

Investigating the medicinal potential and pharmacological applications of *Calotropis gigantea* L.

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Abstract

Different medicinal plants have been used for the treatment of various diseases since the pre-historic period. *Calotropis gigantea* is such a traditional plant that carries various therapeutical use in the field of medicine, it is a wild-growing plant commonly known as giant milkweed growing all over the world and belongs to the family Asclepiadaceae. Methanolic and ethanolic extract of this plant consists of phytochemical constituents that are responsible for the therapeutical treatment of many diseases as it carries anti-venom, anti-cancer, anti-inflammatory, anti-tussive and procoagulant actions, etc., and GC-MS, HPLC, and FTIR are used for the identification and characterization of the active ingredients of this extract. The present study is a review of the extraction of active ingredients from the plant, characterization of these constituents by using different techniques, pharmaceutical application in medicine, and biological properties of *Calotropis gigantea*.

Keywords: *Calotropis gigantea*, Methanol and Ethanol extract, GC-MS, HPLC, Pharmaceutical application.

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Introduction

Different plants, animals, and a lot of natural objects have profound effect on the culture and development of humans since prehistoric times in many parts of the world. At the early age of civilization, some human beings worshiped the different plants, and these plants were preserved as an inherited resource, they also used these plants for food, fertilizer, fuel, feedstuff, and other different ways [1]. *Calotropis gigantea* is one of those plants [2]. It is one of those plants that is found in India, China, and Malaysia and spread in other different countries like Afghanistan, Algeria, Egypt, Eritrea, Ethiopia, Gambia, Ghana, Guinea-Bissau, India, and Iran. Iraq, Israel, Kenya, Kuwait, Lebanon,

Libyan, Arab Jamahiriya, Mali, Mauritania, Morocco, Mozambique, Myanmar, Nepal, Niger, Nigeria, Oman, Pakistan, Saudi Arabia, Senegal, Sierra Leone, Somalia, Sudan, Syrian Arab Republic, Tanzania, Thailand, Uganda, United Arab Emirates, Vietnam, Yemen [6].

Calotropis gigantea is a weed that is known as giant milkweed. *C. gigantea* is a plant from the kingdom Plantae, order Gentianales, belong to the family Asclepiadaceae, subfamily Asclepiadoideae, genus *Calotropis*, and species is *gigantea* [6]. There are following vernacular names of *Calotropis gigantea* in different countries of the world [87,88]. That was shown in (Table 1). *C. gigantea* can grow up

to 8 to 10ft [83]. This plant has oval, light green leaves, a stem with a milky latex, and clusters of waxy flowers that are either white or

lavender in color. *C. gigantea* is frequently available in India and used for medicinal purposes for different diseases [3].



Figure 1: Areal view of *Calotropis gigantea*

It is present in Madagascar, Asia (India, Pakistan, Afghanistan), and tropical and subtropical Africa (Somalia, Egypt, Libya, south Algeria, Morocco, Mauritania, and Senegal). Southern Asia, Indochina, Iran,

Arabia, and Jordan India [98,99]. The plant has naturally grown in South and Central America, the Caribbean, and Australia islands, including those in Indonesia and the Pacific [99] (Figure 2).



Figure 2: The geological distribution of *C. gigantea* in the world: Native Exotic

C. gigantea plant was used for the cure of different diseases and scientifically reported for medicinal application [86], which was shown in (Figure 3).

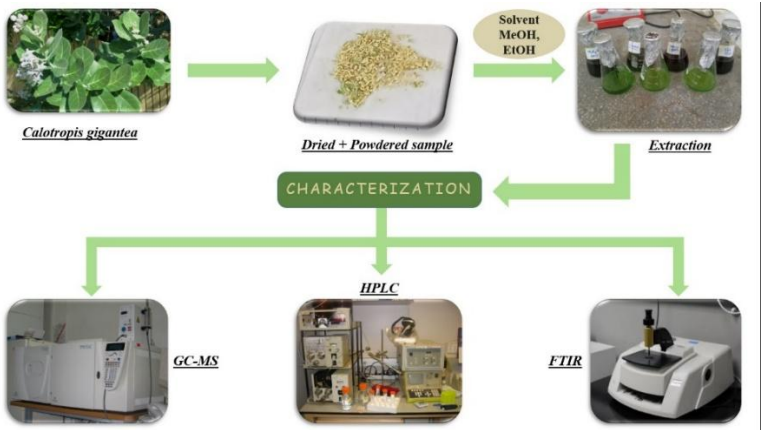


Figure 3: Extraction of leaves of *C. gigantea*

During the early age of medicine, *C. gigantea* was used in Ayurveda for treatment purposes. *C. gigantea* is also known as “Sweta Arka”. It is a perpetual probable herb commonly found in the wasteland in different areas of India [4.]

