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Clerodendrum inerme (L.) Gaertn. (syn. Volkameria inermis): An Integrative Review of its Traditional Uses, Phytochemistry, Pharmacological Activities, and Therapeutic Prospects

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ABSTRACT: Clerodendrum inerme (L.) Gaertn., also known as Volkameria inermis, is an evergreen coastal shrub of the family Lamiaceae that has been used for generations in the traditional medicine of Asia, Africa, and the Pacific islands. Different parts of the plant have been employed to treat fever, skin diseases, venereal and scrofulous infections, rheumatism, asthma, hepatitis, and tumors. Modern investigations have identified a rich array of secondary metabolites, including flavonoids, phenolic compounds, diterpenoids, iridoid glycosides, sterols, and saponins and have begun to explain the biological basis of these traditional uses. Reported activities include anti-inflammatory, analgesic, antipyretic, antioxidant, anticancer and anti-metastatic, neuroprotective, antimicrobial, antidiabetic, and hepatoprotective effects. Noteworthy, the plant and its constituent hispidulin have been shown to ameliorate motor tics, a spectrum of Tourette syndrome, and the leaf extract suppresses the migration, invasion, and adhesion of lung cancer cells at non-cytotoxic concentrations. The plant has also proven useful in the green synthesis of gold and silver nanoparticles with enhanced bioactivity. Although the available evidence is promising, most studies rely on crude extracts, and standardized preparations, mechanistic validation, and clinical data are still lacking. This review brings together the current knowledge on the taxonomy, botany, phytochemistry, and pharmacology of C. inerme, with particular attention to mechanistic evidence and highlights the therapeutic potential of C. inerme and outlines the research needed to translate traditional knowledge into evidence-based applications.

1. INTRODUCTION

Medicinal plants have long been the backbone of traditional medicine systems, and interest in validating their use with modern pharmacology has grown steadily. As more scientific attention turns to combining traditional knowledge with molecular-level confirmation, species with both a long history of use and a rich chemical profile have become attractive starting points for drug discovery [1,2]. *Clerodendrum inerme (L.) Gaertn*., also known as *Volkameria inermis L.,* is one such plant. It is a perennial coastal shrub belonging to the family Lamiaceae (formerly Verbenaceae) and is distributed widely across tropical and subtropical coastal regions of Asia, Africa, Australia, and the Pacific islands [1,2,3].

Traditional healers have used different parts of the plant to treat fever, skin ailments, venereal and scrofulous infections, rheumatism, asthma, hepatitis, and even tumors [4,6]. Modern research has begun to uncover the scientific basis for these uses, reporting anti-inflammatory, antioxidant, anticancer, neuroprotective, antimicrobial, antidiabetic, and hepatoprotective activities [2,3,4]. Several reviews have summarized parts of the phytochemistry and pharmacology of the species, but a synthesis that connects traditional knowledge, chemical composition, and molecular mechanisms is still incomplete [1,3,4].

This review brings together the available information on *C. inerme*, with emphasis on the mechanistic evidence, the unique anti-motor-tic activity, the anticancer and anti-metastatic potential, and the emerging applications in green nanotechnology. It also identifies gaps in the current evidence and outlines directions for future research, with the aim of supporting the rational standardization of the plant as a potential therapeutic agent [2].

2. TAXONOMY AND BOTANICAL DESCRIPTION

Cleodendrum inerme is a scrambling or scandent evergreen shrub that typically reaches 1 to 3 m in height and can sometimes grow as a liana up to 13 m long [2,3]. The stems are woody and smooth. The leaves are ovate to elliptical, 5 to 10 cm long, opposite, simple, with entire margins and pinnate venation, and are green and slightly shiny on the upper surface [4]. The flowers are white and fused with five lobes, arranged in cymes or umbels of three flowers joined at a common base; the four stamens are reddish to purple and curve upward. The fruit is green, turning black as it matures, obovoid, and 1 to 1.5 cm long [4]. The characteristic morphology of the species, including its opposite glossy leaves, white five-lobed flowers with long upward-curving reddish-purple stamens, and black mature drupes, is illustrated in Figure 1..The taxonomy of the species has been revised in recent decades. It was originally placed in the genus *Clerodendrum* within the family Verbenaceae, but phylogenetic studies have since moved it to the genus *Volkameria* in the family Lamiaceae [2,3]. The name *Clerodendrum* is derived from the Greek kleros, meaning chance or fate, and dendron, meaning tree, a reference to the uncertain medicinal qualities attributed to some of the plants [4]. Common names include seaside clerodendrum, wild jasmine, garden quinine, and Indian privet, among many local names across its range [4].



