

Review on Clinical Safety and Efficacy of Giant *Calotropis* in the 21st Century

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Abstract

Calotropis gigantea, a highly valued plant in traditional Indian pharmacology, has emerged as a promising candidate for therapeutic innovation. This review delves into the clinical safety and efficacy of *C. gigantea* in the 21st century, examining its historical use, phytochemical composition, and pharmacological properties. While traditional medicine has long utilized *C. gigantea* for various ailments, modern research has sought to validate these claims through scientific investigation. This review critically analyzes the available clinical evidence, highlighting the plant's potential in managing conditions like inflammation, pain, and microbial infections. However, it also underscores the need for further rigorous clinical trials to establish definitive conclusions regarding their safety and efficacy. Additionally, the review discusses potential toxicity concerns associated with *C. gigantea*, emphasizing the importance of appropriate dosage and administration. In final analysis, *C. gigantea* demonstrates potential as a therapeutic agent, but ongoing research is vital to elucidate its therapeutic efficacy and safety profile, thereby facilitating its responsible and effective utilization in healthcare settings.

Keywords: Antidiabetic, antimalarial, antimicrobial, *Calotropis gigantea*, healing, traditional medicine

INTRODUCTION

Calotropis gigantea, commonly known as Giant *Calotropis*, Sweta Arka, or Madar, is a perennial shrub belonging to the Apocynaceae family. Native to tropical and subtropical Asia, including India, Southeast Asia, and parts of Africa, *C. gigantea* is a hardy plant that excels in challenging conditions. It effortlessly grows in dry, sandy, or rocky soils, showcasing its remarkable resilience. It is characterized by its large, leathery leaves, pale purple or white flowers, and a milky latex, which is a distinguishing feature of the genus *Calotropis*.

In traditional medicine, particularly within the Ayurvedic, Unani, and Siddha systems, *Calotropis gigantea* has been used for its therapeutic properties for centuries. Almost all parts of the plant—the roots, leaves, flowers, and latex—are utilized in various forms, such as powders, decoctions, and extracts. *C. gigantea* is a versatile medicinal plant, providing relief from a range of health conditions, including digestive disorders, respiratory problems, infections, and inflammation. Nonetheless, its toxic compounds require careful handling and precise dosage to ensure safe and effective treatment.

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Phytochemically, *C. gigantea* is rich in a diverse array of bioactive compounds, including cardiac glycosides, alkaloids, flavonoids, terpenoids, tannins, and resins. These compounds are responsible for its various pharmacological activities, such as anti-inflammatory, antimicrobial, antioxidant, and antidiabetic effects. Modern science is increasingly recognizing the value of the

plant's traditional uses, establishing a solid foundation for its integration into contemporary herbal medicine practices.

Despite its widespread use in indigenous medicine, *Calotropis gigantea* also poses certain risks due to the toxic nature of some of its constituents, particularly the cardiac glycosides. These compounds can have harmful effects on the heart if consumed improperly, making careful formulation and dosage essential for safe use.

This review aims to explore the various medicinal applications, chemical constituents, pharmacological activities, and safety considerations associated with *Calotropis gigantea*. By examining both traditional knowledge and contemporary research, the article seeks to provide a comprehensive understanding of this remarkable yet potent plant and its potential for therapeutic use in modern medicine (Figure 1)] [1, 2].



Figure 1. Giant *Calotropis*.

(WHO) World Health Organization report that 80% of world's population mostly in developing country relies on traditional medicine to treat common health problem.

Taxonomical Classification

1.	Kingdom	Plantae
2.	Subkingdom	Tracheobionta
3.	Class	Dicotyledones
4.	Sub class	Asteridae
5.	Order	Gentianales
6.	Family	Apocynaceae
7.	Sub family	Asclepidiaceae
8.	Genus	<i>Calotropis</i>
9.	Species	<i>C. gigantea</i>

Vernacular Name

Common Name

1.	India	Arka, Mandara (in Sanskrit) Aak, Madar (in Hindi)
2.	West Indies	Pillow cotton
3.	Indonesia	Bidhuri, sidaguri, rubik
4.	French	Mercure vegetal

