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Ethnobotanical uses, phytochemistry and pharmacological activities of *Clerodendrum infortunatum* L. (Lamiaceae): A review

Prashith Kekuda T.R.[1*], Dhanya Shree V.S.[1], Saema Noorain G.K.[1], Sahana B.K.[1], Raghavendra H.L.[2]

1 Department of Microbiology, S.R.N.M.N College of Applied Sciences, N.E.S campus, Balraj Urs Road, Shivamogga-577201, Karnataka, India

2 Department of Biochemistry, School of Medicine, Wollega University, P.O. Box: 395, Nekemte, Ethiopia

ABSTRACT

Ethnobotany is the scientific study concerned with the study of relationship between plants and man, in particular, how people use their traditional knowledge with respect to utilization of plant resources for their wellbeing. Plants have been extensively used since time immemorial as an indispensible source such as food, fodder, medicine, dyes, flavoring agents and for construction purposes. The genus *Clerodendrum* is one of the largest plant genera, belongs to the family Lamiaceae and encompasses herbs, shrubs and trees distributed worldwide. *Clerodendrum infortunatum* L. (synonym *Clerodendrum viscosum* Vent.) is one among the important species of the genus *Clerodendrum*. In the present review, we discuss the traditional (ethnobotanical) uses and pharmacological activities displayed by *C. infortunatum*. An extensive literature survey revealed that various parts of *C. infortunatum* are used traditionally by various indigenous communities as green salad, as an ingredient in local wine and to treat ailments or disorders such as headache, toothache, rheumatism, swelling, skin diseases, fever, diabetes, malaria, burns, tumor and epilepsy. Literatures revealed various pharmacological properties exhibited by the plant such as antimicrobial, antioxidant, analgesic, wound healing, antivenom, hepatoprotective, anti-inflammatory, antipyretic, anthelmintic, insecticidal, thrombolytic and cytotoxic activities.

Keywords: *Clerodendrum infortunatum* L., Lamiaceae, Ethnobotany, Phytochemistry, Pharmacological activities

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***Address for Correspondence:**

Dr. Prashith Kekuda T.R, Department of Microbiology, S.R.N.M.N College of Applied Sciences, N.E.S campus, Balraj Urs Road, Shivamogga-577201, Karnataka, India

INTRODUCTION

Plants have been widely used for various purposes such as food, fodder, medicine, flavoring agents, construction tools and dyes. Worldwide, plants have been used by traditional medicinal practitioners to treat human and veterinary ailments. Medicinal systems such as Ayurveda, Siddha, Unani and Chinese medicine employ several plant species to promote health and to combat infectious diseases and certain other disorders. Countries such as India, China, Bangladesh, Thailand, Japan, Malaysia, Bhutan, Sri Lanka, Taiwan, Pakistan and many African countries utilize plant based medicines as primary healthcare. Plants are considered as valuable sources of bioactive compounds (secondary metabolites produced by metabolic pathways such as shikimic acid pathway and malonate/acetate pathway) with therapeutic values. Drugs viz. quinine, morphine, codeine, vincristine, vinblastine, taxol, digoxin, and artemisinin are from plant origin. Besides, medicinal plants have also become a source of income generation in many parts of the world. In recent years, plants have been given much focus owing to some drawbacks such as high cost, adverse effects and emergence of resistance that are associated with the use of modern drugs.[1-6]

Clerodendrum is a large genus of flowering plants (herbs, shrubs and small trees) belonging to the family Lamiaceae found distributed in tropical and subtropical regions of the world. The genus was described by Linnaeus for first time. The flowers of the plants are visited by butterflies and humming bird and the larvae of some insects feeds on certain *Clerodendrum* species. Many species of the genus have been used in indigenous medicine in several countries. Few species have been extensively studied for phytochemicals present and pharmacological properties. Pharmacological properties such as antimicrobial, anticancer, antimalarial, antioxidant, antidiabetic, larvicidal and antidiarrheal activities have been shown by *Clerodendrum* species.[7-17] *Clerodendrum infortunatum* L. (Syn. *C. viscosum* Vent.) is a large tawny-villous shrub with white flowers in large, terminal panicles. The plant distributed in various countries such as India, Thailand, Malaysia, Bangladesh and Sri Lanka. It is known by name perugilai in Tamil, Bhant in Hindi, Ibbane in Kannada and

Bhandira in Sanskrit. The plant is common in the outskirts of semi-evergreen forests. Flowers are often visited by butterflies that play an important role in pollination. The plant is used as medicine for various purposes either singly or in certain polyherbal formulations in various indigenous systems of medicine including Ayurveda, Unani and Homeopathy.[18-20] In this review, we carried out an extensive literature survey to compile information available on the traditional uses, phytochemistry and pharmacological properties of *C. infortunatum* by referring standard flora, journals, and search engines such as ScienceDirect, Google scholar, and Pubmed.

CLERODENDRUM INFORTUNATUM L. – PLANT DESCRIPTION

C. infortunatum (Figure 1) is a large villous shrub (reaching a height of up to 2.5m) with quadrangular branches. Leaves opposite, broadly ovate, 25x20cm, shortly acuminate at apex, cordate at base, denticulate or serrate, pubescent above, pubescent or tomentose beneath.

