

REVIEW

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A systematic review on the biological evaluation of *Calotropis procera* (Aiton) Dryand

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Abstract

Background Humans have used plants as a safe and effective medicine for a wide range of ailments ever since the earliest days of civilization. *Calotropis procera* potential as a treatment for a variety of ailments has been known for quite some time. This xerophytic, upright shrub grows to a height of about 6 m and can be found in the tropics of Africa and Asia. Its parts have been used to cure a variety of ailments, including rheumatism, fever, dysentery, diabetes, malaria, asthma, and many more. Here, we provide a synopsis of the available biological data and discuss the possible ways in which *Calotropis procera* could be used as a novel platform for the treatment of a wide range of diseases.

Main body High antioxidant, antiinflammatory, antianalgesic, antimicrobial, antimalaria, antidiabetic, wound-healing, hepato-protective, nerve-recovery, antiulcer, insecticidal, and anticancer effects have been observed in the latex. The research also found that excessive intake has negative health effects.

Conclusion The review discovered that the biological evaluation of *C. procera* in vitro and in vivo animal models was well documented. Human safety and efficacy, however, have yet to be thoroughly tested, and additional well-designed clinical trials are required to confirm preclinical findings. It is essential to establish a standard dose and assure its safety.

Keywords Antioxidant, Antibacterial, *Calotropis procera*, Pre-clinical, Plants, Traditional

Background

The use of plant-based remedies to treat human and animal illness dates back thousands of years [1]. In many cultures, plants have long been relied upon as an effective means of disease prevention and treatment. Medicinal plants are still the primary source of healthcare in many developing world areas [2]. World health organization (WHO) reports that 80% of the world's population, mostly in developing nations, relies on traditional medicines to treat common health problems [3]. They are used medicinally and as a food source in almost every culture. What's more impressive is that plants provide the basis for nearly 25% of today's pharmaceuticals [4].

They are regarded as invaluable sources of pharmaceutical products including herbal medicines, and their use contributes significantly to primary healthcare delivery. Bioactive plant products have been a major research and development focus in the food and pharmaceutical industries [5]. *Calotropis procera*, it is common in Indonesia, Malaysia, China, and the Indian subcontinent [6]. The medicinal properties of the plant have long been recognized, and its parts have been used to treat a wide range of conditions, including rheumatism, painful muscular spasms, fever, dysentery, diabetes, malaria, asthma, and more. In recent years, studying synergies in phyto-medicine has emerged as an important new field of study. Extensive pharmacological studies were conducted on the biological activities of plant extracts and natural products derived from these plants. Exploring the relevant scientific literature is essential for understanding the potential of industrial use of *Calotropis procera*. With an eye toward industrial formulation of health products,

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this study aimed to compile a comprehensive literature review on the biological potential of its components. This study will facilitate the dissemination of information about the plant's potential applications, which in turn will guide future decisions in the fields of food science, herbal medicine, and pharmaceuticals.

Main text

Search strategy, inclusion, and exclusion criteria

Online databases like Science Direct, PubMed, Springer, Wiley, Sage, Google Scholar, and Hindawi combed through primary scientific research publications to glean relevant data. Selection criteria: a secondary verification of the plant name authenticity was performed using the website World Flora Online (<http://www.worldfloraonline.org>). Papers with only plant accepted names were considered. We used the following terms as search criteria: antioxidant, *Calotropis procera*, traditional medicine, *C. procera*, antidiabetic, antibacterial, medicine, toxicity, antiviral, antimicrobial, ethnopharmacology, cytotoxic activity, chemical composition, isolation, compounds, HPLC, FTIR, GCMS analysis. We did not incorporate any information that may have come from questionable websites into our investigation. We also omitted articles that were reviewed with *C. procera* theses, or were written in a language besides English.

Description and origin

Traditional medicine has used *Calotropis procera*, a plant belonging to the Asclepiadaceae family. It's a shrub that produces latex and thrives in the wild despite the fact that it's constantly exposed to adverse weather [7]. When damaged, the plant secretes a milky latex that is most abundant in its aerial parts. It protects the plant from

harm and is full of useful secondary compounds and enzymes [8]. Swallow wort in English, madar in Hindi, and Tumpapiya in Hausa are just some of the common names for this plant. It reaches a height of 2.5–6 m and has a soft woody, upright form. It prefers warm climates, dry, sandy, and alkaline soils, and is therefore widespread across the globe (Fig. 1). It thrives in a variety of other environments, including landfills, abandoned lots, wastelands, roadside ditches, and sand dunes [9].

Biological activity

Multiple biological assessments of the plant's constituent parts were performed, each employing a unique assay to confirm the plant's efficacy, as discovered by the research (Fig. 2).

Antioxidant

When oxygen is used to produce cellular energy, a redox process occurs that releases free radicals. The reactive oxygen species (ROS) that make up the free radicals include hydroxyl radical, hydrogen peroxide, and superoxide anion [2]. To guarantee the efficacy of such antioxidant materials, the antioxidant properties of plant extracts were evaluated in several model systems using several different indices (Table 1). The DPPH radical scavenging assay found that the extracts had high levels of free radical scavenging activity (42–90%). It was found that the concentration affected the percentage of metal ions chelated (16–95%) [10]. At 500 µg/mL, the methanol extract showed the highest scavenging activity (83.63%) against ferric thiocyanide, followed by hydrogen peroxide and hydroxyl radical assays, and then the DPPH assay, which showed the lowest activity (50.82%) [11]. Dose-dependent reductions in TBARS levels were observed



