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Review

Calotropis procera Shrub: A toxicological review of its potential hazards for human use

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***Calotropis procera*, commonly known as the "apple of Sodom" or "giant milkweed," is a perennial shrub widely distributed across Africa, the Middle East, and South Asia. Traditionally utilized in various ethnomedicinal systems, it has been employed for treating ailments such as fevers, skin disorders, respiratory conditions, and digestive issues. Despite its historical use in folk medicine, recent scientific investigations have raised concerns regarding its safety due to the presence of toxic compounds such as cardiac glycosides, latex proteases, and other bioactive constituents. This review aims to critically evaluate the toxicological profile of *C. procera*, focusing on both preclinical and clinical evidence. Studies on animal models have demonstrated significant toxicity, including hepatotoxicity, nephrotoxicity, neurotoxicity, and cardiotoxic effects, particularly at higher doses or upon prolonged exposure. In humans, cases of dermal irritation, ocular injuries, and gastrointestinal disturbances have been reported, often associated with exposure to the plant's latex. The findings underscore the importance of exercising caution in the therapeutic application of *C. procera*. While it possesses pharmacological potential, its use must be regulated, and further studies are essential to establish safe dosage ranges and administration routes. This review highlights the need for standardized toxicological assessments to ensure the safe integration of this plant in traditional and modern medicinal practices.**

Key words: *Calotropis procera*, toxicity, cardiac glycosides, human poisoning, phytochemical constituents, herbal safety.

INTRODUCTION

Calotropis procera (Aiton) W.T. Aiton, belonging to the Apocynaceae family, is a robust and fast-growing shrub widely distributed in arid and semi-arid regions across Africa, the Middle East, the Indian subcontinent, and parts of Southeast Asia. This hardy plant is easily recognized by its large, greyish-green leaves, milky latex, and striking purple or white flowers (Zaki et al., 2025). Notably tolerant of poor soil conditions, *C. procera* often colonizes disturbed or marginal habitats, where it is sometimes regarded as a weed due to its vigorous growth and invasive tendencies. Its remarkable adaptability has ensured its persistence in diverse ecosystems, while its extensive use in traditional medicine has cemented its importance in various cultural healing systems (Jayasuriya, 2025). In traditional medicinal practices, *C. procera* holds a distinguished position. In Ayurveda, it is

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known as *Arka* and is used to treat a range of ailments, including skin diseases, leprosy, fever, and asthma. The Unani system of medicine utilizes the plant primarily for its anti-inflammatory and analgesic effects. Folk medicine traditions across its growing regions often use different parts of the plant, including leaves, flowers, roots, and, notably, its latex for therapeutic purposes (Nejhad et al., 2023). Topical applications include wound healing and treatment of skin infections, whereas oral administration is commonly used to manage gastrointestinal disorders, respiratory conditions, and sometimes as an antidote for poisoning. However, these traditional uses frequently lack standardized dosing regimens and safety monitoring, which raises concerns about potential toxicities (Iqbal et al., 2023). With the rising global interest in phytotherapy and natural remedies, *C. procera* has attracted scientific attention for its diverse pharmacological properties. Numerous studies have demonstrated its antimicrobial, anti-inflammatory, analgesic, antioxidant, and even anticancer activities, making it a promising candidate for drug discovery (Umair et al., 2022). For instance, extracts from the plant have shown inhibitory effects against bacterial and fungal pathogens, alongside significant reduction of inflammation in animal models. These findings support many of the traditional claims regarding its therapeutic efficacy (Iqbal et al., 2024a). Despite these benefits, *C. procera* also exhibits significant toxicological risks, which have been documented in both experimental and clinical contexts. The plant's latex, in particular, contains a range of bioactive compounds that contribute to its toxicity. Among these, cardiac glycosides such as calotropin have been identified as major contributors to its cardiotoxic effects (Dogara, 2023). These compounds can disrupt cardiac function by inhibiting sodium-potassium ATPase, potentially leading to arrhythmias and other heart-related complications if ingested inappropriately. Additionally, the plant contains proteolytic enzymes and saponins, which may cause skin irritation, mucous membrane damage, and gastrointestinal distress (He et al., 2022).

