

## Dynamic nature of latex of *Calotropis procera* (Aiton) Dryand: A review

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### Abstract

*Calotropis procera* (Aiton) Dryand. is an important member of the Asclepiadaceae family which comprises of 250 genera and over 2000 species. As the members of the family contain clear or milky sap, Asclepiadaceae is universally known as the “The Milkweed Family”. *C. procera* (Aiton) Dryand. is a medicinal plant with numerous therapeutic properties. Since ages the plant is used by the local traditional healers from various parts of the world to treat many ailments. Almost all the parts of the plant are used in some or the other way for therapeutic purposes. This is because the parts are rich in latex content which further comprises of various biologically active components. The review exclusively presents the phytochemical composition, traditional, therapeutic, pharmacological uses and toxicity of the milky sap of the plant. In various industries the milky sap can play an important role as a base material for manufacturing different products.

**Keywords:** milky sap, phytochemicals, pharmacological properties, plant defense, toxicity

### 1. Introduction

*C. procera* (Aiton) Dryand. is a shrub commonly found in the tropical and sub-tropical regions of the world. It is frequently spotted in the Asian countries like India, Bangladesh, Burma, Pakistan etc. It shows its floral presence in the Afro-Asian monsoonal regions to America and drier parts of Australia (Banfield, 1950) [9]. The plant attains a height of 2.5 to 6 m and produces milky white latex in copious amount (Upadhyay, 2014) [81]. The therapeutic properties are directly associated with the latex content (Chundattu, et al., 2016; Batello, et al., 2004). Along with the medicinal components the plant also bears several toxic constituents and this is the reason that self-medication is not at all recommended. The toxic components are equivalently harmful for human beings as well as their livestock's (Upadhyay, 2014) [81].

### 2. Taxonomic classification of the plant According to Bentham and Hooker

Kingdom: Plantae  
Class: Dicotyledones  
Division: Gamopetalae  
Order: Gentianales  
Family: Asclepiadaceae  
Genus: *Calotropis*  
Species: *procera*.

### 3. Phytochemicals present

The milky sap content is loaded with a variety of phytochemicals. Many authors have reported the presence of these active compounds. Here the list is provided in an alphabetical order. 2,6 dimethyl tetra-1,5-decaene; 3, 7,11-Trimethyl-2,6,10, 12-pentadecatrien-1-ol (Doshi, et al.,2012) [23]. (24S)-24-ethyl stigmast-4-en-6 $\alpha$ -ol-3-oneC-6, C-24 diepimer of stigmast-4-en-6 $\beta$ -ol-3-one, 5- hydroxy-3,7-dimethoxy flav one-4'-O- $\beta$ -glucopyranoside, 2 $\beta$ , 19-epoxy-3 $\beta$ , 14 $\beta$ -dihydroxy-19-methoxy- 5 $\alpha$ -card- 20(22)-enolide,  $\beta$ -anhydr oepidigi toxigenin-3 $\beta$ -O-gluco pyranoside 2-tridecanone, Uzarigenine, (24S)-24-ethyl stigmast-4-en-