Fig. 1 Pictures of *Calotropis procera* collected from wild

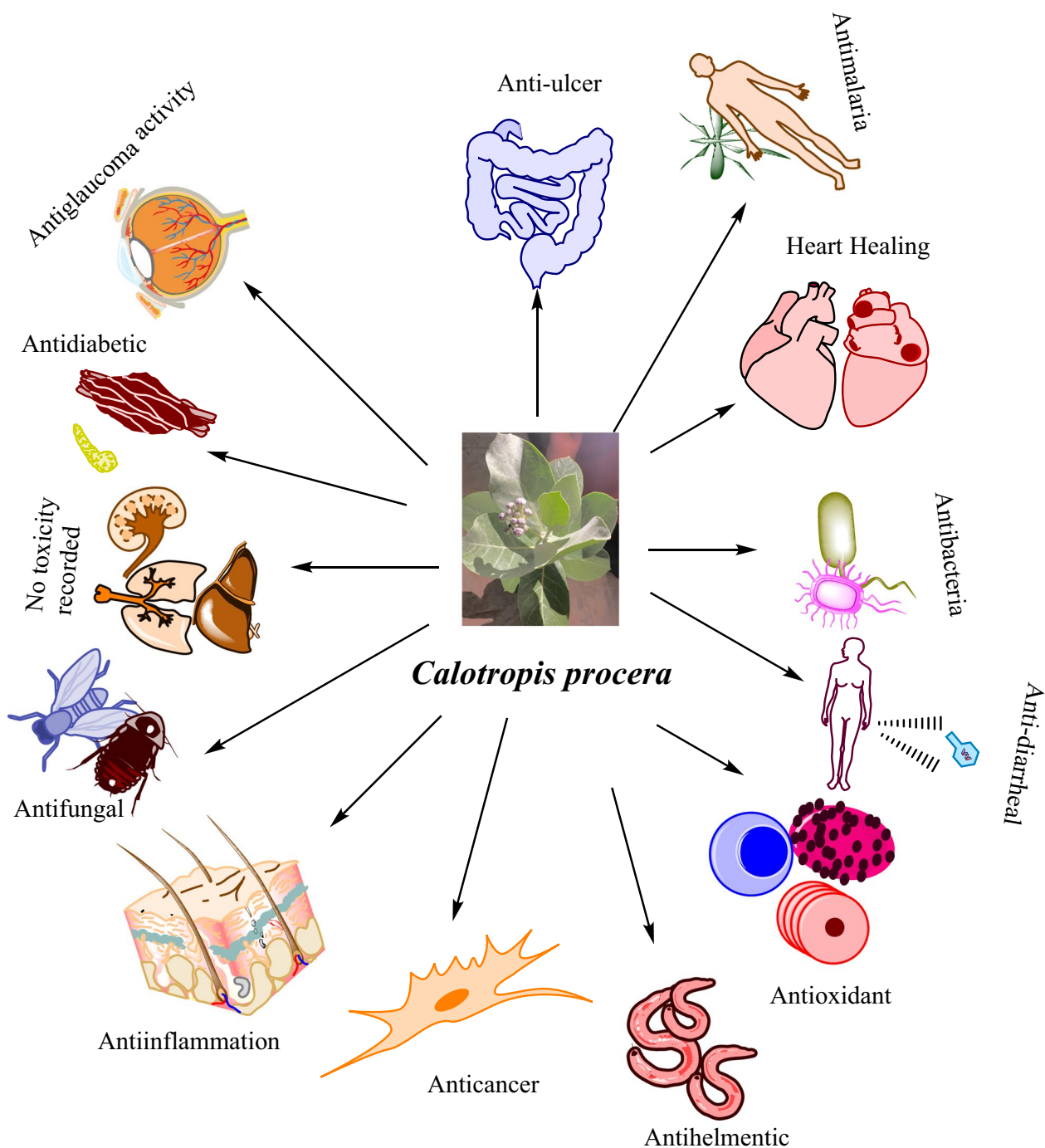


Fig. 2 Diseases treated with different parts of *Calotropis procera*

after 31 days of treatment with dry latex. TBARS levels were brought down to normal levels in both the DL 400 mg/kg and glibenclamide groups [12]. The highest levels of antioxidant capacity were found in lyophilized latex extracts ($IC_{50}=0.060$ mg/mL), while the lowest levels were found in extracts from field-grown plant roots

($IC_{50}=0.27$ mg/mL) [13]. The aqueous flower extract was the most powerful radical scavenger ($IC_{50}=85$ μ g/mL), while the ethanol flower extract was the least effective ($IC_{50}=142$ μ g/mL) [14]. The DPPH radical scavenging activity (%) was the highest (95%) in the ethyl acetate extract, lowest (86% in dichloromethane), and highest

(760%) in water, lowest (32%) in methanol, and lowest (24%) in hexane. The extract of ethyl acetate is the most effective at scavenging ABTS (94%), followed by the extract of water (86%) [15]. 35–39% of free radicals were neutralized by the substance [16]. The isolated compound showed the highest level of inhibition (51.7%), followed by methanol (80%) and water (29.2%) [17]. Using the DPPH radical scavenging assay, the antioxidant activity of both samples was determined to be 81.16 and 80.97% inhibition, respectively [18]. Against DPPH radicals, the aqueous methanol extract showed a very high scavenging activity of 85.5% in vitro [19]. In terms of DPPH scavenging activity (88.19%) and LPOI activity (89.58%), the ethanolic flower extract came out on top, while the aqueous flower extract had the most reducing power (1.827) [20]. Flavanol glycosides, cardinolides, and lignans have all been found in the latex of this species, all of which may contribute to its antioxidant properties [21]. The location of phenolics' functional groups around the nucleus determines their ability to scavenge free radicals and function as antioxidants [22]. The number and arrangement of H-donating hydroxyl groups are the most important structural factors that govern the antioxidant potential of phenolics [22]. Active hydrogen donor ability of hydroxylated substitutions in calotropogenin, calotropin, and calotoxin may account for some of the plant's potential antioxidant properties [23]. It's possible that some effects might be triggered by other active substances. Even though numerous recognized chemicals were discovered, it is still unclear how much each of them contributed to the current levels of antioxidant activity. These results from the present investigation point to the possibility of cooperative or antagonistic interactions between these active chemicals' antioxidant capacities. As a result, more research is needed to determine the most prominent compounds and learn more about the mechanisms and synergistic effects of these substances. This study's findings demonstrated conclusively that latex of *C. procera* has strong antioxidant activity against a range of in vitro antioxidant systems.

Anti-inflammatory activity

The use of therapeutic plants in folk medicine for the treatment of common illnesses including malaria, inflammation, colds, fever, cough, and other medicinal claims are now supported by solid scientific data, which has led to a substantial increase in interest in these plants recently. The inflammatory response is a protective mechanism activated by injured or infected tissues. It is common during the healing process and can also be a problem on its own. Redness, swelling, discomfort, heat, and loss of function are all symptoms of inflammation. An abundance of chemical mediators, such as

kinins, eicosanoids, complement proteins, histamine, and monokines, trigger and regulate the inflammatory events underlying these symptoms. *Calotropis procera* plant have been used medicinally for centuries to treat inflammation-related disorders and/or to manage the inflammatory symptoms of various diseases. When administered at 5 mg/rat, dramatically decreased oedema caused by carrageenin by 71% ($p < 0.005$) and formalin by 32% ($p < 0.05$) [24]. Substantial dose-related activity was shown for a chloroform-soluble fraction in pharmacologic models of carrageenin-induced pedal oedema, cotton pellet granuloma, and formaldehyde-induced arthritis in rats ($p < 0.001$) [25]. The extract (100 mg/kg b.w.) was more efficient than Indomethacin at avoiding the formation of paw oedema [26]. After treatment with MeDL, colonic mucosal damage was significantly reduced in colitic rats, and tissue levels of oxidative stress markers and proinflammatory mediators were restored, as seen by macroscopic and microscopic examinations [27]. The IC_{50} values for compound 4 were 7.6 μ M against 5-LOX and 2.7 μ M against 15-LOX, making it the compound with the highest antiinflammatory action. [28]. The extract had a dramatic antiinflammatory effect at dosages of 100 and 200 mg/kg. The extract demonstrated 21.6 and 71.6% inhibition at the doses of 100 and 200 mg/kg, respectively, whereas the conventional medication dexamethasone reduced e-Complete Freund's Adjuvant-induced arthritis by 99% [29]. Daily administration of MeDL (50 and 500 mg/kg) considerably reduced the inflammatory response and improved the joint abnormalities seen in arthritic rats [30]. In vivo studies using chloroform and hydroalcoholic extracts showed significant antiinflammatory efficacy at doses of 200 and 400 mg/kg, respectively [31]. The plant, *C. procera*, is a potential source of antiinflammatory agents in in vitro and in vivo animal models, which support its traditional usage in the management of inflammation. Non-protein and protein components of latex are responsible for its antiinflammatory effects [27]. The molecular basis for the antiinflammatory effects of a pure chemical or crude extract (1) Tyrosine kinase receptors are induced by several pathologies and stresses (2) which then stimulate IKKs (3) Additionally, active IKKs phosphorylate the inactive $I\kappa B\alpha$ -NF- κ B complex. (4) A phosphorylated form of $I\kappa B\alpha$ is ubiquitylated and eventually destroyed. (5) Chemical or crude extract blocks the entry of the active form of NF- κ B into the nucleus. (6) which promotes the expression of genes involved in (6a), adhesion molecules, receptors, chemokines, and cytokines all have a role in (6b) growth, proliferation of cells and differentiation (7) Arachidonic acid can be converted into prostaglandin with the help of Cox2, but a pure compound or

crude extract will prevent this from happening. (8) This inflammation is caused by prostaglandins (Fig. 3).