Experimental studies in animals have reported symptoms such as vomiting, diarrhea, abdominal pain, and even death at higher doses of *C. procera* extracts or latex. Skin exposure to latex can cause dermatitis and blistering. In humans, accidental poisoning cases have revealed similar adverse effects, underscoring the need for caution in its therapeutic application. Moreover, chronic exposure or improper use may increase the risk of cumulative toxicity, a concern that is often overlooked in traditional settings (Singh et al., 2024). Figure number one show the Overview of *C. procera* Shrub. The objective of this review is to critically evaluate the toxicological data available on *C. procera*, encompassing both in vitro and in vivo studies, as well as documented clinical observations. By analyzing the mechanisms of toxicity and identifying key safety concerns, this assessment aims to guide future research toward developing safe, standardized, and evidence-based therapeutic applications of *C. procera*. Such efforts are essential to harness its medicinal potential while minimizing risks to human health, ultimately supporting the integration of this traditional medicinal shrub into modern phytomedicine frameworks (Nawaz et al., 2024). Figure 1 shows the overview of *C. procera* Shrub.

PHYTOCHEMICAL COMPOSITION

C. procera is a rich source of diverse phytoconstituents that contribute both to its therapeutic potential and toxicological effects. The plant contains a wide array of biologically active compounds, including cardenolides, flavonoids, alkaloids, triterpenoids, and proteolytic enzymes, predominantly found in its latex, leaves, flowers, roots, and bark (Singh et al., 2024).

Major phytoconstituents

Among the most well-studied compounds are cardiac glycosides, particularly calotropin, uscharin, and calotoxin, which exhibit strong pharmacological and toxic effects due to their action on the Na^+/K^+-ATPase pump. Flavonoids such as quercetin, isorhamnetin, and kaempferol are present and have been linked to antioxidant and anti-inflammatory activities (Bankole and Thiemann, 2022). Alkaloids, another significant group, contribute to both therapeutic and adverse effects, depending on concentration and mode of administration. The latex of *C. procera* is particularly potent, containing proteolytic enzymes such as Caltrain, trypsin-like proteases, and cysteine proteases, which play a role in tissue degradation and have shown both wound-healing and cytotoxic properties. Other phytochemicals reported include tannins, saponins, and sterols (Abookleesh et al., 2022). Figure number two show the heatmap of the phytochemical constituents of *C. Procera* Shrub.

Pharmacological relevance vs. Toxic properties

The dual nature of these constituents is a major concern. While cardenolides possess anti-cancer and antimicrobial potential, their narrow therapeutic index makes them dangerous at high doses, leading to cardiotoxicity (Rajput et al., 2022). Similarly, latex enzymes have demonstrated wound-healing and anti-inflammatory effects, yet can also cause dermal irritation, inflammation, and allergic reactions upon contact with skin or mucous membranes. This duality necessitates precise dosing and targeted application to harness benefits while minimizing risks (Iqbal et al., unpublished). Figure 2 shows the heat map for the toxic chemicals of *C. procera* shrub variability based on plant part.

Figure 1. Overview of *C. procera* Shrub.

