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Phyto-pharmacological review of *Calotropis procera* – A natures drug house in tropical countries

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ABSTRACT

Background & Aim: The use of traditional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health, has been widely observed. In the last century, approximately 121 pharmaceutical products have been discovered based on the information obtained from the traditional healers. In the present study, we thoroughly investigated the phyto-pharmacological potential of *Calotropis procera* which is extremely effective as medicine and its phyto-constituents show strong antioxidant properties.

Results: The world health organization has estimated that world population of about 80 % from developing countries depends on herbal medicine for their basic health care needs. *Calotropis procera* is an important drug of Ayurvedic medicine and researchers are exploring the therapeutic potential of this plant. *Calotropis* is a plant with excellent medicinal properties which is used for curing different human ailments.

Recommended applications/industries: The present review article provides a viewpoint on phytopharmacological potential of *Calotropis procera* which could be beneficial for future research on development of better and economically superior therapeutic agents.

1. Introduction

Calotropis procera is a drought resistant, salt tolerant, shrub of India and an important drug of Ayurveda (Anonymous, 2010). It is native of Asia and widely found in China, Malaysia and Vietnam. It is a small, erect and compact shrub, which is used in several traditional medicines to cure various diseases. There are two common species of Calotropis, viz. *Calotropis gigantea* (Linn.) R.Br. and *Calotropis procera* (Ait.) R.Br described by the Sanskrit writers (Parrotta, 2001). Both the species are used as substitutes for one another and are said to have similar effects. It grows in verities of soils and environmental conditions and don't require cultivation practices. Each part of the plant bears excellent medicinal properties and used for curing different human ailments. The decoction of the plant is used in Indian traditional medicine for the treatment of painful muscular spasm, dysentery, fever, rheumatism, asthma and as an expectorant and purgative. Taxonomic Classification of the plant is as follows (Grieve, 1994; Ali *et al.*, 1996):

Kingdom: Plantae
Subkingdom: Tracheobionta (Vascular Plants)
Superdivision: Spermatophyta (Seed Plants)
Division: Magnoliophyta (Flowering Plants)
Class: Magnoliopsida (Dicotyledones)

Sub class: Asteridae
Order: Gentianales
Family: Apocynaceae (Milkweed Family)
Genus: *Calotropis*
Species: *procera*

The various common and popular names of *Calotropis procera* are discussed in Table 1 (Palejkar *et al.*, 2012).

Table 1. Various common names of *Calotropis procera* in different place.

Countries	Synonyms	India	Synonyms
English	Crown flower, Giant Indian milkweed	**Hindi**	Madar, Aak
Malaysia	Remiga, Rembega	**Sanskrit**	Ravi
Indonesia	Bidhuri, Sidaguri	**Assamies**	Akand
Philippines	Kapal-kapal (Tagalog)	**Bangoli**	Akon
Laos	Kok may, Dok kap, Dok hak	**Cannad**	Ekka
Thailand	Po thuean, Paan thuean, Rak	**Kashmiri**	Acka
Vietnam	Bootng	**Malyalm**	Erikku
French	Faux arbre de soie	**Marathi**	Rui
German	Wahre Mudarpflamzer	**Urea**	Arkha
Italian	Calotropo	**Panjabi**	Ak
Spanish	Algodon extranjero	**Urdu**	Madar
Turkish	Ipekag	**Telgu**	Gilledu
Arabic	Oshar	**Gujarati**	Aakando

2. Botanical description

Calotropis procera (CP) is a perennial, evergreen and soft wooded shrub. It usually attends heights of 3 meter and rarely reaches to 5 meter. White coloured latex is obtained when leaves or stems are cut (Rastogi *et al.*, 1997; Kokate *et al.*, 1994; Evans *et al.*, 2005; Alikhan *et al.*, 2005).

2.1. Leaves

The leaves are opposite and externally shorts petioles belongs to hearts shaped base .The blades are broadly elliptic or nearly orbicular, short pointed to blunt at the apex. The leaves are light to dark green and contain nearly white veins. These are 7-18 cm long and 5-12 cm broad, slightly leathery and cover with fine coat of soft hairs that are easy to rub off (Figure 1a).

2.2. Flowers

The species having white flowers is a most common and superior variety and is referred to as *Calotropis procera*. The corolla is slightly succulent and consist of 5 small triangular dirty white sepals, 5 thick ovate petals (1 cm^2) (Figure 1d).

