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A review of toxicity, therapeutic and biological activities of Calotropis

Aicha Blama Merzaia[1], Huma Riaz[2], Rafia Rehman[2], Shafaq Nisar[2]* and Muhammad Waqar Azeem[2]

[1]Agro-food Technologies Division, National Institute of Agronomic Research of Algeria, 2, avenue des Frères Ouadek. BP 200 Hassen BADI. El Harrach CP 16200 - Alger, Algeria and [2]Department of Chemistry, University of Agriculture, Faisalabad, Pakistan

Abstract

Calotropis procera (arka) is an important drug of Ayurveda. The world health organization has estimated that 80 % of world population in developing countries depends on herbal medicine for their basic health care needs. Researchers are exploring the therapeutic potential of this plant as it is likely to have more therapeutic properties than are currently known. Calotropis is a plant with much potential. It is useful in many diseases. It is known by various names like madder in Hindi alarka in Sanskrit and swallows wort in English. It is found in most part of world with warm climate in sandy, alkaline and dry soils. Calotropis is harvested because of its medicinal properties. Calotropis show antimicrobial, anti-malarial, anti-oxidant, antifungal and antiulcer activity. Hindus worship this plant. This is used for flavoring. *Calotropis gigantean* grows in dry, open wasteland and roadsides. Latex of calotropis consists of protease enzyme, ascorbic acid and also nitrogen and sulphur containing fish poison. Flowers of calotropis contain terpenes and cyclisadol. They are used to treat liver problems and skin disorder. Calotropis yields fiber known as bowstrings. The stem of calotropis is used for making carpets, thread and fishing net. The adverse effect of calotropis consumption is reported to cause lesion, eruption and blisters were taken by patients for treatment of joint pain.

Key words: Apocynaceae, Phytochemistry, Terpenes, Arka, Medicine

Full length article **Corresponding Author*, e-mail: shafaqnisar12@gmail.com, Tel: +923237628206

1. Introduction

Calotropis is a perennial plant and belong to family *Apocynaceae***.** Calotropis is a genus of flowering plant. *Calotropis procera* and *Calotropis gigantean* are two common species of calotropis. Both species used as substitute for one another and have similar effects. Calotropis as wild shrub grows in all parts of Pakistan especially in sandy areas and in plains [1]. It is found mostly in drier part of tropical and subtropical regions as well as in arid inland and semi-arid areas. It is found in most part of world with warm climate in sandy, alkaline and dry soils. It grows as weed in cultivated areas and found in waste land. It also grows well by road sides and in sand dunes [2]. Calotropis is a rigid, large, tall, highly branched and perennial shrub or small tree that grows to 5.4 meter height with milky latex. They are pollinated by insects. *Calotropis gigantean* can be propagated by seed or stem cutting. Seeds are dispersed by water and wind. *Calotropis procera* is known by different names depending on the location. In Pakistan, it called Ak. In English language it is called as bowstring, milkweed, rubber bush, apple of Sodom and swallows worth. In India, the common names used for calotropis are madder, sufed aak and akavan. Telugu name of calotropis is Mandran and In Tamil it is known as Erukku. Other common names of calotropis are Aakand (Bengali), Ak (Punjabi), Ushar (Arab name), Kharak (Pharsi), faftan (Senegal), calotropo (Italy), and Ekka (Canada) [2]. The ethanol, water, acetone and other organic solvents extract of this plant have anti-bacterial, larvicidal, insecticidal [3] and anti-parasitic activities. *Calotropis procera* used to make "Hay" has been considered a good animal food because it contains high level of protein contents and highly digestible. This plant also used as a purgative and emetic. It also exhibit carminative and spasmogenic properties. Essential oils can be extracted from the various aromatic plants and can be used for various purpose in number of industries due to their unique antimicrobial [4] or antioxidant activities etc. [5-7]

The essential oil from the leaves and stem of calotropis procera were analyzed by GC/MS analysis. Ten components present in stem and nine present in leaf of calotropis. tyranton , 1- pentadecene and 1-heptadecene were present in leaf oil [8]. The latex is used as abortifacient, spasmogenic and carminative properties,

mullusccide, diaphoretic and for the treatment of leprosy, bronchial asthma, antidysentric, antisyphilitic, antirheumatic, antifungal, and skin infection. Different part of plants has different number of biological activities such as antimicrobial, larvicidal, nematocidal, proteolytic, anti-inflammatory and anticancer activities.

