

Antioxidant and pharmaceutical potential of *Clerodendrum* L.: An overview

Pallab Kar, Arvind Kumar Goyal¹, Abhaya Prasad Das, Arnab Sen

Department of Botany, University of North Bengal, Siliguri, West Bengal, ¹Department of Biotechnology, Bamboo Technology, Bodoland University, Kokrajhar, Assam, India

Clerodendrum, with about 580 species, belongs to the family Verbenaceae and is widely distributed in the tropical and warm temperate regions of the world. The leaves of some species of *Clerodendrum* form an important source of diet in North eastern part of India. Various plant parts such as leaf and root extracts of *C. indicum*, *C. phlomidis*, *C. serratum*, *C. trichotomum*, *C. chinense* and *C. petasites* have been used for the treatment of rheumatism, asthma, inflammatory diseases, coughs, skin diseases, vermifuge, febrifuge, malaria etc. Isolation and identification of different chemical compounds and biological activities of the genus *Clerodendrum* have been studied by few researchers. The major chemical components reported from the genus are phenolics, steroids, flavonoids, terpenes, volatile oils, etc., This paper presents a comprehensive review on the various aspects of *Clerodendrum* species with respect to their traditional usage or use as alternative medicine for the treatment of various diseases.

Key words: Antioxidant, *Clerodendrum*, flavonoids, pharmaceutical, phenolics, steroids, terpenoids

INTRODUCTION

Plants have been used as a source of medicine since ancient time.^[1] The description of the use of a variety of plant-derived medications was written in different ancient literature of India (Veda, Purana and Upanishad) and China.^[2] In ancient Egypt the dead body was preserved as "Mummy" by using some plant extracts, which is unknown till date. According to the World Health Organization (WHO), a variety of drugs are obtained from different medicinal plants and about 80% of the world's developing population depends on traditional medicine for their primary health care needs.^[3] Different plant species are used as a main ingredient for the preparation of modern phyto-medicine, which has exploded in the last few years, and are still being collected from the nature and play an important role in drug development programmes in the pharmaceutical industry. Now-a-days, in increasing population people use herbal remedies which have become more popular in the treatment of minor ailments and are also much fruitful than others.^[4] A significant number of drugs were obtained from different plant precursors, digitoxin (*Digitalis*

spp.), vincristine and vinblastine (*Catharanthus roseus*), quinine (*Cinchona* spp.), atropine (*Atropa belladonna*) and morphine and codeine (*Papaver somniferum*). Now, many medicinal plants are disappearing because of rapid urban development, agriculture, uncontrolled deforestation and indiscriminate collection. Combination of *in vitro* propagation techniques^[5] and cryopreservation is a reliable method for long term storage of germplasm of endangered species and it may help in the conservation of biodiversity.

THE FAMILY VERBENACEAE

The family Verbenaceae, also known as the teak family comprises 35 genera and 1,200 species, which are found mainly in the tropical and subtropical regions of the world.^[6] This family is represented by herbs, shrubs and small trees known for heads, spikes or clusters of small flowers, of which many have aromatic odour.^[7] The family is closely related to the Lamiaceae.^[8] The main difference between the two families is the ovary. Lamiaceae have a deeply four-lobed ovary with gynobasic style while the Verbenaceae have an unlobed ovary and a terminal style.^[9]

Many species of this family have been used in folk medicine; *Verbena hastata* as bitters, species of *Lippia* for the treatment of typhoid and rheumatism.^[10] *Lantana camara* is used as a remedy for malaria and as an antiseptic.^[11] Several compounds such as anthraquinones, terpenes, steroidal saponins, alkaloids and flavonoids are mainly found in members of the Verbenaceae family.^[12]

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Address for correspondence: Dr. Arnab Sen, Department of Botany, University of North Bengal, Siliguri - 734 013, West Bengal, India.

E-mail: senarnab_nbu@hotmail.com.