2.3. Fruits

The fruits are green inflated, and spongy ovoid follicles that split open to release plumed, papery light brown seeds with white filaments. These are 3-4.5 inches long and 2-2.5 inches wide. The main flowering period is from March to October (Figure 1b).

2.4. Root and root bark

Giant milkweed has a very deep, stout taproot with few or no near-surface lateral roots. Giant milkweed roots were found to have few branches and reach depths of 1.7 to 3.0 m in Indian sandy desert soils. The roots are covered with root bark with rounded head and rest of the portion spirally curved. The bark of the older root is cracked at places. The bark is yellowish gray outside and yellowish white inside. The upper cork portion is spongy and rough while the inner portion of bark is smooth and mucilaginous (Figure 1e).

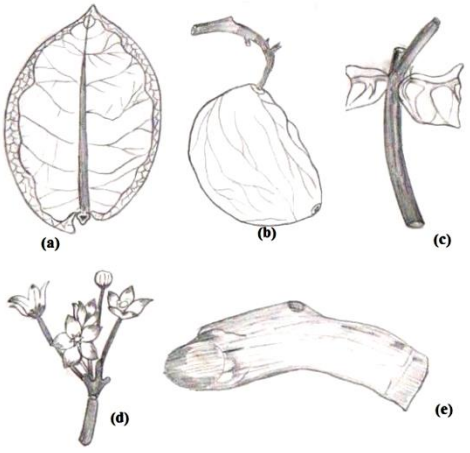

Figure 1. a) Leaf, b) Fruit, c) Stem, d) Flower, e) Root.

3. Phyto-pharmacological discussion

Each part of *Calotropis procera* (CP) contains several phytoconstituents belonging to different classes of natural products, which makes the genus Calotropis as the nature's drug house. About 70 chemicals have been isolated and characterized from different part of this plant. The availability of various compounds and important pharmacological activity associated to each part of *Calotropis procera* is discussed in this paper.

3.1. Flower

Flower of *Calotropis procera* is rich in cardiac glycosides, carbohydrates, enzymes and steroidal contents. The major cardiac glycosides are calotropin (1), calactin (2), calotoxin (3), calotropagenine (4), uscharin (5), voruscharin (6), uscharidine (7), uzarigenin (8), proceragenine (9) (Figure 2). The carbohydrates present in flowers are D-arabinose (10), glucose (11), glucosamine (12), and rhamnose (13). However, the most studied sterols in flower are lupeol (14), stigma sterols (15), cycloart-2,3-ene-3-B-25-diol (16), multiflorenol (17), clycosadol (18), 3-epimoratenol, prosterol (19) (Figure 3). Two enzymes namely 3- protinase, calotropain (20), have also been isolated from the flowers of *Calotropis procera*. The flower also contain one calotropenyl acetate (21) (Figure 3). The flowers of the plant exhibit hepatoprotective activity, anti-inflammatory, antipyretic, analgesic and antimicrobial effect and larvicidal activity (Ansari *et al*., 1999; Meena *et al.*, 2011). Structures of all the phytochemicals are shown in Figure 3.

Zafar *et al.* (2005) studied the effect of crude aqueous and methanolic extract of flowers of *Calotropis procera* on live *Haemonchus contortus* and evaluated the rate and extent of mortality and temporary paralysis. In their experiment, the extracts of *Calotropis procera* flowers showed good antihelmentic activity in sheep infected with nematodes.

Setty *et al.* (2007) reported hepatoprotective effect of ethanolic extract (70%) against paracetamol induced hepatitis in rats. The treatment with ethanolic extract (200mg and 400mg/kg) restored the altered levels of biochemical markers (SGPT, SGOT, ALP, Bilirubin and cholesterol, HDL, and tissue GSH) in a dose dependent manner.

Mukharjee *et al.* (2010) reported the CNS depressant activity of methanolic extracts of fresh flowers of *calotropis procera* in an *in-vivo* model. Administration of Diazapam (1.5mg/kg body weight ip) and flower extracts (100mg/kg oral) produces significant CNS depression to the treated mice.