2. History/origin

Calotrope is native to tropical and subtropical Asia and Africa. The species naturalized range includes California, Central and South America (Brazil), the Seychelles, Mexico, Thailand, Australia and many Pacific Islands, including Hawaii. *Calotropis procera* is native to Nepal, Pakistan, Iran, Iraq, United Arab Emirates, Yemen, Kuwait, Oman, Saudi Arabia, Niger, Nigeria, Israel, India, Algeria, Afghanistan and Zimbabwe. Calotropis is salt tolerant, drought-resistant to high degree and disperse seed through animals and wind. Its becomes established as weed along lagoon edges, roadsides and overgrazed native pastures. It often dominant in area of dumped cultivation, sandy soils in area of low rainfall assumed to be indicator of over cultivation [1]. *Calotropis gigantea* is native to South East Asia and Asia and also in pacific islands, Australia, Central and northern South America and Africa as an decorative near villages and temples and as a weed. In Africa it is recorded from Sudan, Kenya, Tanzania, and Gabon as well as from Mauritius. Their distributions are completely known and occur in other countries.

Calotropis procera is original from India and Persia and is known popularly as jealously cotton, milk, and flower silk. Scientific name of family asclepiadaecae is taken from Asklepios, The Greek God of medicine. Its leaves, stem, fruits and branches covered by serous with strong white latex which floe when tissue is broken. Brazil welcomed this plant development. Sometimes it is classified as invasive plant as they are able to establish themselves in most unlikely places under unfavorable conditions. This plant belongs to a large range of plants that can be used in folk medicine. The leaves of this plant used in worship. Calotropis used very early period in folk beliefs as well as drug of choice for different ailment. Its different formulas found in Vedic book of India, “Sushruta Samhita”. In the period of ved Hindus used it at time of worship of sun in old days. Therefore this plant was awarded name Arka prana which means shining leaf or leaf. Different parts of plant have been used in Indian traditional system of medicine for treatment of tumors, ulcer, abdomen and liver [9]. The plant, however, is not native only to Palestine. It is known to occur tropical belt and is also common in the West Indies (e.g. Jamaica), where the locals be familiar with it as "pillow cotton". When the ripe "apples" fracture the fibrous contents are expelled along with the seeds.

3. Location

It grows on a variety of lands but prefers sandy soil and in different climates but usually with a periodic dry period. Calotropis grows on variety of soil types and survive on salines and alkaline soil [10]**.** *Calotropis procera* is common in semi dry conditions on deep sandy soils, rubbish heaps, fallow land and waste places, from sea level up to 1300m altitude. It is indicator of exhausted soil. It grow in dry habitat with annual rain fall of 300-400mm. It is salt tolerant [11]. During seed inhibition of Calotropis preocera, the percentage and rate of germination can be influenced by temperature. Since 1860, it has been identify that three temperatures like base temperature, optimum temperature and maximum temperature show the temperature range over which the seeds can germinate. The lowest temperature at which crop growth can occur is minimum cardinal temperature. Calotropis can tolerate low rainfall and dry season only upto 10 months. Growth is slow during dry season and rapid during wet season. Age at first flowering is 2 years. Each flower opens for 12 days. Growth can be up to 1m during 1st year. It is propagated by root, seed, root cutting and stem cutting. Each year about 100 to 1000 seeds are produced by per plant.

