex	Anthelmintic activity	[28,26,30]
Plant	*Haemonchus contortus, Schistosoma mansoni, Rhipicephalus (Boophilus) microplus,* Ascaris	
Latex	Antiarthritis and monoarticular arthritis model	[2,36]
Root	Antiangiogenesis	[26]
Flower	Antibacterial and antiparasitic antimicrobial activities	[2,25,27,28,26]
Leaf, latex		
Latex, root barks	Anticancer and *in vitro* cytotoxicity hepatocellular carcinoma, skin melanoma, Antitumor studies	[20,21,33-35,41]
Latex	Anticonvulsant action	[25]
Flowers	Anticoccidial activity *Eimeria tenella*	[26]
Latex	Antidiabetic, diabetic wound, diabetic nephropathy, diabetic neuropathy	[28,52,53]
Latex, ariel part	Antidiarrheal activity	[26]
Whole plant	Antieczema, dermatophytic activity	[2,40]
Latex	Antiedematogenic	[2,26]
Root, Flower, Latex	Antifertility screening	[26]
Leaf	Antifilarial activity (*Setaria digitata*)	[2]
Whole plant	Antifungal activity (*Ceratocystis paradoxa, Candida albicans*)	[26]
Leaves	Antihyperbilirubinemic	[2,53]
Leaves	Anti-implantation activity	[26]
Whole plant	Antilithic	[54]
Whole plant	Antimycoplasmal activity	[55]
Latex, root	Antioxidant and free-radical scavenging activity	[2,25-27,31,32]
Leaf	Antiplasmodial activity	[2]
Latex	Antiseptic - *Salmonella enterica* s Typ	[56]
Latex	Antitermites property	[26]
Leaves stem	Antitussive activity	[57]
Root, root bark, leaf, stem, latex	Antitumor studies Antiproliferative and cell death (Apoptosis)	[25,31]
Latex	Allergic contact dermatitis Immunological and allergenic responses, Immunomodulatory activity	[37-39]
Latex	Asthma	[35]
Latex	Bullous eruption	[35]
Latex	Cardiotonic action	[2,41]
Latex	Clot inducing and dissolving properties	[58]
Latex	Cognition enhancer	[59]
Aerial parts	Effect on diverse muscles	[60]
Latex	Enzyme purification potential	[25,41]
Latex	Enzymatic activity	[61]
Latex	5-fluorouracil-induced oral mucositis	[62]
Latex, stem bark	Gastric ulcers, gastric mucosal protective activity Anti-*Helicobacter pylori* and urease inhibition	[2,26-28]
Leaf, flowers	Glucose tolerance, hypoglycemic Effect	[26]
Latex, flowers	Hepatoprotective activity	[26]
Latex	Hepatorenal functions	[63]
Latex	Hemorrhagic septicemia or poisoning	[26]

(Contd...)

Table 2: *(Continued)*

Part of plant	Activity	References
Latex	Histaminic activity	[2]
Latex	Hyperalgesia effect	[64]
Leaves	Hypotensive	[26]
Whole plant	Insecticidal activity	[2,26]
Latex	Interleukin-1beta inducer	[2]
Whole plant	*In-vitro* spasmolytic effect	[27]
Leaves	Lipolytic, lipoxygenase inhibitors	[65,66]
Leaf Latex	Larvicidal malaria, dengue/dengue hemorrhagic fever and lymphatic filariasis-*Musca domestica*, mosquito larvae, *Culex quinquefasciatus say, Aedes aegypti, Anopheles stephensi*	[25,26]
Latex	Morphogenetic abnormalities	[67]
Whole plant	Molluscicidal activity	[26]
Latex	Myocardial infarction	[28]
Root	Estrogenic functionality	[26]
Latex	Ontogenetical and histochemical	[2]
Aerial parts	Purgative	[2]
Root, latex, flowers	Pro- and anti-inflammatory activities acute inflammation	[2,26-28]
Latex	Pleurisy	[2,25,27]
Latex	Proteolytic enzyme activity	[61]
Latex	Prostaglandins releaser	[2]
Arieal part	Reproductive potential	[68]
Whole plant	Schizontocidal activity	[2,28]
Latex	Toxicity study - Toxic iridocyclitis keratoconjunctivitis. corneal endothelial cytotoxicity ocular toxicity keratitis cytostatic and cytotoxic activity, dermatophytes	[25-26,35]
Latex, leaves, bark	Wound healing, antikeloidal activity, and surgical wounds	[27,32]

Figure 1: Photograph of plant *Calotropis procera*; flowering shoot, inflorescence, stem, leaves

the antioxidant activity and the healing action of the ethanol extract of *C. procera* bark against surgical wounds [27,32].

Antiulcer Activity

The antiulcer activity of *C. procera* using different *in vivo* ulcer models was performed. The results of the study revealed that it significantly inhibited aspirin, reserpine, absolute alcohol, and serotonin-induced gastric ulcerations in rats and also protecting the gastric mucosa from aspirin-induced ulceration in pyloric-ligated rats, and significant protection was observed in histamine-induced duodenal ulcers in Guinea pigs [26].

Antifertility Activity

The effect of an ethanolic extract of the roots of *C. procera* was studied in albino rats to explore its antifertility and hormonal activities. Strong anti-implantation (inhibition 100%) and heterotrophic activity was observed at a dose of 250 mg/kg (1⁄4 of LD_{50}). No antiestrogenic activity was detected [26].

Antidiarrheal Activity

The DL of *C. procera* was evaluated for its antidiarrheal activity. Like atropine and PBZ, a single oral dose of DL (500 mg/kg) was produced a significant decrease in the frequency of defecation and the severity of diarrhea as well as protecting from diarrhea in 80 % rats treated with castor oil [26].

Estrogenic Functionality

The effects of ethanolic and aqueous extracts of *C. procera* roots were studied on the estrous cycle and on some parameters of estrogenic functionality in rats. Both extracts were found to interrupt the normal estrous cycle in 60% and 80% of rats treated [2,26].

Dermatophytic Activity

Fresh latex of *C. procera* was screened for antifungal activity against dermatophytes: *Trichophyton* spp., *Microsporum* spp., and *Epidermophyton* spp. The result shows *Trichophyton* spp. being the most susceptible followed by the *Microsporum* spp. and *Epidermophyton* spp. were least inhibited [40].

Toxicity Studies

The plant is proven as toxic, and it is one of the plants not eaten by grazing animals. The latex from the plant has used by the tribal people to make poison arrows used for hunting purpose. The latex is highly toxic to human eyes cause ocular toxicity and produces loss of vision with photophobia. Latex of *C. procera* was studied for its inflammatory effects using pedal edema and air pouch models of inflammation in rats and could be used to evaluate anti-inflammatory drugs. Furthermore, latex also produces toxic iridocyclitis, keratoconjunctivitis, corneal endothelial cytotoxicity, and keratitis when applied accidentally on the eye.

In a study, DL and flowers of *C. procera* and its ethanolic extracts were evaluated against MCF-7 and HeLa cell line cultures against the MTT assay to determine the inhibitory effects of test compounds on cell growth *in vitro*. The standard drug tamoxifen inhibits 60.46% breast cancer (MCF-7) cells, whereas the ethanolic extract of DL and flowers showed cytotoxic properties against both MCF-7 and HeLa cells in a dose-dependent manner [2,26-28].

CONCLUSION

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

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