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A Review on Pharmacological Activities of *Calotropis Procera*

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ABSTRACT

The plant *Calotropis procera* (Aiton) Dryand belong to the Apocynaceae family it is popularly known as "Rui" in Marathi, " Mudar" in hindi other common name include Rubber Bush, Apple of sodom. (India & Pakistan). The bark and leaves are known to show wound healing, shows anti-Hyperglycemic effect, Analgesic, Anti pyretic, neuromuscular blocking activity, Purgative, anti-cancer activities. The phytochemistry of plant reveals presence of triterpenoids, flavonoids, cardiac glycosides, cardenolides, anthocyanins, α-amyrin, β-amyrin, lupeol, β-sitosterol, flavanols, mudarine, resins, a powerful bacteriolytic enzyme calactin, a nontoxic proteolytic enzyme calotropin, and a wax was isolated from the heartwood of *Calotropis procera.* The present review focuses on pharmacological activities of *Calotropis procera*.

Keywords: *Calotropis procera, anti-* Hyperglycemic effect, wound healing, pharmacological activities.

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Introduction

The human race uses plants or plant products successfully as a mean of treatment of disease and injuries as effective therapeutic snce ages. *Calotropis procera* Linn (Family: Apocynaceae) is a plant mentioned in ayurveda with important medicinal properties. It is known by various vernacular names such as Swallow-Wort (English), Madar (Hindi), Alarka (Sanskrit), and commonly referred to as Ark, Swallow wart or milkweed.

It occurs frequently in Indonesia, Malaysia, China, India as wasteland weed and also found in most parts of the world with a warm climate in dry, sandy, and alkaline soils

Plants as sourse of new drugs has been thrust area for the major pharmaceutical companies and they are currently conducting extensive research on plant materials to introduced new drugs in the medical practice. According to literature survey *Calotropis procera* contains many biological active chemical groups including, cardenolides, steroids, tannins, glycosides, phenols, terpenoids, sugars, flavonoids, alkaloids and saponins. It has showed many pharmacological effects such as antimicrobial, anthelmintic, anti-inflammatory, analgesic and antipyretic, anticancer, anti-angiogenic, immunological, antidiabetic, cardiovascular, hypolipidemic, gastroprotective, hepatic protective, renal protective, antidiarrheal, antioxidant, anticonvulsant, enhancement of wound healing, antifertility and smooth muscle relaxant effect. The present review was designed to highlight the pharmacological effect of *Calotropis procera.* [1-13].

Plant profile:

C. procera (Rui Tree) is an erect, tall large, highly branched, and perennial shrub or small tree that grows to a height of 5.4 m with milky latex throughout the plant.

Synonyms

Calotropis gigantea var. *procera* (Aiton) P.T.Li, *Calotropis heterophylla Wall. ex Wight, Calotropis heterophylla Wall., Calotropis inflexa Chiov, Calotropis persica Gand, Calotro b bpis syriaca Woodson, Calotropis wallichii Wight, Madorius procerus (Aiton) Kuntze, Apocynum syriacum Garsault, Asclepias patula Decne, Asclepias procera Aiton and Calotropis busseana* K. Schum [14].