Figure 1. Botanical illustration of Clerodendrum inerme (L.) Gaertn., showing opposite leaves, white five-lobed flowers with long upward-curving stamens, and black mature drupes.

3. DISTRIBUTION AND ECOLOGY

The plant is native to coastal areas of India, Sri Lanka, Myanmar, Malaysia, tropical Australia, Polynesia, and the Philippines [4]. It thrives in saline environments, coastal sandy soils, and mangrove-associated habitats and shows strong tolerance to salt stress [2]. This ecological flexibility is thought to shape its secondary metabolite profile, favoring the accumulation of stress-responsive phytochemicals that may carry medicinal value [2].

4. TRADITIONAL AND ETHNOMEDICINAL USES

The plant has a wide range of traditional applications across Asian, African, and Pacific cultures [2]. In Ayurvedic medicine, different parts are used to treat rheumatism, skin diseases, venereal infections, beri-beri, and tumors [4]. The leaves have been used as a febrifuge and uterine stimulant, as an antiseptic, and to arrest bleeding; they were also used to treat asthma, hepatitis, ringworm, and stomach pain [4]. The plant was employed against scrofulous and venereal infections and as an antidote to poisoning from fish, crabs, and toadstools [4]. Fresh leaf juice was applied externally for skin diseases, and roots boiled in oil were used for rheumatic affections [4]. The genus as a whole has been known as garden quinine because of its intense bitter taste and historical use as a substitute for quinine [4].

Natural Resources for Human Health
eISSN: 2583-1194

5. PHYTOCHEMISTRY

C. inerme contains a diverse array of secondary metabolites, including flavonoids, phenolic compounds, diterpenoids, triterpenoids, iridoid glycosides, sterols, saponins, tannins, alkaloids, cardiac glycosides, and volatile oils [3,4]. The recurrent presence of polyphenolic compounds points to a conserved biosynthetic emphasis on shikimate- and phenylpropanoid-derived pathways in the genus [3]. Figure 2 summarises the major phytochemical classes reported from the species, and Figure 3 illustrates the chemical structures of key bioactive flavonoids.

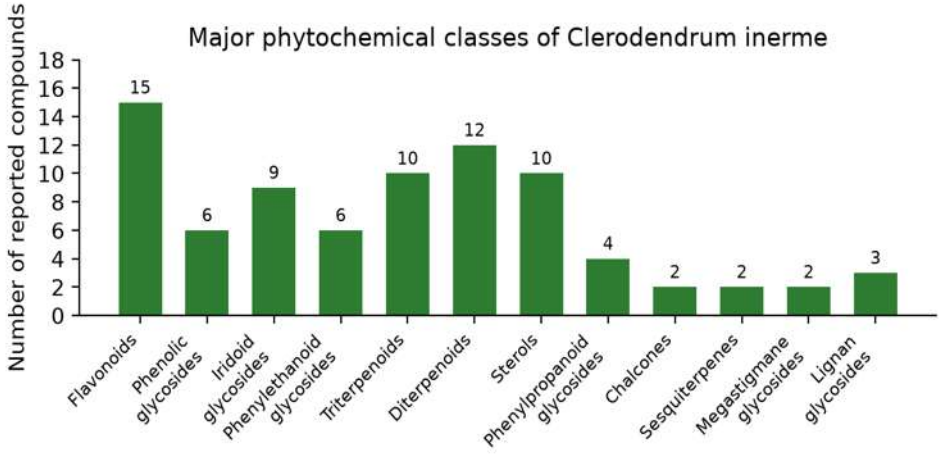


Figure 2. Major phytochemical classes reported from C. inerme, grouped by the number of reported compounds

