RESEARCH PAPER

Calotropis gigantea: From invasive ecology to sustainable pharmacological exploitation

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ABSTRACT

Calotropis gigantea is a long-lived shrub that grows in hot regions of the globe. It is also considered challenging, contagious, and used in folk medicine. The plant can withstand animal feeding, adverse weather conditions, and degraded soil. Nonetheless, its medicine capability has never been thoroughly examined in the field. This review examines the physical characteristics of this plant, including how it survives, its use in traditional medicine, chemical contents it carries, and lab tests that depict its health benefits. It is concentrated on the effects of combating cell damage and minimizing the inflammation. It has been demonstrated through many lab and animal studies to be able to kill microbes, fight cancer, protect the liver, and assist nerves. However, there are no human experiments and no uniform procedures, which entails the existence of enormous knowledge gaps. This article demonstrates Calotropis gigantea as a prospective untapped resource through the association of plant strength in nature with the absence of medical research. The work in the future will involve testing the plant, ensuring its safety, and learning about its functionality. This is required so as to harness its natural power and make effective medicines.

Keywords: Calotropis gigantea, pharmacological review, traditional Indian medicine, Ayurveda, pharmacological activities.

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1. Introduction

Herbs have been used for different diseases in traditional medicines. Certain research has revealed that herbal medicine practices began 60,000 years ago in Iraq and 8,000 years ago in China.[1] The traditional medicine system embraces numerous systems like Chinese, Unani, Ayurvedic, and biomedicine, wherein they employ roots, bark, stems, leaves, etc. of plants in the curing of disease and other health disorders. Traditional medicine has, however, not been integrated in some countries owing to the supremacy of the allopathic medicine system.[2] Calotropis gigantea is a shrub that has been studied and found to represent a multitude of such resources as being anti-inflammatory, anti-oxidative, anti-hyperlipidemic, anti-fungal, anti-bacterial, anti-diarrheal, cytotoxic, hepatoprotective, etc. This herb is traditionally incredibly effective in terms of healing. Calotropis gigantea is also referred to as “Arka” or “sunshine” in Sanskrit; hence, it heals disease by casually touching it and has been in use since time immemorial. It also refers to the Crown flower. Calotropis has two species: Calotropis gigantea and Calotropis procera. Calotropis gigantea is known as “sweta arka” (white flower); Calotropis procera is known as “raktha arka” (purple flower). These are extremely similar botanically, and they share similar pharmacological action. Calotropis procera, though having the same botanical and pharmacological effects, is highly toxic and regarded as more poisonous than cobra venom [3],[4].

2. Taxonomy, morphology, and global distribution

Taxonomy

Calotropis gigantea is a flower-bearing plant that belongs to the Plantae kingdom and subkingdom *Tracheobionta,* which is classified under multicellular and photosynthetic organisms, and is found under *the Spermatophyta* subdivision. The species belongs to the order Gentianales, which is taxonomically very familiar with plants having varied secondary metabolites and high medicinal potential. *Calotropis gigantea* belongs to the family Apocynaceae within this order, which is a big and pharmacologically significant family with many latex-bearing plants that are identified to be abundant in bioactive compounds. More precisely, the plant belongs to the subfamily Asclepiadoideae (previously considered the family Asclepiadaceae) and is characteristic of milky latex, complex floral structures, and the prevalence of steroidal as well as cardiac glycosides. The species is in the genus *Calotropis*, which is a small genus that consists of hardy perennial shrubs with adaptations to arid and semi-arid climates. *Calotropis gigantea* is one of the known species in this genus with several distinguishing characteristics, such as vigorous growth habit, crown-shaped flowers, and extensive ecological adaptability, which have added to its extensive spread and long-term utilization as part of traditional medicinal systems [5],[6].

Kingdom	Plantae
Subkingdom	Tracheobionta
Subdivision	Spermatophyta
Order	Gentinales
Family	Apocynaceae

Subfamily	Asclepiadaceae
Genus	Calotropis
Species	Calotropis Gigantea

Table 1: Taxonomical classification of Calotropis gigantea

Morphology

Habitat

Calotropis gigantea is a shrub, or small tree, with a long life span, and the average height of the plant is approximately 4 to 10 meters. It has a straight, upright growth habit and prefers dry, infertile soils; it naturally sprouts to about 900m or more in height without being watered.