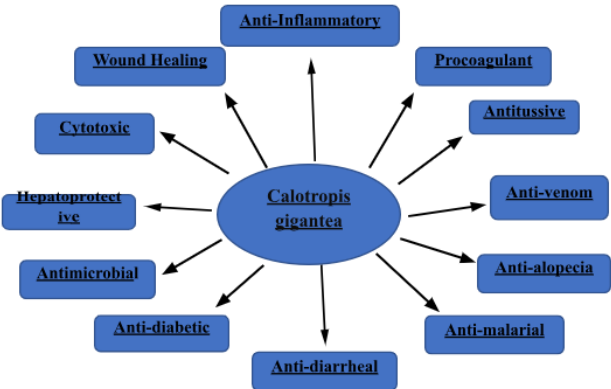


Figure 1: Medicinal application of *C. gigantea*

Calotropis has a high degree of drouth resistance and salt tolerance, it can grow wild up to 900 meters throughout the country [5]. The milky latex is present in the stem of *C. gigantea* which acts as an antinode for venom (snake poison) when it is in dried form. Its dried leaves are used for cough medicine and are anti-inflammatory for the treatment of paralysis [7-10]. Calotropis is considered an aromatic plant having medicinal characteristics. Cardiac poison is present in the latex of the Calotropis [79]. Essential oil is also present in the leaves and stem of the Calotropis plant that is analyzed by GC-MS [80,81,83]. Different parts of the Calotropis plant like leaves, stem flower, and root barks are mostly used in the field of medicine for the treatment of disease that is commonly found in human beings such as fever, Arthritis, digestion problem, cough, looseness, and nausea [11].

Table 1. The vernacular name of *C. gigantea* in the world

Names of countries	Common name of <i>Calotropis gigantea</i> .
India	In Sanskrit it is called as Arka, Vasuki, Alarka, pratapass. In Hindi called Maddar, Aak. In Kannada, it is called Ekka, and in Telugu, it is called as Jilledi Puvvu.
Malaysia	In Malaysia, it is called Rembega, Kemang.
English countries	In almost all the English countries it is called as Giant milkweed, a Crown flower.
Indonesia	In Indonesia it is called as Sidaguri in Javanese, Rubik in Aceh.
Thailand	In Thailand it is called as Paan-theun and Po-theun.
Laos	In Laos it is called as Dok kap, Dok hak and Kok may.
French	In French countries, it is called Faux Arbre de some and Mercure vegetal.

The different chemical constituent is present in various part of the Calotropis plant. The latex contains cardenolide glycoside, calotropin, uscharin, calotoxin, and ushering. This latex also contains calotropin DI and DII and calotropin FI and FII and invertase activity containing enzymes are also present [12]. Leaves of the *C. gigantea* contain

many phytochemical constituents like uscharin, calcium oxalate, alpha and beta calotropeol, fatty acids, hydrocarbons, and acetates [2,14]. *C. gigantea* was methodically observed for different medicinal applications like the flowers were used for cytotoxic, analgesic, and antimicrobial activity [3,16]. Areal parts and the leaves of the plants were used for anti-candida, anti-diarrheal, antioxidant, and antibacterial activity [17-19]. Roots of Calotropis were used for anti-pyretic, cytotoxic, antimicrobial, wound healing, pregnancy interception, and CNS activity [20-26]. Latex of this plant was used for the procoagulant activity, wound healing, and antimicrobial activity [26-29]. The stem of this plant was used as a hepatoprotective agent [30].

Extraction

From root bark

For the separation of the specific compound, the extract was made, the root bark of Calotropis plant dried then powdered, and was imperiled to hot extraction by using methanol as a solvent then extract was fractionated with different solvents like ether, Chloroform, and ethyl acetate. Two compounds were purified and isolated [31].