4. Morphology

The botanical name of calotropis is *Calotropis gigantean***.** It belongs to family *Apocynaceae***.** The subfamily of calotropis is *Asclepiadoideae.* The genus is Calotropis. The species of calotropis is *C. gigantean***.** It belongs to kingdom *Plantae***.** The order of calotropis is Gentian ales. Calotropis occur as a single soft wooded shrub and a tree reaching to 6m. All parts of calotropis give off white milky latex when cut into pieces. Botanical distribution of plant includes following parts. The bark of calotropis is corky, thick and yellow brown colour; twings are flashy and green and may have a white fur like hairs. The leaves of calotropis are simple, ovate to obovate with 6 pair of nerves prominent on surface, acute apex, a pale green colour and a quite large which is about 30cm. Flowers consist of 5 dirty white sepals, 5 petals which are white at base and purple at tips and 5 stamens which surround a white 5 lobed stigma. Fruits of calotropis consist of spongy, green fruits. The main flowering period would be from March to October. *Calotropis gigantea* grows in dry, open wasteland, uncultivated land, roadsides, and railway up to 1000m altitude. *Calotropis procera* and *Calotropis gigantea* are two most common species in the genus, *Calotropis procera* grows to height of 3 to 6 ft while *Calotropis gigantea* grows to 8 to 10 ft.

5. **Chemistry**

Calotropis is an aromatic plant with medicinal properties. The latex of calotropis contain cariac poisons, calcium oxalate and resinols as esters of steam volatile fatty acid [12]. Essential oil present only in leaf and stem of calotropis. GC-MS analysis is used to analyze essential oils [13-15]. *Calotropis procera* is a source of insecticidal, anti-bacterial, larvicidal and cytotoxic chemicals. Flavonoids, organic carbonates, alkaloids, cardenolides and sterols are

present in calotropis. The latex of calotropis contains fatty acids terpenels, sterols and hydrocarbons. Lead, zinc, cadmium, nickel, calotoxin, iron, copper were identified in the latex and leaves of calotropis. Calcium present highest in leaves and magnes present highest in latex of calotropis [16-17].

5.1. Chemical composition

The principle constituent of stem and leaves is latex which consists of protease enzyme, calotropain FI, calotropain F11, calotropsin D1 and D11, ascorbic acid, calotoxin, calactin and also nitrogen and sulphur containing fish poison and gigatin. Stem and root barks contain alpha and beta calotropeols, amyrins and other glycosides. Leaves contain glycolipids, waxes and fatty acids. Various cardiac glycosides including calotropin also identified in roots. Sitosterol has been isolated from the plant. Steroids not present but glycosides and tannins present. Lead and chromium are usually present very trace amounts. Calcium has highest amount in leaves and bark. Flowers consist of cyclisadol and terpenes. Amyrin, amyrin acetate, calotropin, calotropagenin are present in the leaves of calotropis. The latex holds calotropin, calotoxin, uscharin, trypsin, uzarigenin and proceroside [18]. The flowers of *calotropis* contain the retinoside, calactin, calotoxin, calotropin, glucose and L-rhamnose. Other chemical constituents of flower of calotropis are lupeol, gigantin, giganteol and lactucery acetate. Root barks of calotropis contain calotropterpenyl, mundarol isovalerate and rutinoside. Chemical composition of the volatile oil of traditionally useful *Calotropis procera* is as follows. Leaf oil is conquered by tyranton (54.4%), 1- pentadecene (9.5%) and 1-heptadecene (8.2%). Most plentiful compounds in stem oil are Z-13-docosenamide (31.8%), isobutyl nonane (13.7%) [16].

5.2. Phytochemistry

Phyto is Greek word for plants. There are many families of phytochemicals which help human body in many ways. Phytochemical are non nutritive plant chemicals that have disease preventive and protective properties. Plants produce these chemicals to protect themselves but recent research show that phytochemicals can protect human against various diseases [19]. The plants contain proceragenin and bark contains the benzoylinesolone. The stalk and leaves contain calotropin while flower contain calotropenyl acetate and latex contain terpenol ester [2]. Chemical investigation of this plant shows presence of calotropoleanyl ester, cardiac glycosides, cylotoxin and calactin. Anthocyanins also present in calotropis. In leaves mudarine is active constitute as well as bitter yellow acid, resins and 3 toxic glycosides calotoxin, calotropin and uscharin. The latex contains powerfull enzyme, a very toxic glycoside calactin and a non toxic enzyme calotropin. This enzyme is more proteolytic than that of papain. Whole plant calotropis contain gigantin, giganteol and wax [20]. The result of phytochemical screening of leaf extract of calotropis discovered presence of protein, steroids, and flavonoids. The presence of these compounds shows that it may have some medicinal potential. The parts of plants used in medicines are leaves, root bark, roots and the flowers. The powered leaves use for treatment of digestion and for fast healing of wounds as a purgative. They are used to treat liver problems and skin disorder. Tribes of central India were used the leaves of this plant as a curative agent for jaundice. The leaves are used to reduce swelling and treat joint pain. *Calotropis* also used as homeopathic medicine. It is also used by traditional medicine for treatment of ringworm.