MORPHOLOGY

- a. *Seed*: The seeds are small, oval-shaped, about 5 x 4 mm in size, and they have a fluffy white coating (called pappus) that is about 3 cm long, making them look compact.
- b. *Leaves*: The leaves are arranged opposite to each other in pairs, with each pair placed at right angles to the next (decussate). They are relatively simple, without stipules, and have a smooth edge that is oval or obovate (egg-shaped), ranging in size from 5 to 30 cm long and 2.5 to 15.5 cm wide. The tip of the leaf is sharply pointed or has a small point, and the base is heart shaped. The edges are smooth, and when the leaves are young, they are covered with white, soft hair (tomentose), but as they mature, they become smooth and glossy [3–5].
- c. *Flower*: The flowers have bracts (small leaves) at their base, are fully developed (complete), and have both male and female parts. They are symmetrical, with five parts (petals, sepals, etc.), and the ovary is positioned below the flower parts (hypogynous). The flowers are attached to a stalk (pedicel) that is 1–3 cm long [6].
- d. *Fruit*: The fruit is a simple, rounded, and slightly swollen capsule that is either nearly spherical or oval-shaped, and can grow up to 10 cm or more in diameter.
- e. *Calyx*: The calyx (the outer part of the flower) has five separate sepals, which are joined together at the base. The sepals are smooth and lose their hair as they mature. They have a specific arrangement where four of the sepals overlap in a pattern.

The androecium (the male part of the flower) consists of five stamens, which are attached to both the male and female parts of the flower. The anthers (the pollen-producing parts) are two-lobed and release pollen when mature.

The Chief Feature

- It is one plant that grazing animal do not eat [7].
- In environments impoverished by overgrazing, this species exhibits remarkable resilience, thriving in soils of low fertility [8].
- This plant is adaptable to diverse soil conditions and climates.
- Do not require cultivation practice.

Therapeutic Use

Calotropis gigantea, a medicinally multifaceted plant, has been distinguished for its broad spectrum of bioactive properties, underscoring its potential as a valuable therapeutic agent. The juice of this plant is particularly noted for its anthelmintic effects, meaning it helps expel intestinal worms, making it a valuable remedy for parasitic infections. Additionally, this juice is beneficial for treating leucoderma, a skin condition marked by white patches, and it is used to manage various other ailments, including tumours, ascites (fluid buildup in the abdomen), and disorders of the abdomen.

Beyond the juice, the plant itself is known to possess purgative properties, helping to cleanse the digestive system and promote regular bowel movements. It is also alexipharmic, meaning it can counteract poisons or toxins for centuries, *Calotropis gigantea* has been used to treat a multitude of skin-related disorders, including leprosy and vitiligo, as well as other conditions, such as ulcers, growths, and anal fissures (hemorrhoids). Additionally, it has therapeutic effects on the spleen, liver, and abdominal diseases, supporting the overall health of these vital organs.

The leaves of the plant are particularly valuable in treating wounds, both fresh and chronic, promoting faster healing and reducing inflammation. Their therapeutic applications also encompass the mitigation of articular pain, paralysis, and inflammation. The plant's application extends to managing conditions like arthritis or any painful and swollen joints, where it helps alleviate discomfort and promote mobility.

For individuals suffering from intermittent or periodic fevers, the tincture made from the plant's leaves prove to be a highly effective antiperiodic, preventing the recurrence of fever episodes. This tincture is a vital remedy for those facing conditions like malaria or other fever-related illnesses that come in cycles [9, 10].

Biological Activity

Various biological evaluations of the plant *Calotropis gigantea* (milk weed) individual components were conducted, such as antioxidant, antimalarial, anti-ulcer, heart healing, antibacterial, antidiarrheal, anticancer, antiinflammation antifungal, antidiabetic, antiglaucoma activity (Figure 2).