Figure 1: *C. infortunatum* (Photograph by Prashith Kekuda)

Flowers are white, in large terminal panicles. Calyx is deeply 5-lobed, much enlarged in fruit, lobes broadly lanceolate and acute, and silky pubescent. Corolla are white (tinged with pink), *c.* 3cm long, lanceolate, tube *c.* 2.5cm long. Fruit is a drupe (*c.* 8mm across), bluish black when ripe, enclosed in accrescent calyx. Flowering occurs more or less throughout the year.[19,21]

ETHNOMEDICINAL USES OF *C. INFORTUNATUM*

Plants have been widely used in medicine since time immemorial. People especially those from rural areas utilize several plant species as a remedy against several diseases or conditions such as fever, pain, diabetes, inflammation, wounds, rheumatism, deworming, dysentery, diarrhea, snakebite, blood pressure, and cancer. Plants are also an integral part of ethnoveterinary practices. Whole plant or certain plant parts are used either singly or in certain formulations.[3,4,10,22,23] In India and other countries, *C. infortunatum* is widely used in traditional medicine to treat several diseases. Leaves, roots and flowers of *C. infortunatum* are used as medicine in the form of paste, juice and ash. Roots are used to treat bronchitis and asthma in Assam, India.[24] Leaves and flowers are used as antidote for scorpion sting while sprout is used as antidote for snakebite.[18,19]

Tribal communities in Attappady, Kerala, India uses paste made from leaves to treat wounds.[25] Indigenous communities in Bangladesh utilize the plant in conditions such as helminthiasis, pain, sprain, fracture, joint displacement, diabetes and fever.[26] In Manipur, India, the plant is used against boils.[27] Dry leaves together with cow dung is used a mosquito repellent in Orissa, India.[28] In rural community of South Kerala, India, the fresh leaves of the plant are used as one of the ingredients in the formulations of medicated water for bathing women after delivery.[29] The plant is consumed as green salad by Monpa ethnic group of Arunachal Pradesh, India.[30] Extract prepared from leaves are applied to forehead in order to relieve headache in Chota Nagpur Plateau, India.[22] More information on utilization of *C. infortunatum* in traditional medicine is presented in Table 1.

Table 1: Ethnobotanical uses of *C. infortunatum*

Region	Part used	Uses	Reference
Malappuram district, Kerala, India	Roots, flowers	Paste comprising of roots and flowers along with coconut shell ash is used in rheumatism	Chithra and Geetha[31]
Visakhapatnam district, Andhra Pradesh, India	Root	Paste made from root along with *Annona reticulata*, *Jatropa curcas* and *Solanum torvum* is used in Sciatica.	Rao et al.[32]
Jalpaiguri district, West Bengal, India	Leaf, root	The root paste and leaf paste are used to treat pain and skin disease respectively.	Bose et al.[33]
Nadia district, West Bengal, India	Leaf	Used in inflammation and as vermifuge	Banerjee[34]
Sivasagar district, Assam, India	Root	Juice prepared from root is used against tapeworm infection. Paste made from root is used to treat toothache.	Gogoi and Islam[35]
Cox's bazar district, Bangladesh	Leaf	Leaf ash with coconut is applied to get rid of swelling of leg and blister.	Uddin et al.[36]
Wayanad district, Kerala, India	Leaf	Juice prepared from leaves is applied around the vaginal opening of pregnant women to make delivery easy.	Prasad et al.[37]
Barpeta district, Assam, India	Leaf, root	Used in preparation of beer and treatment of fever	Das[38]
Cachar district, Assam, India	Leaf	Used in diabetes, deworming, dysentery	Das et al.[39]
Purulia district, India	Root, leaf	Used in rheumatism and headache	Dey and De[40]
Assam, India	Leaf	Juice made from leaves is used to treat malaria	Paul et al.[41]
Sonebhadra district, Uttar Pradesh, India	Root, leaf	Used to treat helmintiasis, body ache, boils, burns, cuts, skin disease, sores, swelling, ulcer, wounds.	Singh and Dubey[42]

Uttarakhand, India	Root	Root powder together with *Boerhavia diffusa* is taken orally to treat epilepsy.	Sharma et al.[43]
Manipur, India	Leaf, root, flower	Used in diabetes, blood pressure, ascarids, tumor and poisonous bites	Khumbongmayum et al.[44]
Wardha district, Maharashtra, India	Leaf	Used to treat wound and bone fracture	Shende et al.[45]
Hazaribag district, Jharkhand, India	Leaf, root	Used in swelling, stomachic and malaria	Lal and Singh[46]
Arunachal Pradesh, India	Leaf	Leaf infusion taken to purify blood and manage high blood pressure	Khongsai et al.[47]
Assam and Arunachal Pradesh, India	Leaf	Used as heart tonic and as an ingredient of local wine	Shankar et al.[48]
Mymensingh district, Bangladesh	Leaf	Leaves of *C. infortunatum* along with leaves of *Catharanthus roseus* are crushed in water and a teaspoonful of this preparation is taken before meals in order to treat diabetes	Rahmatullah et al.[49]
Assam, India	Leaf	Juice made from leaves is used to treat malaria	Gohain et al.[50]
Assam, India	Leaf	Either raw or mixed with vegetables, leaves are used to treat diabetes, asthma and blood pressure.	Sajem and Gosai[51]
Uttar Pradesh, India	Leaf, stem	Stem is used in toothache. Decoction prepared from leaves is given to women suffering from fever after child birth.	Sharma et al.[52]
Assam, India	Leaf	Leaves are used in the preparation of Apong, a traditional beverage used by Mising tribe.	Gogoi et al.[53]
Tinsukia District, Assam, India	Leaf	Infusion prepared from leaves is used to cure malaria.	Buragohain[54]
Assam, India	Leaf	Juice from leaves is used as a tonic to cure dysentery	Basumatary et al.[55]
Madhya Pradesh, India	Leaf	Leaf paste is used to treat skin diseases.	Choudhary et al.[56]
Assam, India	Leaf	A herbal recipe containing leaf is used to cure respiratory problems.	Deka and Nath[57]
Assam, India	Leaf, twigs	Tender twigs are boiled in water, decoction is taken orally to reduce complicacy of menstruation. Leaves are used as vegetable and also as substrate in the preparation of rice starter cake for fermentation of rice	Terangpi et al.[58]
Rangamati district, Bangladesh	Leaf, root	Used in fever, helminthiasis, severe skin infection and stomach pain	Islam et al.[59]
Joypurhat district, Bangladesh	Leaf	Leaf juice is used in deworming and vomiting	Rahman[60]
Northeast India	-	Used in the preparation of starter cultures used in alcohol fermentation	Tanti et al.[61]
Bhola district, Bangladesh	Leaf, root, fruit	Scabies, fever, anthelmintic	Sohel et al.[62]