6 $\alpha$ -ol-3-one (Upadhyay, 2014) [81]. alkaloids (Shobowale, et al., 2013 [74]; Aliyu, et al., 2015 [4]; Al- Yahya, et al., 1990 [5]; Sabahi, et al., 2008) [68], anthocyanins (Al- Yahya, et al., 1990 [5]; Sabahi, et al., 2008) [68], anthraquinone (Aliyu, et al., 2015) [4], amino acids, anthraquinones (Murugan, 2012),  $\alpha$ - amyirin, amyirin (Khairnar, et al., 2012.) [40], akundaric acid, akundrol (Upadhyay, 2014) [81],  $\beta$ -amyirin,  $\beta$ -sitosterol (Khairnar, et al., 2012.) [40].  $\beta$ -anhydroepidigitoxigenin -3 $\beta$ -O-glucopyranoside,  $\beta$ -anhydro epidigitoxigenin (Upadhyay, 2014) [81], cardenolide (Al- Yahya, et al., 1990 [5]; Sabahi, et al., 2008 [68]; Khairnar, et al., 2012 [40]; Upadhyay, 2014) [81], calotropin D I, calotropin D II, calotropin F I, calotropin F II, calotropin (Meena, et al. [53], 2011),caoutchouc, calotoxin, calactin, (Chopra, et al., 1996 [17]; Baquar, and Tasnif, 1967 [10]; Rastogi, and Mehrotra, 1998 [67]; Grieve,1998) [29], calotropin, cardiac glycosides (Khairnar, et al., 2012 [40]; Upadhyay, 2014) [81], Flavonoids (Shobowale, et al., 2013 [74]; Aliyu, et al., 2015 [4]; Murugan, 2012; Kawo, et al., 2009 [38]; Jucá, et al., 2013) [23], flavanoid glycosides, flavanols (Upadhyay, 2014) [81], gigantol, giganteol, isogiganteol (Khairnar, et al., 2012) [40], lectin, methomyl madarlbium, mudrol ursane triterpenes, osmotin, oleanene triterpenes (Upadhyay, 2014) [81], proteolytic enzymes (Al- Yahya, et al., 1990 [5]; Sabahi, et al., 2008) [68], proceroside (Chopra, et al., 1996 [17]; Baquar, and Tasnif, 1967 [10]; Rastogi, and Mehrotra, 1998 [67]; Grieve,1998) [29], phenolic compounds (Murugan, 2012), pentacyclic triterpinoids, quercetin-3-rutinoside (Upadhyay, 2014) [81], resins, reducing sugar (Kawo, et al., 2009) [38], saponins (Shobowale, et al., 2013 [74]; Kawo, et al., 2009; Aliyu, et al., 2015 [4]; Murugan, 2012), Steroid glycosides (Kawo, et al., 2009) [38], stigmast-4-en-6 $\beta$ -ol-3-one (Upadhyay, 2014) [81], syriogenin (Chopra, et al., 1996 [17], Baquar, and Tasnif, 1967 [10]; Rastogi, and Mehrotra, 1998 [67]; Grieve,1998) [29], steroids (Murugan, 2012; Aliyu, et al., 2015 [4]; Jucá, et al., 2013) [23], tannins (Shobowale, et al., 2013 [74]; Kawo, et al., 2009 [38]; Aliyu, et al., 2015 [4]; tannins (Murugan, 2012), triterpenes (Jucá, et al., 2013) [23], triterpenoids (Al- Yahya, et al., 1990 [5]; Sabahi, et al., 2008

[68]; Aliyu, *et al.*, 2015 [4]; Upadhyay, 2014) [81], trypsin (Chopra, *et al.*, 1996 [17], Baquar, and Tasnif, 1967 [10], Rastogi, and Mehrotra, 1998 [67]; Grieve, 1998) [29], teraxasterol (Khairnar, *et al.*, 2012) [40], uscharin (Meena, *et al.*, 2010 [53]; Chopra, *et al.*, 1996 [17], Baquar, and Tasnif, 1967 [10], Rastogi, and Mehrotra, 1998 [67]; Grieve, 1998) [29], uzarigenin (Chopra, *et al.*, 1996, Baquar, and Tasnif, 1967 [10], Rastogi, and Mehrotra, 1998 [67]; Grieve, 1998) [29], voruscarin (Meena, *et al.*, 2010) [53]. and voruscharin (Chopra, *et al.*, 1996 [17], Baquar, and Tasnif, 1967 [10], Rastogi, and Mehrotra, 1998 [67]; Grieve, 1998) [29].