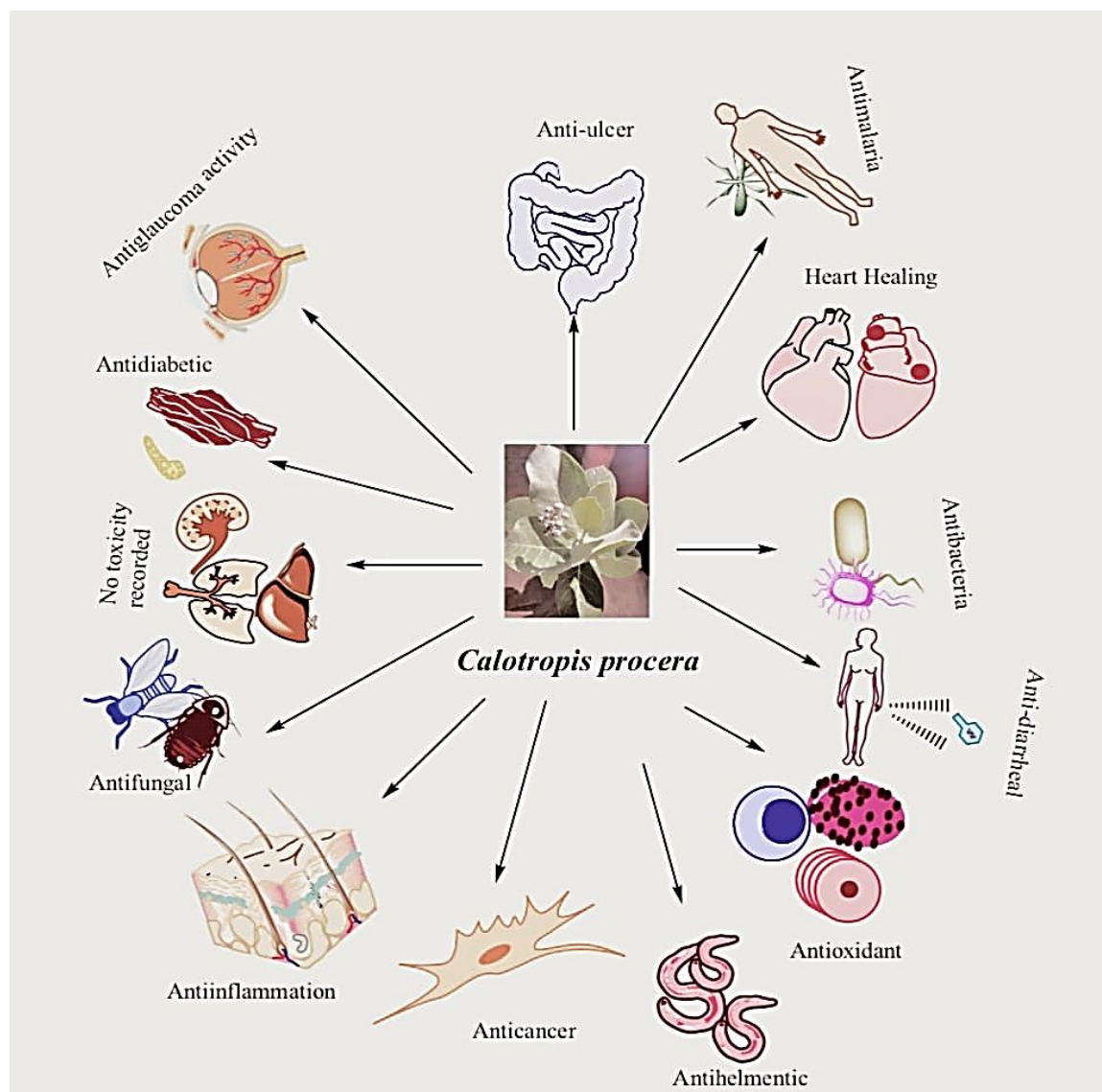


Figure 2. Biological activity.

Clinical Use

Antioxidant

It's possible that other active substances in the plant might also play a role in its effects. While many chemicals have been identified, it's still unclear how much each one contributes to the plant's antioxidant activity. The study suggests that the antioxidants in these chemicals might work together or even against each other in some cases. Additional research is necessary to identify the key bioactive compounds and to comprehend their mechanistic interplay. Overall, the study clearly shows that the latex from *Calotropis procera* has strong antioxidant properties in various test systems.