From the stem bark

The stem bark of *C. gigantea* was taken and then dried and powdered it. 6kg of powdered form were soaked in 95% ethanol and extract had been taken by using an ultrasonicator for 1hr at room temperature. The supernatant was separated, and the remaining solvent should be removed by using a rotary evaporator at 45°C and 336g of crude ethanolic extract of *C. gigantea* was obtained. This extract was dark greenish [39].

From different parts of the plant

Root leaves and flowers of the Calotropis plant were collected and then dried under sunlight by covering them with black cloth. Then powdered was made from this dried part of the plant and collected in a brown bottle. Then the extraction was done by using solvent ethanol 70% with a ratio of 1:5 for 72 hrs. The residue after filtering the extract was re-extracted by 70% of ethanol with a ratio of 1:2 for 3 days. The re-extracted process was taken two times then all filtrate was evaporated by using a technique called rotary evaporator [40].

From the whole plant

The dried massive powdered of the plant *C. gigantea* was taken and 100g of it was imperiled to Soxhlet’s extraction separately and consecutively with methanol. Under reduced pressure and controlled temperature of 40-50°c the solvent was distilled. The semi-solid mass was obtained as a result that was vacuum dried by using a rotary evaporator to get a yield of solid residue that should be taken in an airtight container and stored in a refrigerator [41].

From the leaves

The leaves with complete growth of *C. gigantea* were collected from a resident market. These leaves were identified by the Bangladesh Council of Science and Industrial Research After washing the leaves with water, leaves were dried in air and powdered then 500g of dried powder was used to get extract them by using ethanol for 15 days. Then the extract was filtered and separated in a beaker. The beaker containing the extract was placed in the water bath at 40-50°c for the evaporation of the solvent from the extract, and the semi-solid extract was collected and stored for further analysis [42].

The leaves of the plant *C. gigantea* were washed through tap water after collection, then dried them in shade. Crusher was used to make powder from the leaves. These powders of 25g in weight were used to make an extract by using different solvents of 250ml like methanol, petroleum ether, and acetone by using a technique named Soxhlet Apparatus. Airtight bottles were used to preserve this extract in the

refrigerator at 4°C and then used for further analysis. These solvents were dissolved by the solvent Dimethyl Sulfoxide [50].

Tap water was used for washing the leaves of plant *C. gigantea*, these leaves were cut into small pieces and dried in shade for 7 days at 30 to 40°C, then powdered of 40 mesh size was made by using a grinder [53]. 100g of the dried powdered were soaked in 1L of methanol to get extract using Soxhlet apparatus for 10hr. Whatman filter paper of 125mm was used for the filtration process of the extract. Then this extract was concentrated using techniques named Rotary evaporator under reduced pressure. 1.2g of leaves residue was obtained and Different series (0.15, 0.25, 0.50%) of methanol extract were prepared for further studies [54].

From flowers

The collection of the flowers from the plant *C. gigantea* both white and pink color was done in Poosaripalayam India. Tap water was used for washing the flowers thoroughly and dried them in shade at room temperature. Then fine powdered was made from these shaded dried flowers. 10g of dry powder of the sample was used to get hot extraction for 6hr in Soxhlet Apparatus using methanol as a solvent. 10g of powdered sample were soaked in methanol at room temperature to get cold extraction of the plant *C. gigantea*. A rotary evaporator was used to concentrate the extract and this extract was put into a lyophilizer for freeze-drying and get dry powdered. Then this dry powder was suspended in methanol with a ratio of 100mg/ml (w/v). Both cold and hot extracts of the flowers were stored at 4°C for other analysis [52].

Characterization

GC-MS analysis

The leaves extract of *C. gigantea* using methanol as a solvent was characterized by using GC-MS, more than 52 compounds were eluted, and they were eluted between retention times of 5-32min. there were thirty-two bioactive compounds were isolated. The identification of that compounds was approved by using the NIST library of GC-MS with version 08-S. The main and major phytochemical present in that extract was phenols, sterols, ester, and most of the organic compound. The major compounds that were identified were tridecanedial, palmitic acid, methyl n-undecanoate erucic acid, and trulinolien. There were different ranges of these compounds was found [37].