#### 4. Traditional Uses

Since ancient times the latex of the plant has been used by the traditional healers and local people. The stem latex was used to empoison the hunting arrows during wars (Upadhyay, 2014) [81]. In Sokoto the fresh latex of *C. procera* (Aiton) Dryand. is being used since ages as a topical antimycotic treatment (Ameh and Okolo 2004) [6]. In northern Nigeria, it is utilized by indigenous people to treat topical fungal diseases, convulsion, asthma, cough and inflammation (Aliero, *et al.*, 2001 [3]; Hassan, *et al.*, 2006) [32]. People in Senegal use the milky sap for treating cutaneous diseases such as ringworm, syphilitic sores and leprosy. Preparations from latex with honey is used as anti-rabies medicine. The preparation is also used in treating cough and toothache (Burkill, H. M. 1985) [15]. The leaf latex finds its application in the removal of thorns from the body (Rai, *et al.*, 2000) [62], to treat boils and is also applied on fresh cuts to stop bleeding instantly (Vohra, 2004) [83]. Topical application of the extract is used in relaxing the muscles of uterus or to increase uterine contractility in mothers to ease safe childbirth or to cause abortion in women (Attah, *et al.*, 2012 [7]. The dried sap is utilized by many local healers as an antidote for snake poisoning (Basu, *et al.*, 1992) [45].

#### 5. Therapeutic Uses

In Homeopathy the milky sap is used as a purgative and an emetic for treating ascites of kapha type and hepatosplenomegaly ascites (Upadhyay, 2014) [81]. The leaf and flower latex of the plant is processed and used in the preparation of commercial eye tonics (Vohra, R. 2004) [83]. Calotropin is an important constituent present in the sap which is used as a remedy of painful tooth ache and is topically applied to cure various skin ailments (Badruzzaman, *et al.*, 1989 [8]. Properties like spasmogenic, carminative, antidyseric, antifungal, antirheumatic, antisiphilitic, molluscicidal (Sharma, 1934) [72], diaphoretic, abortifacient are present in the latex (Banfield, 1950 [9]; Basu, *et al.*, 1992) [45]. The *C. procera* (Aiton) Dryand. milky sap is used in treating disorders like hair loss, baldness, toothache, vertigo, intermittent fevers, paralysis, rheumatoid swellings (Meena, *et al.*, 2011) [53], boils, infected injuries, rushed skin (Khare, 2007), piles (Gupta, *et al.*, 1996) [28], intestinal worms (Singh, *et al.*, 1980), neoplasia (Alencar, *et al.*, 2006 [2]; Choedon, *et al.*, 2006) [16], enlarged spleen and liver (Singh, *et al.*, 1996), bronchial asthma, leprosy and skin infection (El- Badwi 1997).

#### 6. Pharmacological Properties

##### 6.1. Anti-microbial property

The plant latex is an effective antimycotic agent against dermatophytes i.e., *Microsporum spp.* and *Epidermophyton*

*spp.* Therefore, in the dermatomycotic infection the latex use is highly recommended (Aliyu, *et al.*, 2015) [4]. Manoorkar, *et al.*, 2015 reported that the aqueous and ethanol latex extracts of *C. procera* (Aiton) Dryand. displayed positive results against the seed-borne fungi of some oil seeds namely *Alternaria altrenata*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, *Cucularia lunata*, *Fusarium solani*, *Rhizoctonia solani* and *Penicillium chrysogenum*. Halu, and Vidyasagar, 2012 observed inhibition of the spore germination of *Fusarium solani* when treated with Osmotin (protein purified from *Calotropis procera* latex). Adoum, *et al.*, 1997 reported antibacterial activity against *E. coli*, *S. aureus*, *Salmonella* and *Pasteurella species*. Correspondingly Shobowale, *et al.*, 2013 [74]. testified positive results against *E. coli*, *S. typhi*, *B. subtilis*, *C. albicans*, and *A. niger* of the ethanolic and aqueous extracts of the latex.