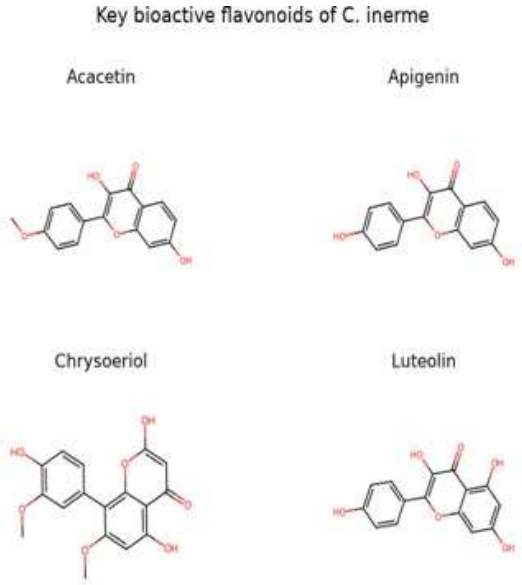


Figure 3. Chemical structures of key bioactive flavonoids (chrysoeriol, acacetin, apigenin, luteolin) reported from C. inerme.

5.1 Flavonoids

Flavonoids are among the most abundant and most studied constituents of the plant. Reported compounds include hispidulin, acacetin, diosmetin, apigenin, quercetin, kaempferol, pectolinarigenin, salvigenin, scutellarin, 4'-methylscutellarein, 7-O-methylwogonin, and 7-hydroxyflavone, along with several methylated flavones and chalcones [3,4]. These compounds are associated with antioxidant, anti-inflammatory, and anticancer activities and are considered major contributors to the biological effects of the plant [2,3].

5.2 Phenolic compounds

Phenolic acids and polyphenols are widely present and contribute substantially to the antioxidant capacity of the plant [2]. Quantitative analysis of a leaf extract reported a polyphenol content of about 120 mg gallic acid equivalents per gram of dry weight and a flavonoid content of about 4.5 mg hispidulin equivalents per gram [31].

5.3 Terpenoids and diterpenoids

Several clerodane-type diterpenoids have been isolated, including inermes A and B, 14,15-dihydro-15-methoxy-3-epicaryoptin, clerodermic acid, harwickiic acid, and uncinatone [3,4]. A novel lupene-type triterpenic glucoside, lup-1,5,20(29)-trien-3-O-beta-D-glucopyranoside, together with n-octacosane, friedelin, and beta-amyrin, has been isolated from the leaves [4,21]. These terpenoids have drawn interest for their cytotoxic, antibacterial, and anti-inflammatory properties and may also carry chemotaxonomic significance [2].

5.4 Iridoid glycosides

Iridoid glycosides such as inerminosides A, A1, B, C, and D, melittoside, and monomelittoside have been reported from the plant [3,4,22]. These compounds are common in the Lamiaceae and are recognized for hepatoprotective, neuroprotective, and anti-inflammatory effects [2].

5.5 Other constituents

The plant also contains sterols such as beta-sitosterol, saponins, tannins, alkaloids, chalcones, phenylethanoid and phenylpropanoid glycosides including verbascoside and isoverbascoside, lignan glycosides, fatty acids, and volatile oils [3,4,23]. Gas chromatography-mass spectrometry analysis of an ethanolic leaf extract identified more than twenty compounds, including fatty acids, alkanes, and squalene [4].

6. PHARMACOLOGICAL ACTIVITIES

6.1 Anti-inflammatory, analgesic, and antipyretic activities

Alcoholic and aqueous leaf extracts have shown significant antinociceptive activity in standard analgesic tests [4]. A methanol extract of the aerial parts, given at 200 mg/kg, produced a maximum inhibition of 60.17% in carrageenan-induced paw edema after 3 h and significant analgesic activity in the acetic acid writhing model [4,11]. The total methanolic extract showed anti-inflammatory activity greater than that of indomethacin at 200 mg/kg in the formalin-induced hind paw edema model [4,11]. In vitro, the extracts stabilized erythrocyte membranes and inhibited protein denaturation, with ethyl acetate and ethanol extracts showing the strongest effects [4]. In an adjuvant-induced arthritis model, a flavonoid fraction containing apigenin, scutellarin, and pectolinarigenin improved body weight, serum ionic levels, and liver glycogen content and reduced radiological signs of bone degeneration, suggesting long-term relief from arthritis [4,12].