PHYTOCHEMICALS DETECTED IN *C. INFORTUNATUM*

Plants produce myriad chemicals that are collectively referred as phytochemicals. Many of such metabolites are secondary metabolites and have profound effect on the health of an individual. Alkaloids, terpenes and polyphenolic compounds including flavonoids are few among the secondary metabolites produced by plants. Plant secondary metabolites are significant and play important roles such as protection of the plants from pathogens, insects and herbivores, contribute to fragrance and vibrant color which may aid in pollination. These secondary metabolites are responsible for therapeutic potential of plants as it is experimentally shown that purified phytochemicals exhibit wide range of bioactivities.[63-66] Various parts of *C. infortunatum* are investigated for the detection of phytochemicals. Many methods such as standard phytochemical analysis, HPLC, HPTLC and GC-MS have been employed to detect and quantify phytochemicals present in various parts of *C. infortunatum*.[67-71]

Many chemical species such as limonene, phytol, catechol, hexadecanoic acid, squalene, dodecanoic acid, vitamin E, hydroxymethylfurfural, stigmasterol, cinnamic acid, guaiacol, eugenol, vanillic acid have been detected in *C. infortunatum* by GC-MS analysis.[69] Three clerodane diterpenoids namely Clerodin, 15-methoxy-14,15-dihydroclerodin and 15-hydroxy-14,15-dihydroclerodin having insecticidal activity have been detected in *C. infortunatum*.[72] The ethanolic extract of root was found to contain 1.4% w/w of alkaloid as estimated by spectrophotometric method.[73] A tannin content of 166.6±5.607mg tannic acid equivalents/g dry extract of root bark was estimated by Folin-denis assay.[74] More information on the presence of various phytochemicals in different parts of the plant and the structures of some of the compounds identified is shown in Table 2 and Figure 2.

Table 2: Phytochemicals detected in various parts of *C. infortunatum*

Part	Phytochemicals	Reference
Root	Alkaloids, flavonoids, terpenoids, glycosides	Haris et al.[75]
Leaf	Tannins, phenolics and flavonoids	Nayak et al.[76]
Leaf	Gallic acid	Verma and Gupta [68]; Gupta and Singh[77]
Leaf	Sterols, tannins, terpenoids, flavonoids and saponins	Verma and Gupta[68]
Root	Tannins, flavonoids, saponins and steroids	Sumi et al.[78]
Leaf	Alkaloids, flavonoids, steroid, tannin, terpenoid, phenolics	Dey et al.[79]
Whole plant	Flavonoids, tannins, sterols, terpenoids, anthraquinone glycosides	Prakash et al.[80]
Leaf	Alkaloids, flavonoids, steroid, saponins, terpenoid, phenolis, glycosides, phytosterols	Florence et al.[81]
Leaf	Alkaloids, saponins, flavonoids, triterpenes	Sannigrahi et al.[82]
Leaf	β-sitosterol	Gupta and Singh[83]
Root	Quercetin	Chacko et al.[84]
Leaf	Flavonoids, tannins, saponins	Das et al.[85]
Leaf	Oleanolic acid, Clerodinin A	Sannigrahi et al.[67]
Root	Tannins, phenols	Helen et al.[74]
Leaf	Phenolics, alkaloids, flavonoid, saponin, tannin and anthraquinone	Devi and Kumar[86]
Leaf	Steroids, triterpenoids, glycosides, flavonoids, polyphenolics and tannins	Panda et al.[70]
Flower	Antisal 1a, β-cubebene, tyranton, 2-trans-β-ocimene, 3-allyl methoxy phenol, 4H-1, 3-oxazin and others	Islam and Rahman[71]
Root	Alkaloids, flavonoids and tannins	Joly et al.[87]
Leaf	Alkaloids, steroids, triterpenoids, cardiac glycosides, flavonoids, tannins and phenolic compounds	Prusty et al.[88]
Leaf	Alkaloids, flavonoids, terpenoids, steroids, tannins, saponins and glycosides	Haris et al.[89]
Root	Alkaloids, flavonoids, terpenoids, steroids, tannins and saponins	Haris et al.[89]
Flower	Apigenin, acacetin and methyl ester of acacetin-7-O-glucuronide	Sihna et al.[90]
Whole plant	(22E,24S)-Stigmasta-5,22,25-trien-3b-ol	Das et al.[91]
Aerial parts	Viscosene (I-methyl-3-(2,6, 14, 18-tetramethylnonadeca-7, 17~dien-9-yl)benzene)	Choudhury et al.[92]
Root	Clerodolone, Clerodone, Clerodol and Clerosterol	Manzoor-Khuda and Sarela[93]
Leaf	Flavonoids, glycosides, polyphenolics, steroids and triterpenoids	Ghosh et al.[94]
Leaf	Alkaloids, glycosides and flavonoids	Rippon et al.[95]
Seeds	Quercetin	Eluru and Koumaravelou[96]
Aerial parts	24-ethylcholesta-5,22E-dien-3β-ol	Akihisa et al.[97]

