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Calotropis procera: A Promising Candidate in Cancer Pharmacology

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Abstract *Calotropis procera*, a plant belonging to the Asclepiadaceae family, with significant therapeutic potential. Indigenous to the arid regions of India, Africa, and China, *Calotropis procera* is recognized for its diverse biological activities, including anti-inflammatory, antimicrobial, hypoglycemic, and anticancer properties. This review focuses on the anticancer potential of *Calotropis procera*, highlighting its relevance in traditional medicine and its emerging role in modern therapeutic applications. Despite its promising medicinal value, *Calotropis procera* is also associated with toxicity, particularly its immunomodulatory effects, which can lead to severe conditions, such as delayed-type hypersensitivity and rheumatoid arthritis, if not managed properly. Plant taxonomy, widespread geographical distribution, and botanical characteristics are outlined, emphasizing its adaptability to various environments. Additionally, the traditional uses and folklore surrounding *Calotropis procera* are explored, illustrating its historical significance in treating ailments such as snake bites gynecological disorders and as a component in ritualistic practices. However, the potential risks associated with its use underscore the importance of careful application in therapeutic context. This review consolidates the existing knowledge on *Calotropis procera*, providing a foundation for further research into its mechanisms of action and potential as a pharmaceutical-grade treatment for cancer.

Key Words *Calotropis procera*, apoptosis, Anticancer, Natural, Traditional

INTRODUCTION

Calotropis procera (*C. procera)*, a plant of great therapeutic value in the Asclepiadaceae family, is referred to as "Ushar" in Saudi Arabia and "Safed Aak" in Indian traditional medicine [1]. It is associated with numerous biological activities such as anti-inflammatory, anti-ulcer, pain-relieving, wound-healing, antimicrobial, and hypoglycemic effects. the plant thrives in arid regions of the Middle East, Pakistan, India, Africa, and China [2]. Building on its prominence in ethnopharmacology, recent studies have explored its potential as an anti-cancer agent [3]. Currently, chemotherapy remains the primary treatment for cancer, a complicated disease caused by genetic mutations that impair normal cellular apoptosis and lead to aberrant metabolic pathways [4]. As an adjunct to cancer therapy, there is growing interest in plant-based medications, particularly those with a long history of traditional use, such as *C. procera*.

Although *C. procera* has notable therapeutic potential, it also poses risks [4]. This plant is well known for its toxicity and strong immunomodulatory properties, which, if left unchecked, can result in serious illnesses such as rheumatoid arthritis and delayed-type hypersensitivity [5]. Its exact mechanism of action remains unknown, although numerous have used both *in vitro* and *in vivo* studies have demonstrated its anticancer activity [5]. The progression of *C. procera* from a historically recognized medicinal plant to a promising pharmaceutical-grade cancer treatment reflects ongoing efforts to harness its medicinal advantages while tackling the obstacles presented by its toxicity [6].

Bio-active compounds of *C. procera*, which have shown efficacy in targeting the mechanisms driving cancer progression, as primarily responsible for its potential as a cancer treatment [7]. However, a better understanding of how these substances interact with the cellular pathways implicated in cancer is necessary to realize their potential in clinical settings. Studies have indicated that plant extracts can trigger apoptosis, suppress tumor growth, and interfere with several signaling pathways essential for cancer cell survival [8]. It is difficult to isolate and improve these substances in order to reduce their toxicity and increase their therapeutic efficacy [8]. Future research should focus on maximizing the use of *C. porcera* by balancing its powerful medicinal qualities with the need to mitigate its side effects. This will eventually help *C. procera* become a useful natural anticancer agent.

Additionally, thorough clinical trials are required to verify the safety and effectiveness of *C. procera* before it can be integrated into contemporary medicine. Although early research has produced encouraging results, further investigation is required to identify the best dosages, delivery strategies, and possible interactions with currently available treatments. Traditional uses of the plant provide a useful foundation, but rigorous scientific validation is essential to translate this knowledge into a standardized pharmaceutical product [9]. Furthermore, exploring *C. procera's* synergistic effects with other chemotherapeutic agents may enhance their therapeutic potential with minimizing toxicity [9]. The growing popularity of complementary and alternative therapies makes *C. procera* an intriguing subject for additional research, which could help close the knowledge gap between conventional medicine and modern cancer treatment methods.