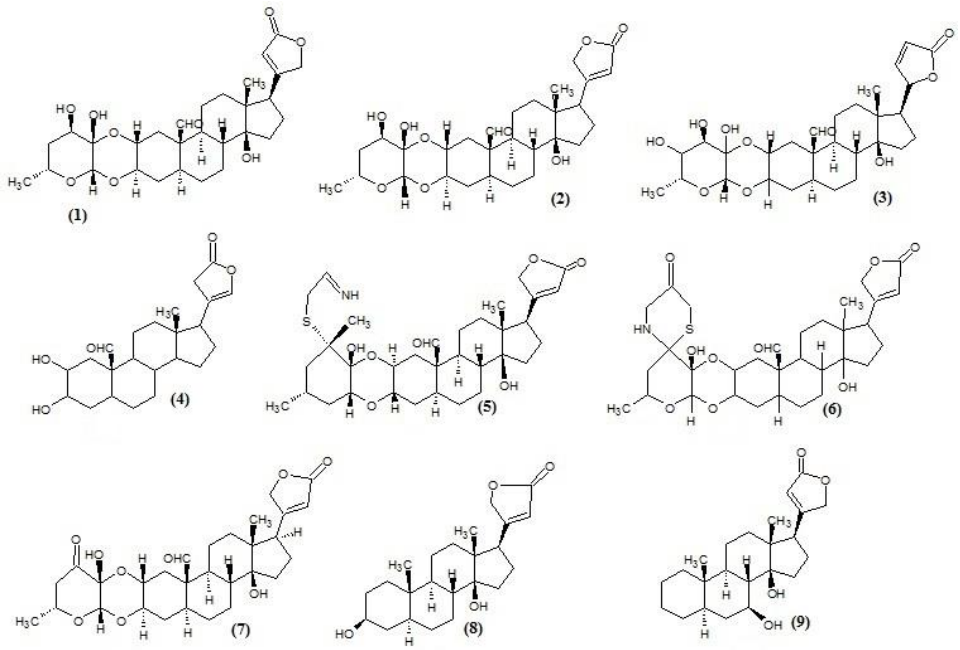

Figure 2. Structures of phyto-constituents present in *Calotropis procera* flower. calotropin (1), calactin (2), calotoxin (3), calotropagenine (4), uscharin (5), voruscharin (6), uscharidine (7), uzarigenin (8), proceragenine (9).

Sharma and Sharma (2000) studied the antimalerial effects of ethanolic extracts of different parts of *calotropis procera* .The IC_{50} values were obtained from 0.11-0.47mg/ml against *P. falciperum.* It was observed that flower and bud extracts are most active antimicrobial component in *Calotropis procera*.