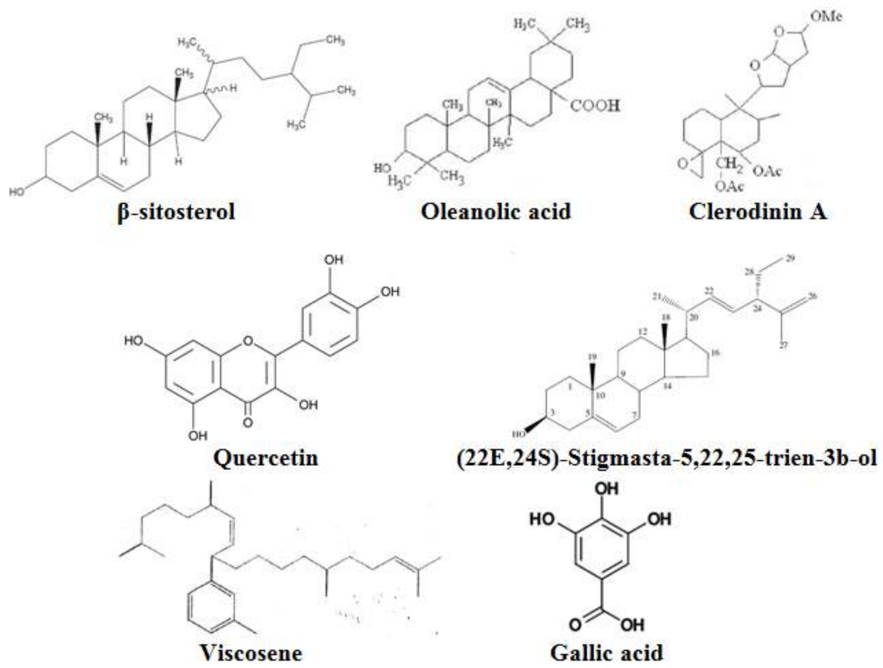

Figure 2: Structures of some compounds

PHARMACOLOGICAL ACTIVITIES OF *C. INFORTUNATUM*

A number of studies have revealed a wide range of pharmacological activities displayed by various parts of *C. infortunatum*. Biological activities (in vitro and in vivo) such as antimicrobial, anthelmintic, insecticidal, analgesic, antipyretic, insecticidal, hepatoprotective, wound healing, thrombolytic, antidiabetic, cytotoxic and anti-inflammatory activity have been displayed by *C. infortunatum*. A brief detail on the biological activities displayed by the plant is discussed below.

Cytotoxic activity

Many studies have been undertaken to investigate in vitro and in vivo cytotoxic/anticancer nature of different parts of *C. infortunatum* by various assays such as MTT assay, SRB method, brine shrimp lethality assay and inhibition of colony forming ability of cancer cell lines. Solvent extracts from leaf and bark were shown to exhibit concentration dependent cytotoxic activity against brine shrimp larvae.[98] A water extract fraction from the root was evaluated for its anticervical cancer cell bioactivity. It was found that the fraction displayed pro-apoptotic, anti-proliferative, and anti-migratory activity in a dose-dependent fashion against cervical cancer cell lines. The major component in fraction was identified as a glycoprotein via SDS Page and Concanavalin-A binding studies.[99] The hexane, chloroform, ethyl acetate and water fractions of 70% methanolic leaf extract displayed significant cytotoxicity against human glioblastoma (U87) cells. The fractions were able to arrest the cells at G2/M phase as well as induce apoptosis.[100] Waliullah et al.[101] revealed the potential of ethanol and chloroform extracts of leaf, stem and root of to exhibit cytotoxicity against brine shrimp larvae. Ethanol extracts were most active than chloroform extracts. The cytotoxicity of various parts was in the order: root extract > leaf extract > stem extract. The study carried out by Chacko et al.[84] revealed dose dependent antiproliferative activity of root extract against murine tumor cells (Dalton's lymphoma ascites cells) by the induction of intrinsic pathway of apoptosis however the extract was not shown to be toxic to mouse spleenocytes. Helen et al.[74] showed a dose dependent cytotoxicity of tannins isolated from roots against HCT 15 cancer cell lines by MTT assay.