When oxygen is used to generate cellular energy, a redox reaction takes place that results in the production of free radicals. These reactive oxygen species (ROS) consist of molecules, such as the hydroxyl radical, hydrogen peroxide, and the superoxide ion.

To verify the efficacy of these antioxidant substances, the antioxidant capabilities of plant extracts were evaluated in various systems using different techniques. The DPPH test showed that the extracts had strong ability to neutralize free radicals, with activity ranging from 42% to 90%. Additionally, it was found that the concentration of the extract influenced the amount of metal ions it could bind, ranging from 16% to 95% [11].

The isolated compound had the strongest effect, inhibiting 51.7%, while methanol was slightly higher at 80%, and water showed the least inhibition at 29.2%.

The way the chemical groups on phenolic compounds are arranged around their core structure affects how well they can neutralize free radicals and act as antioxidants. The ability of certain chemical groups (like hydroxyl groups) in calotropagenin, calotropin, and calotoxin to donate hydrogen atoms might explain why these compounds in the plant have antioxidant properties. This means they could help protect cells from damage by neutralizing harmful molecules called free radicals [12].

Anti-Diarrheal Activity

Several mechanisms contribute to the anti-diarrheal effects of Giant Calotropis:

- *Reduced Intestinal Motility:* The plant extract slows down the contractions of the intestinal muscles, allowing more time for water absorption and reducing the frequency of bowel movements.
- *Inhibition of Intestinal Fluid Secretion:* Giant *Calotropis* helps reduce fluid secretion in the intestines, leading to a decrease in stool volume.
- *Anti-Inflammatory Properties:* The plant contains compounds with anti-inflammatory effects that can alleviate gut inflammation, commonly linked to diarrhea. The latex from its roots is used in various remedies to treat this condition [13].
- *Safety Considerations:* While Giant *Calotropis* is generally safe when used correctly, it contains toxic compounds. It is vital to use the plant under the supervision of a qualified healthcare provider to prevent potential adverse reactions. Pregnant and breastfeeding women should avoid using it.
- *Conclusion:* Giant *Calotropis* shows promise as a natural treatment for diarrhea, supported by both scientific research and traditional practices. However, it is important to consult a healthcare professional before using it, particularly for children and pregnant women.

Antimalarial Activity

Giant *Calotropis* (*Calotropis gigantea*) has shown promising potential as a natural remedy for malaria. Several studies have investigated its anti-malarial properties, particularly focusing on its extracts. The spread of malaria strains resistant to many drugs has made finding new treatments very important. The ethanolic extracts from the flowers and buds of a plant showed varying levels of effectiveness against malaria. The IC₅₀ values (the concentration needed to inhibit 50% of the parasite growth) ranged from 0.11 to 0.47 mg/mL for the regular *P. falciparum* strain and from 0.52 to 1.22 mg/mL for strains resistant to chloroquine (CQ). When tested against two different malaria strains (MRC 20 and MRC 76), the extracts showed different levels of inhibition. For MRC 20, inhibition ranged from 7.51% to 61.38% at doses of 62–125 mg/ml. For MRC 76, inhibition ranged from 3.43% to 41.08%. These results were observed for extracts from the flowers, buds, and roots of the plant [14].

- *Antiplasmodial Activity:* Extracts of *Calotropis gigantea*, especially the methanolic leaf extract, have demonstrated significant antiplasmodial activity against both *Plasmodium falciparum* and *Plasmodium berghei*, the parasites responsible for malaria.
- *In Vitro and In Vivo Studies:* The anti-malarial effects have been observed in both in vitro (laboratory) and in vivo (animal) studies.
- *Mechanism of Action:* While the exact mechanism of action is not fully understood, it is believed that the bioactive compounds present in the plant extract may interfere with the parasite's life cycle or disrupt its metabolic processes.

- **Safety:** The extracts have been found to be relatively safe, with minimal toxicity observed in studies.