METHODS

Relevant studies were identified through comprehensive searches of electronic databases, including PubMed, ScienceDirect, Scopus, Google Scholar, and Saudi Digital Library. Relevant articles were studied in detail, and the manuscript was prepared and written. The databases were searched using the keywords: "*Calotropis procera*" or "*C. procera*" or "Ushar" and "Cancer" or "Anticancer" or "Antitumor" were the main keywords used to search for articles.

Taxonomy and Botanical Description

Taxonomy: Members of the Asclepiadaceae family, including *C. procera*, are widely dispersed throughout many nations in the Middle East, Africa, and the Indian subcontinent, including Saudi Arabia, Egypt, Algeria, and Cyprus [10]. Furthermore, the plant has been introduced to areas such as Bangladesh, Italy, and several Pacific Islands (Figure 1) [10]. The phytochemical, pharmacological, and clinical qualities of *C. procera* have been the subject of extensive research, especially in Africa, the Gulf, and India, where its widespread use is primarily attributed to its substantial ethnopharmacological use [10]. This plant is native to several states of the US, including Arizona, Texas, and California [10].

C. procera, also referred to as "Ushar," "apple of Sodom," "madar," and "crown flower," is a small tree or erect shrub that can grow to a height of 4 meters (Figure 2) [10,11]. Structurally, it has a robust main stem that is usually unbranched at the base before maturing into a dense, asymmetrical canopy [11]. The plant grows well in a range of habitats, including steppes and deserts [11]. It is frequently found on rocky, dry slopes or sandy places that receive direct sunlight [11,12]. Its adaptability extends to seasonally dry zones, making it a resilient species in harsh climates [12]. It is especially well-suited to arid and semi-arid regions [12].