The study by Chandra and Sanjib[102] revealed the antiproliferative potential of solvent extracts of leaves against Dalton's lymphoma cells by MTT assay. Haris et al.[75] studied the effect of chloroform and hexane extract of roots on inhibition of colony forming ability of A549 cells (lung cancer cell line) and effect against nuclear morphology. Extract treatment resulted in inhibition of colony forming abilities of cancer cells and also exhibited a direct influence on the nuclear morphology of cells. Further, it was also observed that the extract treatment had a direct effect on the motility of A549 cells (i.e. motility of cells was inhibited) as indicated by the result of scratch motility or wound healing assay. Waliullah et al.[103] carried out cytotoxicity determination of leaf, root and stem extracts by brine shrimp lethality bioassay. All extracts exhibited cytotoxic potential. Ethanol extract of root and ethyl acetate extract of stem displayed marked cytotoxicity in terms of causing mortality of brine shrimp larvae. Mohandas and Narayanan[104] observed dose dependent cytotoxic activity of ethanol extract of leaves against L929 cell line by MTT assay. A study on anticancer activity of methanolic extract of leaves against Ehrlich's ascites carcinoma (EAC) bearing Swiss albino mice was carried out by Sannigrahi et al.[67] Treatment with extract resulted in a significant decrease in the tumor cell volume and increase in the life span of animals. Besides, all the hematological parameters, malonaldehyde content and activity of antioxidant enzyme were restored. Haris et al.[89] revealed dose dependent cytotoxic potential of extracts of leaves and roots against cell lines viz. T47D (breast), PC-3 (prostate), A549 (lung) and HCT-116 (colon) cancer cell lines by SRB method. Table 3 shows more details on the cytotoxic potential of *C. infortunatum* as evaluated by brine shrimp lethality bioassay.

Table 3: Cytotoxic efficacy of *C. infortunatum* by brine shrimp lethality assay

Part	Extract	LC_{50} value	References
Leaf	Methanol extract	3.696µg/ml	Shamsul et al.[105]
Root	Methanol extract	10.235µg/ml	Rahman et al.[106]
Leaf	Methanol and chloroform extracts	10.58µg/ml (methanol extract), 13.68µg/ml (acetone extract)	Amin et al.[107]
Root	Ethanol extract	20.845ppm	Oly et al.[108]

Antibacterial activity

The antimicrobial potential of *C. infortunatum* has been investigated by several researchers. In the study of Rajakaruna et al.[109], the extract of *C. infortunatum* was shown to exhibit antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Enterobacter faecalis* however no activity was observed against *Escherichia coli* and *Pseudomonas aeruginosa*. Prusty et al.[88] evaluated antibacterial activity of various solvent extracts of *C. infortunatum* leaves against a panel of test bacteria by disc diffusion and MIC determination method. Extracts were effective against test bacteria with marked activity against gram positive bacteria when compared to gram negative bacteria. Benzene extract was more inhibitory to bacteria followed by ethanol and aqueous extracts. Modi et al.[110] evaluated antibacterial activity of ethanolic extract of leaves against gram positive and gram negative bacteria by disc diffusion method. The extract exhibited highest inhibitory activity against *E. coli*. A mixture of extracts of *C. infortunatum*, *Vitex negundo* and *Argyreia nervosa* was shown to exhibit marked antibacterial activity when compared to leaf extract of *C. infortunatum* alone. Choudhury et al.[92] revealed the antibacterial potential of a compound called viscosene isolated from aerial parts against bacteria viz. *Klebsiella pneumoniae*, *E. coli* and *Proteus vulgaris*. Table 4 shows more information on the antibacterial activity of various parts of *C. infortunatum*.

Table 4: Antibacterial activity of *C. infortunatum*

Part	Activity against	Reference
Leaf	Gram positive and gram negative bacteria	Shukla et al.[111]
Leaf	Gram positive and gram negative bacteria	Nayak et al.[76]
Root, stem, leaf	Gram positive and gram negative bacteria	Oly et al.[108]
Root, stem, leaf	Gram positive and gram negative bacteria	Waliullah et al.[112]
Leaf	*E. coli*, *Sarcina lutea* and *Shigella sonnei*	Amin et al.[107]
Root	Gram positive and gram negative bacteria	Joly et al.[87]
Leaf	Gram positive and gram negative bacteria	Devi and Kumar[86]
Leaf	*P. aeruginosa*	Mohandas et al.[113]
Leaf	Gram positive and gram negative bacteria	Lobo et al.[114]
Leaf	Gram positive and gram negative bacteria	Tamta et al.[115]
Aerial parts	*K. pneumoniae*, *E. coli*	Choudhury et al.[92]
Leaf	Gram positive and gram negative bacteria	Ghosh et al.[94]
Leaf	*B. subtilis*, *E. coli*	Banerjee[34]

Antifungal activity

Besides antibacterial activity, results of many studies have revealed the antifungal potential of various parts of *C. infortunatum* against a range of human and plant pathogenic and storage fungi. A brief description on the antifungal activity being exhibited by various parts of *C. infortunatum* is presented in Table 5.

Table 5: Antifungal activity of *C. infortunatum*

Part	Activity against	Reference
Leaf, root, stem	*Aspergillus niger*, *A. flavus*, *A. fumigatus*, *Fusarium oxysporum*, *F. vasinfactum*, *Mucor* sp. and *Candida albicans*	Waliullah et al.[112]
Leaf	*A. niger*, *A. flavus* and *C. albicans*	Modi et al.[110]
Leaf	*A. niger* and *C. albicans*	Rana et al.[116]
Leaf	*A. niger*, *Penicillium notatnum* and *C. albicans*	Prusty et al.[88]
Root, stem, leaf	*A. niger*, *A. flavus*, *A. fumigatus*, *Mucor* sp., *F. oxysporum* and *C. albicans*	Oly et al.[108]
Leaf	*A. niger*, *A. flavus*	Haris et al.[117]
Leaf	*A. niger*, *P. notatum*, *P. frequentance*, *Botrytis cinera*	Kharkwal et al.[118]
Leaf	*A. niger*, *A. flavus*, *F. oxysporum*, *Penicillium chrysogenum*, *Trichophyton mentagrophytes*	Devi and Kumar[86]

Antipyretic activity

Prusty et al.[88] evaluated the antipyretic potential of benzene, ethanol and aqueous extracts of *C. infortunatum* leaves by yeast-induced pyrexia in rabbits. Extracts were shown to display significant reduction in hyperthermia with marked activity being exhibited by benzene extract followed by ethanol and aqueous extracts.