Antibacterial activity

The steadily rising number of microorganisms that are resistant to chemical antimicrobial drugs poses a serious threat to the control of infectious diseases, even though

new antibiotics are being synthesized steadily by industry. As a result, new multi-resistant bacterial strains emerge, which poses a serious threat, especially to those with compromised immune systems. As a result, natural plant products serve as a constant source of inspiration for the development of bioactive antimicrobial agents that have low toxicity, a broad spectrum, and

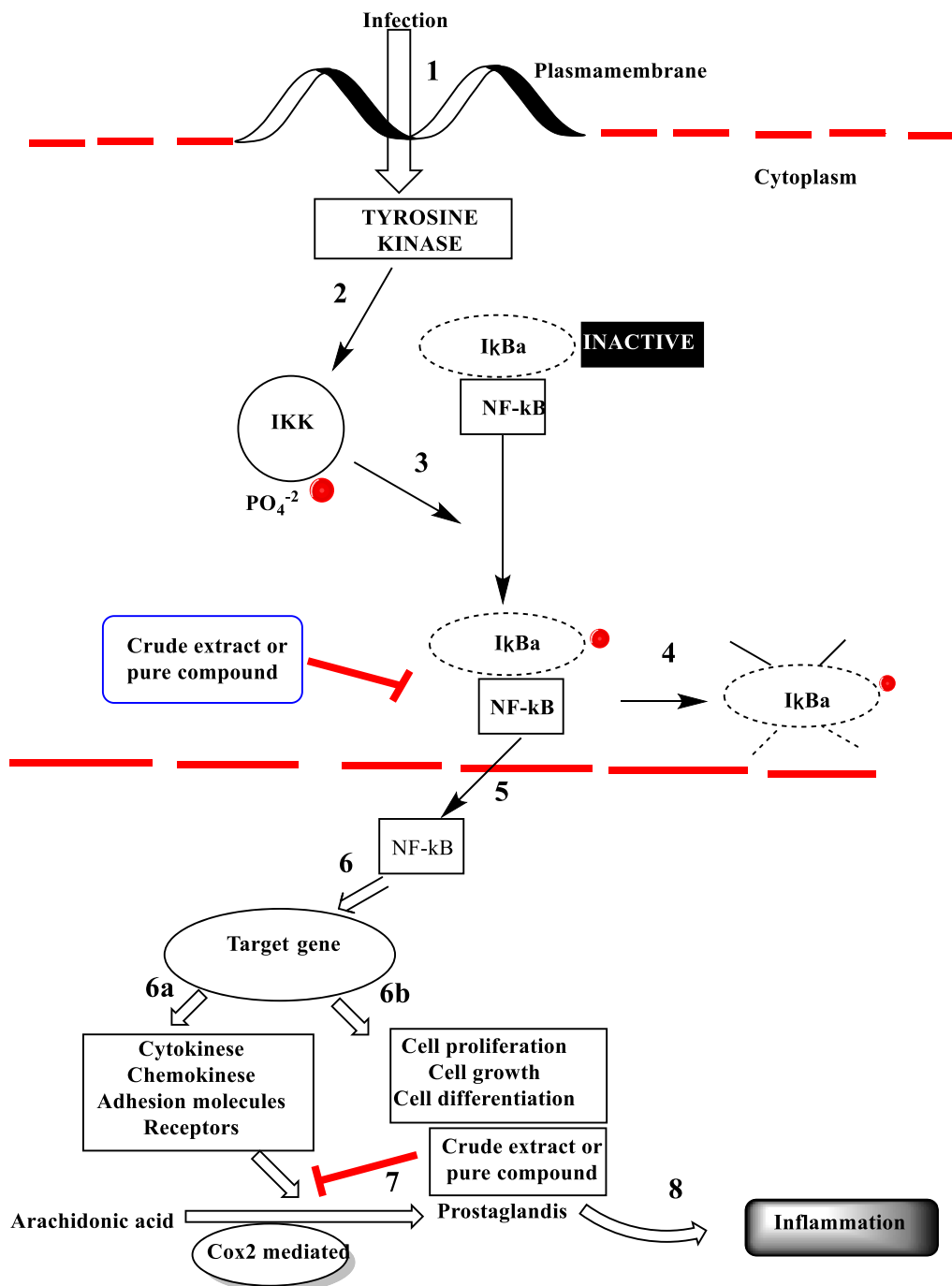


Fig. 3 Antiinflammatory mechanism of action of crude extract or pure compounds from *C. procera*

good pharmacokinetics and may be employed in clinical settings without requiring any chemical modification. There has been a recent push to publicize the use of plants as alternative medicines for combating infectious diseases. Promising antibacterial activities were observed in these natural compounds (Table 1). For *Staphylococcus saprophyticus* and *S. aureus*, the greatest inhibitory zones for aqueous leaf extracts at 500 µg/well were 22 mm and 10 mm, respectively [32]. Against all five of the tested strains, proceragenin has shown activity. The zone of inhibition at doses of 150 and 200 mcg per well was between 20 and 35 mm, and the minimum inhibitory concentration (MIC) of the sensitive species was between 100 and 150 mcg [33]. The most effective inhibition (11 mm) against *Escherichia coli* was seen in the leaves after they were extracted with ethanol [6]. The MIC for *E. coli* E1 at 511 µg/mL showed greater antibacterial effectiveness when methanol extracts were used [34]. The inhibitory zone against *E. coli* has a diameter of 9.8 mm at 100 µg/mL Cuonp, which is bigger than the zone seen in the control without nanoparticles [35]. At a concentration of 250 µg/mL, the water-soluble extract exhibited strong antibacterial activity against the pathogens *Clostridium perfringens* and *Streptococcus faecalis* [36]. *Staphylococcus aureus* and *Streptococcus pyogenes* were significantly inhibited by the extract, with inhibition zones measuring more than 15 mm in diameter [37]. Overall, the test organisms were effectively inhibited by the ethanolic latex extract, with *B. subtilis* showing the largest zone of inhibition (21 mm) [38]. At 100 µg/mL of an ethanol extract, the maximum zone of inhibition against *Pseudomonas aeruginosa* was observed [39]. Ethanol performed much better than chloroform and water ($p < 0.05$). Latex ethanolic extract showed the biggest zone of inhibition (14 mm) when tested against *E. coli* with 9 mm zone [40]. The largest inhibition zones against *B. subtilis* when utilizing leaf and bark extracts made with 50% methanol were 20 and 21.66 mm [41]. All fractions were effective at inhibiting *Klebsiella pneumoniae*. The most effective flower extract fractions are the n-hexane and ether fractions, which had inhibition zones of 23 and 24 mm, respectively [42]. The MIC of the ethanolic extract of leaves was 1000–2000 µg/mL, but the MBC of the ethanolic extract of latex was 2000 µg/mL [43]. The crude flavonoid fraction has shown the maximum efficacy, with inhibition zones' diameters against the investigated bacterial strains ranging from 15 to 28 mm [44]. *C. procera* antibacterial activity may be due to one or more components of the latex, either alone or in concert with others [45]. The latex of *C. procera* contains a wide variety of compounds, including proceroside, proteolytic enzymes, syriogenine, cardenolides, carbohydrates, cardioactive glycosides calactin, calotropain, calotoxin,

and alkaloids, tannins, flavonoids, and procerain, a stable cysteine protease [45]. It is theorized that the synergistic effects of a variety of bioactive compounds and their byproducts found in plant extracts contribute to the improved efficacy of numerous extracts. Specifically, CuONPs cause protein denaturation and cell death in bacteria by releasing Copper (Cu) ions from nanoparticles, which bind efficiently to the negatively charged bacterial cell wall and break it (Fig. 4). The released Cu ions from the nanoparticles may bind to the negatively charged bacterial cell wall, causing it to rupture and, in turn, leading to protein denaturation and cell death [35]. This study provides evidence of the plant's antibacterial properties and suggests it may be useful in the treatment of bacterial diseases in humans and other animals.