Root

Its root system is not complicated, yet it branches widely toward the base, becoming woodier. It is wrapped in a thick, corky, bumpy, thick-barked layer. Little branches are also fleshy with white fuzz; however, the fuzz disappears as they age, leaving them smooth. When you chop it or thrust a needle into it, the roots and the other parts spout a milky, white sap.

Stem

The stem is straight, stout, and round, 20 cm or so when fully developed. One of its family characteristics is that it emits a milky latex. Initially it is hairy but smoothed out as it grows up.

Leaves

There are simple leaves, opposite-decussate stems, nearly without leaves, and no minute stipules. The form of both leaves changes to elliptical and rounded at the upper end, with the length of the leaf measuring 9-30 cm and the width 2.5-15.5 cm. The foundation is heart-shaped, and the end is slightly pointed or rounded. The lines are soft, and the texture is fat and plump. The whitish fuzz packs the young leaves, which then become smooth and bluish-green, but with a light green appearance.

Inflorescence

The flowering cluster is thick, baggy, multi-flowered, and umbrella-shaped. They grow on heavy stalks from the nodes, on one side or the top.

Flowers

The flowers are bracted, complete, bisexual, radial, and consist of five parts, with the lower parts located at the bottom. Tiny stalks with a length of 1-3 cm. The flowers are in bunches and are waxy, hence a characteristic appearance.

Calyx

It has five fused sepals in the calyx. They are oval in general, being approximately 4-6 mm long and 2-3 mm wide, and are organized in the form of a quincunx. They are rather smooth and somewhat fuzzy.

Corolla

The corolla is approximately 2.5-4 cm in size, and the five petals are sharply pointed and make a crown-like shape in the middle. The petals are triangular with a length of 5-8 mm and a width of 10-15 mm, being covered with cream, white, buff, or pale lavender colors, particularly at the ends.

Androecium

It has five stamens, which are joined with the female ones to form a gynandrous structure. The anthers are grouped together, thus having a distinctive flower appearance.

Fruit

The fruit is a unique, puffed, spongy pod that is roundish or slightly ovoid and has a maximum diameter of 10 nm or more when in full bloom.

Seeds

The seeds are tiny, flattened, inverted egg-shaped, and approximately 6 x 5 mm. The seeds have a tuft of silky white fluff that generally measures 3 cm or more, and this assists them in drifting with the wind.

Ecological Adaptation

Grazing animals tend to avoid the area because of the toxic milky sap and other harmful chemicals present. It grows well in degraded and bad soils, particularly in overgrazed areas where the native grasses are not competitive [5]-[7].

Habitat	Shrub or small tree
Height	4-10m
Stem	Straight stem, 20cm in diameter
Leaves and Size	Elliptical, sub-sessile, light green (9-20×6-12.5)
Flowers and Peduncle length	Waxy-textured, buff, white, or lavender (2.5-4 cm)
Sepals	Wide ovate,4-6mm×2-3mm
Corolla Diameter	2.5-4cm
Petal size	5.8mm long, 10-15 mm long

Table 2: Morphology of Calotropis Gigantea

Figure 1.1

Figure 1.2

Figure 1.3
Figure 1.4
Figure 1: *Calotropis Gigantea*

Global Distribution and Habitat

Calotropis is predominantly a weed prevalent in India in fairly dry, warm weather. It is a member of the Asclepiadaceae family [5]. *Calotropis gigantea* is a plant native to the Indian subcontinent and parts of South Asia, China, and Malaysia. Beyond the native range, species have spread widely across countries like Bangladesh, Pakistan, Sri Lanka, Nepal, Cambodia, Vietnam, Thailand, Afghanistan, Algeria, Antigua and Barbuda, Argentina, Australia, Burkina Faso, the Antilles, the Bahamas, Barbados, Bolivia, Brazil, Cameroon, Chad, Colombia, Cuba, the Republic of Congo, Dominica, the Dominican Republic, Egypt, Eritrea, Ethiopia, Ecuador, French Guiana, Iran, Iraq, Israel, Jamaica, Kenya, Kuwait, Lebanon, Libya, Martinique, Mexico, Montserrat, Mauritania, Morocco, Mozambique, Myanmar, Mali, Nigeria, the Netherlands, Nicaragua, Oman, Panama, Peru, Saudi Arabia, Senegal, Somalia, Sudan, Syrian Arab Republic, Surinam, Tanzania, Uganda, Uruguay, the United Arab Emirates, Venezuela, and Yemen.[8] In India, it occurs from the northern states, like Punjab and Rajasthan, to the south until Kanyakumari. It is a type of shrub that grows naturally up to 900 meters without irrigation. This plant mainly grows well on poor soils and needs fewer nutrients to grow [5].