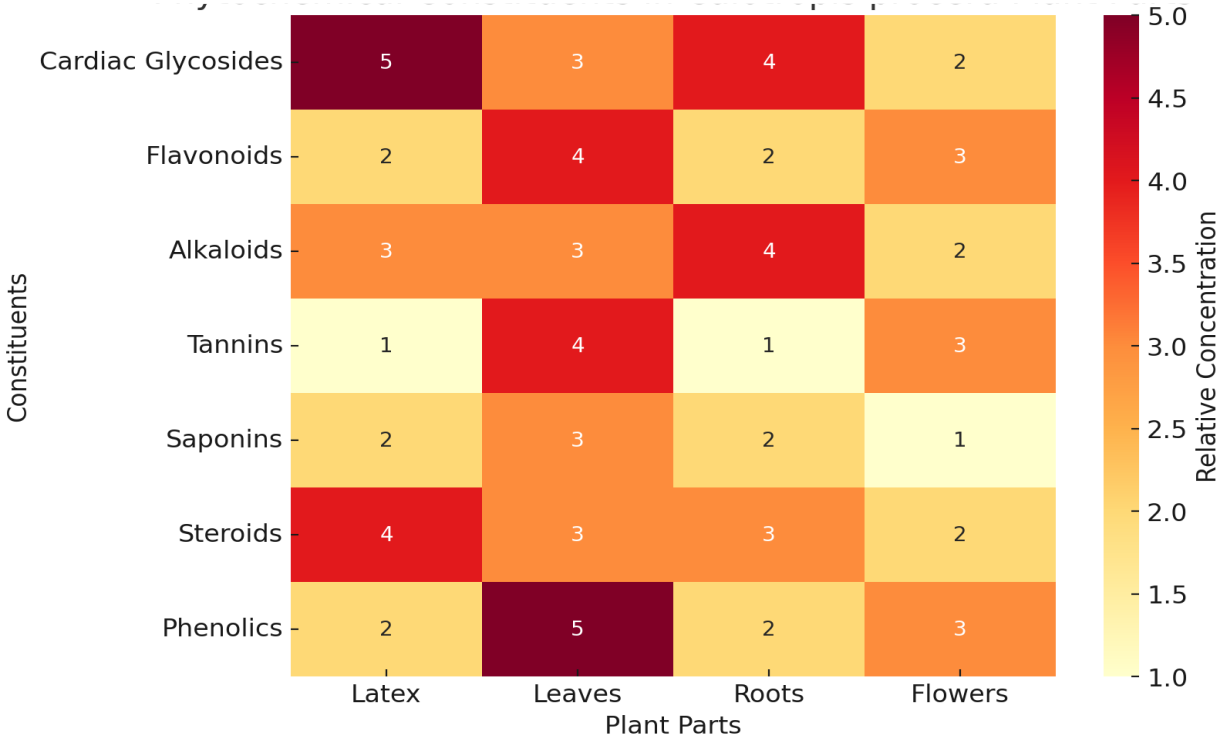

Figure 2. The heatmap of the phytochemical constituents of *C. procera* Shrub.

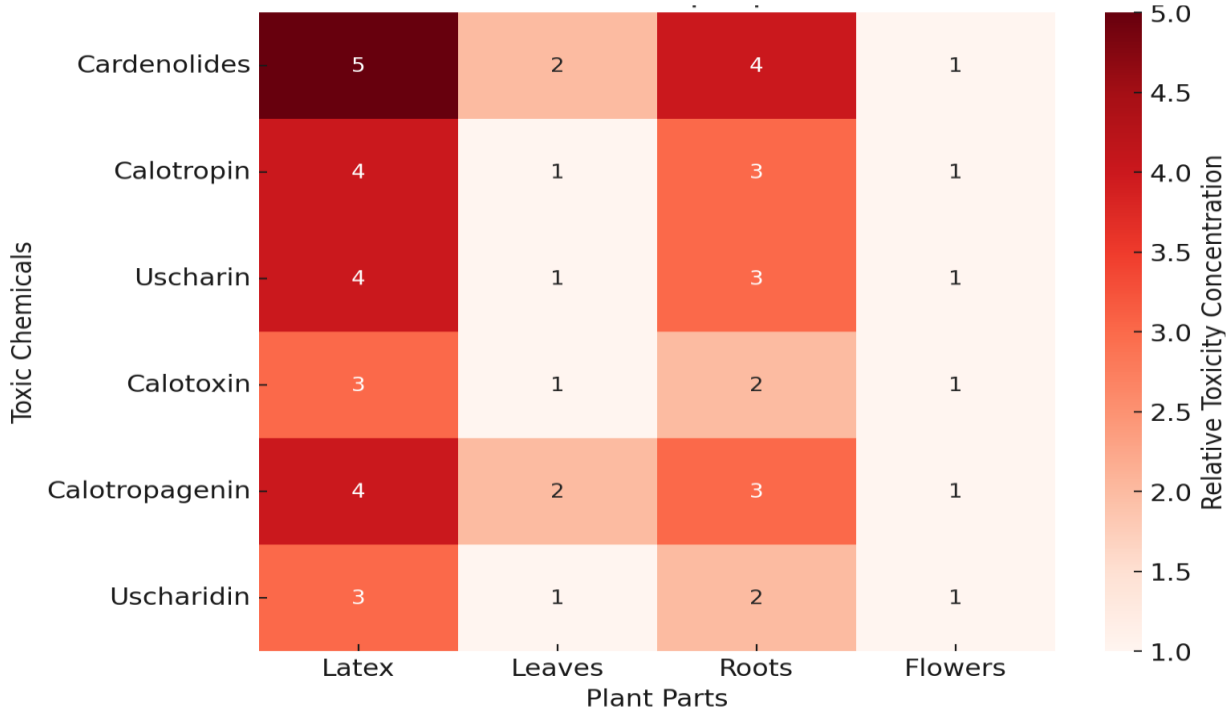

Figure 3. The heatmap for the toxic chemicals of *C. procera* Shrub.