Mechanistically, hispidulin, acacetin, and diosmetin inhibited nitric oxide production in RAW264.7 macrophages with IC50 values of 44, 43, and 57 micromolar, respectively, and hispidulin suppressed prostaglandin E2 production as well as inducible nitric oxide synthase and cyclooxygenase-2 expression by inhibiting the NF-kB and JNK pathways [13].

6.2 Antioxidant activity

Extracts of *C. inerme* have shown strong free radical scavenging activity in DPPH, ABTS, reducing power, and total antioxidant assays [14,15]. Among the solvents tested, methanol extracts consistently showed the strongest activity, with DPPH IC50 values of about 24 to 28 micrograms per mL [4,31]. This antioxidant capacity is largely attributed to the phenolic and flavonoid content of the plant [4]. Figure 4 organises the principal pharmacological activities and their underlying molecular or cellular bases.

Natural Resources for Human Health
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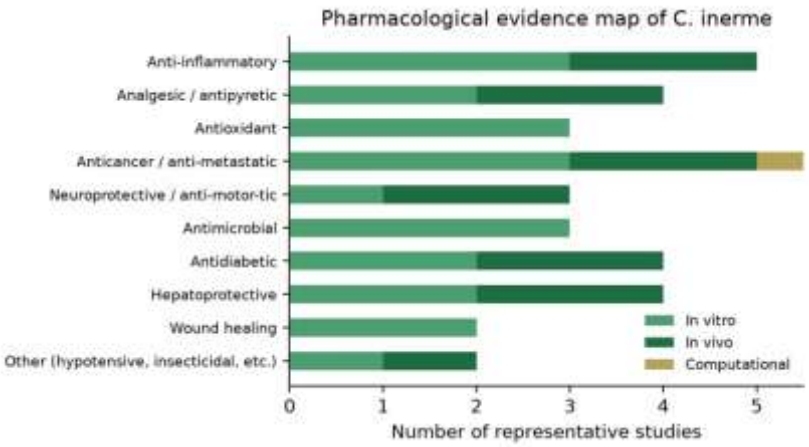


Figure 4. Distribution of pharmacological activities of C. inerme across in vitro, in vivo, and computational evidence levels.

6.3 Anticancer and anti-metastatic activities

The anticancer potential of the plant has been examined in several models. An ethanolic leaf extract was cytotoxic against A549 lung adenocarcinoma cells with an IC50 of about 16 micrograms per mL [16]. An aqueous methanol aerial part extract was weakly cytotoxic against A549 cells (IC50 260 micrograms per mL) and Burkitt's lymphoma cells (IC50 213 micrograms per mL), compared with doxorubicin as the positive control [17,18]. An ethyl acetate fraction inhibited MCF-7 breast and HepG2 liver cancer cells by 68% and 53%, respectively, at 300 micrograms per mL [19]. Hardwickiic acid from the methanol leaf extract showed strong cytotoxicity against HCT116 colon cancer cells with an IC50 of 3.5 micromolar [3]. In animal models, aqueous and ethanolic leaf extracts reduced DMBA-induced buccal pouch and skin tumors in hamsters and mice, inhibited lipid peroxidation, and improved antioxidant defenses [3].

Of particular interest is the anti-metastatic activity. Tayeh and colleagues demonstrated that a methanolic leaf extract, at non-cytotoxic concentrations of 200 and 400 micrograms per mL, significantly suppressed the migration, invasion, and adhesion of A549 human lung adenocarcinoma cells in a dose-dependent manner, as shown by wound healing, transwell, Matrigel-coated Boyden chamber, and cell adhesion assays [20]. The extract was not cytotoxic at these concentrations, with IC20 and IC50 values above 400 micrograms per mL, indicating that it can restrain metastatic behavior without killing cells [20]. The authors proposed that the extract may serve as an anti-metastatic agent for lung cancer, although the active compounds and underlying mechanisms remain to be identified [20]. Related flavonoids such as acacetin have been shown in other systems to inhibit invasion and migration through inactivation of the p38 MAPK signaling pathway [20]. Figure 5 illustrates the anti-metastatic mechanism of the leaf extract at non-cytotoxic doses.