3. Traditional and Ethnomedicinal Uses of Calotropis Gigantea

In folk medicine, the Calotropis gigantea plant as a whole has been used to treat numerous skin ailments, including boils and sores as well as being believed to have a tonic and purgative effect. The plant has different parts that are utilized in various ways. The stem bark is used to induce sweating and looseness of mucus in people; treat dysentery, swollen spleen, seizures, scabies, ringworm, and pneumonia; and assist people in giving birth. Fruit pulp is alleged to be a cause of abortion, and powdered root is a treatment of elephantiasis, leprosy, and dysentery. Calotropis gigantea is used as a remedy in the form of the milky juice (latex). It is used to treat stings, toothaches, cavities, leprosy, ringworm, syphilis, tumors, rheumatism, and wounds. It is also anti-germic and anti-wormic, and it can cleanse the body. It has also been reported to harden the heart like digitalis, to treat abortions, and to kill the babies. The plant's flowers are used in folk medicine to treat jaundice, inflammation, ulcers, asthma, cough, and rheumatism. For the treatment of intestinal worm infections and seizures, the flowers are steeped into tea as well as boiled in combinations that are used to treat cough and asthma.

The leaves are typically flattened, heated, and used in the treatment of skin burns, headaches, rheumatic pains, and inflammation. A leaf preparation is also used to treat fever. In other cultures, a powdered plant combined with cow milk is used to treat rheumatism, diarrhea, dysentery, syphilis, ulcers, and leprosy. The uses of the plant documented by researchers include toothache, inflammation of the eye, runny nose, wounds, boils, and syphilis. The plant is used in the Hainan Islands of China as an anti-asthma, worm-removing, gas-relieving, cough-reducing, and leprosy medicine. In India they boil the dried ends of the flower with molasses and swallow them to cure asthma. An oil known as "Arka taila," a blend of sesame oil, plant juice, and turmeric, is used in eczema and various skin eruptions, insect and scorpion bites, and also in the alleviation of pain and burning. The twigs and seeds are also used to prevent pregnancy as well as to abort, and the latex is mostly used to prevent bleeding, decrease inflammation, aid in childbirth, and treat numerous skin ailments. Child convulsions, earaches, and rheumatic pains are also treated using fresh leaves. The Western Ghats of Karnataka have an aboriginal population that uses latex as a skin infection and root juice during delivery to relieve labor pain and warmed root juice with coconut oil to treat scabies [4],[6],[9]. It's also helpful in the treatment of eruptions on the body and enlarged liver and spleen [10].

Table 3: Traditional and Ethnomedicinal uses of *Calotropis gigantea*

Plant part	Traditional uses	Community reported/Region
Whole plant	Heals skin infections such as boils and sores; taken as a tonic and to cleanse the body.	General Folk Medicine
Stem Bark	Treats loose mucus, dysentery, enlarged spleen, seizures, scabies, ringworm, and pneumonia.	Traditional Medicine System
Root (powdered)	Treatment of elephantiasis, leprosy	Traditional Medicine
Root Juice	Ease of labor pain during childbirth	Western Ghats, Karnataka
Root juice (infused with coconut oil)	cures scabies and plague	Western Ghats, Karnataka
Fruit pulp	Serves as abortion agent	Folk medicine
Latex (milky juice)	Stings, toothache, dental cavities, syphilis, tumors, wounds, anti-germ, stops bleeding, aids childbirth.	Widely used in folk medicine
Flower	Treats Jaundice, inflammation, asthma, ulcers, and cough	Folk medicine
Flower (tea)	Can be used as a treatment for intestinal worms and seizures	Traditional use
Flower (boiled preparation)	Cough, asthma	Traditional use
Leaves (heated)	Leaves were used on burns and for headache, rheumatic pains, and inflammation.	Folk medicine
Leaves (Fresh)	Child convulsions, earache, rheumatic pain	Folk medicine
Whole plant (powder with cow milk)	Treats Rheumatism, diarrhea, dysentery, syphilis, ulcers, and Leprosy	Cultural Practices
Oil Preparation (Arka-Taila; sesame oil + plant juice + turmeric)	Eczema, skin eruptions, insect and scorpion bites, pain, burning, and abortion	India