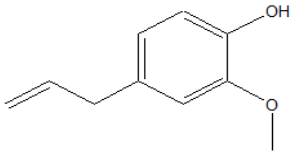

Fig.1. Structure of Eugenol

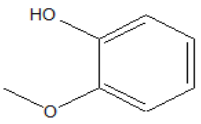

Fig.2. Structure of Guaiacol

6. Post harvesting technique and processing

The leaves, flowers and roots of *calotropis* gigantean harvested all the year. In Thailand, it reaches the height of 166cm in 1 year and 56 Kg of latex per hectare. The leaves of calotropis are cleaned with cloth to remove hair before use fresh or dried in sun [21]. The seed are not initially responsive to light but affected by light quality and responsible after long exposure to radiation. Mature fruits collected just before the dehiscence and hairs removed from the seeds. The seed should be dried in sun for 3 to 4 days before storage. Seeds lose their viability after one year. Vegetative propagation through root and stem cutting is very useful in large scale multiplication of preferred genotype [22]. *Calotropis procera* is well suited for energy forming in arid regions where frost is not limited factor. In area where calotropis not wanted chemical control is difficult and expensive. Roots, barks and leaves of plants are harvested throughout the year according to availability and need. Plants are completely uprooted after which the roots are separated from plant and both parts are processed separately in some cases. To obtain seed flows, green and unopened fruits are pick and opened. When seeds rubbed against palm of hand they fall off from flows. Report from India where it is planted as source of biofuel suggest that it has potential crop yield 90t/ha two times in year. Anual yield of 600kg are reported. The aerial parts, roots and barks are cleaned after which they can directly use or dried in shade, powdered and then stored [23].

7. **Value addition**

Calotropis yields fiber known as bowstrings. The

stems of calotropis are used for making ropes, carpets, thread and fishing net. Fibers from the inner side of bark are used in manufacturing of cloth for nobility. The stem of calotropis has been used to extract natural rubber and oil. Calotropis act as a source of pulp for paper making. The stem of calotropis used as charcoal and firewood. The pith of stem make tinders. The flos of calotropis mixed with longer fiber e.g. cotton, for spinning. Root form good tooth cleanser [24].

8. Uses

For improving soil fertility and soil water holding capacity, calotropis are used. The powder root of calotropis is useful in dyspepsia, asthma and bronchitis. Full dried plant of calotropis is good depurative and tonic. Calotropis used as antitode. The flowers of calotropis last long and used in various floral arrangements in Thailand. They were also popular with Hawaiian Queen who believes them as symbol of royality. They also used in funerals to decorate urn and in interior of house holding funerals in Cambodia. In Ayurvedic medicine, it is used for many purposes; the powdered leaves help wounds heal are good for indigestion, liver disorders, constipation, intestinal worms and skin disorder. The fruit of this plant is follicle and when dry seed spread by wind. The latex is used as antiseptic [25]

8.1 General Uses

8.1.1. Ritualistic uses

Hindus worship the plant calotropis. Pooja to Lord Hanuman is not complete without offering of garland made with arka leaves. The leaves of calotropis used while having bath on festival of sun God. Arka is mentioned as healing plant. Ratha Saptami is practical by first taking a ritualistic bath. The important feature of ritualistic bath involves the use of the leaves of plant *Calotropis gigantea.* In the Sanskrit language this plant is called Arka. The *calotropis* was popular in Hawaiian Queen who belief them as symbol of royalty. In India in every village, young married girls move in groups in afternoon for complete forth night start from mauna and collect variety of green leaves of calotropis which offered in puja in next day [2].