Antifungal activity

Despite the great developments in human medicine, infectious diseases created by microorganisms like fungi continue to pose a significant threat to public health. Although fungal infections may seem manageable under optimal hygiene conditions, the use of antifungal drugs has led to the almost inevitable emergence of resistant strains of the fungi they were designed to combat. Once a microorganism has developed resistance to an antimicrobial drug, it can no longer be treated with that drug, which can have serious consequences in the clinic. The increasing prevalence of drug-resistant fungal illnesses has increased the urgency of developing effective alternatives to chemosynthetic drugs for treating human illness. Extracts that prove useful may pave the way for new, eco-friendly antifungal drugs. Of the three extracts tested, the aqueous one was the weakest. On the other hand, the extracts made with ethanol and chloroform performed exceptionally well. An ethanol extract of latex proved to be the most effective antifungal agent against *Candida albicans*. The minimum inhibitory concentration (MIC) for this ethanol extract was 5–20 mg/mL [40]. With inhibitory zones measuring 30 mm in diameter, the crude flavonoid fraction was the most efficient against *C. albicans* [44]. Treatment with LAg-NPs caused *T. rubrum*, *C. albican*, and *A. terreus* to grow by 24 mm, 26 mm, and 23 mm, respectively [46]. The average diameter of a fungal colony exposed to CuONPs at a concentration of 100 µg/mL was 3.6 mm, and the colony size barely altered. As opposed to the control's 21.2 mm, three different studies with 30 and 50 µg/mL demonstrated inhibition of 17 and 14.3 mm, respectively [35]. All extracts prevent all organisms from proliferating. The MIC of the latex extract ranged from 5 to 7 mg/mL. For leaf extract, the MIC ranged from 11 to 15 mg/mL [38]. All peptidases that were

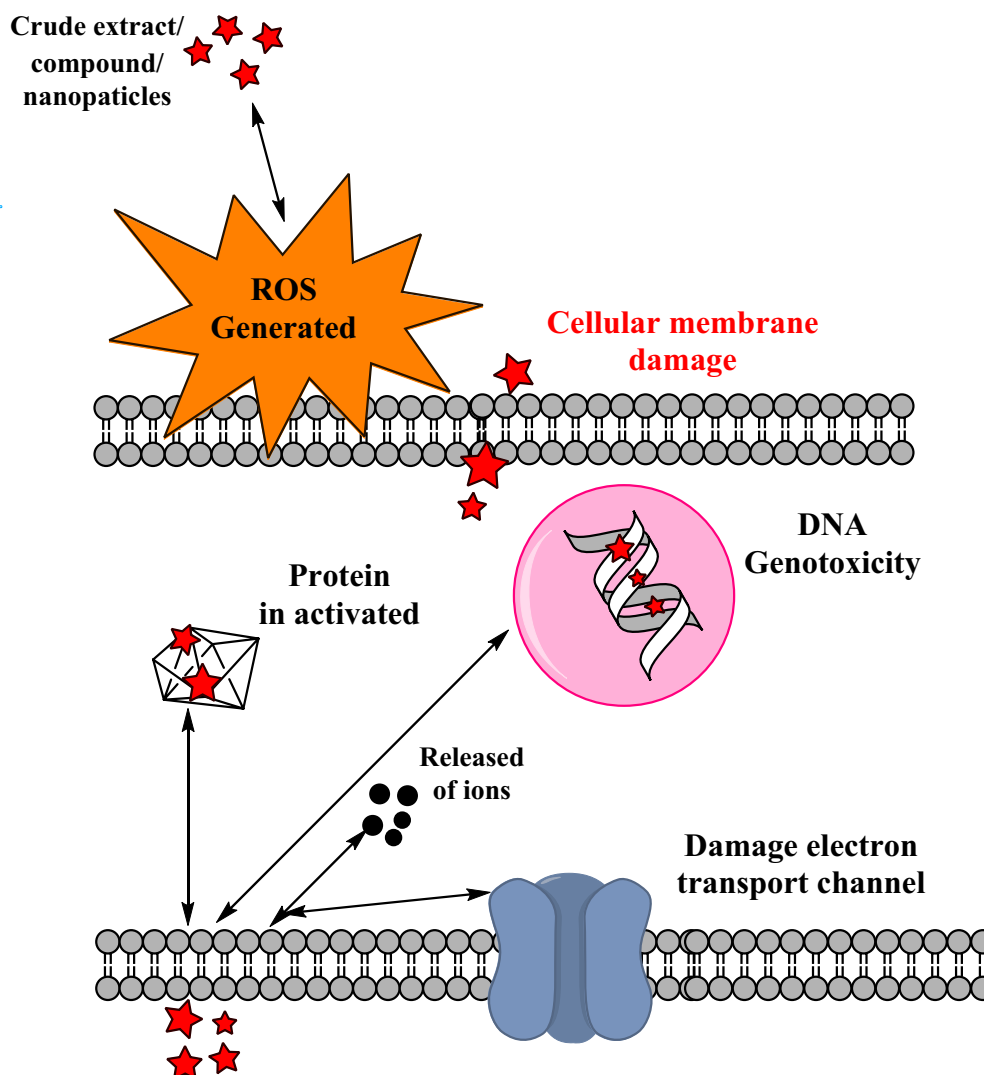


Fig. 4 Mechanism of action of *C. procera* part nanoparticles on bacteria

tested had IC_{50} values of roughly $50 \mu\text{g}/\text{mL}$ for the two tested fungi [47]. The crude extract proved effective against *E. floccosum* and *T. gypseum* at a concentration of $4.0 \text{ mg}/\text{mL}$ [48]. The lowest inhibitory and fungicidal values, respectively, were 0.5 and $0.9 \text{ mg}/\text{mL}$, 2.0 and $4.0 \text{ mg}/\text{mL}$ (Table 1). Antimicrobial resistance mechanisms include enzymatic changes in antibody activation and receptor modifications, as well as restrictions on drug delivery to susceptible hosts of pathogens [48]. The mechanism of action revealed CuONPs are able to penetrate fungal hyphae and destroy them by interfering with DNA replication and protein synthesis at the macromolecular level [35]. The amount of NPs used to suppress the fungus is also crucial because larger NPs have higher concentrations that cause enhanced membrane permeability and cell death. Fungi are inhibited by *Calotropis procera* in vitro. The effectiveness in the

treatment of fungal infections, however, has not been demonstrated in clinical trials.

Anthelmintic activity

A major contributor to significant production losses in grazing animals, helminthiasis, is one of the most significant animal illnesses worldwide. As a result of weak management methods and control measures, the disease is disproportionately widespread in underdeveloped countries. A multimodal strategy that incorporates both long- and short-term anthelmintic treatment is necessary for effective helminth management. Natural product controls have been investigated because of a rise in anthelmintic-resistant parasites (Table 1). When exposed to either fresh or aqueous extracts of dried latex, both spontaneous motility (paralysis) and pin-evoked responses were reduced in a dose-dependent manner.

100 mg/mL (aqueous extract of dried latex) and 100% of the standard dose (300 mg/mL) produced results similar to those achieved with 3% piperazine (fresh latex) [49]. Sheep treated with aqueous extract (3 g/kg) or crude powder (3 g/kg) for 7 or 10 days experienced an 88 and 77% reduction in egg count, respectively. The methanolic extract group experienced the least severe drop in egg count, at 20%, on day 7 post-treatment [50]. The discovered activities should be confirmed through additional studies, and the individual compounds should be isolated for a deeper dive into the underlying processes. In addition, the extract's therapeutic potential must be assessed throughout a broad range of concentrations to establish the optimum therapeutic doses and treatment duration.