Potential Benefits

- **Natural Alternative:** *Calotropis gigantea* offers a potential natural alternative to synthetic antimalarial drugs, which can have side effects and contribute to drug resistance.
- **Accessibility:** The plant is widely available in tropical regions, making it a readily accessible source of potential antimalarial compounds.
- **Future Studies:** The preliminary findings are encouraging, but additional research is required to fully unravel the anti-malarial potential of *Calotropis gigantea*. This includes:
 - **Identification of Active Compounds:** Isolating and identifying the specific compounds responsible for the anti-malarial activity would allow for targeted drug development.
 - **Clinical Trials:** Conducting clinical trials in human subjects is essential to evaluate the safety and efficacy of *Calotropis gigantea* extracts as a treatment for malaria.
 - **Formulation and Dosing Strategy:** Developing an effective and safe dosing strategy, including the optimal formulation, is critical for successful therapeutic outcomes.
- **Conclusion:** *Calotropis gigantea* shows potential as a possible source for new antimalarial medications. However, further research is needed to fully explore its capabilities and create safe and effective malaria treatments.

Antidiabetic Activity

Diabetes is an increasingly prevalent condition, leading to a rising number of fatalities. The disease interferes with the body's ability to use sugar (glucose) for energy, disrupting the metabolism of carbohydrates, fats, and proteins. In India, millions are affected by diabetes, and this figure is projected to continue rising. Globally, the incidence of diabetes is also on the rise.

Giant *Calotropis* (*Calotropis gigantea*) is a plant that may help manage diabetes. Studies have shown that extracts from this plant can lower blood sugar levels in both normal and diabetic animals. It might work by helping the body use insulin better or by slowing down the breakdown of carbohydrates into sugar.

Although these results are encouraging, further studies are necessary to gain a complete understanding of how Giant *Calotropis* functions and to confirm its safety for human use.

This means that when diabetic rats were given extracts from the *Calotropis procera* plant (root methanol, stem methanol, and leaf ethyl acetate), it helped to reduce the symptoms of diabetic neuropathy. These symptoms include increased sensitivity to pain (hyperalgesia), sensitivity to light touch (allodynia), and elevated blood sugar levels (HbA1c) [15].

The study showed that administering the extracts at doses of 100 and 250 mg/kg over an extended period significantly alleviated these symptoms. This indicates that the plant extracts could hold promise as a treatment for diabetic neuropathy.

Another potential mechanism: Pure compounds or crude extracts may trigger the production of inflammatory cytokines, which can induce apoptosis in macrophages in the bloodstream, leading to the eventual release of secreted insulin. On the other hand, the stimulation of dendritic cells in the brain could signal the release of insulin in response to hypoglycemia. However, the presence of fat surrounding the insulin receptor might contribute to insulin resistance and diabetes mellitus by obstructing the interaction between the insulin receptor on cells and the release of insulin [16].

Anthelmintic Activity

Helminthiasis is a major disease that causes big production losses in grazing animals like cattle and sheep. It's caused by parasitic worms and is common in many parts of the world, especially in poorer

countries where management and control methods are weak. To effectively manage this disease, both long-term and short-term treatments with medicines called anthelmintics are needed. Researchers are also looking into natural products to help control the disease, especially since some parasites have become resistant to traditional medicines. In one study, it was found that extracts from dried latex (a natural substance) could reduce the movement of worms in a dose-dependent way, meaning the effect increased with higher doses.

Giant *Calotropis* (*Calotropis gigantea*) has shown potential as a natural anthelmintic, meaning it can help control parasitic worm infections in animals.

Key Points

- **Paralysis and Reduced Response:** Studies have shown that both fresh and dried latex extracts of *Calotropis gigantea* can cause paralysis in parasitic worms and reduce their response to stimuli.
- **Dose-Dependent Effect:** The effectiveness of the extract increases with higher concentrations, suggesting a dose-dependent relationship.
- **Potential for Natural Control:** This plant-based approach could be a valuable tool in managing parasitic worm infections, especially in regions where drug resistance is a growing concern.

However, it's important to note: Additional studies required: Although the preliminary results are encouraging, further research is essential to gain a complete understanding of the anthelmintic properties of *Calotropis gigantea*.

Safety Considerations

The safety and efficacy of the extract for animals need to be thoroughly evaluated before widespread use. Overall, *Calotropis gigantea* offers a potential natural solution to a significant problem in animal health. Continued research and development could lead to effective and sustainable strategies for controlling parasitic worm infections.