The methanolic and ethyl acetate latex extract showed positive results against bacterial strains i.e., *Bacillus subtilis*, *Micrococcus luteus*, *Pseudomonas aeruginosa* and *Serratia marcescens*. The extracts also showed effective results against fungal strains i.e., *Aspergillus niger*, *Aspergillus flavus*, *Alternaria sp.*, *Fusarium sp.*, *Penicillium sp.* and *Rhizopus sp.* (Murugan, 2012). Kareem, *et al.*, 2008 used paper disc and agar well diffusion methods for revealing the antibacterial and antifungal properties of aqueous, ethanol and chloroform latex extract. The test organisms chosen for this experiment were *E. coli*, *S. aureus*, *S. albus*, *P. aeruginosa*, *S. pyogenes*, *S. pneumoniae*, *A. niger*, *A. flavus*, *C. albicans* and *M. boulardii*. The result displayed strong inhibitory effect on the test organisms. Moreover, the results revealed that ethanol extract presented the best result among the extracts. In similar experiments reported by Kawo, *et al.*, 2009 [38]. it was testified that the ethanolic extract of the latex displayed antibacterial result against *E. coli*.

##### 6.2. Analgesic activity

In various animal models' analgesic activity of the latex has been observed (Choedon, *et al.*, 2006) [16]. Kumar, *et al.*, 2011. evaluated the analgesic activity of the dry latex on mice model. The effect was examined against acetic acid generated writhing. A single oral dose ranging from 165 to 830 mg/kg was used in this research. In another experimentation reported by Das, *et al.*, 2011 [20]. at doses of 250 and 500 mg/kg the latex inhibited the writhing responses which was caused by intraperitoneal administration of acetic acid. The standard used for this experiment was Sodium diclophenac. The results obtained were better in comparison to the standard used. Analgesic properties of the latex have been attributed to the protein and non-protein constituents derived from the plant latex. It was further reported that the proteins derived from the latex are effective when parenteral administration was used while the non-protein constituents were effective when delivered orally (Soares, *et al.*, 2005 [79]; Dewan, S., *et al.*, 2000 [22]; Kumar and Basu 1994 [45]; Kumar, *et al.*, 2017) [47].

##### 6.3. Anti-inflammatory activity

In the aqueous and alcoholic latex extracts of *C. procera* (Aiton) Dryand., anti-inflammatory activity was reported by Kumar and colleagues (Kumar, and Roy, S. 2009 [48]; Kumar, 2011) [49]. A study conducted on the water-soluble latex of the plant by Seddek, *et al.*, 2009 [70]. reported

inflammatory and immune response effector cell activation in murine macrophages. The study concluded that this was possible due to the enhancement of iNOS gene expression and NO production in the macrophages. In another study the fractions of dichloromethane and ethyl acetate latex extract exhibited anti-inflammatory properties in adult male Wistar rats (Jucá, *et al.*, 2013) [23]. The non-protein and protein constituents of the latex were attributed for the anti-inflammatory properties (Soares, *et al.*, 2005 [79]; Dewan, S., *et al.*, 2000 [22]; Kumar and Basu 1994 [12]; Kumar, *et al.*, 2017) [56].

#### 6.4. Anticancer activity

Laticifer proteins from *C. procera* (Aiton) Dryand. have shown selective cytotoxic effects on different human cancer cell lines, the proteins have shown effective results against sarcoma cell proliferation (Oliveira, *et al.*, 2007). In the work by Jucá, *et al.*, 2013 [23], it was reported that the *C. procera* (Aiton) Dryand. latex dichloromethane and ethyl acetate fractions exhibited potential toxicity against the cancer cell lines HL-60, Ovc8-8, HCT-116, SF-295. Choedon, *et al.*, 2006 [16], reported the Methanolic extract of the latex is cytotoxic to cancer cell lines and display chemo preventive activity in hepatocellular carcinoma. The phytochemicals uscharin and voruscarin were reported as highly antiproliferative against the cancer cell lines Hs683, U373, HCT-15, LoVo and A549 (Meena, *et al.*, 2010) [54].