Anthelmintic activity

Benzene, ethanol and aqueous extracts of leaves were shown to exhibit dose dependent anthelmintic activity in terms of paralysis and death of earthworms. Benzene and ethanol extracts were effective while aqueous extract displayed weaker anthelmintic potential.[88] Various concentrations of aqueous and ethanol extracts of leaves were screened for anthelmintic activity by using earthworm *Pheretima posthuma*. Ethanol extract displayed marked anthelmintic potential as it caused paralysis and death of worms in relatively shorter time when compared to time taken by aqueous extract and standard anthelmintic piperazine citrate.[119] Methanolic extract of leaves was shown to display dose dependent paralysis and death of *P. posthuma*.[120]. Methanolic and aqueous extracts from roots displayed anthelmintic activity against *P. posthuma* in terms of causing paralysis and death of worms. Among extracts, methanolic extract exhibited marked activity when compared to aqueous extract.[106] Shamsul et al.[105] showed dose dependent anthelmintic activity of methanol and aqueous extract of leaves using *P. posthuma*. Methanol extract displayed marked anthelmintic potential than aqueous extract. Haris et al.[117] revealed dose dependent anthelmintic activity of leaf extracts in terms of paralysis and death of *P. posthuma*. Among solvent extracts ethanol extract displayed marked anthelmintic effect as ethanol extract took less time to cause paralysis and death of worms. Das et al.[121] have also shown the potential of ethanolic and aqueous extract of roots and leaves to exhibit dose dependent anthelmintic activity. Activity observed was marked against *Ascardia galli* (recovered from fowls) when compared to *P. posthuma*. Recently, Nandi et al.[122] revealed anthelmintic potential of ethanolic extract of leaves against fowl tapeworm *Raillietina tetragona* in terms of paralysis and death of worms. Electron microscopic observations showed disruptions in the tegument and parenchymal layer, accompanied by deformities in cell organelles indicating anthelmintic efficacy of leaf extract.

Thrombolytic and membrane stabilizing activity

Ali et al.[123] revealed thrombolytic activity of methanol extract and solvent fractions viz. petroleum ether, chloroform, carbon tetrachloride and aqueous fractions of leaves by clot lysis assay. Carbon tetrachloride fraction and chloroform fraction displayed highest and least percentage of clot lysis. Joly et al.[87] showed thrombolytic and membrane stabilizing activity of various solvent fractions of root by clot lysis assay and heat and hypotonic solution induced hemolysis assay respectively. Fractions were shown to exhibit inhibitory activity against hemolysis induced by heat and hypertonic solution. Ethyl acetate extract was shown to exhibit marked thrombolytic and membrane stabilizing activity. The study of Rippon et al.[95] also showed membrane stabilizing activity of leaf extract in terms of dose dependent inhibition of hemolysis of human erythrocytes. The extract also caused dose dependent clot lysis activity indicating thrombolytic activity.

Nootropic (memory enhancing) activity

Two concentrations viz. 100mg/kg and 200mg/kg of methanolic extract obtained from leaves were evaluated for nootropic activity in mice using interoceptive behavioral models (rectangular maze and Y maze). At higher dose, the extract revealed a promising nootropic effect which closely approximated the result for the standard drug Brahmi.[124]

Antioxidant activity

The study carried out by Sannigrahi et al.[82] revealed the dose dependent scavenging potential of methanolic extract of leaves against DPPH, nitric oxide, superoxide and hydroxyl radicals with an IC_{50} value of 86.7, 76.1, 90.1 and 65.8µg/ml respectively. The extract also showed ferric reducing activity. Prakash et al.[80] observed scavenging of DPPH radicals by ethanol extract of whole plant with an IC_{50} value of 50.905µg/ml. The study by Kumar et al.[125] revealed dose dependent scavenging of DPPH radicals by methanol extract of roots with an IC_{50} value of 34.46µg/ml. The extract also exhibited reducing potential. Sumi et al.[78] revealed marked dose dependent scavenging of DPPH radicals by root extract with an IC_{50} value of 32.5µg/ml. More information of antioxidant activity of *C. infortunatum* is presented in Table 6.