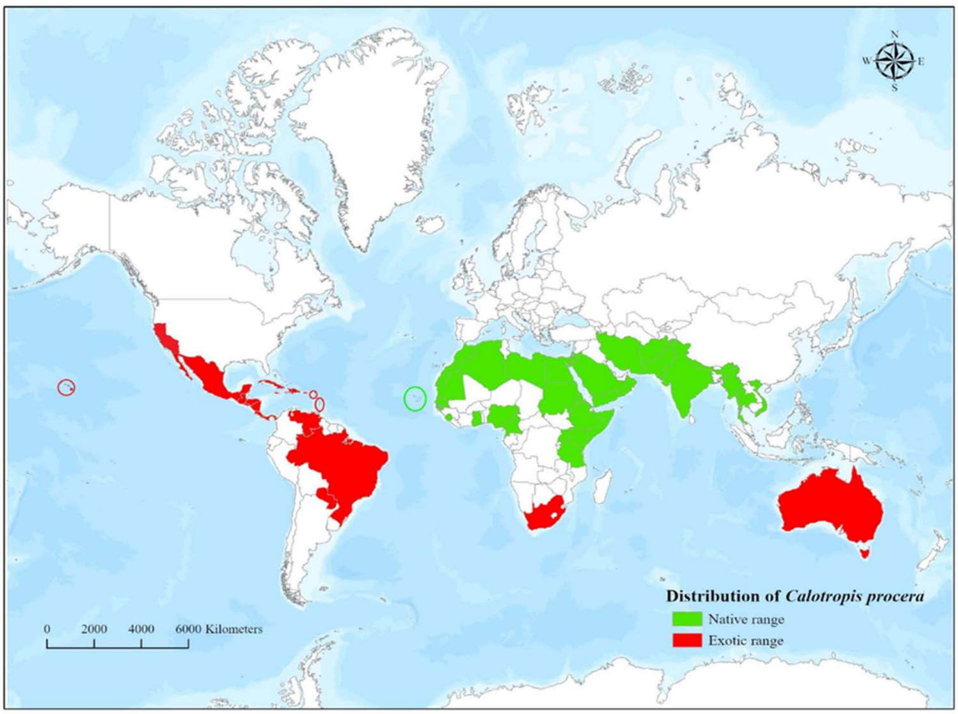

Figure 1: Worldwide distribution of *Calotropis procera*

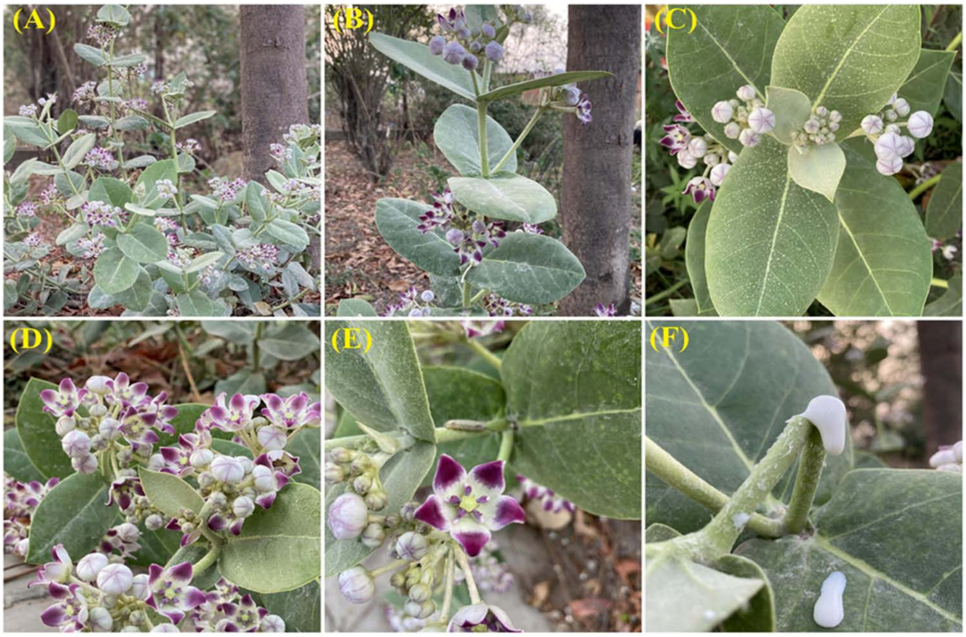

Figure 2: *C. procera*: (A) Flowering plant; (B) Phyllotaxy; (C) Reproductive buds; (D) Inflorescence; (E) Individual flower; and (F) Latex oozing out of the wounded stem

Traditional Uses and Folklore

Traditional medicine has long used *C. procera* to treat a wide range of illnesses. The powdered leaves of the plant are applied to snakebite wounds and used as a hemostatic agent for postsurgical care in places such as Pakistan and southern Africa [13]. The milky juice of *C. procera* was thought to have divine properties by ancient Egyptians, who used it in rituals to seek healing and spiritual protection [14]. In the first century CE, the Greek herbalist Dioscorides identified the plant and documented for treating thorn wounds and animal bites [15]. The root bark of *C. procera* has been used in southern Africa to produce amulets, which are thought to fend off evil spells [16]. Zulus was especially known for this practice, appreciating the protective properties of amulets [16].

C. procera has been traditionally used in India to treat various gynecological conditions, including lactation and menstruation disorders, leukorrhea, and abnormal vaginal discharge [17]. If consumed during the menstrual period, latex induces severe cramps or menstruation owing to strong uterine contractions [17]. The emetic qualities of latex have also been used to treat problems associated with milk production, irregular menstruation, and appetite loss [18,19]. Furthermore, because of *C. procera* latex's diuretic properties, conventional medicine is used to treat ailments such as renal failure, filariasis, dropsy, and chronic nephritis [20].

Chemical Composition of *C. procera*

Many studies have been conducted on the chemical composition of *C. procera*, with particular emphasis on its many bioactive compounds. The study of *C. procera* identified 14 types of chemical compounds through the analysis of various studies [4]. These compounds include alkaloids, flavonoids, phenolic compounds, terpenoids, lipids, proteins, saponins, phytosterols, carbohydrates, reducing sugars, xanthoproteins, amino acids, resins, and gums [9]. Triterpenes, flavonoids, and alkaloids are the three most abundant bioactive compounds [9]. Studies on plant leaves, fruits, flowers, roots, and latex have revealed a wide range of chemical components [9].