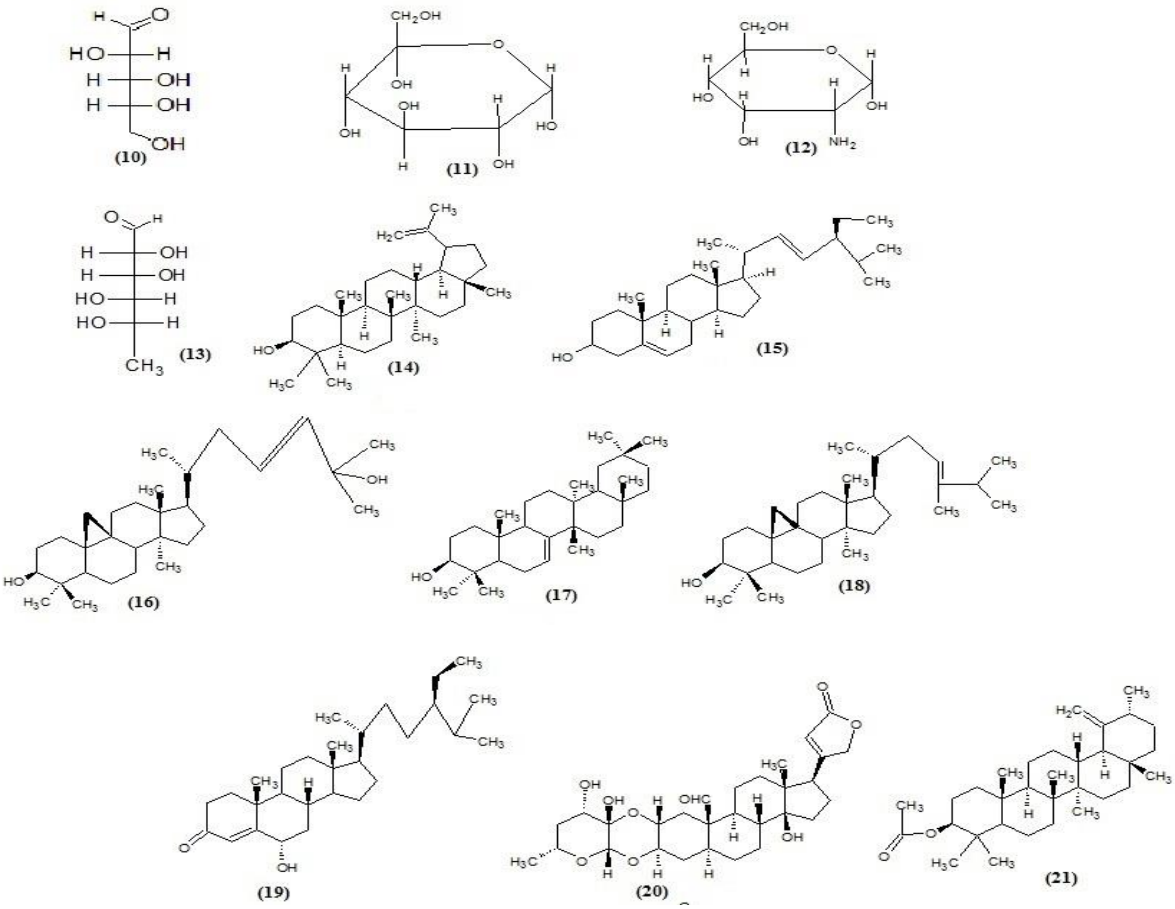

Figure 3. Structures of carbohydrates, sterols and enzymes present in flowers of *Calotropis procera*. D-arabinose (10), glucose (11), glucosamine (12), rhamnose (13), lupeol (14), stigma sterols (15), cycloart-2,3-ene-3-B-25-diol (16), multiflorenol (17), clycosadol (18), 3-epimoratenol, prosterol (19), 3- protinase, calotropain (20), calotropenyl acetate (21).

3.2. Latex

Latex is a complex mixture of more than 9 cardiac glycosides which are calotoxin, calactin, uscharine, voruscharine, uzarigenine, syriogenin (22), proceroside (23), cholin (24). One enzyme named as trypsine was also isolated from latex of *calotropis procera* (25) (Figure 4). The presence of these compounds enables latex to use as anti-inflammatory, analgesic, antinociceptive and antidiabetic remedy in folklore medicines. The Latex of the plant is reported to posses antiasthmatic, antileprotic, antirheumatism, anticold activity (Murti *et al.*, 1943; Atef *et al.*, 1999; Kew *et al.*, 1985).

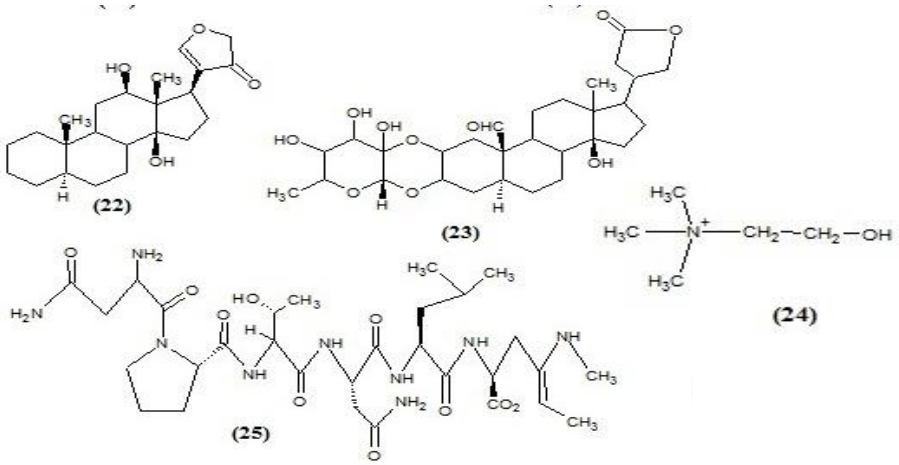

Figure 4. Glycosides and enzyme isolated from latex of *calotropis procera*: syriogenin (22), proceroside (23), cholin (24), trypsine (25).

Kumar *et al.* (2000) studied the analgesic effect of *calotropis procera* latex against acetic acid induced writhing drug. Administration of dry latex at a dose of 830 mg/kg produces marginal analgesia in a tail- flick rodent model. This dose of latex did not show any toxic effects in mice and LD_{50} was found to be 3000 mg/kg.