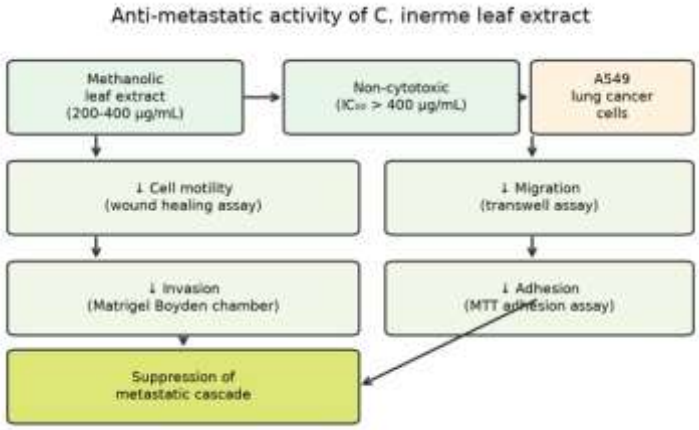


Figure 5. Anti-metastatic mechanism of C. inerme methanolic leaf extract on A549 lung cancer cells at non-cytotoxic concentrations (200-400 µg/mL).

In silico studies have also explored the antiangiogenic potential of *C. inerme* phytochemicals. Molecular docking and dynamics simulations suggested that cirsimaritin and salvigenin bind stably to vascular endothelial growth factor receptor 2 and neuropilin receptors involved in tumor angiogenesis, with favorable binding free energies, and density functional theory analysis indicated that salvigenin is chemically more reactive [38]. These computational findings support a possible antiangiogenic role but require experimental confirmation [38].

6.4 Neuroprotective and anti-motor-tic activities

The most distinctive pharmacological property of *C. inerme* is its ability to ameliorate motor tics, a spectrum of Tourette syndrome [3]. The story began with a case report of a 13-year-old girl with intractable chronic motor tic disorder who had not responded to multiple medications. Her tics subsided dramatically about an hour after she took an aqueous extract of ground leaves, and her symptoms remained suppressed with intermittent use over more than two years, with no adverse effects on blood counts or liver and renal function [3,24]. Subsequent in vivo studies showed that an ethanol leaf extract dose-dependently inhibited methamphetamine-induced hyperlocomotion and prepulse inhibition disruptions in mice, improving sensorimotor gating, without affecting spontaneous locomotion or motor coordination [25]. Hispidulin, a flavonoid from the plant, remitted motor tics and alleviated methamphetamine-induced hyperlocomotion without motor impairment, and it acted through GABAA receptors in the cerebellum [3,26]. Apomorphine-induced hyperlocomotion was not affected, indicating pathway specificity [3]. Together these findings suggest therapeutic potential for Tourette syndrome and possibly schizophrenia [25]. Figure 6 depicts the clinical and mechanistic pathway supporting the anti-motor-tic activity.