The alkaloid calotropin and its analogs, such as calotropagenin and keto-calotropin, which are also present in latex, are present in both the leaves and flowers of *C. procera* [21]. Flavonoids and phenolic compounds are abundant in the aqueous extracts of leaves and latex, with flavonoid glycosides being the main flavonoids present in latex [21]. Furthermore, latex and roots have been found to contain luteolin and quercetin [23]. The protein content of *C. procera* seeds has been investigated because it can be used in poultry feed [23]. The overall medicinal value of the plant is bolstered by a diverse range of bioactive agents found in the seeds, including hydrocarbons, proteins, vitamins, starches, glucose, glycerides, reducing sugars, phytosterols, fixed oils, alkaloids, flavonoids, and various acids [22].

Alkaloids

Alkaloids are important plant compounds that have been shown to be effective in treating a variety of tumour conditions [21]. These compounds typically consist of basic nitrogen atoms within a heterocyclic ring structure with molecular weights ranging from 150 to 400 Da [5,23]. Some alkaloids found in *C. procera*, particularly in the plant roots, have shown promising anticancer activities [23]. Calotropins and calotropins are the two most common alkaloids found in plants [23]. However, further exploration and characterization of the alkaloids in *C. procera* is required to fully understand their therapeutic potential.

Calotropine N-O-oxide, a yellow amorphous powder, was first isolated from *C. procera's* methanolic extract using column chromatography [24]. The compound was identified based on its physical, chemical, and spectral characteristics. Calotropine N O-oxide exhibited significant anticancer activity against human cancer cell lines (MCF-7, and A549) *in vitro* [14,25]. The half-maximal inhibitory concentration (IC50) values were 17.34±0.025 μM, and 18.928±0.632 μM [24,25]. Owing to its low toxicity and strong cytotoxic effects, Calotropine N O-oxide appears to be a promising source of anticancer drugs [7]. Furthermore, although alkaloids play an important role in pharmacology and therapeutics, their presence in the nectar of Calotropis species may affect their suitability as a food for nectarivorous organisms, an area that has received little attention in biological research [26].

Flavonoids and Phenolic Compounds

Flavonoids are a broad class of phenolic compounds abundantly produced by plants [37]. They primarily neutralize harmful free radicals and reactive nitrogen species, thereby reducing oxidative stress [27]. These compounds have been identified as potential anticancer agents because of their ability to influence cancer cell growth [28]. They can induce apoptosis, stop the cell cycle, and have anti-angiogenic and anti-migratory properties, all of which are important for preventing tumor growth and progression [28,29]. *C. procera* flavonoids, such as Calotropin aglycone, Calotropagenin aglycone, and Calotropin, have demonstrated cytotoxic activity against various cancer cell lines, including KB, MCF-7, colon carcinoma, T-47D, and MDA-MB-231 [30,31, 32,33].

C. procera is well known for its anticancer properties, and all parts of the plant-roots, stems, leaves, flowers, and latex-exhibit cytotoxic activity [33]. This plant contains several chemopreventive compounds, including Calotropiscin, Giganteol, and Giganteone A and B [34]. Furthermore, the alkaloid ω-undecalactone isolated from its latex, demonstrated dose-dependent cytotoxicity against oral and esophageal squamous cell carcinoma [35]. This plant also contains oleanolic acid, a triterpenoid with antioxidant, anti-inflammatory, and anticancer properties [36]. The nutritional content of the leaves, including pro-vitamin carotenoids like β-carotene, contributes to its antioxidant properties [34,35]. Calotropis has been shown to affect cancers, such as breast, cervical, colorectal, and prostate cancers, and its potential is supported by its historical use in traditional medicine for a variety of conditions [36].

C. procera's anticancer potential has been investigated, revealing its role in the treatment of estrogen-induced cancers, as well as its potential influence on genetic factors such as BRAC2 gene mutations [37]. Its cytotoxic activity, combined with its laxative, anthelminthic, and anti-pneumonia properties, demonstrates its therapeutic versatility [37]. Extracts from the latex of plants have also been found to contain bioactive compounds, such as calotropin, calotropagenin, giganteol, and giganteones A and B, demonstrating their diverse pharmacological benefits [34,37]. The ability of this plant to produce anti-cancer compounds makes it a promising candidate for future research and therapeutic applications.