Vasconcelos *et al.* (2005) administered fraction of *calotropis procera* latex prote in to male mice and observed a dose-dependent antinociceptive effect compare with the respective controls in all assays. Different doses of latex protein reduced the nociception produced by formaline and the effect was not reversed by pretreatment with naloxone. They observed that protein fraction of latex possesses good antinociceptive activity.

Kumar *et al.* (2005) observed that daily of oral administration of latex in diabetic rats at 100 and 400 mg/kg caused a dose dependent decrease in blood glucose and an increase in hepatic glycogen. It also restores the body weight and daily water consumption capacity of the treated animals. Dry latex also increases hepatic levels of endogenous antioxidants such as superoxide dismutase (SOD), calatase, glutathione and reduces the levels of thiobarbeturic acid reactive substance (TBARS) in alloxan- induced diabetic rats.

Al-Yahya *et al.* (1985) studied the latex of *Calotropis procera* for its inflammatory activity in rats using pedal oedema and air pouch models of inflammation. Subcutaneous injection of aqueous solution of dry latex into the plantar surface of paw induces inflammation. Maximum inflammation obtained one hour after the injection and maintained for next one hour. The inflammatory activity (response) accompanied by an increase in vascular permeability that reaches its maximum within 15 minutes. The model characterized for the exudates volume and its protein concentration and wet and dry weights of granuloma. Their results indicated maximum exudates volume and weight of granuloma on day 5 after dry latex injection and the protein concentration peaked on the 3rd day. Further study of both the model for the anti inflammatory effect of various drugs, they observed that in padel oedema model, phenyl butazone was more effective than prednisolone and almost complete inhibition was observed by mepiramine and cycloheptadine. In air pouch model, prednisolone was more effective than phenylbutazone in inhibiting the inflammation.

Kumar *et al.* (2001) studied the anti-diarrhoeal activity of *Calotropis procera* dry latex. They evaluated its effect on intestinal transit, castor oil-induced intestinal fluid accumulation and electrolyte concentration in intestinal fluid. Dry latex caused a decrease in intestinal transit (27%-37%) compare with normal and castor oil treated animals. Dry latex significantly inhibited castor oil induced enter pooling, but it didn't alter the electrolyte concentration in the intestinal fluid compared with castor oil- treated rats.

Uddin *et al.* (2012) studied the antibacterial effect of various extracts of milky latex of *Calotropis procera* using modified agar well diffusion method. Streptomycin was used as standard drug at the concentration of 2mg/ml. The crude methanolic extract

exhibited good antibacterial activity with zone of inhibition ranging from 12-20 mm diameter.

3.3. Roots and root bark

Root and root bark of *Calotropis procera* is rich in terpenoids, steroids, heterocyclics and napthalene derivatives. Terpenoids were mainly Calotropaleanyl ester (26), proceroleanol A and B (27, 28), Calotropsesquiterpenol (29), Calotropsesterpenol (30), Calotropursenyl acetate, quercetine -3- ratinoside (31). One napthalene derivative namely Calotropnapthalene (32) was isolated from the root bark. Few sterols like benzoyllineolone (33), benzoylisolineolane (34) and teraxasterol (35) have been isolated and characterized from the roots of *Calotropis procera*. One heterocyclic compound named as chlorobenzofuranone (36) has also reported from the roots. Compounds like procerursenyl acetate (37), proceranol -2 (38), n- tetradecanyl palmitoleate (39), proceraursenolide (40), pyrocatechuic acid (41) are also isolated from the root of *Calotropis procera* (Figure 5). The root and root bark of plant are reported to have antidiarrheal and anticholeral activity (Ansari *et al.*, 2001; Akhtar *et al.*, 1998; Murti *et al.*, 1945; Gupta *et al.*, 2000; Alam *et al.*, 2009; Ansari *et al.*, 2000; Mittal *et al.*, 2011; Parrota et al. 2001).

Jalalpure *et al*. (2009) studied anticonvulsant activity of root extract of *Calotropis procera* in rats induced by seizures using maximal electroshock seizures (MES), pentylenetetrazol (PTZ), lithiumpilocarpine and kindling seizures. Chloroform extract of *Calotropis procera* roots showed the most significant ($P<0.01$) anticonvulsant effect by decreasing the duration of hind limb extension in the MES test. In the PTZ test, chloroform extract exhibited highly significant effect ($P<0.001$) and aqueous extract exhibited most significant ($P<0.01$) effect. By the study, they observed that the chloroform extracts and aqueous extract of roots are useful in the absence and tonic clonic (grand mal), (petitmal) types of seizures.