#### 6.5. Anti-diarrheal activity

In an experiment conducted by Kumar, and Shivkar, 2004, rats were treated with castor oil. A single oral dose of dry latex (500 mg/ kg) produced decrease in the frequency of severity of diarrhea and defecation. Das, *et al.*, 2011 [20] reported the ethanol extracts at doses 250 and 500 mg/kg produced effective anti-diarrheal effects. The latent time was  $81.8 \pm 2.38$  min and  $106.08 \pm 7.22$  min, respectively. In another experimental study conducted by Kumar, *et al.*, 2001, the aqueous suspension of the dried latex had stopped diarrhea and further decrease in the intestinal transit and affected contractility of gastrointestinal smooth muscles was also observed.

#### 6.6. Anti-hyperglycemic effect

Alloxan-induced diabetic rats when treated with dried latex of *C. procera* showed better results when compared with glibenclamide (standard antidiabetic drug). 100 and 400mg/kg oral dose produced increase in the content of hepatic glycogen and decrease in the blood glucose content. The dried latex also checked the loss of body weight in the diabetic rats. Increase in the hepatic levels of the antioxidants namely catalase, superoxide dismutase, and glutathione were also observed (Kumar, *et al.*, 2005) [47].

#### 6.7. Antinociceptive effect

In an experiment conducted by Vasconcelos, 2005. with three different models of nociception in mice exhibited that the protein fraction derived from the latex possesses antinociceptive effects. In the experiment male mice were administered intraperitoneally with the latex proteins at doses of 12.5, 25 and 50 mg/kg. Antinociceptive effect was observed in a dose dependent manner compared to that of the control sets.

#### 6.8. Anti-colitis activity

The study conducted by Kumar, *et al.*, 2019 [50], revealed that the latex provides protection to the rat model in which colitis was induced using acetic-acid by the suppression of the oxidative stress and NFκB mediated pro-inflammatory signal. It was concluded that the latex bears therapeutic potential in inflammatory disorders of the colon.

#### 6.9. Anti-helminthic

Nagaty, *et al.*, 1959 [57], reported that the milky sap of *C. procera* (Aiton) Dryand. had an *in vitro* ascaricidal effect when compared with the latex of *Ficus carica* and *Papaya carica*. The ascaricidal effect was considered to be caused by enzymes present in the latex.

#### 6.10. Antioxidant activity

Antioxidant potential of extracts from the latex of *C. procera* (Aiton) Dryand. has been reported by Patel *et al.*, 2014. Positive results were obtained from the DPPH [1, 1-diphenyl -2- picryl hydrazyle] assay, reducing power assay, FRAP [Ferric Reducing Antioxidant Power] assay and ferrous ion chelating activity.

#### 6.11. Wound healing activity

In various animal models wound healing activity of the latex has been observed (Choedon, *et al.*, 2006) [16]. Based on the traditional use of *C. procera* wound healing potential of the plant was evaluated by Rasik, *et al.*, 1999 [66]. Guinea pigs were chosen as the experimental model for this experimentation. 4 full thickness wounds of diameter 8.0mm were inflicted on the back of the pigs. For a time period of 7 days daily 2 times 1% sterile 20 ul latex solution was applied topically. It was observed that the latex significantly enhanced the healing process by epithelization, heading towards the reduction of the wound area.

#### 6.12. Pro-coagulant activity

Thrombin and plasmin-like activity is produced by the latex proteases. The subunits of the cross-liked fibrin are hydrolyzed by the proteases derived from latex (Hemalatha and Padmini 2010) [37]. These proteases exhibit similar actions on fibrinogens and fibrins (Shivaprasad, *et al.*, 2009 [63]; Freitas, C. D. 2007) [58] and are involved in homeostasis, inducing blood clot and dissolving properties (Rajesh, *et al.*, 2007) [63].