Anticancer Properties of *C. procera*

C. procera has diverse and unique properties. In Egypt, this plant is used to treat a variety of ailments, including cancer, and is an important component of traditional medicine [38]. It is valued for both its tonic properties and its ability to repel pests [38]. *C. procera's* anticancer potential has been studied extensively, and several mechanisms of action have been identified, including antiangiogenic and antiproliferative effects [36,37,38]. This review examines the anticancer properties of plants from modern pharmacological and phytochemical perspectives.

The anticancer properties of *C. procera* have been well documented in numerous studies. From 2010 to 2021, researchers have conducted extensive *in vivo* and *in vitro* experiments on animals and cells to investigate the potential of the plant as an anticancer agent [36-39]. These studies have investigated a variety of therapeutic indicators, including their involvement in carcinogenesis, antioxidant activity, and effects on inflammatory cytokines [36-39]. The contributions of plants to cancer therapy are constantly being refined and evaluated, particularly when combined with other compounds, to increase their biological activities [7,26,37].

C. procera remains an active research topic, with ongoing studies focusing on its modern scientific applications in cancer therapy [40]. The therapeutic potential of this plant is being studied in terms of several key factors, including its effect on carcinogenesis and its role in regulating necrotic factors and anti-fibrotic responses [38, 39]. C. procera holds promise for the development of effective anticancer therapies as evidenced by its long history of use and emerging scientific research [38, 40].

***In Vitro* Studies:**

In vitro studies have provided valuable insights into the potential effects of *C. procera* on cancer and its underlying mechanisms in controlled laboratory settings [39]. Researchers used a variety of *in vitro* models to investigate the effect of *C. procera* leaf extracts or their purified components on cancer cell replication and apoptosis. Experiments were conducted to determine the effects of these extracts, either alone or in combination with other therapeutic agents, on cancer cells with high proliferation rates [33,35,36, 37].

Researchers examined the antiproliferative and anticancer effects of *C. procera* extracts and isolated components in a variety of cancer cell lines, including MCF-7, MDA-MB-231, MDA-MB-435, BEL-7402, and Hep3B [3,41,42,43,44]. These studies examined factors such as extract concentration, culture conditions, observed anticancer effects, and mechanisms of action. *C. procera* has been shown to have a variety of anticancer effects, including the inhibition of cell proliferation, cell cycle arrest, and apoptosis [42-44]. These effects are thought to be caused by mechanisms such as increased reactive oxygen species (ROS) production, reduced mitochondrial membrane potential (MMP), and modulation of signaling pathways involving PARP, caspases, PI3K, AKT, p53, ERK, and JNK [41-44].

in vivo Studies

Significant findings were reported in an *in vivo* study investigating the effects of *C. procera's* defatted hydroalcoholic extract on Ehrlich tumor growth and metastasis [4,7,39,45]. Mice treated with 50 or 100 mg/kg of the extract showed a significant reduction in tumor volume compared to untreated controls [7]. Furthermore, the number of metastatic tumor sites was reduced, which may be due to the ability of the extract to stimulate immune responses in Ehrlich tumor-bearing mice [7,45]. This extract also reduced the number of metastatic sites, suggesting an immunostimulatory effect that may contribute to its antitumor properties [7,45]. Other study found an increase in tumor volume after *C. procera* treatment; however, this study focused on using the plant's tumor-suppressive potential to develop new drug delivery systems rather than evaluating its direct therapeutic efficacy [2].

Mechanisms of Action

C. procera has been traditionally used to treat various types of cancer [13]. Numerous studies have investigated the pharmacological properties of this plant and revealed its promising anticancer potential [37,2]. *C. procera's* anticancer mechanisms have been studied in cell cultures and *in vivo* animal models [39]. This section discusses *C. procera's* anticancer mechanisms and summarizes recent research on its effects on various cancer cell lines, including solid and blood cancers.

Apoptosis Induction

Both synthetic and herbal chemotherapeutic agents frequently cause programmed cell death, or apoptosis, in cancer cells [46]. Understanding this mechanism is critical for assessing the anticancer potential of these agents. The activation of caspase enzymes initiates apoptosis, which is a key indicator of the ability of an agent to inhibit cancer [43]. Recent studies have focused on developing strategies to induce apoptosis in cancer cells as a form of cancer treatment [43,47]. Natural anticancer agents have been used to treat cancer for over three centuries, and their therapeutic potential is well recognized [31].