Mathura *et al.* (2009) studied the anti-tumor activity of various root extracts of *calotropis procera*. Treatment of step 2 cancer cells with these extracts at different dosage of 1,5,10 and 25 mg/ml revealed that all the extracts, except aqueous, possesses good cytotoxic effects. Among them, ethyl acetate extract showed strongest cytotoxic effect (96.3%) followed by methanolic (72.7%) and hexane extract (60.5%).

Danmalam *et al.* (2007) studied the anticonvulsant of 70% ethanolic extract of root bark of *Calotropis procera* using maximum electroshock induced seizeures in chicks. The extracts proved to be effecting in inhibiting electroshock induced seizures in chicks. The observed inhibition effect in hind limb tonic extension chicks was comparable to the effect of phenitoine (100% protection) in this model .Thus, they suggested the usefulness of ethanolic extracts of *Calotropis procera* root bark in management of grandma epilepsy.

3.4. Leaves

The leaves of *Calotropis procera* have been reported to possess cardiac glycosides, terpenoides and sterols. Two major cardiac glycosides isolated from the leaves are calotropin and calotropagenin, where as terpenoids were mainly alpha-amyrin (42), beta-amyrin and amyrin acetate (43). Beta sitosterol (44) was the only steroid present in the leaves of *Calotropis procera.* Ursolic acid (45), ratinoside (46) and 3-thiozoline (47) was also isolated from the leaves of *Calotropis procera* (Figure 6). The leaves of plant exhibit antirheumatism and antiasthmatic activity (Palejkar, *et al.*, 2012; Jan, *et al.*, 2008). Phytopharmacological details of *Calotropis procera* are summarized in Table 2.