4. Invasive Ecology and Botanical Adaptations of *Calotropis Gigantea*

As the well-known 10-10 rule of biological invasions implies, most introduced plant species fail to establish themselves in non-native habitats, and even fewer of the established ones become invasive. It is approximated that around 10 percent of the introduced species can naturalize, and out of these, roughly 10 percent end up developing invasive properties [11]. This means that out of these, about 1 percent of the plants that were inaugurated become invasive. The typical features of successful invasive species are associated with beneficial life-history characteristics, such as a large reproductive potential, intense phenotypic plasticity, and high competitive intensity. These qualities allow them to establish, persist, and expand in new ranges [12]-[13].

Ecological plasticity

Calotropis gigantea grows throughout the country and is well adapted to survive in quite dry and salty areas. It grows easily in an average 300–400 mm of annual rainfall and loves well-distributed sandy soil [14]. Sometimes it is the only plant that grows in some areas where nothing else grows. The extremely branched system of roots and the presence of waxy-like coverage on the leaves are xerophytic adaptations. It does not require any cultivation process [15]. Wide habitats with low competition are preferred for *Calotropis gigantea.* It is readily distributed as weed along deteriorated roadside and lagoon edges. It prefers mostly dry, abandoned agricultural sites [16]-[17].

Reduced Grazing and Biotic Resistance

Calotropis gigantea does have milky secretions and poisonous latex, but the stem (latex) and branched root of the plant are more poisonous; that's why its latex is also called plant mercury because on exposure it shows mercury-like effects on the body. The sap and latex are very bitter and sour in taste, causing burning pain, irritation, collapse, and death. The leaves contain toxins such as calotoxin, glycosides, calotropin, and uscarin, which are corrosive in nature. These types of toxins increase its natural defense; that's why cattle or other livestock animals don't eat this plant. Even this plant is protected against locust or insect attacks. Due to these reasons, this plant species is reduced to grazing [17]. Latex exposure to the eyes causes ocular toxicity and results in vision loss. That's why animals don't eat this plant. *Calotropis gigantea* is nasty to eat, so not many grazers prefer it, and it has an advantage and will multiply fast in places with lots of grazers. It accumulates toxic materials, particularly cardiac glycosides, which not only keep away animals but also reduce other biological stresses to the plant. Having fewer herbivores chewing on it, the plant will be able to continue growing, reproduce more, and migrate in disturbed areas and wastelands. This hardy perseverance allows *C. gigantea* to triumph in marginal habitats where excessively grazed species perish because of the less favorable conditions [16]-[17].

Reproductive Efficiency

Calotropis gigantea flowers throughout the year. During the hot season, it grows very fast. This plant is mainly pollinated by bees, wasps, and butterflies. The seeds are also dispersed by water and wind [18]. A single fruit of the Calotropis plant produces nearly 433.2 ± 19 seeds; that's why this plant spreads very fast [19]. There are some common insect visitors of this plant because the *Calotropis* flower is a spellbinding source of nectar, so they are responsible for the huge production of seeds throughout the year. *Xylocopa caerulea* (blue carpenter bee) and *Xylocopa fenestrate* (windowed carpenter bee) mostly visit the *Calotropis* throughout the year and play a notable role in the pollination of the *Calotropis* flower [20].

Factors Contributing to Invasiveness

- *Calotropis gigantea* is a wasteland weed [21].
- Spreads in a wide range of climates and soils [22].
- The presence of an extremely branched root system and thick leaves with waxy coverage are the xerophytic conditions [8].
- Grazing animals do not eat this plant, allowing it to thrive in the areas where overgrazing has reduced competition from other vegetation.
- Plant growth to standard height, harvest fruits, and collect seeds. ineffectual management system [23].
- If it is repeatedly cut back to ground level, it will resprout vigorously. This system maintains the soil's organic carbon [24].