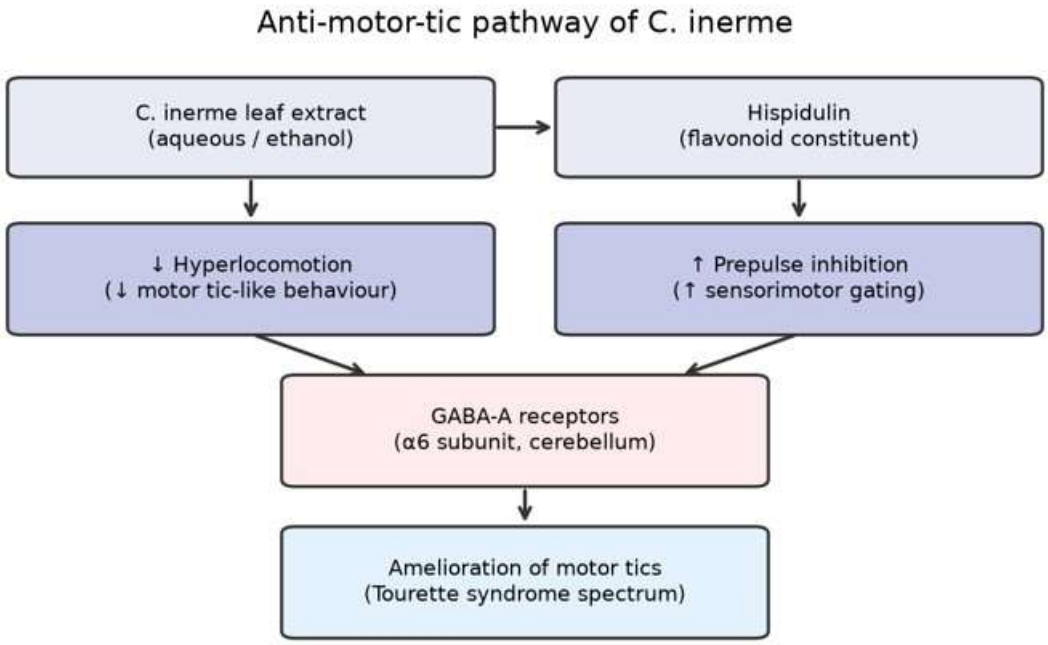


Figure 6. Clinical and mechanistic pathway supporting the anti-motor-tic activity of C. inerme leaf extract and hispidulin.

The plant also shows broader neuroprotective promise. Acacetin inhibits amyloid-beta aggregation, a hallmark of Alzheimer's disease, and protects neurons by inhibiting glutamate release in rat hippocampal synaptosomes and against kainic acid-induced excitotoxicity [3,27]. Dichloromethane extracts of the leaves and roots inhibited amyloid-beta aggregation by about 90% [3]. Animal studies have reported neuroprotective, anticonvulsant, and anxiolytic-like effects, possibly mediated through modulation of neurotransmitter systems, antioxidant mechanisms, and suppression of neuroinflammation [2].

6.5 Antimicrobial activity

Extracts of *C. inerme* have shown antibacterial activity against a range of Gram-positive and Gram-negative bacteria [2,4]. Methanol, ethyl acetate, and aqueous aerial part extracts significantly inhibited 15 of the 18 bacterial species tested [3]. Methanol extracts of the leaf and root showed the strongest activity against Staphylococcus aureus [3]. The plant also exhibits antifungal

activity; ethyl acetate and hexane extracts were effective against Trichophyton mentagrophytes and Trichophyton rubrum [3]. Antiviral activity has been reported for extracts from plants collected in southern India [33], and UPLC-MS profiling linked the plant's constituents to activity against Mycobacterium tuberculosis [34].

6.6 Antidiabetic activity

The hypoglycemic activity of *C. inerme* has been demonstrated in streptozotocin-induced diabetic models. Oral administration of a leaf extract at 343 and 686 mg/kg for seven days significantly reduced fasting plasma glucose by 53.1% and 56.7%, respectively, and improved glucose tolerance in mice [31]. The extract also protected the liver, kidneys, and pancreas from oxidative damage, reducing malondialdehyde and restoring glutathione levels, and increased the size and number of pancreatic islets [31]. A methanol extract of the aerial parts at 400 mg/kg reduced fasting blood glucose by 54.32% after 10 h in diabetic rats [32]. These effects are attributed partly to antioxidant mechanisms and possibly to inhibition of carbohydrate-digesting enzymes [2].

6.7 Hepatoprotective activity

Ethanol and aqueous leaf extracts protected against carbon tetrachloride- and paracetamol-induced liver injury in rats, significantly lowering serum AST, ALT, and ALP, reducing cholesterol and triglycerides, and increasing glutathione levels [3,29,30]. These effects are attributed to antioxidant and membrane-stabilizing properties [2].

6.8 Wound healing

Leaf extracts have demonstrated in vitro wound healing potential together with antimicrobial activity, supporting their traditional use for skin ailments [7].

6.9 Other activities

Other reported activities include a hypotensive effect, with an aqueous leaf extract lowering blood pressure in rabbits [35]; anti-tyrosinase activity, with a methanol leaf extract showing 17% tyrosinase inhibition [3]; antipyretic activity [10]; insecticidal and larvicidal activity against dengue and filarial vector mosquitoes [36]; a diuretic effect [4]; and anti-allergic activity [4].