Hepatoprotective Activity

Liver diseases are a major global health concern, affecting the liver, which plays a crucial role in digestion and detoxification. These conditions can result in severe complications, such as liver failure, cancer, or cirrhosis, and their prevalence is rising. Many individuals are unaware of their liver disease until it reaches an advanced stage, making it a critical public health challenge.

Giant *Calotropis*: A Potential Hepatoprotective Agent

Liver diseases pose a serious health threat worldwide, with various causes, such as viral infections, alcohol consumption, and toxin exposure leading to liver damage.

In the search for effective treatments, researchers have turned to natural remedies, including plants like Giant *Calotropis* (*Calotropis gigantea*) [17, 18].

- **Hepatoprotective Properties of Giant *Calotropis*:** Several studies have demonstrated the hepatoprotective potential of Giant *Calotropis*. Here are some key findings:
- **Antioxidant Activity:** The plant is rich in powerful antioxidants that can neutralize harmful free radicals, alleviating oxidative stress on the liver. These antioxidants help safeguard liver cells from damage caused by oxidative stress.
- **Liver Enzyme Reduction:** Extracts from Giant *Calotropis* have been shown to lower elevated levels of liver enzymes, such as ALT (alanine aminotransferase) and AST (aspartate aminotransferase), which are markers of liver damage.
- **Reduced Inflammation:** The plant's anti-inflammatory properties can help decrease liver inflammation, a common factor in many liver conditions.
- **Promotion of Liver Regeneration:** Some studies suggest that Giant *Calotropis* may stimulate the liver's regenerative capacity, aiding in the repair of damaged liver tissue.

- **Mechanism of Action:** While the exact mechanisms underlying the hepatoprotective effects of Giant *Calotropis* are not fully understood, several factors may contribute:
- **Antioxidant Properties:** Counteracting free radicals and minimizing oxidative stress.
- **Anti-inflammatory Effects:** Alleviating inflammation in the liver.
- **Modulation of Immune Response:** Regulating immune responses that may contribute to liver damage.
- **Direct Protective Effects on Liver Cells:** Protecting liver cells from toxins and other harmful agents.
- **Conclusion:** Giant *Calotropis* holds potential as a natural treatment for liver diseases. However, additional studies are necessary to fully comprehend its mechanisms and determine safe and effective dosages. It is crucial to seek advice from a healthcare provider before using any herbal treatments, particularly for liver-related issues.

Wound Healing Activity

Giant *Calotropis* has been traditionally used in India for wound healing, and recent scientific studies have validated its wound-healing properties. Here are some key findings:

- **Wound Contraction:** Topical application of *Calotropis gigantea* extracts significantly enhanced wound contraction compared to control groups.
- **Epithelialization:** The extracts of *Calotropis gigantea* reduced the time required for wound closure.
- **Scar Formation:** *Calotropis gigantea* extracts reduced the size of scars and improved the quality of the scar tissue.
- **Collagen Synthesis:** *Calotropis gigantea* extracts promoted collagen production, a crucial component for effective wound healing.
- **Antimicrobial Activity:** The extracts possess antimicrobial properties, which can help prevent infection and support the healing process.

These findings suggest that *C. gigantea* could serve as a promising natural remedy for wound healing. However, more research is needed to fully understand its mechanisms and determine the appropriate dosage and formulation for clinical use.

It's important to note that *Calotropis gigantea* is toxic and should not be used internally. Always consult a healthcare professional before using any herbal remedy, particularly if you are pregnant, breastfeeding, or on other medications [19, 20].

CONCLUSIONS

Calotropis gigantea is a natural remedy that aids in wound healing. The plant improves wound contraction, epithelialization, and collagen synthesis. Its antimicrobial properties help prevent wound infections. *Calotropis gigantea* can be a safe and effective treatment for wound healing. However, some precautions should be taken:

Calotropis gigantea is a toxic plant and should not be consumed internally. It is essential to consult with a healthcare provider before using it, particularly if you are pregnant, breastfeeding, or taking other medications.

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