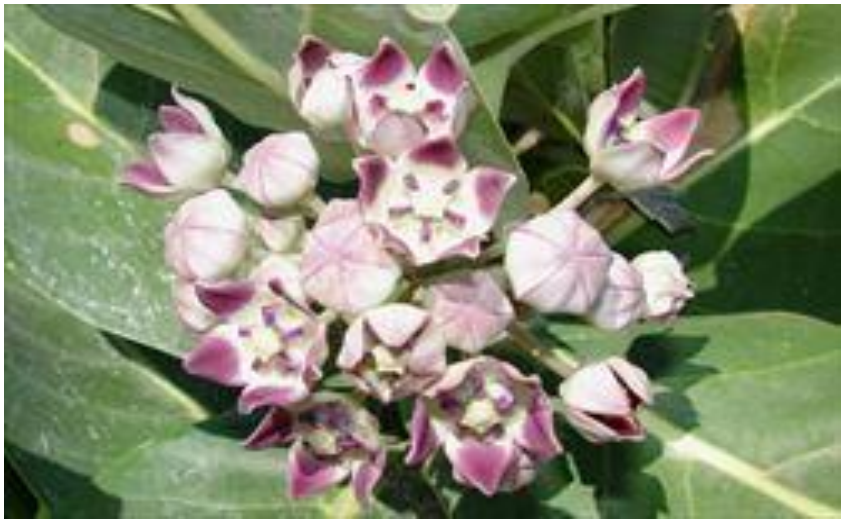

Fig 1: *Calotropis procera* plant

Common names

Arabic: Dead Sea plant, debaj, usher, oshar, kisher;

English: calotrope, calotropis, dead Sea fruit, desert wick, giant milkweed, swallow-wort, mudar fibre, rubber bush, rubber tree, sodom apple;

French: pomme de Sodome, algodón de seda, arbre á soie, coton soie, arbre a soie du Senegal;

German: wahre mudarpflanzer, gomeiner;

Hindi: madar, akada, akdo,aak;

Italian: calotropo;

Marathi: rui, mandara;

Punjabi: aK;

Sanskrit: arka, alaka, ravi;

Somali: boah, bo'ah;

Spanish: bomba, algodón extranjero, cazuela;

Swahili: mpamba mwitu;

Tamil: vellerukku;

Telgu: jilledu;

Turkish: ipekag

Urdu: madar, aak [15-17]

Taxonomic classification

Kingdom: Plantae,

Subkingdom: Tracheobionta,

Superdivision: Spermatophyta,

Division: Magnoliophyta,

Class: Magnoliopsida,

Subclass: Asteridae,

Order: Gentianales,

Family: Asclepiadaceae,

Genus: Calotropis,

Species: *Calotropis procera.* [18-19].

Pharmacological Activities of *Calotropis procera*

Antimicrobial activity

The aqueous and ethanolic extract of roots and leaves of *Calotropis procera* against various strains like *Staphylococcus aureus, Streptococcus pyogen, Escherichia coli* and *Pseudomonas aeruginosa* was studied on disc Diffusion method. Both ethanolic and aqueous extracts of *Calotropis procera* had inhibitory effect on the growth of isolates. The effect exhibited by ethanolic extract of leaves and roots was significantly greater than that of the aqueous extract of leaves and roots. [20].

The petroleum ether extract of *Calotropis procera* exhibited the best antibacterial activity against Pseudomonas aeruginosa ATCC and Klebsiella pneumonia while the chloroform extract was more potent antibacterial against Pseudomonas aeruginosa ATCC with 19 mm, 16 mm and 17 mm inhibition zone diameters respectively. [21].

The methanolic and aqueous extract of leaves of *Calotropis procera* were subjected to the potential antibacterial against both Gram-positive bacteria (*Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus* and *Streptococcus pyogenes*) and Gram-negative bacteria (*Plesiomonas shigelloides*, *Shigella dysenteriae*, *Vibrio cholerae*, *Salmonella typhi*, *Shigella flexneri*, *Shigella boydii*, *Shigella sonnei and Pseudomonas aeruginosa*) in agar diffusion method. It was evident that both extracts are active against the bacteria at low concentrations. [22]