The instrumentation of the GC-MS was based on Shimadzu 2010 with the autosampler. There were the following conditions used by GC-MS: Column diameter was 0.32 mm, length of the column was 30m, the thickness was 0.5µm, electron impact mode of 70eV was operating, Carrier gas used at the constant flow of 1.73ml/min was Helium gas with 99.99% purity, 0.5µl of injection volume was used, the temperature of the injector was 270°C and the temperature of the ion-source was 200°C. the temperature of the oven was managed from 40°C isothermally for 2 min, then increased temperature at 8°C/min to 150°C and then used an isothermal process at 280°C for 20min at the end. The spectra of MS were taken at 70eV in which there were scan intervals of 0.5s and 40 to 450Da fragments were obtained. The total running time of GC was 51.25min. A comparison between the average peak area and the total area was used to calculate the relative percentage amount of each component. The Mass spectra and Chromatogram were handled by the software called Turbo Mass Ver 5.2.0 [51].

FT IR analysis

For the Fourier transmission Infrared Spectrophotometer analysis, the extract of the plant *C. gigantea* was used as a sample after being centrifuged at 3000rpm for 10 min and then filtered by using Whatman

filter paper no.1 at a high-pressure vacuum pump. Diluted the sample by using the same solvent with a ratio of 1:10. The wavelength range of 260 to 900nm was used for scanning the extract of plants with the help of Perkin Elmer A Spectrophotometry (PES) to detect the characteristic peaks. PES was used for the FTIR analysis. It had ranges from 400 to 4000cm⁻¹, which helped in the detection of characteristic peaks and the functional group also. The peaks were recorded after the FTIR analysis, and this analysis was repeated more than two times for the confirmation of the spectrum [50].

HPLC analysis

HPLC was an analytical technique that was used for the qualification and quantification of the chemical compound. It was used to find the amount of chemical compound that was present in the mixture of the chemicals. The instrumentation of HPLC was used as L-4000 UV detector, intelligent pump L-6200, reverse-phase column (RP-C18) from Hitachi and the solvent that was used as mobile phase was 0.4% acetic acid with a ratio of 80:20, the flow rate of the HPLC was 0.5ml/min and 290nm wavelength was maintained, the injected sample was 20µl in the instrumentation of HPLC for analysis [52].

HPLC was used for the characterization of the extraction of the plant, and air-dried powdered with the size of 20mesh of the Calotropis leaves of both *C. gigantea* and *C. procera* was used as a sample. The sample was reflexed with 99% methanol at a temperature of 80-85°C for 2 to 3 hrs. in a water bath, then the sample was filtered and again refluxed with methanol more than two times. All the extracts were collected and concentrated using a Rotary evaporator. In the end, the sample was air-dried after the removal of the solvent methanol [59].

The extract of the plant was analyzed by using RP-HPLC system with instrumentation based on Shimadzu Corporation coupled with a UV-photodiode array detector. 40°C temperature was used during chromatographic separation using a C18 column size (250 x 4.6mm, 5µm). There were two types of mobile phases A and B. The mobile phase A consisted of 1:1 (v/v) of acetonitrile: methanol and the mobile phase B consist of 0.1mM of ammonium acetate in water with a flow rate of 1ml/min and injected volume was 20µl. The column effluent was analyzed by using a UV-UV detector of 280nm [60].

Phytochemical constituents

Phyto was a Greek word that relate to plant. Phytochemicals carried such groups of chemicals that were responsible for the help of human beings in many ways. These were non-nutritive chemicals of plants that had the capability of disease prevention and protective nature. These chemicals were produced by the plant for the protection of themselves, but recent studies showed that these chemicals called phytochemicals were responsible for the protection the humans from different diseases [84]. Different chemical groups were confirmed by using primarily test for the identification of phytochemical that was present in the sample of the ethanolic extract [85].