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The Genus *Clerodendrum*

Clerodendrum is a genus of flowering plants belongs to the family Verbenaceae. It is widely distributed in the tropical and warm temperate regions of the world, with most of the species occurring in tropical and northern Africa, Asia, Egypt and Madagascar. The genus represents herbs, shrubs and small trees and is well-known for its ornamental uses. In 1753, Linnaeus first described the genus, with the identification of *C. infortunatum*. After a decade later, in 1763, Adanson changed the Latin name "*Clerodendrum*" to its Greek form "*Clerodendron*"; in Greek 'Klero' means chance and 'dendron' means tree.^[13] After a big gap of about two centuries, in 1942, Moldenke readopted the Latinised name '*Clerodendrum*', which is currently used for the classification and description of the genus and species.^[14-17]

Clerodendrum is a very large and diverse genus with about 580 identified species is distributed throughout the world.^[13] It is the largest genus of the tribe Teucriaceae.^[17] In India 23 species were recorded by Rajendran and Daniel,^[18] of which 16 were recorded from Arunachal Pradesh by Srivastava and Choudhary.^[19]

ETHNOMEDICINAL USES

A number of species from this genus have been used in traditional systems of medicine by various tribes in many countries like China, India, Japan, Korea and Thailand.^[13] Different plant parts such as leaf and root extracts of *C. indicum*, *C. phlomidis*, *C. serratum*, *C. trichotomum*, *C. chinense* and *C. petasites* have been used for the treatment of rheumatism, asthma, febrifuge, incephalalgia, ophthalmia and other inflammatory diseases.^[3,20-24] Plant species such as *C. indicum* and *C. inerme* are used for the treatment of coughs, venereal infections, skin diseases, elephantiasis, rheumatism, tropical burns, vermifuge, febrifuge, malaria etc.^[25-28] *C. phlomidis*, *C. colebrookianum*, *C. calamitosum* and *C. trichotomum* have been used for anti-diabetic, anti-hypertensive and sedative properties.^[21,23,29-34]

CHEMICAL CONSTITUENTS

Clerodendrum, an ethnomedicinally important genus is used for the treatment of various diseases. A number of researches have been performed to identify and isolate biologically active compounds from different species of *Clerodendrum*. Research report revealed that steroids, terpenoids and flavonoids are major among them.^[35] Some of the important chemical compounds encountered in *Clerodendrum* are depicted in Figure 1.

Flavonoids

Flavonoids are another class of compounds that have been isolated from different species of *Clerodendrum*.

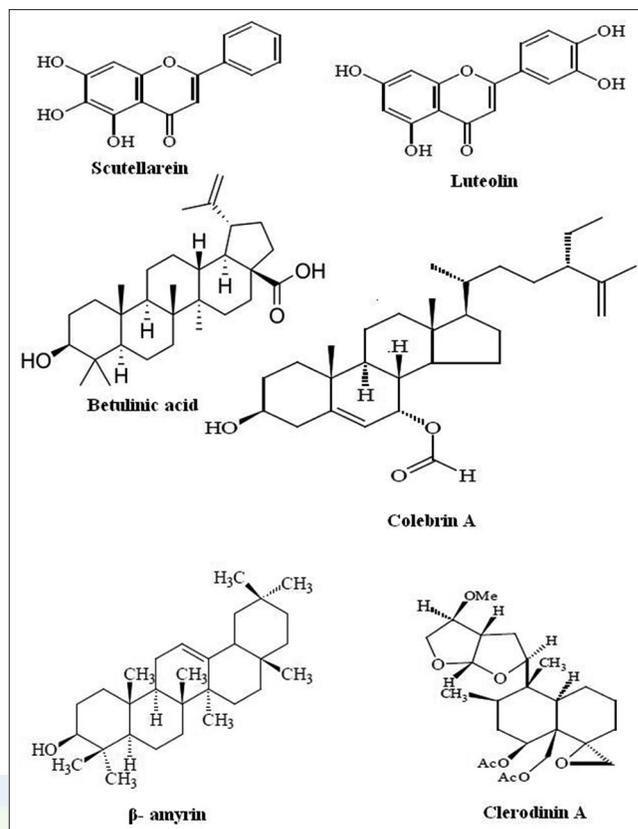


Figure 1: Some important chemical compounds found in *Clerodendrum* L.