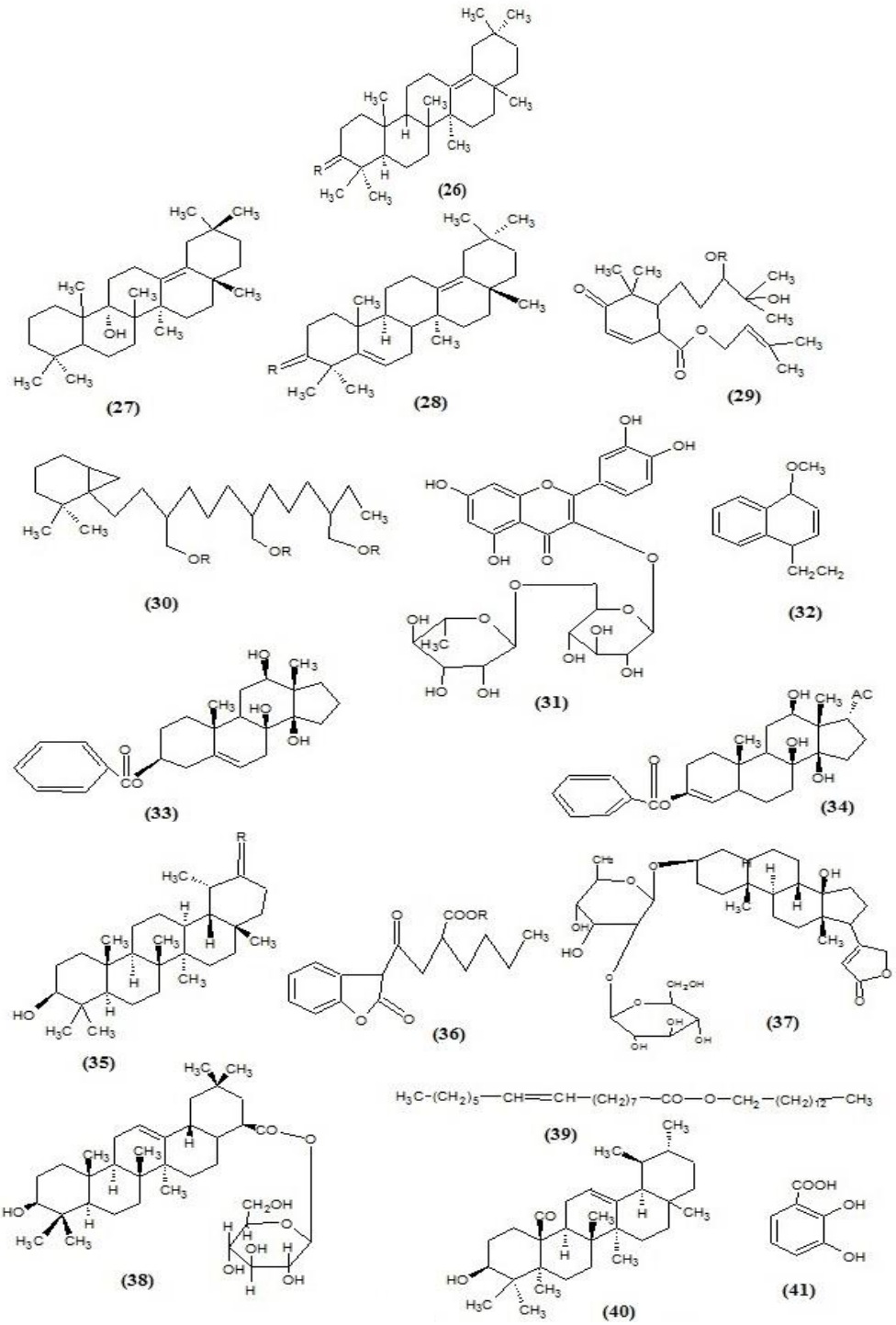

Figure 5. Terpenoids, steroids, heterocyclics and napthalene derivatives in root and root bark of *Calotropis procera*: Calotropaleanyl ester (26), proceroleanol A and B (27, 28), Calotropsesquiterpenol (29), Calotropsesterpenol (30), Calotropursenyl acetate, quercetine -3- ratinoside (31), Calotropnapthalene (32), benzoyllineolone (33), benzoylisolineolane (34), teraxasterol (35), chlorobenzofuranone (36), procerursenyl acetate (37), proceranol -2 (38), n- tetradecanyl palmitoleate (39), proceraursenolide (40), Pyrocatechuic acid (41).

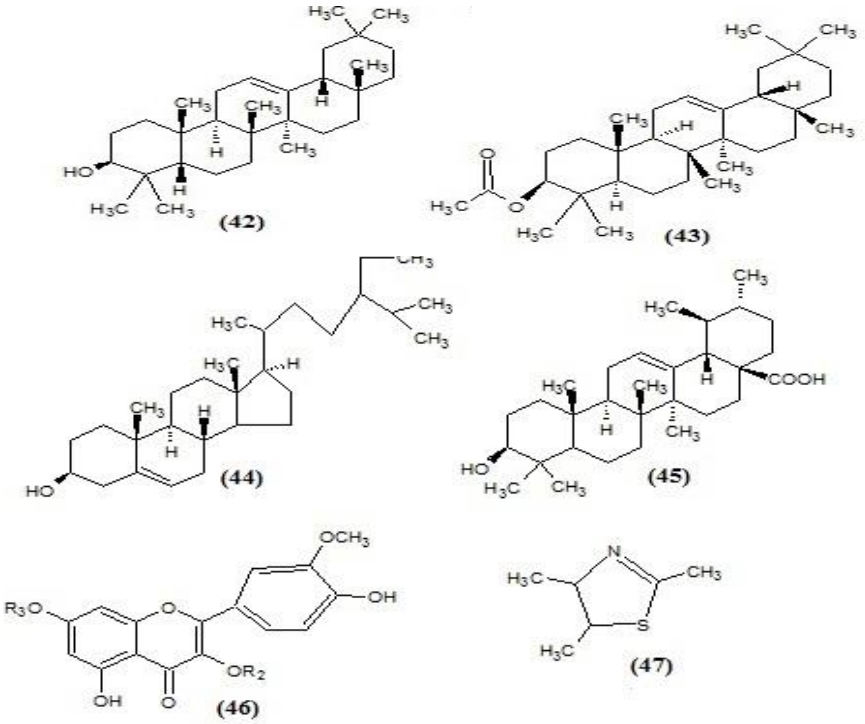

Figure 6. Cardiac glycosides, terpenoides and sterols of *Calotropis procera* leaves: alpha-amyrin (42), beta-amyrin, amyrin acetate (43), beta sitosterol (44), ursolic acid (45), ratinoside (46) and 3-thiozoline (47).