The phytochemical composition of *C. procera* varies significantly across its plant parts. Leaves are abundant in flavonoids, tannins, and glycosides, while latex contains proteolytic enzymes, cardiac glycosides, and sterols. Roots and bark are rich in alkaloids and saponins, commonly used in traditional remedies (Radhaboy et al., 2022). Flowers possess volatile oils, glycosides, and smaller amounts of flavonoids and alkaloids. This variation influences the plant's pharmacological and toxicological properties, making it essential to conduct part-specific investigations to ensure an accurate assessment of its therapeutic potential and safety. Tailored research is critical for the effective and responsible use of each plant part (Kandar, 2020).

TOXICOLOGICAL PROFILE

The toxicity of *C. procera* has been well-documented across various biological systems. While it possesses several pharmacologically active constituents, numerous studies have reported toxic effects, especially when used in non-standardized doses or without proper preparation. The toxicological profile includes acute and chronic toxicity, cytotoxicity, genotoxicity, neurotoxicity, and dermal and ocular hazards (Dogara, 2023). Figure 3 shows the heatmap for the toxic chemicals of *C. procera* Shrub.

Acute toxicity

Animal studies have established the acute toxicity of *C. procera* through LD_{50} evaluations. The reported LD_{50} values vary depending on the route of administration and plant part used. For instance, the oral LD_{50} of latex in rats ranges between 1.5 and 2 g/kg, while for leaf and root extracts, values range from 3 to 5 g/kg, indicating moderate to high toxicity (Kumar et al., 2022). Symptoms of acute toxicity observed in both animals and humans include nausea, vomiting, diarrhea, excessive salivation, tremors, and dermatitis. Contact with the plant's milky latex is particularly hazardous, often causing skin irritation, burning sensation, blisters, and ocular inflammation. Cases of conjunctivitis, corneal ulcers, and temporary vision loss have been reported following accidental eye exposure to the latex (Beck et al., 2020).

Sub-chronic and chronic toxicity

Repeated dose studies in rodents have revealed significant toxicity from prolonged exposure to *C. procera* extracts. Sub-chronic administration notably impacts the liver, kidneys, and gastrointestinal tract. Histopathological analyses from chronic studies report hepatic degeneration and necrosis, renal tubular damage with glomerular atrophy, and mucosal erosion accompanied by

Table 1. Data table example (Constituent levels by plant part).

Constituent	Leaves	Latex	Root	Bark	Flowers	References
Calotropin	Low	High	Medium	Low	Medium	Rajkovic et al. (2023)
Uscharin	Absent	High	Medium	Low	Low	Minj et al. (2025)
Cardenolides	Medium	High	Medium	Low	Medium	Minj et al. (2025)
Flavonoids	High	Medium	Low	Medium	High	Micek et al. (2021)
Alkaloids	Medium	Low	Medium	Low	Low	Uzor (2020)
Latex Enzymes	Absent	High	Absent	Absent	Absent	Long et al. 92021)

gastrointestinal inflammation (Kumar et al., 2022). These findings indicate that long-term or high-dose use of *C. procera* extracts can lead to systemic toxicity and severe organ damage. Consequently, caution is advised in its therapeutic application, and further studies are essential to establish safe dosage limits and duration for clinical use (Taychaworaditsakul et al., 2024).

Cytotoxic and genotoxic effects

In vitro assays, including 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and trypan blue exclusion assays, have confirmed the cytotoxic nature of *C. procera* latex and extracts against several mammalian cell lines (Iqbal et al., 2024b). Some studies have shown dose-dependent inhibition of cell viability and induction of apoptosis. Genotoxicity has also been demonstrated using comet assays and Deoxyribonucleic acid (DNA) fragmentation tests, indicating possible DNA damage (Al-Zahrani et al., 2024). Studies using chromosomal aberration analysis in *vivo* and *in vitro* systems revealed structural chromosomal changes and increased frequency of micronuclei, suggesting potential mutagenic effects. These findings raise concerns about the long-term safety of the plant, especially with unregulated use, and point to its possible carcinogenic risk, although further investigation is required (Siri et al., 2021). Table 1 shows the data constituent levels by plant part.