Phytochemical Composition (Chemical-Ecological Perspective)

Phytochemical class	Compound	Plant parts	Ecological Role	Pharmacological Relevance
Cardenolides (Cardiac Glycosides)	Calotropin, Calcatin, Uscharin	Latex, leaves, root	Herbivore deterrence, toxic to grazing animals, defense against insects	Cardiotonic activity, anti-cancer, anti-inflammatory, and neuroactive effects: effects
Flavonoids	Quercetin Kaempferol derivativess	Leaves, Flowers	UV protection,oxidative stress tolerance, pollinator attractor	Antioxidant,neuroprotective,antiinflammatory
Terpenoids	B-amyrin,Lupeol	Leaves, Latex	Alleopathic interactions, membrane stabilization,under stress	Antiinflammatory,analgesic,hepatoprotective
Alkaloids	Calotropiane(Reported)	Roots, Latex	Chemical defence,Deterrence of herbivory	CNS activity,antimicrobial potential
Phenolic Acids	Gallic acid, Caffeic acid	Leaves, Flowers	Alleopathy,inhibition of competing vegetation, ROS defence	Antioxidant,antiinflammatory neuroprotective

Table 4: Phytochemical Composition (Chemical-Ecological Perspective)

5. Ecology Role of Secondary Metabolites

Defense against pathogens

The spectrum of classes of secondary metabolites synthesized by plants is quite extensive, and they represent a plethora of chemical classes. Most of these compounds are only made when the plant is stimulated by environmental or biological factors. In invasive plants, these secondary metabolites may have several biological purposes in the ecology, such as herbivore repulsion, fungus and microbial pathogen resistance, and allelopathy to surrounding vegetation. A blend of these bioactive compounds increases the ecological competitiveness and adaptation capacity of invasive plants in the nonnative conditions [25]-[26]. *Calotropis gigantea* is a plant related to plant defense (presence of secondary metabolites). These secondary metabolites act as anti-nutritious, repellant, deterrent, and toxic agents against herbivorous animals, such as alkaloids, saponins, tannins, terpenoids, phenols, etc. [27]. The presence of these chemical factors adds on to reduce disease factors and enhance plant longevity under natural environmental conditions [28],[29].

Allopathic interactions

Alleochemicals are non-nutritive substances mainly produced by plants as secondary metabolites [30]. Allelopathy is an interference mechanism by which plants release chemicals that affect other plants. Invasive plant species having allelopathic properties alters the environment through the production of secondary metabolites [31]. Phenols, alkaloids, tannins, terpenoids, flavonoids, cyanohydrins, benzoquinones, etc. are various allelochemicals [32]. On average, chemicals released by one plant reduced the growth and survival of other plants by 25%. Allelopathic effects are stronger at first but decrease over a long period of time due to degredation of the plant over time [33]. *Calotropis gigantea* is a type of plant that is rich in secondary metabolites. Cardenolides are cytotoxic and may exhibit allelopathic properties, but further empirical validation is needed. There are several types of secondary metabolites present in *Calotropis gigantea, which act* as allochemicals [34].

Stress Tolerance and Environment Adaptation

Some plants have developed and evolved diverse adaptation mechanisms to survive under adverse conditions, including some pathways that play a crucial role in stress tolerance [35]. There are some bioactive polyphenol compounds that help the plant to survive under tense conditions and provide various functions, like chemical defense and mostly protecting the plants from biotic and abiotic stress conditions [36]-[37]. Abiotic stress includes drought, heavy metals, salinity, extreme temperatures, UV light, and oxidative stress, which hinders plant growth [38]. With the climate changes, plants and crops are affected by changes in the earth's climate, elevated CO_2, changes in precipitation, cloud patterns, etc. [39], phenylpropanoid pathway, which, after various enzymatic reactions, yields compounds like phenols, flavonoids, lignin, and hydrobenzoic derivatives [36],[40]. *Calotropis gigantea* is a plant that contains these secondary metabolites, such as phenols, flavonoids, etc., which provides a mechanism against reactive oxygen species, etc. [41].