White and pink colored flowers of plant *C. gigantea* were hot and cold extracted by using methanol as a solvent. This extract was used for phytochemical analysis. There was a different kind of constituent was subjected, the soluble protein was measured [43], carbohydrate was quantified [44], free fatty acid was present [45], vanillin hydrochloride method was used for Tannin's quantification, [46] and the method was used for Flavonoid estimation [47], saponin and Alkaloid were also determined by different methods [48,49]. Calotropis plant was reported for different phytochemicals such as cyanogenic, glycosides, tannins, cardenolides, different types of flavonoids, sterol, terpenes, and nonproteinic amino acids [89-97]. There were following phytochemical constituent was reported from different parts of the plant that was shown in (Table 2).

Table 2. List of the phytochemical constituents present in different parts of the plant

Phytochemical constituents	Parts of the plant	Chemical nature	References
18,20-Epoxy and 19-Nor-cardenolides	Leaves of the plant	Cardenolide nature	[90]
Hydroxy-cardenolides	Leaves of the plant	Cardenolide nature	[91]
Hydroxy-calactinic acid and CH ₃ -ester.	Leaves of the plant	Cardenolide nature	[91]
Taraxasterol acetate	Aerial parts of the plant	Flavonoid nature	[92]
F1-Calotropin	Latex of the plant	Enzyme related to protein-hydrolyzation of the peptide bond.	[96]
Fii-Calotropin	Latex of the plant	Enzyme related to protein-hydrolyzation of the peptide bond.	[96]
3-methyl-butanoate of amyrin	Latex of the plant	Easter nature is like triterpene.	[13]
D1-Calotropin	Latex of the plant	Enzyme related to protein-hydrolyzation of the peptide bond.	[17]
Dii-Calotropin	Latex of the plant	Enzyme related to protein-hydrolyzation of the peptide bond.	[17]
Anhydrosophoradiol-acetate	Flowers of the plant	Terpenoid nature	[57]
Caolotropone	Roots of the plant	Cardiac glycoside	[54]
Calotropises juiterenol	Roots of the plant	Terpene nature	[93]
Esterpenolcalotropis	Roots of the plant	Terpene nature	[93]
Calotrop-benzofuranone	Roots of the plant	Products was Aromatic in nature	[93]
Coroglaucigenin	Roots of the plant	Cardenolide nature	[54]
Frugoside	Roots of the plant	Cardenolide nature	[54]
Gigantincine	Rootbark of the plant	Non-protein amino acid	[97]

Pharmaceutical Application

It was reported that the stigmasterol was isolated from the extract of the root bark of *C. gigantea* by using solvent methanol, the basic aim of this study is to characterize and identify the bioactive particles present in the rootbark of this plant. It has a wide range of medicinal uses [31].

Wound Healing

The extract of the root bark of *C. gigantea* was used for the healing purpose of the wounds in Albino Rats. These rats were used as wound healing models articulated with extract as an ointment, this extract was orally injected in Albino Rats by using different amounts of that extract (100-400 mg/kg dose). This experiment showed that the wound healing activity was speedup by using the root extract of *C. gigantea* [32].

Cytotoxic Activity

The most important ingredient present in the root of *C. gigantea* was reported as cardenolide glycoside which was used for cytotoxic activity against mouse cells and numerous human cells. Calotropin, and Frugoside were reported as the active ingredient for cytotoxic activity in the root extract of the Calotropis plant [33].

Hepatoprotective activity

Ethanollic extract of the stem of *C. gigantea* was used for hepatoprotective activity in Wister Male Rats in contradiction to CCl₃ tempted liver damage. This extract was helpful for the protection of the liver by decreasing lipid peroxide, Aspartate transaminase, and Alanine transaminase levels. These rats were protected from oxidative damage by the implementation of this extract [34].

Procoagulant activity

The latex of the plant *C. gigantea* was used as a procoagulant activity. The hydrolyzed protein extract of the latex was treated with human fibrinogen and clot of crude fibrin in a specific dose manner. This crude extract was strongly associated with papain and trypsin. The protein that was isolated from the latex of *C. gigantea* was strongly proteolytic and used for procoagulant activity [35].

Anti-Inflammatory activity

Ethanollic extract of the Calotropis plant was used as an anti-inflammatory agent. Wistar Albino Rats with tempted paw edema was

treated with this ethanolic extract. The used oral administration of 400mg/kg doat showed anti-inflammatory activity significantly, this activity was more than that of the 100mg/kg dose of Isobutylphenyl propionic acid was used [36].