Neurotoxicity and cardiovascular effects

The cardiac glycosides present in *C. procera*, including calotropin and uscharin, exert effects similar to digitalis compounds by inhibiting the Na^+/K^+-ATPase pump, potentially leading to arrhythmias, bradycardia, and cardiac arrest at toxic doses. Animal studies have reported neurobehavioral changes, including lethargy, tremors, and loss of motor coordination. Severe Central Nervous System (CNS) effects such as convulsions, depression of reflexes, and respiratory distress have been observed in experimental rodent models at higher doses (Singh et al., 2022).

Dermatological and ocular hazards

One of the most immediate and well-known toxic effects of *C. procera* is its dermatological impact. The latex is a potent irritant and vesicant, capable of causing blistering, erythema, and ulceration upon skin contact. Allergic contact dermatitis has been frequently reported in individuals exposed occupationally or during traditional medicine preparation. Ophthalmic exposure is particularly dangerous. The latex can cause severe conjunctivitis, photophobia, keratitis, and corneal opacity, potentially resulting in temporary or permanent vision impairment if not promptly treated (Rasul et al., 2023).

HUMAN CASE REPORTS AND EPIDEMIOLOGICAL EVIDENCE

Although most toxicological studies on *C. procera* have been conducted in animal models, there are also several documented cases of toxicity in humans, ranging from accidental exposure to intentional therapeutic use. These reports provide valuable insight into the real-world hazards associated with the plant (Kumar et al., 2022).

Documented poisoning cases

Cases of *C. procera* poisoning have been recorded across various regions, particularly in areas where traditional medicine is commonly practiced. Accidental ingestion—especially by children and therapeutic misuse by traditional healers have led to episodes of acute toxicity. In several reports, ingestion of plant parts or latex has caused symptoms such as vomiting, diarrhea, excessive salivation, and in severe cases, bradycardia, hypotension, and loss of consciousness (Khan, 2021). In one instance, oral administration of latex to a patient for treating jaundice led to multi-organ failure and death due to cardiac arrest. There are also reports of intentional use of latex as an abortifacient, resulting in uterine bleeding, systemic toxicity, and hospitalization. Deliberate or accidental ophthalmic exposure has been associated with corneal burns, conjunctivitis, and temporary vision loss (Minjares,

Martin and Bhamidimarri, 2024). Table number two show the toxicological review of *C. procera* shrub.

Symptoms in humans

Clinical manifestations of *C. procera* toxicity in humans closely resemble findings from animal studies. Common symptoms include gastrointestinal distress such as nausea, vomiting, abdominal pain, and diarrhea. Cardiac complications may arise, including arrhythmias, hypotension, and, in severe cases, cardiac arrest. Neurological effects range from dizziness and seizures to altered mental status and coma in extreme exposures (Singh et al., 2024). Dermal contact with the plant's latex can cause skin rashes, vesicle formation, and allergic reactions. Additionally, ocular exposure may result in redness, excessive tearing, blurred vision, and photophobia. These manifestations underscore the need for caution and proper handling of the plant (Interpretation, 2021).

Occupational exposure among traditional healers and farmers

Traditional healers, herbalists, and rural farmers frequently encounter *C. procera* and often handle the plant without protective equipment. Repeated skin contact with its latex has led to chronic dermatitis, ulcerations, and eczema. In some cases, long-term exposure has resulted in sensitization and delayed hypersensitivity reactions. Field workers involved in harvesting the plant and extracting its latex are at heightened risk, particularly during the flowering and sap-extraction seasons. Epidemiological surveillance in endemic regions remains limited; however, isolated case series and surveys indicate a higher burden of dermal and ocular complaints among individuals with occupational exposure (Emmanuel, 2021). Table 2 shows the toxicological review of *C. procera* shrub.