Anti-diarrheal activity

A primary contributor to both child mortality and morbidity is diarrhea, which is characterized by three or more watery or loose stools per day [51]. Diarrhea is a factor in one out of every ten fatalities of children under five worldwide [51]. Children in sub-Saharan and South Asian nations have a higher rate of diarrhea-related mortality (78%) than those in other developing nations. Scientists' interest in natural product-based drug development has been rekindled considering the widespread emergence of resistance to standard therapeutic drugs among many prevalent diseases. For thousands of years, people have relied on medicinal herbs as a natural remedy for health issues. Natural compounds originating from plants, or chemicals that mimic their effects, are the basis for many modern pharmaceuticals. Decreased bowel motion by 2.2 times as much as the castor oil-treated control group (6.8) minimized castor oil-induced diarrhea and kept the bowels from moving too frequently [52]. More scientific investigation is needed.

Antimalarial activity

Malaria is one of the most widespread infectious diseases in the tropics. Approximately 1.5–3 million individuals lose their lives every year due to malaria infections, out of an annual infection rate of 300–500 million [53]. The rapid global spread of malaria strains resistant to numerous drugs has made the need for novel antimalarial an urgent public health priority [54]. The IC_{50} values for the ethanolic extracts of the flowers and buds were 0.11 to 0.47 mg/mL against *P. falciparum* and 0.52–1.22 mg/mL against CQ-resistant strains (Table 1). The percentage of inhibition against MRC 20 ranged from 7.51 to 61.38% within a dose range of 62–125 mg/mL, while the percentage of inhibition against MRC 76 aged between 3.437 and 41.08%. These results were seen for flower, bud, and root fractions [54].

Antidiabetic activity

A rising number of people are developing diabetes mellitus, and the associated death rate keeps climbing. Insulin deficiency, insulin resistance, or both contribute to the metabolic abnormalities in carbohydrates, lipids, and proteins that define diabetes mellitus. It is estimated by the International Diabetes Federation that there are currently 41 million people with diabetes in India, with that number expected to rise to 70 million by the year 2025 as the prevalence of diabetes mellitus continues to skyrocket around the world [55]. The use of medicinal plants with hypoglycemic effects has been widely documented to be beneficial in the treatment of diabetes mellitus. Most prospective lead candidates for future drug development programs can be found in natural products. Oral administration of 100 and 400 mg/kg of dry latex per day resulted in a decrease in blood glucose and an increase in hepatic glycogen content. Additionally, the diabetic rats' daily water intake was decreased to that of the non-diabetic rats, which helped to arrest their weight loss. Normal rats had blood glucose levels of 11.5 mmol/l ($p < 0.01$), while the diabetic rats had 12.9 mmol/l ($p < 0.01$). [12]. The half-maximal inhibitory concentration (IC_{50}) of the 80% ethanolic extract for various enzymes ranged from 0.78 mg/mL for beta-glucosidase to 0.93 mg/mL for alpha-amylase [56]. When compared to the control group's mean glucose level of 15.5 mmol/L, the leaf extract treated group's mean glucose level of 5.9 mmol/L ($p < 0.05$) was considerably lower [57]. Chronic administration of *Calotropis procera* root methanol, stem methanol, and leaf ethyl acetate extracts in 100 and 250 mg/kg doses resulted in a substantial ($p < 0.01$) reduction in mechanical hyperalgesia, thermal hyperalgesia, tactile allodynia, and HbA1C% level in Streptozotocin diabetic rats [58]. Antioxidant action, insulin level interference, and the protein kinase B and AMP-activated protein kinase enzymatic pathways have all been proposed as potential mechanisms of action [21]. Another possible mechanism: Pure compounds or crude extracts will produce inflammatory cytokines, which will cause macrophages to undergo apoptosis in the blood and eventually release secretory insulin. On the other hand, stimulation of dendritic cells in the brain will signal the release of insulin due to hypoglycemia there. However, it is possible that the presence of fat that covers the insulin receptor contributes to insulin resistance and diabetes mellitus by preventing the interaction between the insulin receptor in the cells and insulin release. Complications from diabetes mellitus are highlighted in the state shown in Fig. 5: Nephropathy, Retinopathy, and Neuropathy all result in harm to the nervous system (damage to nephrons).

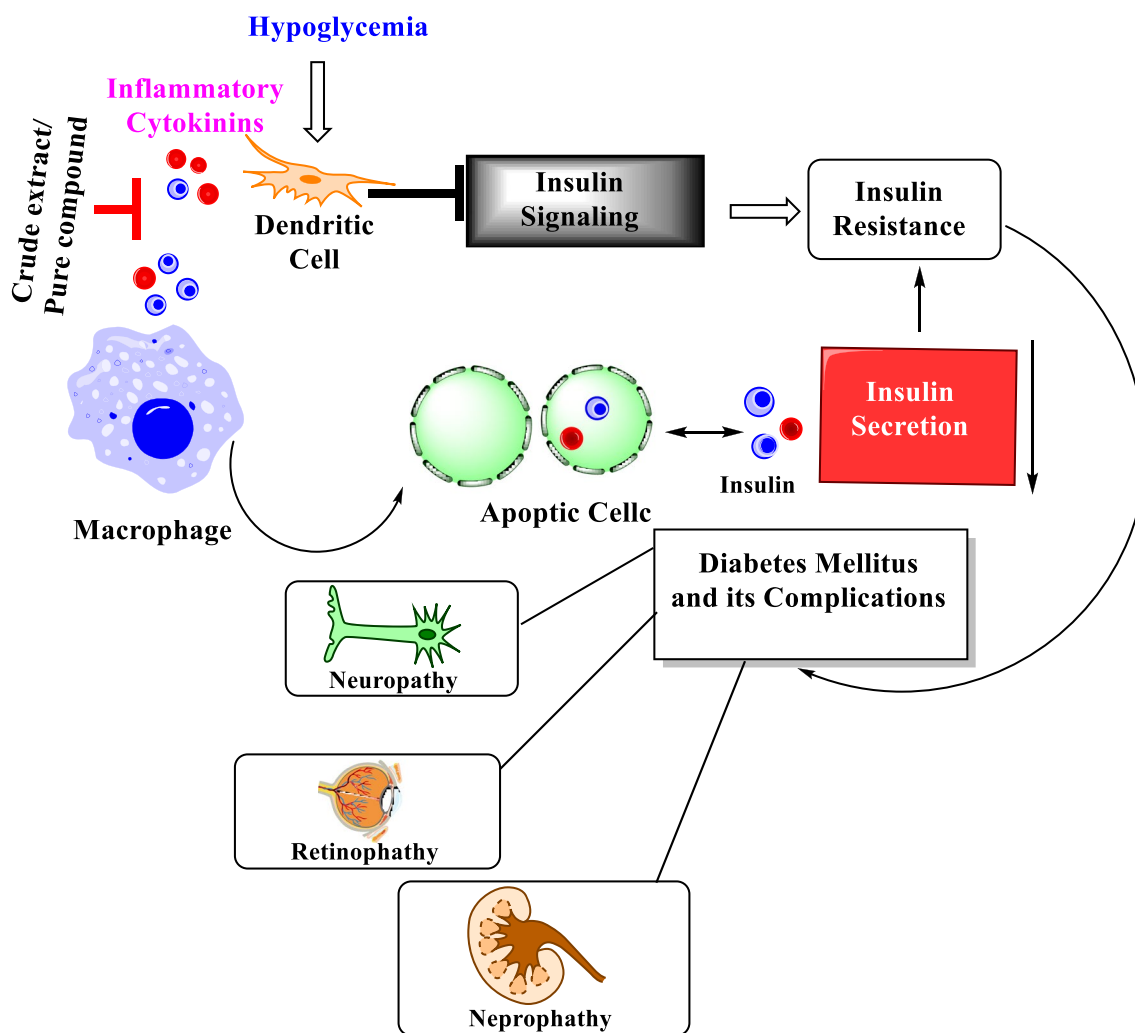


Fig. 5 Mechanism of action of *C. procera* parts against Hypoglycemia

Wound healing activity

As a result of damage to the skin or other soft tissues, the body undergoes a repair process known as wound healing. When the skin is damaged, the underlying cells undergo an inflammatory response and ramp up collagen production. In time, new epithelial cells form. Once a day, for seven days, a sterile latex solution (20 μL each time) was applied topically. The wound size was reduced as a result of the latex’s stimulation of collagen, DNA, and protein synthesis, and epithelization [59]. Normal and dexamethasone-treated rats showed a statistically significant ($p < 0.001$) decrease in epithelialization time after administration of the extract. This cut down the time needed to complete the task from 28 days to between 17 and 18 days. The consumption of the same extract led to similar increases in breaking strength in dexamethasone-treated rats [60]. After 7 days, the wounds were much smaller in the 50% latex in the honey and triamcinolone