Table 6: Free radical scavenging and antioxidant activity of *C. infortunatum*

Part	Extract or compound	Method	Reference
Leaf	Methanol extract	DPPH scavenging assay, nitric oxide scavenging assay, total antioxidant capacity, reducing power assay	Rahman et al.[126]
Leaf, bark	Solvent extracts	DPPH radical scavenging assay	Bhatnagar and Pattanaik[98]
Leaf	Petroleum ether, chloroform and ethanol extracts	DPPH scavenging assay	Gouthamchandra et al.[127]
Leaf	Ethanol and chloroform extracts	DPPH scavenging assay, ferric reducing power assay	Devi and Kumar[86]
Leaf	Methanol extract and solvent fractions	DPPH scavenging, ABTS scavenging, nitric oxide scavenging, hydrogen peroxide scavenging assays	Ghosh et al.[94]
Root	Tannin	DPPH scavenging assay, reducing power assay and total antioxidant activity	Helen et al.[74]
Leaf	Ethanol extract	DPPH radical scavenging assay, FRAP assay and the Hydrogen peroxide radical scavenging assay	Modi et al.[128]
Leaf, stem, root	Methanol extract	Total antioxidant capacity, hydrogen peroxide scavenging, radical scavenging assays, singlet oxygen scavenging assay, metal chelating assay, ferric reducing assay, lipid peroxidation assay	Dey et al.[129]
Leaf	Methanol extract	DPPH radical scavenging assay	Rippon et al.[95]
Leaf	Solvent fractions of methanol extract	Total antioxidant activity, scavenging of DPPH, hydroxyl, superoxide, nitric oxide, peroxynitrite and hypochlorous radicals.	Ghate et al.[100]

Insecticidal activity

Several studies have been undertaken to investigate insecticidal activity of various parts of *C. infortunatum*. The study carried out by Abbaszadeh et al.[72] revealed the potential of three clerodane diterpenoids viz. clerodin, 15-methoxy-14,15-dihydroclerodin and 15-hydroxy-14,15-dihydroclerodin isolated from *C. infortunatum* to exhibit insecticidal activity against *Helicoverpa armigera* with GI_{50} values of 13, 21 and 11 ppm respectively. In a study, the leaf powder mixed with cow dung at various concentrations (5, 10 and 20% w/w) was fed to third instar grubs of rhinoceros beetle *Oryctes rhinoceros*. A dose dependent mortality of grubs was observed. Further, the plant has adverse effects on the reproduction capability of male insect.[130] Insecticidal activity of leaf powder was evaluated against fourth instar larvae of banana pseudostem borer *Odoiporus longicollis*. A dose dependent mortality of larvae by plant was observed with an LD_{50} value of 3.987%.[131]

Dinesh et al.[132] revealed the insecticidal activity (by adulticidal and larvicidal assays) of whole plant, root, bark and leaf against the sand fly *Phlebotomus argentipes*. Hexane extract of root exhibited stronger insecticidal activity against adult insect (77%) while larvae were not affected. A fraction obtained from the leaf extract was shown to be effective against *P. argentipes* (63% effective). The study of Mondal et al.[133] revealed the larvicidal potential of leaf extract against filarial vector *Culex quinquefasciatus*. The leaf extract was effective in causing larval mortality dose dependently with LC_{50} value of 0.075%. Roy et al.[134] showed the insecticidal effect of aqueous extract of *C. infortunatum* against 3rd instar larvae of *Hyposidra talaca* an emerging major pest of tea by leaf dip method. Table 7 presents more information on the insecticidal efficacy of *C. infortunatum*.

Table 7: Insecticidal activity of *C. infortunatum*

Part	Method	Activity against	Reference
Leaf	Repellent activity	*Tribolium castaneum* (flour beetle)	Husain and Rahman[135]
Leaf	Larvicidal activity	*Orthaga exvinacea* (a pest of mango trees)	Nambiar et al.[136]
Leaf	Repellant and oviposition deterrent activity	*Callosobruchus chinensis* (pulse beetle)	Valsala and Gokuldas[137]
Root, leaf, stem	Residual film assay and repellency test	*Tribolium castaneum*	Waliullah et al.[138]
Root, leaf, stem	Residual film assay and repellency test	*Sitophilus oryzae* (rice weevil)	Waliullah et al.[139]

Antidiabetic activity

Kalita et al.[140] evaluated antidiabetic property of methanol extract of roots by streptozotocine induced diabetes in rats. Administration of extract caused a reduction in the elevated blood glucose level. An increase in the body weight was also observed. Study of Devi and Kumar[86] revealed the inhibitory effect of ethanol and chloroform extract of leaves against the activity of α-amylase and α-glucosidase. Kalita and Chakraborty[141] revealed antidiabetic activity of methanolic extract of leaves in rats with diabetes induced by streptozotocine. A significant increase in the body weight and reduction in blood glucose level was observed in animals administered with the extract indicating the potential to act against diabetes. Further, administration of extract to diabetic rats also exhibited a dose dependent protective effect against testicular damage caused by diabetes induced by streptozotocine. A significant improvement in sperm parameters such as sperm motility, sperm viability and sperm count was observed. Panigrahi et al.[142] have also revealed antidiabetic activity of leaf extract against hyperglycemia in rats induced by streptozotocin. A significant decrease in fasting blood glucose level in diabetic rats was observed at the extract dose of 400mg/kg body weight. The study of Das et al.[143] revealed the antihyperglycemic potential of leaf extract against streptozotocin-induced diabetes in rats. Extract administration showed a significant and dose dependent reduction in blood glucose level when compared to control group animals. Further, a decrease in lipid peroxidation and a recovery of GSH level and catalase activity was observed in extract treated animals.

Wound healing activity

The study of Kuluvar et al.[144] revealed the wound healing potential of roots by excision, incision and dead space wound models in rats. Topical application of ointment cream bases of root extracts showed significant wound healing activity in terms of increased area of epithelialization, followed by an increase in wound contraction, skin breaking strength and tissue granulation dry weight.