Antimicrobial activity of solvent extracts of *Calotropis procera* growing wild in Saudi Arabia was evaluated against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Pseudomonas aeruginosa* and *Salmonella enteritidis*) using agar well-diffusion method. A bioassay-guided fractionation of the crude flavonoid fraction (Cf3) of methanol extract which showed the highest antimicrobial activity led to the isolation of four flavonoid glycosides as the bioactive constituents. Most of the isolated extracts showed antimicrobial activity against the test microorganisms, where the crude flavonoid fraction was the most active, diameter of inhibition zones ranged between 15.5 and 28.5 mm against the tested bacterial strains, while reached 30 mm against *Candida albicans*. The minimal inhibitory concentrations varied from 0.04 to 0.32 mg/ml against all of the tested microorganisms in case of the crude flavonoid fraction. Quercetin-3-O-rutinoside showed

superior activity over the remainder flavonoids. The Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) were more susceptible than the Gram-negative (*Pseudomonas aeruginosa* and *Salmonella enteritidis*), and the yeast species were more susceptible than the filamentous fungi. Calo-protein was purified from the most-active aqueous extracts of *C. procera* and showed broad-spectrum antibacterial activity. Calo-protein inhibited the growth of *S. aureus* and *E. aerogenes* effectively at 25µg/ml concentration. Ethyl acetate, methanol, and aqueous extracts (20µL of the extracts, containing 100 µg of residues), displayed high antimicrobial activity against *E. coli E. aerogenes P. vulgaris P. mirabilis P. aeruginosa* and *S. aureus.* Methanolic extract appeared as the most potent antimicrobial extract, with a diameter of inhibition zone (mm) of 14±0.31, 19±0.2, 23±0.4, 20±0.6, 8±0.12 and 27±0.06 against *E. coli, E. aerogenes, P. vulgaris, P. mirabilis, P. aeruginosa* and *S. aureus* respectively. [23,24]

The differential antimycoses activities of chloroform, methanol and ethyl acetate extracts of *Calotropis procera* (50,100 and 150 mg/ml) were studied against *Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophyte, Epidermophyton floccosum* and *Aspergillus.* Ethyl lactate extract produced the potent activity followed by chloroform extract, while methanol extract had no antifungal activity in all concentrations used in the study. [25]

The osmotin purified from *Calotropis procera* latex, inhibited the spore germination of *Fusarium solani*. Osmotin interacted with the negatively charged large unilamellar vesicles (LUVs) of 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-rac-1-glycerol (POPG), inducing vesicle permeabilization by the leakage of calcein. Osmotin induced the membrane permeabilization of spores and hyphae from *Fusarium solani*, allowing for propidium iodide uptake.[26]

Anthelmintic effects

Different extracts of *Calotropis procera* leaves were evaluated for *in-vitro* anthelmintic activity against Indian earthworms *Pheritima posthuma.* The perusal of the anthelmintic activity data reveals that 70% hydroethanolic extract at the concentration of 12.5 mg/ml showed paralysis and death in 18.58 and 29.05m. respectively. Similarly *n*-butanol and chloroform extract at the concentration of 12.5 mg/ml showed both paralysis in 21.03 and 48.26 and death in 26.53 and 51.25m. respectively. The effect was positively correlated with concentration [27].

The anthelmintic effect of crude aqueous (CAE) and methanolic extracts (CME) of *Calotropis procera* flowers was evaluated by *in vitro* and *in vivo* models in comparison with levamisole. The *in vitro* studies demonstrated the anthelmintic effects (P<0.05) of (CAE) and (CME) of *Calotropis procera* flowers on *Haemonchus contortus* as evaluated by mortality or temporary paralysis. For the *in vivo* studies, *Calotropis procera* flowers were administered as a crude powder (CP), CAE and CME to sheep naturally infected with a mixed sample of gastrointestinal nematodes. The percentage reduction in egg count (ECR) was recorded as 88.4 and 77.8 % in sheep treated with CAE and CP at a dose of 3000 mg/kg body weight respectively. CME was the least effective producing only a 20.9 % reduction in ECR on day 7 after the treatment. The anthelmintic activity of *Calotropis procera* against nematodes, was less than that exhibited by levamisole (97.8 %-100 %) . [28]

Antiinflammatory, analgesic and antipyretic effects:

The anti-inflammatory effect of the chloroform (CH) and hydroalcoholic extract (HE) of the stem bark of *Calotropis procera* against carrageenan-induced paw oedema has been studied by using two acute models, aspirin (100 mg/kg, po) and ethanol (96%) in albino rats. CH and HE extracts showed significant anti-inflammatory activity at 200 and 400 mg/kg. As part of investigations to obtain compounds with anti-inflammatory effects, a bioassay was carried out with fractions obtained from the CH extract with n-hexane (NF1), 1-butanol (BF1), ethyl acetate (EF1) and chloroform (CF1). The HE extract of the stem bark was fractionated with n-hexane (NF2), 1-butanol (BF2), ethyl acetate (EF2), chloroform (CF2) and water (WF2). The fractions were evaluated for their anti-inflammatory effects. Fractions NF1, CF1, BF2 and EF2 (20 mg/kg) showed significant anti-inflammatory activity. The latex of *Calotropis procera*, ethanol extract of its flowers and the chloroform soluble fraction of its roots possessed significant anti-inflammatory activity. [29]

The methanolic extract of plant *Calotropis procera* roots has been reported to exhibit potent anti-inflammatory activity against carrageenan induced paw oedema and cotton pellet induced granuloma in albino Wistar rats. The different extracts of the roots of *C. procera* and standard anti-inflammatory drugs were administered orally 1 hour before inducing of inflammation. The methanolic extracts (180mg/kg, po) of roots of *C. procera* has potential to inhibit sub-acute inflammation by interruption of the arachidonic acid metabolism in both paw oedema as well as cotton pellet model and showed inhibition of inflammation (p<0.01 and p<0.001) very close to the inhibitory effect of diclofenac sodium (25 mg/kg, ip). [30]

Anti-hyperbilirubinemic and wound healing activity

Albino Wistar rats of either sex were used for the study. Bilirubin lowering property of *C. procera* leaves was evaluated using phenylhydrazine and paracetamol as inducing agents followed by measuring the concentration of serum total bilirubin in hyperbilirubinemic rats. Wound healing property was evaluated using incision and excision models by measuring tensile breaking strength, percentage wound contractions, and epithelization days, respectively. AECP showed significant bilirubin lowering and wound healing property in Wistar rats.[31]

***Calotropis procera* leaf extracts on glucose tolerance in glucose-induced hyperglycemic rats and mice.**

Calotropis procera (leaves) are used in folk medicine of Bangladesh to control blood sugar in patients suffering from diabetes mellitus. The hypoglycemic effects methanol extract of leaves of *Calotropis procera* were investigated in oral glucose tolerance tests in Long Evans rats and Swiss albino mice, respectively. The methanol extract of leaves of Calotropis procera, when tested at doses of 100 and 250 mg/kg body weight did not demonstrate any oral hypoglycemic effect when tested in glucose-loaded mice. [32]

Anticancer Activity

Latex of *Calotropis procera* has been described as a relevant source of pharmacologically active proteins, including proteins with anticancer activity. A previous *in vitro* study of laticifer proteins (LP) from *C. procera* reported that they had selective cytotoxic effects on human cancer cell lines. The aim of this study was to determine the effects of LP in vivo using mice transplanted with sarcoma 180. Biochemical, hematological, histopathological, and morphological analyses were performed in animals given LP by oral or intraperitoneal routes. LP significantly reduced tumor growth (51.83%) and augmented the survival time of animals for up to 4 days. Tumor growth inhibitory activity

was lost when LP fraction was submitted to proteolysis, acidic treatment, or pretreated with iodoacetamide. However, LP retained its inhibitory activities on sarcoma 180 growth after heat treatment. Thus, it seems that heat-stable proteins are involved in tumor suppression. Biochemical parameters, such as the enzymatic activity of aspartate aminotransferase and alanine aminotransferase and urea content in serum were not affected in treated mice. It is worth noting that LP completely eliminated the 5-FU-induced depletion of leukocytes in mice even when given orally. The active proteins were recovered in a single fraction by ion exchange chromatography and still exhibited anticancer activity. This study confirms the pharmacological potential of proteins from the latex of *C. procera* to control sarcoma cell proliferation.[33]