COMPARATIVE TOXICITY OF DIFFERENT PLANT PARTS

C. procera displays a variable toxicological profile depending on the specific plant part, reflecting significant differences in phytochemical composition. This variability creates a toxicity gradient—Latex > Root > Leaves > Flowers requiring careful consideration for both medicinal use and safety assessments. The latex is the most toxic component, rich in cardenolides, proteolytic enzymes, and alkaloids. It causes severe dermatological reactions, ocular inflammation, and cardiac toxicity, and is known for its cytotoxic, genotoxic, and neurotoxic properties. Accidental exposure can result in systemic poisoning, especially if ingested or absorbed through mucous membranes. The root ranks next in toxicity due to its high content of alkaloids, glycosides, and tannins (Dogara, 2023). Experimental and traditional use studies have shown that root extracts can cause hepatorenal toxicity, gastrointestinal damage, and adverse cardiovascular effects, particularly with prolonged use or high doses. The leaves, while less toxic, still carry risks due to the presence of flavonoids, saponins, and small amounts of cardenolides. Reports of moderate hepatotoxicity, gastric irritation, and dermal sensitivity highlight the need for dose regulation and careful preparation in therapeutic applications. The flowers are the least toxic part of the plant, containing glycosides, essential oils, and low concentrations of alkaloids. Although generally safe in limited amounts, improper extraction or excessive use can still lead to adverse effects. Understanding this toxicity gradient is crucial for the safe use of *C. procera* in traditional and modern medicine. Detailed toxicological evaluation of each part is essential to ensure therapeutic efficacy without compromising patient safety (Francis, 2025).

Differential organ-specific toxicity based on plant part used

Each part of *C. procera* exhibits distinct organ-specific toxicity, necessitating careful consideration in therapeutic use. The latex predominantly affects the cardiovascular system, skin, and eyes. Cardiac glycosides within the latex can disrupt heart rhythm, while proteolytic enzymes cause local tissue irritation and inflammation. The root primarily targets the liver and kidneys, with histopathological studies showing centrilobular hepatic necrosis, renal tubular degeneration, and inflammatory cell infiltration (Iqbal et al., 2024c). The leaves mainly impact the gastrointestinal tract and liver, often resulting in mucosal irritation, nausea, and elevated liver enzymes. Flowers, although least toxic, may trigger allergic responses or mild gastrointestinal discomfort, particularly in sensitive individuals. This organ-specific toxicity highlights the critical need to select appropriate plant parts, control dosage, and apply proper preparation techniques. Special caution is warranted when using raw latex or root extracts, which are most commonly associated with severe toxic effects. Rigorous safety evaluations are essential to balance therapeutic benefits with potential risks (Nyamwamu et al., 2020).

MECHANISMS OF TOXICITY

The toxicological effects of *C. procera* are mediated through multiple biochemical and molecular pathways. Its phytochemical constituents particularly cardiac glycosides, proteolytic enzymes, and alkaloids

Table 2. The toxicological review of *C. procera* shrub.

Aspect	Plant part	Toxicity level	Remarks	References
Botanical description	Whole plant	N/A	Known for milky latex	Hani et al. (2024)
Ethnomedicinal uses	Leaves, roots, latex	Variable	Traditional use vs. toxicity concern	Khodaie et al. (2025)
Major phytochemicals	Leaves, latex, root	Medium to high	Both therapeutic and toxic effects	Tariq et al. (2021)
Acute toxicity	Latex, root	High	Causes nausea, vomiting, dermatitis	Marisetti et al. (2025)
Sub-chronic toxicity	Various	Medium to high	Histopathological damage observed	Kokova (2023)
Cytotoxic and genotoxic effects	Extracts from leaves	Medium	Potential cancer risk	Interpretation (2021)
Neurotoxicity and cardiotoxicity	Latex, whole plant	High	Risk of convulsions and arrhythmias	Micek et al. (2021)
Dermatological and ocular hazards	Latex	High	Occupational hazard	Kandar (2020)
Human case reports	Accidental or therapeutic	High	Limited clinical documentation	Abookleesh et al. (2022)
Comparative toxicity	Different plant parts	Gradient	Latex most hazardous	Jayasuriya (2025)
Toxicity mechanisms	Whole plant	Mechanistic insights	Explains cardiac and cellular effects	Singh et al. (2022)
Management of toxicity	N/A	No specific antidote	Treatment mostly symptomatic	Micek et al. (2021)
Regulatory status	N/A	Regulatory gaps	Need for standardization	Siri et al. (2021)
Research gaps	N/A	Research needed	Emphasis on safety evaluation	Uzor (2020)

interact with key physiological systems, leading to cellular damage and systemic toxicity. The major mechanisms include Na^+/K^+-ATPase inhibition, oxidative stress induction, enzyme inhibition, and mitochondrial dysfunction (Nawaz et al., 2024).