Different chemical intermediaries were responsible for inflammation. Prostaglandins were the major cause of inflammation. Mediators and prostaglandins were reduced by using *C. gigantea*, so this plant was reported to reduce the inflammation. The albumin denaturation study method was used to check the anti-inflammatory profile of the Calotropis plant [4].

Antitussive activity

The leaves extract of *C. gigantea* showed antitussive activity because alkaloids and glycosides were present in this extract, so it was used as antitussive activity [38].

Anti-venom activity

Different pathophysiological changes that occur in a human were caused by the bite of the snake like edema, inflammation, brain hemorrhage, and blood coagulation process also changed and lead to death. There were different constituents present in the Calotropis plant like flavonoids, saponin, steroids, triterpenoids were responsible for anti-venom activity. A noxious effect like necrotizing and hemorrhage activity of venom was neutralized by using alcoholic extract of *C. gigantea* [4].

Anti-alopecia

It was reported that *C. gigantea* was used for hair growth activity as compared with other herbs. Recent studies showed the use of different herbs like Calotropis spp. Hibiscus rosa-Sinensis and their polyherbal formation for hair loss prevention and were also used for disorders like stress-induced alopecia [56].

Anti-malarial activity

Malaria was a parasitic disease that led to death. Anti-malarial activity against plasmodium falciparum was exhibited by *C. gigantea*. It showed the best anti-malarial activity result against Chloroquine sensitive Plasmodium falciparum [4].

Anti-diabetic activity

C. gigantea plant extract showed a hypoglycemic effect. *C. gigantea* was used for the prevention of weight loss during diabetes mellitus.

Cellular population like granulated and normal beta cells was increased in pancreatic islets by *C. gigantea*. The extract of the Calotropis plant was used as an effective agent in reducing elevated serum sugar levels in the animals in the experiment [4].

Biological activities

Different parts of the *C. gigantea* were used for different types of biological activities. Calotropis plant was considered a highly potent plant source for biological activity [2], which was shown in the following (Table 3).

Table 3. Biological activities of the different parts of the plant

Sr.no:	Biological Activities	Parts of the plant used	References
01	Arrow poison used in hunting	Latex of plant was used	[61, 62]
02	Biocidal activity for micro-organisms	Latex of plant was used	[63]
03	To produce Biogas	The whole plant was used	[64]
04	For brewing and curdling milk	The latex and bark were used	[65]
05	Cleansing purpose	Leaves of the plant and its sap were used	[65]
06	To produce energy	The whole plant was used	[65]
07	As fodder for animals	Seed holding ponds and old leaves were used	[74]
08	As a fungicide and insecticide	The whole plant was used	[66, 67, 68, 69]
09	As a rubber	Latex of plant was used	[70]
10	In tanning of leather	The whole plant was used	[70]
11	Like sugar and liquor as Manna	The sap of the plant was used	[65]
12	As repellent of the pest	Leaves of the plant was used	[65, 71]
13	As Molluscs killing by pesticide	The whole plant was used	[72, 73]
14	Help in the indication of heavy metals	Leaves and stem of the plant were used	[75]
15	Mosquitoes killing capability	A whole plant with petroleum ether extract was used	[76, 77]
16	In contamination of poly-aromatic hydrocarbon	Leaves of the plant were used	[78]
17	Reclaiming Salt-land	The whole plant was used	[65]
18	Cooling process near the home	Plantation of the plant was used	[65]
19	As a substitute for paper	Leaves of the plant were used	[65]

Conclusion

C. gigantea is a plant that has the capability to grow all over the world and in different types of soils. It is mostly present in the wasteland, but it has an excellent therapeutic value in the treatment of different diseases. The methanolic and ethanolic extracts of the different parts of the plant are used in medicine as these are an excellent alternative to the antibiotics for the dealing of different kinds of infectious diseases by carrying anti-bacterial, anti-fungal, and anti-viral actions, etc. Calotropis plant has also pharmaceutical applications like anti-cancer, anti-inflammatory, anti-venom action, etc. It contains a lot of phytochemical constituents that are responsible for human welfare. This plant needs more investigation at the molecular level to understand the exact mechanism of action of these phytochemical constituents that helps in the development of the different products that will be used for better economical and therapeutical application.

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