Hepatoprotective activity

Sannigrahi et al.[145] evaluated hepatoprotective potential of methanolic extract of leaves against carbon tetrachloride induced hepatotoxicity in rats. Extract administration resulted in reduction in MDA concentration and an increase in liver antioxidative enzyme activity. In addition, histopathology of liver tissue showed reduction of fatty degeneration and liver necrosis indicating hepatoprotective activity. Singh et al.[146] revealed ameliorative efficacy of methanolic extract of leaves against arsenic induced hepatotoxicity in albino rats. Administration of extract to animals revealed hepatoprotective activity in terms of increase in liver weight and SOD level and a decrease in the level of MDA, ALT and AST.

Analgesic activity

Khatry et al.[147] observed a dose dependent antinociceptive activity of methanol extract of whole plant in acetic acid induced writhing in swiss albino mice. In a study, saponin isolated from the leaves was screened for analgesic activity by acetic acid induced writing and hot plate method. Saponin was found to exhibit marked analgesic effect in terms of inhibition of writhing induced by acetic acid and production of analgesia (in terms of increase in retention time) in mice in hot plate method.[8] Das et al.[148] revealed the analgesic potential of leaves by tail flick method. Rahman et al.[126] showed antinociceptive activity of methanolic extract of leaves by acetic acid induced writhing in mice. A significant activity was observed when compared to standard drug Diclofenac. The root extract was shown to produce 38.59% and 59.07% writhing inhibition at the doses of 250mg/kg and 500 mg/kg respectively.[78] Ethanolic extract of root was shown to exhibit an appreciable analgesic activity in mice as evaluated by methods viz. hot plate, tail immersion, acetic acid induced writhing and formalin test.[73] The study of Chandrashekar and Rao[149] revealed analgesic potential of ethanol extract of leaves by acetic acid induced writhing in swiss albino mice, however, the extract failed to produce analgesia by tail immersion method.

Antivenom activity

Lobo et al.[150] evaluated antisnake venom activity of alcoholic root extract in *Naja naja* venom by in vitro (using human blood) and in vivo (in mice) methods. In vitro studies revealed only interaction with but do not stabilize membrane protein. However, in in vivo study, the extract displayed significant activity which was attributed to the possible interference of extract with the acetyl choline binding sites.

Antiinflammatory activity

Khatry et al.[147] showed concentration dependent anti-inflammatory potential of whole plant extract by carrageenan induced paw edema method in rats. Extract administration showed statistically significant inhibition of paw volume. The study carried out by Prasanth et al.[73] revealed anti-inflammatory activity of root extract by carrageenan induced paw edema in mice. At dose 200mg/kg and 400mg/kg, the ethanol extract produced significant reduction in the edema when compared to standard drug. In another study, Chandrashekar and Rao[151] showed significant and dose dependent anti-inflammatory activity of ethanolic extract of leaves by carrageenan induced paw oedema model in Wistar rats. Helen et al.[152] revealed anti-inflammatory activity by carrageenan induced paw oedema of various extracts of root bark. Aqueous acetone extract was shown to exhibit marked anti-inflammatory activity. It was observed that the phenolic content of extract correlates with the anti-inflammatory activities. Rippon et al.[95] evaluated in vitro anti-inflammatory activity of leaf extract in terms of inhibitory activity against protein denaturation in egg albumin assay. The extract was shown to cause inhibition of protein denaturation with an IC_{50} value of 127.7±0.5μg/ml.

Anticonvulsant activity

Pal et al.[8] investigated anticonvulsant activity of saponin isolated from the leaves by leptazol-induced seizure method in mice. Saponin was shown to reduce the duration of seizures and also provided protection against leptazol-induced convulsions in a dose dependent manner. The study carried out by Das et al.[85] also revealed significant anticonvulsant activity of leaf extract by methods viz. pentylenetetrazole- and strychnine- induced convulsion in mice. The extract significantly delayed the onset and antagonized seizures. Further, the extract significantly increased pentobarbitone-induced sleeping time in a dose dependent manner.

Diuretic activity

Khatry et al.[147] evaluated diuretic activity of whole plant extracts by recording urinary output from 1 to 4 hours of extract administration (at an interval of 1 hour). The results showed that the extract lacks diuretic activity as the extract exhibited a score of <0.72. Further, it was observed that the extract lacks natriuretic or saliuretic properties and the extract had no inhibitory property on carbonic anhydrase enzyme.

Effect on germination of seeds

A study on the effect of leaf extract on the germination and growth of root and shoot of some vegetable crops was carried out by Islam et al.[153] It was observed that the chloroform extract showed significant effect and enhanced the germination, growth of shoot length and root length of yard long bean and swamp cabbage while it reduced and delayed the germination, growth of shoot length and root length of lady's finger seeds compared with control. Datta and Chakrabarti[154] revealed allelopathic effect of decaying plant-parts of *C. infortunatum* against weed seeds as evaluated by inhibition of germination of seeds and root and hypocotyl growth of weeds.

CONCLUSIONS

An extensive literature survey on various aspects of *C. infortunatum* revealed high medicinal value in various geographical areas and various pharmacological properties displayed by the plant as revealed by in vitro and in vivo studies. The studies have given justification to the traditional uses of the plants by various indigenous communities. A number of phytochemicals have been identified which can be attributed to the observed biological activities of the plant. Overall, it appears that the plant *C. infortunatum* is suitable for the development of therapeutic agents against various ailments or disorders.

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CONFLICTS OF INTEREST

None declared

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