8.1.2. Culinary uses

In Java, the central part of the flower of calotropis used to make sweetmeat. Inner part of the flower used for flavoring. The flower of plant used as drink with milk for curing colds, cough and asthma. Young leaves and shoots are cooked as a vegetable. Fruits are infused to make tea. Calotropis extract used for traditional cheese making in Nigeria and Benin.

8.1.3. Traditional medical uses

Ayurvedis medicine is traditional practice of healing. Various plants are used for this purpose [26]. In India, this plant is used to treat leprosy. Madar root use for diarrhea. Calotropis is used as medicinal plant with unique properties. Traditinally calotropis use alone or with other medicines to treat common disease like fever, indigestion, cough, cold, asthma, vomiting, and nausea. The whole dries plant is a good tonic and depuravate. The flowers are bitter and tonic [2]. Root of this plant are crushed well and applied well by rubbing firmly over the Bitten area. Latex of this plant is used to cure dental problems, rat bite, swellings, gonococcal arthritis and other rheumatic complaints. Flowers are used to cure bronchial asthma [27].

8.1.4. Insecticidal properties

The methanol extract of root bark of calotropis and chloroform and petroleum ether soluble fractions show insecticidal activity and toxicity to adults. Larvae were more susceptible than adult. Methanol extract are more toxic than other fractions in adult and larval stages. The repellent effect of extract of root was investigated. It shows moderate repellent to *T.castanem* [28]. *Calotropis procera* latex show larvicidal activity against larvae of *Anopheles stefensi* and *Musca domestica* at very low application of latex. Their sub lethal doses also show effect on survival of larvae and pupae, inhibit growth and reduction in weight of larva. Latex components toxins, acetogenins, flavonoids, triterpenes and proteins act at the cellular level and made organogenesis default, which guide to formation of abnormal pupae with weak quality weight loss and structural deformity in various organs. All these effects were irreversible and growth and development inhibitory in nature. Furthermore, laticifer fluid from *C. procera* contains endogenous soluble proteins and different proteases, which linked with insecticidal activity [29].

8.2. Pharmacological uses

The plant has involved much awareness due to following activities.

8.2.1. Anti-cancerous activity

In both developed and developing countries, cancer is the main case of the death which is increases rapidly. There are number of side effects associated with the drugs involved in hemotherapy that is why the use of traditional herbal medicines for the treatment of cancer is becoming popular in developed countries. The extract of calotropis root has been observed to have cytotoxic effect on COLO 320 tumor cells. The cardiotonic steroid UNBS1450 was observed as potent sodium pump inhibitor, showing cell death inducing activity [30].

8.2.2. Hepatoprotective activity

An aqueous ethanolic extract (70 %) of calotropis flowers was made and hepatoprotective effect against paracetamol-induced hepatitis in rats was observed. Changes in biochemical markers levels of hepatic damage, such as SGOT, SGPT, cholesterol, tissue GSH, HDL, ALP, and bilirubin were examined in treated as well as untreated groups. Paracetamol (2000 mg/kg) was observed to enhance cholesterol, SGPT, bilirubin and SGOT levels and reduce HDL serum levels and GSH tissue level while treatment with an aqueous ethanolic extract of calotropis flowers re-establish the changed biochemical markers levels to almost

normal levels in a doze needy manner [31].

8.2.3. Analgesic activity

The calotropis plant latex was traditionally used for toothache (root juice decreases the labour pain in pregnant women). Antinociceptive effect of protein extracted from the calotropis plant latex was observed by some researchers using three different nociception experimental models in mice. Results showed that latex protein reduces the nociception produced by formalin in 1st phase and 2nd phase, and this effect was not changed by the pretreatment with naloxone [32].

8.2.4. Antifertility activity

The effect of ethanolic extract of calotropis roots was studied in albino rats by some researchers to discover its hormonal and anti-fertility activities. Strong utereotropic and anti-implantation was observed at 250mg/kg dose. No antiestrogenic activity was detected.