groups, and smaller still after 14 and 21 days [61]. According to the plant’s phytochemistry, it contains triterpenoids -amyrin, flavonoids, cardiac glycosides, cardenolide anthocyanins, mudarine, lupeol, -sitosterol, flavanols, resin, potent bacteriolytic enzyme called calactin, a nontoxic proteolytic enzyme called calotropin, and a wax [62]. Strength upon breaking was much improved by the extract. The rate of wound contraction was also greatly accelerated, and epithelialization occurred more quickly in extract-treated wounds.

Hepatoprotective activity

Liver diseases are widely recognized as one of the world’s most pressing public health concerns [63]. The current medical management of these conditions is inadequate despite their high rates of prevalence, morbidity, and mortality [64]. Historically, it has been believed that medicinal plants, particularly those with long histories

Table 1 Biological activity of *C. procer*

S/N	Activity	Methods	Part	Solvents	Reference
1	Antioxidants	DPPH	Leaves	Methanol, aqueous	[32]
		LPOI, DPPH	Root	Aqueous	[10]
		In vivo	Dry latex		[12]
			Leaves	Methanol, petroleum ether, aqueous	[75]
		DPPH, DDA	Bark	Ethanol	[60]
		DPPH, (OH-), FRAP,	Flowers (Polyphenolic)	Methanol	[11]
			Leaves	Aqueous, aqueous ethanol	[56]
		DPPH, FRAP	Leaves, root, flower	Methanol	[76]
		DPPH,	Root, leaf, latex		[77]
		DPPH, FRAP	Leaf, stem, flower		[18]
			Leaves, flowers	80% aqueous methanol, 80% aqueous ethanol, 80% aqueous acetone	[78]
			Latex		[79]
		DPPH	Leaves		[19]
		DPPH	Leaves, flower	Ethanol, chloroform, aqueous	[14]
			Leaves	Ethanol, aqueous, petroleum ether, ethyl acetate, butanol and aqueous	[80]
			Leaves	Aqueous	[81]
		DPPH	Root, leaf, latex		[13]
		In vivo	Stem	Aqueous	[82]
		DPPH	Leaves	Aqueous, methanol, n-hexane	[9]
		DPPH	Latex		[83]
		DPPH, FRAP	Leaf	Methanolic, d ethyl acetate, chloroform, hot aqueous	[84]
		DPPH	Leaves	Methanol, ethanol	[64]
		H ₂ O ₂ scavenging, DPPH	Leaves	DMSO, ethanol, petroleum ether, chloroform, ethyl acetate	[85]
			Root	Methanol	[86]
		DPPH	Flower, leaf, fruit, latex		[87]
					[88]
		DPPH	Root (Dihydroquercetin-glucoside)		[17]
		In vivo	Root	Ethanol	[89]
		DPPH, ABTS	Flower	Hexane, dichloromethane, ethyl acetate, methanol, aqueous	[15]
		DPPH, FRAP	Bark, leaves		[41]
DPPH	Methanol, hexane, chloroform		[16]		
	Essential oil		[90]		
DPPH, FRAP, LPOI	Leaf, flower	Hexane, ethyl acetate, aqueous and ethanol fractions	[20]		
DPPH	Root, leaf, stem	Pet ether, ethanol (75%), aqueous	[91]		
2	Antiinflammatory	In vivo	Latex	Aqueous	[24]
			Leaves	Ethanol	[26]
		In vivo	Roots	Petroleum ether	[25]
		In vivo	Latex	Aqueous, methanol	[92]
		In vivo		Protein fraction	[7]
		In vivo			[27]
			Leaves, bark		[41]
		Lipoxygenase	Latex		[28]

Table 1 (continued)

S/N	Activity	Methods	Part	Solvents	Reference
			Rootbark	Ethanol	[29]
			Latex		[93]
		In vivo	Latex	Methanol	[30]
					[94]
		In vivo	Latex		[95]
		In vivo	Stembark	Chloroform, hydroalcoholic	[31]
3	Analgesic	In vivo	Roots	Petroleum ether	[25]
			Latex		[96]
4	Antibacterial		Leaves, stems, roots, flowers, fruits and root bark, steroids, flavonoids, cardenolides, anthocyanins, the essential oil from flowers, and latex	Ethanol	[97]
		Agar diffusion	Leaves	Methanol, aqueous	[32]
		Agar diffusion, disk diffusion	Leaf, latex	Ethanol, aqueous and chloroform	[40]
		Agar well			[33]
		Agar well-diffusion			[44]
		Agar-well	LAg-NPs		[46]
					[37]
			Leaf	Ethanol	[6]
		Agar well diffusion	Leaves	Methanol, petroleum ether, aqueous	[75]
		Broth microdilution			[34]
		Disc diffusion	Leaves	Aqueous, methanol, n-hexane	[9]
		Discs diffusion	Leaves	Methanol	[98]
		Disc diffusion	Leaves, bark		[41]
		Disc diffusion	CuONPs		[35]
		Disc	Latex	Ethanol, aqueous	[43]
			Latex		[45]
					[36]
		Well diffusion	Leaves	Ethanol, methanol, aqueous	[39]
		Agar well	Leaves, latex	Aqueous ethanol	[38]
			Cerium oxide nanoparticles		[99]
		Well plate			[100]
			Leaves, fruit, stems, flowers, roots		[42]
				Ethanol, n-butanol, chloroform, aqueous, petroleum ether	[101]
		Disc	Leaves, root		[102]
5	Antifungal	Agar well diffusion, disk diffusion	Leaf, latex	Ethanol, aqueous and chloroform	[40]
		Agar well-diffusion			[44]
		Agar-well	LAg-NPs		[46]
					[37]
		Corn borer	CuONPs		[35]
			Latex		[103]
					[104]
		Agar diffusion	Stembark	Aqueous	[48]
			Latex		[105]
		Agar dilution	Leaves, root, stembark		[106]
		Agar well	Leaves, latex	Aqueous ethanol	[38]
					[47]
6	Anthelmintic	In vivo	Latex	Aqueous	[49]

Table 1 (continued)