#### 6.13. Larvicidal activity

In an experiment conducted by Singhi *et al.*, 2006 it was observed that the milky sap was effective against the three vector species i.e., *Aedes aegypti*, *Anopheles stephensi* and *Culex quinquefasciatus*. In this experimentation 14 solvents were used to dissolve latex at 1000 ppm. It was observed that 100 % mortality rate was produced by the methanolic extract against *Aedes aegypti* larvae. In another experimentation conducted by Shahi, *et al.*, 2010 [71] it was observed that the larvicidal efficacy against *Anopheles stephensi* and *Culex quinquefasciatus* generated LC<sub>50</sub> 13.06 and LC<sub>50</sub> 86.47.

#### 6.14. Insecticidal effects

The natural latex acts as a good pesticide and effectively

kills a lot of pests in the field of agriculture and household. The milky sap shows larvicidal and growth inhibitory activity in pests. In male insect's latex induces spermicidal activity and controls the reproductive behavior (Hifsa, *et al.*, 2010) <sup>[34]</sup>.

### 7. Proteolytic enzyme content and effects

The enzyme Calotropin is more powerful in comparison to Papain and Bromelain. The enzyme effectively coagulates milk, processes and breaks down meat, Gelatin and Casein (Meena, *et al.*, 2011) <sup>[53]</sup>. The proteolytic enzymes derived from the latex are used by the leather and tanning industries for removing hair from the hides. The "nari leather" that is used for book-binding purposes is prepared and processed from the fermented-salted latex. The fermented latex is used to remove the hairs from goatskins (Singh, U., *et al.*, 1996).

### 8. Plant defense

Unpleasant components such as alkaloids, tannins, saponins, resins, enzymatic proteins, (Yeang, *et al.*, 2002) <sup>[84]</sup> monoterpenes, phenolic glycosides, (Hagel, *et al.*, 2008) <sup>[30]</sup> and 2-tridecanone (Braga, *et al.*, 2007) <sup>[14]</sup> are present in the latex. These components are extremely allergic to the insects and by producing these phytochemicals the plant easily protects itself from the pests (Ramos, *et al.*, 2011) <sup>[65]</sup>. Among all the components Calactin is produced in greater amount as a defense mechanism against insect attacks (Meena, *et al.*, 2011) <sup>[53]</sup>.

### 9. Toxicity

*C. procera* (Aiton) Dryand. is best known as a poisonous plant; the constituents of the latex play important role in this. The aerial parts are highly toxic to livestock due to the milky sap content (Parsons and Cuthbertson 2001). Poison arrows are made traditionally using the stem latex extracts since ages (Upadhyay, 2014) <sup>[81]</sup>. The constituents of the milky sap make it highly harmful to human eyes and produces immediate painless blurriness of vision with photophobia (Basak, *et al.*, 2009) <sup>[11]</sup>. The content of cardenolides in the latex is directly connected with toxic effects in mammals (Elgamal, *et al.*, 1999) <sup>[26]</sup>. Sharma, 1934 <sup>[72]</sup>. reported Calotropin derived from the sap slowed down the heart beat and caused gastroenteritis in the frog used as a model in the experiment. Jucá, *et al.*, 2013 <sup>[23]</sup>. reported the dichloromethane and ethyl acetate fractions of the latex extract exhibited potential toxicity against Brine shrimp nauplii (*Artemia sp.*). Latex induces skin and mucous membrane irritation, slows down heartbeat, causes difficulty in breathing, severe bullous dermatitis, increase in blood pressure and convulsions. Consumption of 4-5 ml of latex may result into lethality (Crout, *et al.*, and Duke, 1986) <sup>[24]</sup>.

### 10. Discussion

The Natural latex of *C. procera* (Aiton) Dryand. can be used as a base material for preparing commercial products. Many pharmacological properties have been observed in the latex. It can be served as a primary source in preparing various medicines by the pharmaceutical industries. The insecticidal properties provide a platform in making pesticides from it. The proteolytic enzymes are very useful in comparison with the other alternatives present in the markets. Low cost and effective herbal solutions are therefore encouraged from the

*C. procera* (Aiton) Dryand. latex. Further evaluation of the latex can lead to many new discoveries helpful to mankind.

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