Scutellarein has been isolated from the aerial parts of *C. indicum*.^[36] Apigenin has been obtained from the leaves and stem of *C. inerme*.^[37] Hispidulin has been recorded from the flowers of *C. phlomoides*^[38] and the aerial parts of *C. indicum* is known to contain hispidulin 7-O-glucuronide.^[36] Luteolin, another major flavonoid was found to be present in the flowers of *C. phlomoides*.^[38]

Other Group of Compounds

Several other chemical compounds have been found in different species of *Clerodendrum*. Benzoic acid, cabsurin, and quercetin have been noted in the aerial parts and roots of *C. infortunatum*.^[39] Ceryl alcohol and pectolarigenin have been isolated from *C. phlomidis*.^[38] 3, 4-dihydroxyphenyl ethanol, cupafolin, larcirecinol 9-O-β-D-glucoside have been recorded for the first time from *C. indicum*.^[36] Friedelin, betulinic acid, syringic acid, ρ-methoxy benzoin acid have been obtained from *C. inerme*.^[40] Martinoside, monoacetyl martinoside have been found in *C. japonicum* and *C. bungei*.^[41,42] Glycerol-1-docosate, acetoside, maslinic acid have been isolated from *C. colebrookianum*.^[34] *C. fragrans* is known to contain Racemic renygolone, racemic dihydro renygolone, renyoxide, renyoside B, cornoside, dihydro cornoside.^[24] Betulinic acid and octadecanoic acids were reported from *C. bungei*.^[42]

Steroids

Steroids are a group of secondary metabolites.^[43] Steroids are present in considerable amount in *Clerodendrum* in various forms. Researchers have reported that β -sitosterol is present in the roots of *C. infortunatum*, roots also contain clerosterol, clerodolone, clerodone, which is identified as 5, 25-sigmastadien-3 β -ol, lup_20 (30)-en-3 β -diol-12-one and 3 β -hydroxylupan-12-one.^[39] β -sitosterol is also found in the roots of *C. phlomides*,^[38] *C. serratum*,^[44] *C. paniculatum*,^[45] *C. fragrans*^[46] and stem of *C. indicum*.^[47] *C. indicum* also contain clerodendrol.^[36] γ - sitosterol and clerosterol is present in the roots of *C. phlomides*.^[38] Clerodenoside-A is present in *C. japonicum*, and it is identified as [β -3'-hydroxyl-4'-methoxyphenyl)-ethyl]-2',3'-di-o-acetyl-3-o- α -L-rhamnopyranosyl)-(4-o-feroloyl)- β -D-glucopyranoside.^[41] Clerosterol is also present in entire plant of *C. bungei*^[42] and leaves and stem of *C. inerme*.^[48] Colebroside-A, colebrin A, and B have also been isolated from the aerial parts of *C. colebrookianum*.^[34] Stigmasterol, cholesterol, poriferasterol, and 22-dehydroclerosterol have been isolated from the aerial parts, leaves and stem of *C. fragrans*.^[49] Bungein-A, cleroindicin-A, cleroindicin-C, cleroindicin-E, and cleroindicin-F have been isolated from *C. bungei*.^[42]