Na^+/K^+-ATPase inhibition by cardenolides

A key mechanism underlying *C. procera* toxicity is the inhibition of Na^+/K^+-ATPase, a critical enzyme that maintains cellular ion gradients. Cardenolides such as calotropin, uscharin, and frugoside bind to and inhibit this enzyme. In cardiac tissue, this inhibition raises intracellular sodium levels, disrupting calcium regulation and enhancing contractility, which can result in arrhythmias, bradycardia, or cardiac arrest at high doses. In neuronal cells, altered Na^+/K^+ balance impairs action potential conduction, leading to neurotoxic effects such as seizures, confusion, and central nervous system depression. This mechanism underscores the potent and systemic toxicity of *C. procera* compounds (Yosif et al., 2024).

Oxidative stress and lipid peroxidation

C. procera has been shown to induce oxidative stress in both in vitro and in vivo studies. Exposure to its latex or ethanolic extracts results in excessive generation of reactive oxygen species (ROS), leading to lipid peroxidation and subsequent damage to cellular membranes and organelles. A significant increase in oxidative stress markers, such as malondialdehyde (MDA), has been observed, while key antioxidant defenses including glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) are markedly reduced. This oxidative imbalance contributes to membrane destabilization, mitochondrial dysfunction, and the activation of apoptotic pathways, particularly affecting liver and kidney tissues, and amplifying the plant's toxicological impact (Dogara, 2023).

Enzyme inhibition and mitochondrial dysfunction

Various extracts of *C. procera* exhibit broad-spectrum enzyme inhibition, significantly impairing cellular metabolism. The plant's latex contains proteases and oxidases that can deactivate essential cellular enzymes and disrupt intracellular signaling pathways. Notably, inhibitory effects have been reported on acetylcholinesterase, cytochrome P450 enzymes, and digestive enzymes, thereby affecting neurological processes

and hepatic detoxification (Nawaz et al., 2024). Furthermore, mitochondrial dysfunction results from both ROS-induced damage and inhibited ATP synthesis, culminating in energy depletion, cellular swelling, and apoptosis. These interlinked toxic mechanisms emphasize the critical need for strict dose regulation, purification, and formulation when considering *C. procera* for therapeutic use. Despite its pharmacological promise, the associated risks demand comprehensive toxicological assessments before clinical application (Hagel et al., 2022).

ANTIDOTES AND MANAGEMENT OF TOXICITY

Toxic exposure to *C. procera*, whether through ingestion, dermal contact, or ocular exposure, can lead to serious health consequences. Currently, there is no specific antidote for poisoning caused by this plant. Management is primarily supportive and symptomatic, with a focus on minimizing absorption, stabilizing vital functions, and treating specific complications such as cardiac arrhythmias and organ dysfunction (Dogara, 2023).

Current approaches in managing calotropis poisoning

Clinical management of *C. procera* toxicity depends on the route and severity of exposure. The initial priority is to assess and stabilize airway, breathing, and circulation (ABCs), followed by rapid decontamination if the exposure is recent. In cases of oral ingestion, activated charcoal is recommended within 1 to 2 h to limit absorption of toxic constituents. Inducing emesis is generally avoided due to the risk of aspiration and further mucosal injury (Kumar et al., 2022). For dermal exposure, the affected area should be thoroughly washed with soap and water to remove plant residues and reduce skin irritation. In the event of ocular contact, immediate and copious irrigation with saline or clean water is essential to minimize the risk of corneal damage. Supportive care should be tailored to the presenting symptoms, with continuous monitoring of vital signs and organ function. Cardiac monitoring, fluid-electrolyte balance, and symptomatic management are crucial in moderate to severe toxicity cases to prevent complications (Bates, 2021).

Role of activated charcoal, fluid therapy, and anti-arrhythmics

Activated charcoal effectively binds glycosides and other toxic compounds, reducing their systemic absorption. Intravenous fluid therapy is crucial for managing hypotension, correcting electrolyte imbalances, and enhancing renal toxin clearance. Electrocardiographic monitoring is recommended for all symptomatic patients, particularly those with cardiac symptoms linked to Na^+/K^+-ATPase inhibition by cardenolides. In cases of cardiac toxicity, anti-arrhythmic medications such as lidocaine or phenytoin may be administered under medical supervision to control ventricular arrhythmias. Atropine can be used to treat symptomatic bradycardia, helping to stabilize heart rate. These interventions are essential to manage and mitigate the severe cardiac effects associated with *C. procera* poisoning (Zhang et al., 2022).