6. **Pharmacological Activities of Calotropis gigantea (Pre-Clinical Studies)**

There are a number of preclinical studies that provide data that *Calotropis gigantea* is a potent drug for human use. It is capable of treating various health conditions.

Free radical scavenging activity

Leaf and flower extract (chloroform) of *Calotropis gigantea* shows free radical scavenging activity. Ethanolic extracts of leaf and latex of *Calotropis gigantea* were tested for free radical scavenging activity using 1,1-diphenyl-2-picrylhydrazyl radicals, and the latex exhibits greater capacity for scavenging DPPH while the leaf extract shows moderate activity [42]. The present investigation on the leaf extract of

Calotropis gigantean has demonstrated strong antioxidant potential along with effective metal-chelating capacity, contributing to the reduction of reactive oxygen species. These findings suggest that the antioxidant effect operates through multiple complementary mechanisms. The presence of bioactive constituents in the leaves allows free-radical neutralization via both electron-donating and hydrogen-transfer pathways [43].

Anti-inflammatory activity

Calotropis gigantea is a potent drug capable of reducing inflammation. Different leaf extracts were prepared, such as ethanol extract, n-butanol extract, chloroform extract, etc., and tested against carrageenan-induced paw edema, which showed anti-inflammatory action [44]. The methanolic extract of *Calotropis gigantean* revealed better anti-inflammatory action than other aqueous extracts [45]. It is indicated that there is a reduction in the inflammation and chronic inflammation (arthritis) model. It showed peak activity~ 2 hours after the administration. The alkaloid fraction showed notable early anti-inflammatory activity [46]. A single dose of dried latex (aqueous suspension) revealed significant effective levels against acute inflammatory response [47].

Anti-cancer activity

The nanoemulsions prepared from essential oils of *Calotropis gigantea* show selective cytotoxicity towards cancer cells, with comparative lower toxicity to normal cells. The presences of bioactive secondary metabolites (terpenoids and related compounds) are known to induce oxidative stress imbalance and apoptosis in cancer cells [48]. *Calotropis* has demonstrated potential as an anti-tumorigenesis compound. Calotropis potentially controls the HSC-3 cell progression and significantly reduces the migration and invasive means, showing potential to inhibit cancer metastasis [49]. The stem bark extract of *Calotropis gigantea* exhibited cytotoxicity against HCT116 and HT-29 cells, while Calotropis gigantean dichlormethane (CGDCM) showed higher potency in both cell lines [50]. Coroglaucigenin, a cardenolide from *Calotropis gigantea,* inhibits lung cancer proliferation and enhances radiosensitivity by modulating the Nrf2/ROS oxidant pathway with comparatively low toxicity to normal cells [51].

Hypoglycemic activity

The chloroform leaves and flowers extract of *Calotropis gigantea* were evaluated against streptozotocin-induced diabetes, which was effective in lowering serum glucose levels and improving oral glucose tolerance [52]. Methanolic seed extract of *Calotropis gigantea* significantly reduced hyperglycemia in streptozotocin-induced diabetic rats [53]. The essential oils from *Calotropis gigantea* leaves demonstrated significant in vitro anti-diabetic potential by inhibiting the α-amylase in a dose-dependent manner, and computational studies supported interactions of major oil constituents with the enzyme's active site, indicating mechanistic relevance to blood glucose regulation [54].

Antimicrobial activity

Calotropis gigantea exhibited antimicrobial capacity against a significant proportion of the pathogenic micro-organisms. Intrinsic experiments have revealed that crude extracts of *Calotropis gigantea* have antimicrobial effects against Gram-positive and Gram-negative microorganisms, and this is one of the reasons why it has been used as an antimicrobial agent against infections in practice [55]. Other solvent systems confirmed the reliance of activity of antimicrobial activity on extraction method and organ in the plant, with leaves and latex persistently showing the greatest activity in comparison to the others. Species-specific differences in *Calotropis gigantea* and *Calotropis procera* focused on the contribution made by the phytochemical composition to antimicrobial activity were also identified in the comparison. Both chemical metallographic profiling and GC-MS analysis have gone as far as to attribute the presence of bioactive secondary metabolites (which include phenolics, flavonoids, terpenoids, and volatile compounds) to higher beneficial antibacterial activities in specific leaf and flower extracts. Independently, use of aqueous extracts in the research indicated the presence of an activity of antibacterial properties, which explained the use of traditional water-based preparations and generalized the application of the plant in the light of ethnomedicine. All these findings lead to the identification of *Calotropis gigantea* as a naturally occurring antimicrobial plant, the activity of which is specific to different parts of the plant, the polarity of the solvent, and its wide repertoire of secondary metabolites [56]-[57].