Terpenoids

Terpenes are another class of secondary metabolites, which include monoterpenes, diterpenes, triterpenes, iridoids and sesquiterpenes. α -amyrin is isolated from the roots and stem of *C. fragrans*^[46] and *C. inerme*.^[50] β -amyrin is isolated from the roots of *C. colebrookianum*,^[45] the leaves and stem of *C. inerme*^[51] and the roots of *C. paniculatum*.^[45] Luperol has been obtained from *C. viscosum*.^[39] Clerodendrin A is a diterpene, which have been reported from the roots of *C. phlomoides*.^[38] Clerodendrin B, C, and friedelin have been recorded from the leaves of *C. inerme*.^[52] Clerodin, which is also a diterpene have been found to be present in the flowers of *C. infortunatum*, *C. phlomides*, and the leaves of *C. brachyanthum*.^[38,39,53] Lupeol another triterpene has been isolated from the stem bark of *C. infortunatum*.^[39] The diterpenes clerodinin A, B, and C have been obtained from the leaves of *C. brachyanthum*.^[53] Melittoside, monomelittoside, and harpagide from *C. fragans*,^[46] ajugoside from the leaves of *C. thomsonae*.^[54] Oleanolic acid is obtained from the leaves and stem of *C. colebrookianum*,^[34] clerodinin A and oleanolic acid from *C. infortunatum*.^[55]

PHARMACEUTICAL POTENTIAL

Clerodendrum is an ethnomedicinally important genus, which is used in various traditional healthcare systems for the treatment of wide spectrum of disorders globally. A number of *in vitro* and *in vivo* assays have been performed to validate these traditional claims. These studies showed that the

different species of the genus possess potent antimicrobial, anti-inflammatory, anti-malarial, anti-diabetic, anti-cancer, analgesic and anti-oxidant activities^[13] [Figure 2]. Some major activities are described below.

Anti-oxidant Activity

Reactive Oxygen Species (ROS) and many of the free radicals are natural by-products, which are constantly generated *in vivo*, both by "accidents of chemistry" and for specific metabolic purposes.^[56] ROS has a high reactive potential and is responsible for many of the human diseases like diabetes, cancer, viral infections, cardiovascular diseases, and inflammations, and also damages the biological molecules like DNA, lipids, and proteins.^[57] The antioxidants present in the medicinal plants minimise the formation of ROS.^[58] The ethanolic extract of aerial parts of *Clerodendrum serratum* showed good antioxidant properties against 1,1-diphenyl, 2-picryl hydrazyl (DPPH) and nitric oxide radical whereas *Clerodendrum serratum* roots extract showed considerable antioxidant properties against DPPH.^[59] The ethanolic extract of the leaves of *Clerodendrum infortunatum* Linn showed significant antioxidant activity against DPPH-free radical scavenging activity, reducing power assay and scavenging of hydrogen peroxide.^[60] The methanolic extract of leaves of *Clerodendrum inerme* showed higher free radical and antioxidant activity.^[28] The ethanolic extract of roots of *Clerodendrum viscosum* showed notable scavenging of the radical cation, nitric oxide radical, ferric-ion radical and DPPH. However, the aqueous extract showed moderate antioxidant activity.^[61] The ethanolic extract of roots of *Clerodendrum phlomidis* showed best free radical scavenging activity compared to other three extracts *viz.* petroleum ether, chloroform, and ethyl acetate.^[62]

Anti-microbial Activity

Many species from the genus *Clerodendrum* were documented in ancient literature and have showed potent anti-microbial activity. Ethanolic extracts of leaves of *Clerodendrum infortunatum* showed potent anti-microbial activity against some Gram positive, Gram negative bacteria (*Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*) and fungal strains (*Aspergillus niger*,

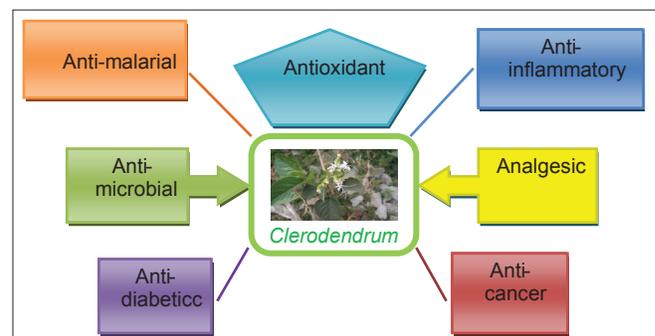


Figure 2: Pharmaceutical potential of *Clerodendrum* L.