Lack of specific antidote

Unlike digoxin toxicity, which can be managed with digoxin-specific antibody fragments (digoxin Fab), there is no analogous antidote for cardenolides derived from *C. procera*. Experimental studies have yet to identify a compound with selective neutralizing capacity for its toxic glycosides. In the absence of a specific antidote, early recognition, symptomatic management, and supportive care remain the cornerstones of treatment. Public health education and preventive measures, especially in communities where traditional use is prevalent, are crucial in reducing the risk of accidental or therapeutic poisoning (Hack et al., 2025).

RISK ASSESSMENT AND REGULATORY PERSPECTIVES

The increasing use of *C. procera* in traditional and herbal medicine has raised important concerns regarding its safety profile and regulatory oversight. Effective risk assessment and regulatory frameworks are critical to ensuring consumer safety while facilitating the responsible use of this plant in medicinal preparations (Praneeth et al., 2024).

Current regulatory status

The World Health Organization (WHO) acknowledges the global importance of traditional medicines but does not currently list *C. procera* among its officially recommended medicinal plants. WHO emphasizes rigorous evidence-based evaluation of herbal products, focusing on their safety, efficacy, and quality. In India, *C. procera* is widely used within Ayurveda and Unani systems and appears in several classical formulations. However, the AYUSH Ministry stresses the need for thorough toxicity screening and advises caution due to the plant's known irritant and cardiotoxic properties (Kumar et al., 2024). Regulatory frameworks outside India vary considerably, with many countries lacking specific guidelines on safe dosage, extraction methods, or labeling requirements for *C. procera* products. This regulatory inconsistency contributes to variability in product safety and highlights

the urgent need for standardized regulations to ensure consumer protection and promote safe therapeutic use of this potent medicinal plant (Ali and Sinha, 2024).

Gaps in toxicological data and lack of clinical trials

Despite extensive preclinical research, there is a significant lack of robust clinical trials evaluating the safety and efficacy of *C. procera* in humans. Major gaps include limited data on long-term toxicity and effects of chronic exposure, insufficient understanding of dose-response relationships distinguishing therapeutic from toxic ranges, and a scarcity of well-designed randomized controlled trials (RCTs) to systematically validate traditional uses and assess adverse effects. Additionally, comprehensive pharmacokinetic and pharmacodynamics studies are lacking. These critical data gaps hinder accurate risk assessment and prevent the establishment of clear, evidence-based guidelines for safe human use of *C. procera* (Singh et al., 2024).

Need for standardization and quality control in herbal formulations

Variation in the phytochemical composition of *C. procera* arises from differences in the plant part used (latex, leaves, root, flowers), geographical location, harvesting conditions, and extraction or processing techniques. This variability leads to inconsistent toxicity profiles and therapeutic outcomes. To address these challenges, it is essential to implement standardized extraction procedures that ensure consistent concentrations of both active and potentially toxic constituents (Kyada *et al.*, 2023). Quality control protocols, including chromatographic fingerprinting and quantification of key toxic compounds like cardenolides, must be established. Clear labeling specifying plant parts, dosage, and warnings is also critical. Additionally, post-marketing pharmacovigilance should monitor adverse events associated with *C. procera* products. These regulatory and research measures are vital to maximizing therapeutic benefits while minimizing risks for safer phytotherapy integration (Lu et al., 2020).

CONCLUSION

C. procera is a medicinal shrub with a long history of use in traditional systems such as Ayurveda and Unani. It contains a wide range of bioactive compounds, including cardiac glycosides, flavonoids, and alkaloids, which contribute to its therapeutic potential. However, the plant also poses significant toxicological risks, primarily due to the presence of cardenolides in its latex and roots. Toxic effects have been documented across multiple organ systems, including the cardiovascular, hepatic, renal, neurological, and dermatological systems. Reported symptoms range from mild gastrointestinal irritation and skin dermatitis to severe cardiac arrhythmias and neurotoxicity. These effects vary depending on the part of the plant used and the method of preparation, making safe use and treatment more complex. Because there is no specific antidote for *Calotropis* poisoning, careful consideration is essential when using this plant medicinally. Rigorous toxicological evaluation, standardization of herbal preparations, and strict quality control are critical to balancing its benefits with safety. Future research should focus on understanding the molecular mechanisms underlying its toxicity, developing safer extraction methods, exploring potential antidotes, and strengthening regulatory oversight to ensure standardized and safe use. Addressing these challenges will help maximize the therapeutic benefits of *C. procera* while minimizing risks to human health.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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