Anti-ulcerative colitis activity

The aim of the present study was to evaluate the anti-ulcerative colitis activity of *Calotropis procera*. Different extracts of the investigated plant were evaluated; total alcohol extract, polar extract and non-polar extract. All the investigated extracts at doses 200 &400 mg/kg possessed a dose-dependent anti-ulcerative colitis potential when administrated for 5 consecutive days after colitis induction by acetic acid in rats. They reduced different parameters of UC. Only polar extract at both doses (200, 400 mg/kg) was more effective than the standard drug Prednisolone (50 mg/kg), it produced percent protection of control colitis by 63.8% and78.4% respectively, while the standard drug Prednisolone produced 54.9% protection. The anti-ulcerative colitis activity may be attributed to the active principles i.e. flavonoids. Preliminary phytochemical screening showed that the plant contains flavonoids, unsaturated sterols and/or triterpenoides, cardiac glycosides, carbohydrates or glycosides, proteins and/or amino acids, tannins and coumarins. The total alcohol extract was safe up to 4000 mg/kg and there were no side effects reported on liver and kidney functions.[34]

Effect on reproductive system

The effect of ethanolic extract of the roots of *Calotropis procera* has been studied in albino rats to explore its antifertility and hormonal activities. A strong antiimplantation (inhibition 100%) and uterotropic activity was observed at the dose level of 250 mg/kg (1/4 of LD(50)). No antiestrogenic activity could be detected.[35]

Effect on acute inflammation

The non-dialysable proteins present in the latex of plant *Calotropis procera* possess anti-inflammatory and analgesic properties. The aim of this study was to evaluate the effect of latex proteins (LP) on the level of inflammatory mediators, oxidative stress markers and tissue histology in the rat model of carrageenan-induced acute inflammation. This study also aimed at evaluating the anti-inflammatory efficacy of LP against different mediators and comparing it with their respective antagonists. Paw inflammation was induced by subplantar injection of carrageenan, and the effect of LP was evaluated on oedema volume, level of TNF-α, PGE(2), myeloperoxidase, nitric oxide, reduced glutathione, thiobarbituric acid-reactive substances and tissue histology at the time of peak inflammation. Paw inflammation was also induced by histamine, serotonin, bradykinin and PGE(2), and the inhibitory effect of LP against these mediators was compared with their respective antagonists at the time of peak effect. Treatment with LP produced a dose-dependent inhibition of oedema formation, and its anti-inflammatory effect against carrageenan-induced paw inflammation was accompanied by reduction in the levels of inflammatory mediators, oxidative stress markers and normalization of tissue architecture. LP also produced a dose-dependent inhibition of oedema formation induced by different inflammatory mediators, and its efficacy was comparable to their respective antagonists and more pronounced than that of diclofenac. Thus, our study shows that LP has a potential to be used for the treatment of various inflammatory conditions where the role of these mediators is well established.[36]

Antioxidant activity

Dry latex (DL) of *Calotropis procera* possessing potent anti-inflammatory activity was evaluated for its antioxidant and anti-hyperglycemic effects against alloxan-induced diabetes in rats. Daily oral administration of DL at 100 and 400 mg/kg doses produced a dose-dependent decrease in the blood glucose and increase in the hepatic glycogen content. DL also prevented the loss of body weight in diabetic rats and brought down the daily water consumption to values comparable to normal rats. DL also produced an increase in the hepatic levels of the endogenous antioxidants, namely superoxide dismutase (SOD), catalase and glutathione, while it brought down the levels of thiobarbituric acid-reactive substances (TBARS) in alloxan-induced diabetic rats. The efficacy of DL as an antioxidant and as an anti-diabetic agent was comparable to the standard anti-diabetic drug, shows significant effect.

Conclusion:

The present review suggests that the plant *Calotropis procera* has been extensively studied for different biological activities. There is further scope for exploring different medicinal uses of *Calotropis procera*.

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