8.2.5. Antimalarial activity

Calotropis is a medicinal plant and show antimalarial activity. The ethanolic extract of different parts of plant show IC_{50} value range from 0.11 to 0.47 against *P.falciparum* senstive flowers and buds extract being most active. Although 220-440 time less than CQ, these extracts deserve study aim at identity of active constituents. The result supports the ethno botanical use of calotropis.

8.2.6. Antimicrobial activity

The chloroform extract of calotropis seed show better antimicrobial activity [33]. This plant is used for leprosy, tuberculosis, and lupus bacterial infections. Some laboratory study revealed that bacterial strain have developed resistant against drugs that is why there is a need for the alternative anti biotic and traditional medicinal herbs are thought to be best replacement. Ethyl acetate extracts of calotropis was found to have inhibition action against gram positive as well as gram negative bacteria.

8.2.7. Anti-asthmatic activity

Stem bark of calotropis plant can be used for the treatment of pneumonia. However, flowers and flowers decoction of calotropis plant has proved to have asthmatic activity. This activity was observed in paw oedema. Flowers, roots and barks of calotropis were used to check its anti-asthmatic and results revealed that calotropis has good anti-asthmatic activity [34].

8.2.8. Anti-oxidant activity

Calotropis plant is also considered to a rich source of anti-oxidant agents which are responsible for scavenging activity. Antixidant properties of plant are due to the presence of phenolic or flavonoid components [7]. Ethanolic flower extract of calotropis was studied for antioxidant activity by hydrogen peroxide radical assay and hydroxyl radical activity at various concentrations. This plant show anti-oxidant activity due to presence of terpenoids and flavonoids.

8.2.9. Anti-inflammatory and antipyretic activity

Chloroform, distilled water, n-butanol and ethanol extracts of calotropis leaves were observed for anti-inflammatory and antipyretic activities. These extracts were observed to have good anti-inflammatory and antipyretic activities [35].

8.2.10. Antifungal activity

Ethanolic extract of calotropis latex tested in vitro against fungi strain. Disc diffusion method was used to assess inhibitory effect of the extract. Results revealed that latex extracts have fungicidal activity (due to the presence of biologically active constituents in ethanolic extract of calotropis latex) [36].

8.2.11. Anti-diarrheal activity

The hydroalcohlic extract of aerial part of calotropis plant was used to study anti-diarrheal effect against castor oil induced diarrhea model in rats. The noteworthy anti-diarrheal effect of hydroalcohlic extract of aerial part of calotropis plant was observed [37].

8.2.12. Wound healing activity

The wound healing activity of calotropis root bark was observed in rats by excision and dead space and incision wound healing models. The wound closure percentage; epithilization time and scar area on whole epithelization were examined. Topical application of calotropis in wound model increased the wound concentration percentage. Scar area and time were decreased and wound breaking strength was increased.

8.2.13. Antiulcer activity

The antiulcer activity of calotropis was reported. The result of this study reveal that it significantly inhibited aspirin, reserpine and serotonin induced gastric ulceration in rats and protect gastric mucosa from aspirin ulceration in pyloric ligated rats [38].

9. Adverse effect

The adverse effect of calotropis consumption is reported to cause lesion, eruption and blisters when taken by patients for treatment of joint pain. The preparations of calotropis need to use under careful surveillance of qualified medical practitioner.

10. Conclusion

Calotropis procera (arka) is an important drug of Ayurveda. The world health organization has estimated that 80 % of world population in developing countries depends on herbal medicine for their basic health care needs. Researchers are exploring the therapeutic potential of this plant as it is likely to have more therapeutic properties than are currently known. Calotropis is a plant with much potential. It is useful in many diseases. It is known by various names like madder in Hindi alarka in Sanskrit and swallows wort in English. It is found in most part of world with warm climate in sandy, alkaline and dry soils. Calotropis is harvested because of its medicinal properties. Calotropis show antimicrobial, anti-malarial, anti-oxidant, antifungal and antiulcer activity. Hindus worship this plant.

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