S/N	Activity	Methods	Part	Solvents	Reference
			Flowers	Aqueous, methanol	[50]
		In vivo	Latex		[107]
7	Antidiarrheal	In vivo	Latex		[52]
8	Antimalaria		Leaves, stems, roots, flowers, buds		[108]
		Desjardins method	Flower, bud and root	Ethanol	[54]
			Leaves	Aqueous methanol with petroleum ether, chloroform, and ethyl acetate	[109]
9	Antidiabetic	In vivo	Dry latex	Dry latex	[12]
		Glucosidase and α -amylase	Leaves	Aqueous, aqueous ethanol	[56]
		In vivo	Latex	Aqueous	[55]
		In vivo	Leaves	Methanol	[57]
		In vivo	Leaves		[21]
		In vivo	Leaves	Methanol, chloroform	[110]
		In vivo	Roots, stem, leaves	Petroleum ether, chloroform, ethylacetate and methanol,	[58]
10	Wound healing	In vivo		Latex	[59]
		In vivo	Bark	Ethanol	[60]
			Latex		[61]
		In vivo	Leaves		[62]
11	Oestrous cycle and on oestrogenic evaluation	In vivo	Roots	Ethanol, aqueous	[111]
12	Antifertility	In vivo	Roots	Ethanol	[112]
13	Antinociceptive	In vivo	Latex	Latex	[113]
14	Hepatoprotective activity	In vivo	Flowers	Ethanol	[66]
15					[114]
			Latex	Ethanol	[115]
		In vivo	Leaves		[64]
		In vivo	Flowers	70 ethanol %	[116]
		In vivo	Flowers		[65]
16	Antiglaucoma activity	In vivo	Leaf		[117]
17	Anticonvulsant	In vivo	Root	Petroleum ether, chloroform and alcohol	[118]
18	Nerves recovery	In vivo	Leaves		[119]
19	Antiulcer	In vivo			[68]
		In vivo	Root	Chloroform	[69]
20	Insecticidal	dipping method	Leaves	Ethanol	[70]
			Leaves	Aqueous	[53]
					[71]
			Flavonoids latex		[74]
			Latex		[72]
			Leaves	Acetone, ethanol, petroleum ether, aqueous	[120]
			Leaves		[121]
					[73]
			Latex		[122]
			Leaves		[123]
21	Anticancer	In vivo	Dry latex	Aqueous	[124]
		MTT, in vivo	Stem	Hexane, dichloromethane, ethyl acetate, acetone, and methanol	[125]
					[126]

Table 1 (continued)

S/N	Activity	Methods	Part	Solvents	Reference
			Latex		[127]
		MTT	Flowers (Polyphenolic)	Methanol	[11]
		MTT	Dry latex	Aqueous	[124]
			Latex		[128]
			Leaves		[129]
			Leaves	Aqueous, methanol, n-hexane	[9]
		MTT	Leaves		[130]
			Root	Methanol	[86]
			Root (Dihydroquercetin-glucoside)		[17]
		MTT	Copper nanoparticles	Aqueous	[131]
				Laticifer proteins (LP)	[132]
			Latex	Hexane, chloroform, ethyl acetate and aqueous	[133]
			Latex		[134]
			Rootbark		[135]
					[136]
			Leaves	Aqueous methanol with petroleum ether, chloroform, ethyl acetate	[109]
					[137]
22	Toxicity evaluation	In vivo	Latex protein		[138]
			Leaves		[64]
		In vivo	Leaves		[139]
		In vivo	Latex		[140]
		In vivo	Flower	Aqueous	[23]
		In vivo	Flower	Hexane, dichloromethane, ethyl acetate, methanol, aqueous	[15]
		In vivo	Leaves		[141]
		In vivo	Latex		[142]
		In vivo			[68]
		In vivo	Leaves		[143]

of traditional use, contain a wealth of untapped potential in the form of new, effective drugs that could aid in the treatment of liver conditions. These results demonstrated that CP has a hepatoprotective effect against INH and RMP administration, protecting the liver from long-term toxicity [65]. Hydro-ethanolic extract (200 mg/kg and 400 mg/kg) therapy dramatically increased unusually low levels of biochemical markers [66] (Table 1).

Antiulcer activity

Gastric and duodenal ulcers are subtypes of peptic ulcer disease (PUD), the most common GI condition. Every year, PUD is responsible for around 15 thousand deaths [67]. Both DL and MeDL reduced gastric acidity in the pyloric ligation model, with DL reducing it to 163 mequiv./l and MeDL reducing it to 201 mequiv./l. In this model, the gastric pH was raised by these extracts, but the gastric mucosa was not protected (Table 1). Both

the 200 mg/kg and 400 mg/kg doses of the extracts under study demonstrated dose-dependent antiulcerative colitis potential when administered to rats for 5 days in a row following acetic acid-induced colitis [68]. The extract considerably decreased the severity of gastric ulcers that were generated in rats by absolute alcohol, aspirin, reserpine, and serotonin [69]. Histamine also greatly prevented the stomach mucosa from being damaged by aspirin in pyloric-ligated rats, demonstrating the similar protective effect that resulted in duodenal ulcers in guinea pigs [69].

Insecticidal efficacy

Recently, there has been a heightened awareness of the risks associated with using synthetic organic insecticides, prompting a flurry of activity to investigate viable alternative products for pest management. In the quest to discover new biological insecticides, one strategy involves

screening plant extracts for their toxic effects on insects. It has been shown that many plants have insecticidal activity against various insects. Several plant extracts, both those from seeds and those from leaves, have a toxic and potent growth-reducing activity against insects. Plant extracts or pure natural/synthetic compounds can have negative effects on insects in several ways, such as through toxicity, mortality, antifeedant, growth inhibition, suppression of reproductive behavior, and decreased fecundity and fertility. Based on these findings, it is likely that natural biocides derived from *C. procera* leaves could be utilized to combat the spread of *An. Arabiensis* and *Cx. Quinque fasciatus* [53]. The extracts had LC_{50} values of 550 mg/l for insecticidal activity [70]. While some test subjects were able to successfully inhibit egg hatching, most test subjects either did not survive to the second instar or remained in the first instar. Furthermore, the percentages were so poisonous that all third-instar larvae died within 24 h [71]. The alcoholic extract was found to be less toxic than latex in experiments involving two mosquito species. Concentrations of 109 and 387 mg/L were found to be half-lethal (LC_{50}) for *An. stephensi* and *Cx. quinquefasciatus*, respectively. The latex of the plant had concentrations of 13 and 86 mg/L [72]. The maximum concentration of methanolic leaf extract (7%) tested resulted in a 38% reduction in *M. phaseolina* diameter [73]. Death rates of 86.0%, 77.6%, and 61.0% were attained after seven days of exposure to the extract at a concentration of (5 mL cm²). Mortality rates for *R. dominica*, on the other hand, were between 53.8% and 64.2% [74]. Using plant extracts instead of synthetic chemicals to kill off disease-spreading insects and other pests is a large step toward protecting human health and the natural world.

Anticancer activity

In 2012, there were 14.1 million new instances of cancer, 8.2 million deaths from cancer, and 32.6 million people living with cancer globally, according to figures from the International Agency for Research on Cancer. It is estimated that there would be 26 million new instances of cancer and 17 million cancer-related deaths annually by the year 2030 [144]. Consequently, there is always a need for the discovery of novel anticancer medications that are both effective and reasonably priced. For ages, one of the most vital parts of human knowledge has been the pursuit and development of medicines derived from plant raw materials. Liver cancer never developed in DL-treated mice. There were no injuries visible on these animals. The serum VEGF level of treated mice was much lower than that of untreated mice [124]. Extracts of acetate and acetone showed increased capability for killing tumor cells, with IC_{50} values ranging from 0.8 to 4.4 g/