Reactive oxygen species (ROS) are important regulators of apoptosis in a variety of cancer cells. It has been demonstrated that plant-based chemical extracts increase anticancer activity by encouraging the production of ROS [48-52]. When ethanolic extracts from *C. procera* were applied to non-small cell lung cancer lines like A549 and NCI-H1299, ROS production occurred, which in turn caused apoptotic cell death [53]. Moreover, a substance found in the stems and leaves of *C. procera* called coroglaucigenin reduced antioxidant defenses and raised ROS levels [54]. Moreover, during the apoptosis of ovarian and colon cancer cells, ROS play a crucial role in controlling intracellular ATP [55, 56].

Cell Cycle Arrest

The mechanism by which a potential anticancer agent induces apoptosis in cancer cells is critical for determining its efficacy against cancer. The extensively documented *C. procera's* ability to induce apoptosis in various types of cancer cells has been extensively documented [46-52]. Two apoptotic pathways have been identified: the NF-κB death receptor-mediated extrinsic pathway and the caspase-9 apoptosome intrinsic pathway [57]. Although these apoptotic pathways are important, another critical factor is the ability of anticancer agents to induce cell cycle arrest in cancer cells [57]. This arrest can occur at any stage of the cell cycle, including G1, S, G2, and M, where tumor suppressor proteins and regulatory complexes play critical roles in maintaining cell cycle integrity and repairing damaged DNA [57, 58]. Cell cycle regulation is inextricably linked to molecular mechanisms underlying cancer development and progression, making it an important target for cancer detection and treatment [58].

C. procera has been extensively studied for its effects on cell cycle phases, specifically G0/G1, G1, and G2/M [60-63]. Understanding the effect of *C. procera* on these specific phases could lead to the development of targeted therapeutic strategies for tumors [57]. Regulation of the cell cycle, particularly the transition from G1 to S phase, is critical for limiting cancer growth [58]. *C. procera*-derived substances have been shown to downregulate cyclin D1, upregulate p21, and increase the expression of p53, both of which are important cell cycle regulatory factors [58].

In summary, *C. procera's* ability to induce apoptosis and cell cycle arrest in cancer cells demonstrates its potential as an anticancer agent [55-58]. By targeting specific cell cycle phases and apoptotic pathways, *C. procera* may be a promising cancer treatment option [57, 58]. However, further research is needed to improve our understanding of the molecular mechanisms involved and optimize their use in clinical settings.

Conclusion and Implications for Cancer Therapy

C. procera, like other species in the Calotropis family, has a long history of traditional use, particularly in the treatment of infectious diseases. Their medicinal properties have been validated in animal, cellular, and clinical studies. Furthermore, its potential as an antitumor agent has been investigated in various cancers, with discussions centered on the active compounds derived from its extract. Despite these promising findings, the available data and patents for anticancer applications remain limited. *C. procera* is well-known in Ayurveda because of its numerous medicinal properties. Modern studies have attempted to determine the efficacy of plants in the treatment of various health conditions. This review examines recent literature and patents to identify potential areas for future research on this flowering plant. This evaluation aimed to lay the groundwork for further scientific investigation into *C. procera's* medicinal properties and its potential role in modern medicine.

According to a systematic review, *C. procera* preparations are widely used in India to treat and prevent various diseases. Most of the evidence comes from *in vitro* studies on both normal and cancerous cells; however, some *in vivo* studies and clinical applications have shown promise. However, many studies have not fully elucidated the precise mechanisms of action or the biological effects of C. procera, highlighting a gap in our current understanding of how *C. procera* functions at the molecular level.

Further research and clinical trials are required to determine the cost-effectiveness and therapeutic potential of *C. procera* in Asia. Based on the available literature and findings of this review, *C. procera* shows promise as a novel anticancer agent that can be incorporated into future chemotherapeutic regimens. Further research may pave the way for its use as an effective cancer treatment option.

Conflicts of Interest

The authors declare that there were no commercial or financial relationships that could lead to a conflict of interest.

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