A. flavus *Candida albicans*).^[63] Ethanol, hexane, chloroform and aqueous extracts of root, leaf and stem of *Clerodendrum viscosum* showed potent antibacterial activity against some Gram positive, Gram negative bacterial and fungal strains viz., *Staphylococcus aureus*, *Sercinia lutea*, *B. subtilis*, *B. megaterium*, *B. cereus* and *Streptococcus-β-haemolyticus*, *Salmonellae typhi*, *Shigella dysenteriae*, *E. coli*, *S. shiga*, *S. boydii*, *S. sonnei*, *Proteus sp.*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Agrobacterium tumefaciens*, *Erwinia chrysanthemi*, and *Xanthomonas phaseoli*.^[64,65] Petrol, benzene, ethanol, methanol, ethyl acetate and aqueous extracts of leaves and roots of *Clerodendrum inerme* exhibited anti-microbial activity against some human pathogenic bacteria.^[66,67] Ethyl acetate and hexane extracts of leaves and stems of *Clerodendrum inerme* and *Clerodendrum phlomidis* exhibited anti-fungal activity against some fungal pathogen.^[68] The ethanol extract of roots of *Clerodendrum serratum* showed potent anti-microbial activity against some Gram-positive and Gram-negative bacteria.^[3] Various extracts of leaves of *Clerodendrum paniculatum* showed potent anti-microbial activity against some Gram-negative bacteria.^[69] Ethanolic extracts of leaves of *C. philippinum* exhibited anti-microbial activity against *E. coli*, *S. aureus*, *Bacillus* and *Klebsiella*.^[70] Chloroform extracts of the flowers of *Clerodendrum chinense* and *Clerodendrum splendens* were active against *Plasmodium falciparum* with an IC_{50} value of $<10 \mu\text{g mL}^{-1}$. Chloroform extracts of the stem and flowers of *C. chinense* were active against *Trypanosoma cruzi* with an IC_{50} = 1.21 and 1.12 $\mu\text{g mL}^{-1}$ respectively. Chloroform extracts of the leaves of *C. chinense* and *C. splendens* showed promising activities against *T. cruzi* with an IC_{50} = 3.39 and 1.98 $\mu\text{g mL}^{-1}$, respectively.^[71]

Anti-inflammatory Activity

Inflammation is the complex biological disorder caused by physical pain, poisonous chemical or different microbial agents.^[72,73] Many species of the genus have showed potent anti-inflammatory activity. In 1988, Surendrakumar^[74] showed that *C. phlomoidis* significantly reduced paw oedema induced by carrageenan in rats at a dose of 1 g/kg. The anti-inflammatory activity of methanol extract of *Clerodendrum inerme* exhibited sub-chronic (cotton pellet-induced granuloma) models significantly.^[72] The ethanolic root extract of *C. serratum* showed significant anti-inflammatory activity in carrageenan-induced oedema in rats, and also in the cotton pellet model in experimental mice, rats, and rabbits.^[3] *C. petasites* was reported to show moderate anti-inflammatory activity in the acute phase of inflammation in rats. The ED_{50} values of the experiment were reported to be 2.34 mg/ear and 420.41 mg/kg in rats.^[22] The methanolic extracts of leaves of *C. trichotomum* showed significant anti-inflammatory activity in experimental rat, mice, and Raw 264.7 macrophage cells.^[23] The methanol extract of leaves of *C. infortunatum* showed significant anti-inflammatory activity against the carrageenan, histamine and dextran induced rat paw oedema.^[73] The

aqueous extract of root bark of *C. phlomidis* showed anti-inflammatory activity against carrageenan induced rat paw oedema and acetic acid induced peritonitis in mice.^[75]