mL. Evaluation of in vivo anticancer activity showed that ethyl acetate and acetone, respectively, inhibited tumor growth in treated rats by 64.3% and 53.1%, with only mild, reversible toxicity to the liver and kidneys in both cases [125]. UNBS1450 01, an inhibitor of the sodium pump, has been demonstrated to have antiproliferative and cell death-inducing effects [126]. Cell death was significantly promoted by DL methanol extract and fraction 8 in Huh-7 and COS-1 cells but not in AML12 cells. Both Huh-7 and COS-1 cell lines had extensive DNA fragmentation with this event (Table 1). The oxidative homeostasis of normal rats was very different from that of rats whose colons had been genetically altered to imitate cancer. The immunoreactivity of IL-1, nitrite, MPO, TNF-, and prostaglandin E2 was also elevated in these animals. The rats' health improved after having these markers adjusted with MeDL or the antiinflammatory medication aspirin [128]. HeLa, A549, and BHK21 cells were all still alive after being exposed to copper nanoparticles at a concentration of 120 μ M [131]. Leaf extract supplementation reduced the progression of postnatal phenytoin-induced damage in the rat cerebellum [139]. Both brine shrimp (LD_{50} 10.9–65.7 g/mL) and cancer cell lines (0.05–3.9 g/mL) were extremely sensitive to these fractions [137]. The extract stimulated a growth rate of over 70% in some cell lines. Against the lung (A-549) cell line, it was 79% effective. It was also discovered that liver cell lines (Hep-2) were susceptible to the effect. The human liver cancer cell line HT-29 and the neuroblastoma cell line IMR-32 were both shown to be inhibited by the extracts in a cytotoxic manner [136]. Cell viability data suggest that *C procera* has the potential to be used as a drug candidate for the treatment of lung cancer, as it effectively inhibits H1299 cancer cell lines in a dose-dependent manner [130]. Phenolic compounds have anti-ulcer properties [64]. UNBS1450 01's anticancer potential arises from its ability to bind to the sodium pump in the cell membrane and thereby disrupt the actin cytoskeleton, induce autophagy-related cell death, suppress NF-kappaB activation, and reduce c-Myc expression in cancer cells.

Other activities

Being the fragile long bundles of thousands of axons that they are, nerves are more susceptible to injury after any kind (both endogenous and exogenous) of traumatic situation [119]. Naturally occurring therapeutically effective compounds found in local flora have a long history of use as therapeutic agents in the treatment of a wide range of diseases. Researching such compounds would open the possibility of a new treatment option for patients. Leaves significantly reduced oxidative stress and sped up functional recovery, as evidenced by improvements

in behavioral parameters [119]. After ingesting either extract, the oestrous cycle was disrupted in 60% and 80% of treated rats, respectively. Ovulation was temporarily suppressed in rats due to a prolonged dioestrous period of the oestrous cycle. On the contrary, no oestrogenic activity was detected in the extracts [111]. It was reported that uterotrophic and antiimplantation action was very strong (inhibition 100%) at the dose of 250 mg/kg (1/4 of LD₅₀) [112]. Acetic acid-induced abdominal constriction was inhibited by 67.9% at 12.5 mg/kg, 85.0% at 25 mg/kg, and 99.5% at 50 mg/kg, relative to controls. Pretreatment with naloxone (1 mg/kg) at either dose of 25 (39.8%; 42% reversal) or 50 (66.6%; 99.3% reversal) had no influence on the effects of latex protein on formalin-induced nociception [113]. After 3–14 days of treatment with topical corticosteroids, antiglaucoma medications, cycloplegics, hypertonic saline, and tear supplements, 27 eyes (93 percent) were cured. After 3 months, the endothelial cell count was considerably reduced in 17 (74%) of the 23 eyes analyzed when compared to the normal fellow eye [117]. In the maximal electroshock seizure test, the chloroform extract was the most efficient ($p < 0.01$) anticonvulsant, decreasing the duration of the extensor phase, clonus, and the stupor phase compared to the control group [118].

Toxicity evaluation

People use therapeutic herbs all around the world, but mainly in less developed areas. They are particularly well-liked due to their low price and abundance in the region. Because they are natural, people everywhere assume that plant-based therapies are risk-free. The data, however, suggests otherwise. If the wrong ones are picked or they are not prepared properly, they can be highly hazardous. Thus, determining the safety of plant extracts is crucial. Researchers have demonstrated that a wide range of chemicals from medicinal plants have advantageous biological effects. For gauging the plant extracts' safety and establishing the tested doses, an acute toxicity study was crucial. Up to 3 g/kg of the leaf extract was safe. None of the treated animal groups demonstrated any evidence of morbidity or altered behavior during the course of the trial [64]. Supplementation with leaf extract delayed the rate of postnatal phenytoin-induced damage in the rat cerebellum [139]. Histological alterations in the testes of treated rats were attributed to the same cardiac glycosides in *C. procera* latex extract that were previously linked to pathological and ultrastructural kidney tubule changes in Wistar rats [143]. Aqueous suspension of DL at doses of 5, 50, and 100 mg/kg daily reduced serum levels of inflammatory mediators and liver enzymes in a dose-dependent manner while

attenuating liver necro-inflammatory alterations [140]. Mice that were given different extracts orally at doses up to 1000 mg/kg did not exhibit any toxicity for 48 h or for as long as 14 days afterward. No deaths were reported, and it was determined that all extracts were safe at the levels utilized [15]. Despite receiving the maximal dose, none of the rats in the other groups perished. During a gross pathological examination, sheep who received 60 g/kg per day for 10 days displayed mild ascites, exudates on the trachea, pulmonary edema, slight liver hemorrhage, hydropericardium, flaccid heart, ulcers on the abomasum, and pale juxtamedullary cortex in their kidneys [141]. After receiving latex at doses of 1 ml/kg of body weight or 0.005 ml/kg of body weight per day intravenously or intraperitoneally, goats typically died 20 min to 4 days later. To our knowledge, neither the intramuscular nor oral administration of the incredibly low dose of latex (0.005 ml/kg body weight/day) resulted in any goat deaths [142]. At doses of total alcohol extract up to 4000 mg/kg, there were no reports of harmful effects on the liver or renal function [68]. The results of this study suggest that using latex extract in excess could have toxicological effects; as a result, only minimal amounts should be used. The basis for every medicine development or herbal composition is the evaluation of each compound's level of toxicity.

Conclusions

There is a rich trove of substances in nature that could be utilized to develop treatments for many long-term illnesses. The neuraceutical and pharmacological value of a wide range of medicinal plants and their constituents has been established. This analysis critically evaluated the existing research suggesting *C. procera* has therapeutic and pharmacological effects. According to the literature, *Calotropis procera* is used as a traditional medicine in many different cultures and has been the subject of much research into its biological properties. Its pharmacological significance meant it was an extremely powerful competitor in the medical arena. Like other plant parts, latex has been demonstrated to possess several therapeutic qualities, including antidiabetic, antiinflammatory, analgesic, hepatoprotective, antimalaria, antiulcer, anthelmintic, and anticancer effects. Preclinical investigations have already been conducted on a variety of biological activities. The latex was found to have significant biological activity, and this is due to the presence of high contents of flavonoid and polyphenol compounds. Latex must be explored further in terms of the mechanism of action of the compound, in vivo cytotoxicity, and clinical trials to obtain more conclusive evidence about its usefulness.

Abbreviations

LPOI	Lipid peroxidation inhibition assay
TBARS	Thiobarbituric acid-reactive substances
DL	Dried latex
MIC	Minimum inhibitory concentrations
UNBS1450 01	Cardiotonic steroid
LAg-NPs	Latex silver nanoparticles
DPPH	2,2-Diphenylpicrylhydrazyl
DDA	Deoxyribose degradation assays
(OH ⁻)	Determination of hydroxyl radical scavenging activity
MeDL	Methanol extract of dried latex
CP-P	<i>Calotropis procera</i> protein
TOS	Peripheral nerve injury
TAC	Total oxidant status
CuONPs	Mediated synthesis of copper oxide nanoparticles
MeDL	Methanol extract dried latex
LP	Latex protein

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Author contributions

The author searched, analyzed, and drafted the manuscript. The authors read and approved the final manuscript.

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Declarations

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