Hepatoprotective activity

The stem extract of *Calotropis gigantea* has shown significant effects on liver injuries as well as on oxidative stress, which results in lipid peroxidation and improved serum biochemical parameters such as ALT and AST. There was also a reduction in the elevated levels of SOD, CAT, and GSH when treated with *Calotropis gigantea* [58]. The methanolic and chloroform leaf extracts of *Calotropis gigantea* showed hepatoprotective activity against hepatic damage induced by acetaminophen (paracetamol). Acetaminophen-induced damage caused elevation in the levels of SGPT, SGOT, ALP, and bilirubin; these levels further caused necrosis, which, after treating with leaf extract, significantly reduced the levels of elevated serums [59]. Carbon tetrachloride-induced liver injury was attenuated by leaf extract of *Calotropis gigantea,* which normalized serum liver enzymes, reduced lipid peroxidation, enhanced endogenous antioxidant defenses, and potently modulated *CYP2E1*-mediated oxidative stress [60].

7. Ecological Dominance vs. Pharmacological Neglect

Calotropis gigantea is a bushy medicinal plant that thrives in dry climates [61]. This is a type of plant that is found nearly everywhere: on mountains, in dry-season areas, grasslands, active volcanic foothills, and beaches [62],[63]. It is an indicator of overgrazed, disturbed lands; this indicates that in areas where animals eat or graze other plants, *Calotropis* dominates [64]. In some countries, *Calotropis gigantea* has become an emerging problem where it has been introduced because of its invasiveness [65]. Although it is an invasive and dominant plant, it has not been much utilized in modern science. Before the advent of penicillin, the milky sap was thought to be effective against syphilis [66]. Various chemical constituents such as Di-(2-ethylhexyl) Phthalate [67], lupeol [68], β-amyrin and β-amyrin acetate [69], and isorhamnetin [70] have been extracted from *Calotropis gigantea.* There were some rare and traditional uses of *Calotropis gigantea,* which include treatment of blood clots [71], treatment of menstrual disorders [72], as a diaphoretic [73], treatment of smallpox, pneumonia infection [74], increased breast milk [75], treatment of tuberculosis [76], etc. These were the traditional uses, but activities such as antibacterial, anticonvulsant, anticancer, antidepressant, antifungal, anti-inflammatory, antioxidant, antitumor, cytotoxic, etc. have been reported. Although *Calotropis gigantea* possesses such beneficial effects, there are no clinical studies reported on either the *Calotropis* genus or the *gigantea* species [77]. The proven preclinical studies have not been extrapolated to clinical studies [78].

8. Conclusion and future perspectives

Despite the limited pharmacological study of Calotropis gigantea on a translational scale, its invasive success and widespread ecological distribution are evident. Future research should also focus on systematic bioactivity-driven studies to establish disease-relevant therapeutic applications beyond initial in vitro and animal models. To overcome variability in the existing studies, standardization of plant material and extraction procedures and dose optimization are necessary to ensure reproducibility. Since there are no clinical trials involving humans, overall toxicological assessment and safety profiling are essential preclinical stages leading to clinical translation. Techniques like systems pharmacology, network analysis, and omics-based profiling can assist in explaining synergistic effects of bioactive components and clarifying multi-target action mechanisms. The redesigning of *Calotropis gigantea* as a sustainable bioresource rather than an invasive species of the exotic organism may align ecological management with the drug discovery activities. All in all, this review demonstrates that *Calotropis gigantea* is a potentially valuable but an underemphasized target of future therapeutic research, and there is a necessity to reconcile ecological supremacy with evidence-supported pharmacological advancement.

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Gurkirat Singh: Original draft, conceptualization. **Rohit Kumar**: Review and editing. **Devinder Kumar**: Review and editing. **Harsimran Singh**: Review and editing, conceptualization.

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