Anti-malarial Activity

Malaria is one of the most important parasitic infections of humans and every year 863,000 deaths occur throughout the world.^[76,77] Many species of *Clerodendrum* have been reported for its anti-malarial activities because of the presence of a bitter principle. The methanol extract of the leaves of *C. myricoides* significantly ($P < 0.05$) inhibited parasitaemia of *Plasmodium berghei*.^[77] The ethanolic extract of leaves of *C. violaceum* showed anti-malarial activity against *Plasmodium berghei*.^[76] The alcoholic extract of *C. phlomidis* showed anti-malarial activity against *Plasmodium falciparum* with an IC_{50} value of 48 $\mu\text{g mL}^{-1}$.^[78] The petroleum ether and ether extract of *C. inerme* also inhibited the growth of larvae of *Ades aegypti*, *Culex quinquefasciatus*, and *Culex pipien*.^[79,80]

Anti-diabetic Activity

Diabetes Mellitus (Type 2) is a metabolic disorder characterized by hyperglycaemia, due to dysfunction of insulin producing β -cell.^[81] According to the WHO, 200 million cases of diabetes were reported worldwide in the year 2000 and the number is estimated to rise to 300 million by 2030.^[82] In India, it is becoming a killer disease next to coronary heart disease. So far, study on *C. phlomidis* has been investigated for its anti-diabetic properties. A decoction of the entire *C. phlomidis* plant has been reported to have anti-diabetic activity. A dose of 1g/kg showed anti-diabetic effect in alloxan induced hyperglycemia in rats. It further showed anti-hyperglycaemic activity in human adults at a dose of 15-30 g/day.^[30] The methanolic extract of leaves of *Clerodendrum inerme* showed anti-diabetic activity. A dose of 200 mg/kg showed a very significant and progressive reduction in glucose level induced by streptozotocin in rats.^[81]

Anti-cancer Activity

Cancer is the second leading cause of death in many of the developed countries and every year it is increase exponentially. The aqueous extract of leaves of *Clerodendrum inerme* showed anti-cancer activity. A dose of 500 mg/kg body weight significantly prevented the tumour formation (oral carcinogenesis) induced by 7, 12-dimethylbenz (a) anthracene (DMBA) in rats.^[83] The leaf extracts of *Clerodendrum serratum* showed anti-cancer activity against skin carcinogenesis induced by 7, 12-dimethylbenz (a) anthracene (DMBA) in mice.^[84] The ethanolic extract of roots of *Clerodendrum paniculatum* showed anti-cancer activity but to a lesser extent.^[85]

Analgesic Activity

Analgesic is a very common term, which includes pain, inflammation, fever etc. and creates many complications in day-to-day life of human beings. Many species of

Clerodendrum have been reported for analgesic activity. Petroleum ether, ethyl acetate, and methanolic extract of aerial parts of *Clerodendrum phlomidis* showed analgesic activity in mice.^[86] The methanolic extract of *Clerodendrum inerme* showed significant analgesic activity in acetic acid induced writhing in rats.^[72] The ethanolic extract of leaves of *Clerodendrum viscosum* showed analgesic activity induced by pethidine in rats.^[87] The ethanolic extract of the leaves of *Clerodendrum viscosum* at a dose of 200 mg/kg ($P < 0.01$) exhibited significant peripheral analgesic activity in mice.^[88]

CONCLUSION AND FUTURE PERSPECTIVES

Clerodendrum forms an important part of traditional medicine in many countries like China, India, Japan, Korea, and Thailand. A few works conducted on the anti-oxidant potential of *Clerodendrum* by various researchers reflects its huge potential as ethnomedicine, although deep investigation through scientific validation and experimentation is still scarce. *Clerodendrum* spp. possesses multiple pharmacological and therapeutical activities such as anti-microbial, anti-inflammatory, anti-malarial, anti-diabetic, anti-cancer, analgesic. However, there are limited numbers of studies describing the bioactivities of *Clerodendrum* and this opens up new horizon for researchers working in this field to explore this raw material as potent nutraceutical and pharmaceutical product.

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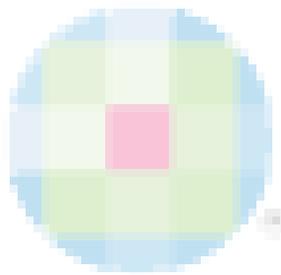
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