7. GREEN SYNTHESIS OF NANOPARTICLES

C. inerme has emerged as a promising agent for the green synthesis of metal nanoparticles. Using the leaf extract as both a reducing and a capping agent, researchers have synthesized gold (CI-Au) and silver (CI-Ag) nanoparticles that carry the plant's bioactive functional groups [37]. The nanoparticles were characterized by X-ray diffraction, UV-visible spectroscopy, Fourier-transform infrared spectroscopy, transmission electron microscopy, energy-dispersive X-ray analysis, and dynamic light scattering, and they showed better antioxidant, antibacterial, and antimycotic performance than commercial nanoparticles [37]. The antimicrobial action was linked to the generation of reactive oxygen species and membrane permeabilization [37]. Silver nanoparticles synthesized from flower and fruit extracts also showed antibacterial activity against Klebsiella pneumoniae, Micrococcus luteus, Mycobacterium smegmatis, and Rhodococcus rhodochrous, with strong DPPH scavenging activity (IC50 values of about 101 to 117 micrograms per mL) [3]. These findings position *C. inerme* as a renewable and eco-friendly source for nanomedicine and related applications [37]. Figure 7 outlines the green synthesis workflow and the key characterisation endpoints.

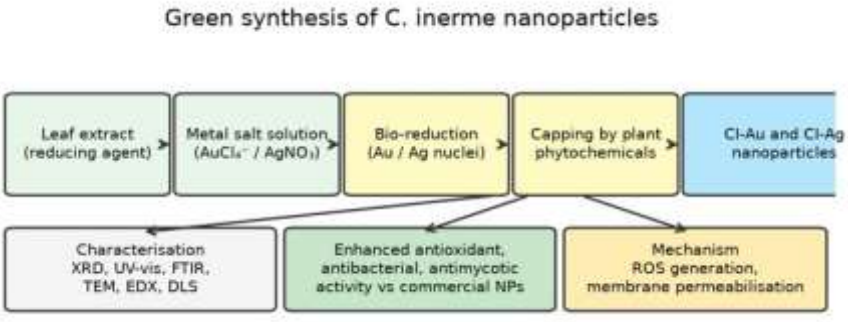


Figure 7. Green synthesis workflow and characterisation endpoints for CI-Au and CI-Ag nanoparticles of C. inerme.

8. TOXICITY AND SAFETY

Available data suggest that the plant is relatively safe. An ethanolic leaf extract caused no mortality in Swiss albino rats up to a dose of 2000 mg/kg [4,30], and the powdered plant produced no ill effects at doses as large as 8 g/kg body weight [4]. In the motor tic case report, the patient's blood counts and liver and renal function remained normal after two years of intermittent use [3,24]. Nevertheless, systematic toxicological and clinical studies are lacking, and the safety of long-term use remains to be established [2].

9. RESEARCH GAPS AND FUTURE DIRECTIONS

Despite the breadth of reported activities, several limitations constrain translation of these findings [2]. Most studies rely on crude or partially characterized extracts, making it difficult to attribute effects to specific compounds [2]. There is considerable methodological variability and a lack of standardized preparations [2]. Many proposed molecular pathways are inferred rather than directly demonstrated, and the limited application of pathway-specific inhibitors, gene expression analysis, and molecular docking hampers definitive target identification [2]. Systematic toxicological evaluation and clinical studies are also missing [2].

Future research should focus on bioassay-guided isolation of the active compounds, mechanistic validation using omics technologies and systems pharmacology approaches, standardization of extracts, and well-designed toxicological and clinical studies [1,2,3]. Such efforts would help bridge the gap between traditional knowledge and evidence-based therapeutic application [2].

CONCLUSION

Clerodendrum inerme is a medicinal plant of considerable ethnopharmacological value, supported by a growing body of phytochemical and pharmacological evidence [2]. Its diverse secondary metabolites, including flavonoids, diterpenoids, phenolics, and iridoid glycosides, underlie a wide range of activities, notably anti-inflammatory, antioxidant, anticancer and anti-metastatic, neuroprotective, antimicrobial, antidiabetic, and hepatoprotective effects [2,3,4]. The unique ability of the plant and its constituent hispidulin to ameliorate motor tics, together with the emerging applications in green nanotechnology, make it a promising candidate for further development [3,37]. Realizing this potential will require concerted efforts to standardize preparations, validate mechanisms, and establish safety and efficacy in clinical settings [1,2,3].

Declarations

Conflict of interest: The authors declare no conflict of interest.

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