Yashmin *et al.* (2008) evaluated antioxidant potential of methanolic and aqueous extract of leaves of *Calotropis procera* using scavenging activity of the stable DPPH free radical. IC_{50} of the methanolic extract was 110.25 mg/ml indicating strong antioxidant effect of aqueous extract.

Table 2. Phyto-pharmacological detail of various parts of *Calotropis procera*

Parts	Chemistry	Pharmacolical Activity	Reference
Flower	**Cardiac glycoside**	Heptoprotective,	(Setty *et al.*, 2007)
	Calotropagenin	Anti- inflammatory	(Markouk *et al.*, 2000; Mascolo *et al.*, 1989)
	Calotropin	Antimicrobial,	
	Uscharin	Larvicidal	(Markouk *et al.*, 2000; Mascolo *et al.*, 1989)
	Calotoxins	Antimalerial	
	Calactin	Antiasthamatic	(Jain *et al.*, 2008)
	Voruscharin	Antimoebic activity	(Kumar *et al.*, 2009)
	Uscharidin		(Anis *et al.*, 2000)
	Uzarigenin		
	Proceroside		
	Proceragenin		
	Syriogenin		
	Carbohydrates		
	D- Arabinose		
	Glucose		
	L- Rhamnose		
	Glucosamine		
	Sterols		
	Proesterol		
	Multiflorenol		
	Cyclosadol		
	Cycloart-23-Ene-3b-25 Diol		
	Lupeol		

	Stigmasterol Calotropain Calotropenyl acetate		
Latex	**Cardiacglycosides**		
	Calotropin	Antirabies	(Kumar, *et al.*, 1994)
	Calotoxin	Arthritis	(Negi, *et al.*, 2002)
	Calactin	Analgesic, Anti-inflammatory,antimicrobial, Antiliprotic	
	Uscharin		
	Voruscharin		
	Uzarigenin		
	Syriogenin		
	Proceroside		
	Trypsin		
	Choline		
Leaves	**Cardiac glycosides**		
	Calotropagenin	Antigout	(Reddy, *et al.*, 2008)
	Calotropin	Antileprotic	(Reddy, *et al.*, 2008)
	α-Amyrin	Antimalarial	(Bhogaonkar, *et al.*, 2007)
	β-Amyrin	Antirhumatism	(Reddy, *et al.*, 2008)
	Amyrin Acetate	Analgesic	(Sha, *et al.*, 2006)
	β-Sitosterol		
	Urosolic Acid		
	Ratinoside		
	3-thiozolin		
Root and root bark	**Sterols**	Anticanceractivity	(Dhar, *et al.*, 1968)
	Benzoyllineolone	Antimalarial	(Joshua, *et al.*, 2006)
	Benzoylisolineolane	Antirheumatism, Antiasthmatic, Antileprotic	(Sen, *et al.*, 2007)
	Proceranol-2		
	Teraxasterol		
	Triterpenoids		
	Calotropsesquiterpenol		
	Calotropsesterpenol		
	Calotropleanyl Ester		
	Proceraleanol A		
	Proceraleanol B		
	Others		
	Calotropnaphthalene		
	Calotropbenzofuranone		
	Procerursenyl Acetate		
	N- Tetradecanyl Palmitoleate		
	Proceraursenolide		
	Pyrocatechuric Acid		
	Queretin–3-retinoside		

From the above vast literature search it was observed that *Calotropis procera* itself contains enormous potential to cure various chronic ailment and is being recommended by various popular systems of medicines. Keeping this aim in mind, *Calotropis procera* latex was taken and preliminary phytochemical screening and antimicrobial activity assay was performed with various extracts of *Calotropis procera* latex. Significant effect was found in petroleum ether extract and the study further elaborated for investigation of antimicrobial principal (if any), which is under progress.

4. Conclusion

Treatment of a number of chronic diseases is still a big challenge before modern medicinal system and World Health Organization has recognised that there are strict requirements of alternative medicines in treatment and cure of such complex diseases. *Calotropis procera* and other species of this plant are well known for a number of phyto-pharmaceutical agents which are been used for their excellent therapeutic properties by Ayurvedic and other traditional practitioners. The present detailed review article thus provides a viewpoint on

phytopharmacological potential of *Calotropis procera* which could be beneficial for future research on development of better and economically superior therapeutic agents.

5. Acknowledgment

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