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Biological and Pharmacological Activity of the Leaves Extract of Clerodendrum Colebrookianum Walp, (Fam: Verbenaceae)

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ABSTRACT:
Clerodendrum colebrookianum Walp is a seasonal perennial shrub which is native to South and Southeast Asia. Different species within the Clerodendrum genus possess tremendous pharmacological and medicinal properties. These emanate from the presence of many unique bioactive secondary metabolites traditionally; it is used in the treatment of various diseases due to its immense therapeutic potential. In view of extensive ethno-medicinal importance and utilization in various forms of ethnomedicinal uses of Clerodendrum colebrookianum in the north eastern region, the present paper is an effort to compile the existing information on folklore medicine uses by different communities of north eastern India. It is extensively used by the indigenous people of Northeast India as a remedy for treatment of various diseases like high blood pressure, diabetes, stomachache, jaundice, cough, rheumatism, dysentery and various skin diseases. The plant possesses different pharmacologically active components like Colebrin A, Colebrin B, Colebrin D, Colebrin E, β-Sitosterol etc. This review reported various pharmacological activities of the plant such as antidiabetic, antihypertensive, anti-inflammatory, analgesic, hepatoprotective, antioxidant, anthelmintic and some other activities which provide scientific evidence for some traditional therapeutic claims.

Keywords: Clerodendrum colebrookianum, ethnomedicinal, Pharmacological, antihypertensive, therapeutic

INTRODUCTION:

Since ancient time, in search for the remedy for the various ailments, people always looked for potential drugs in medicinal plants and over the generations the plant-derived products have been a vital part of our traditional health care system. The uses of plant-derived products provide a large source of natural drug for treatments of several metabolic disorders and infectious diseases. World Health Organization (WHO) estimated that 80% of the developing and under developing countries population depends on plant derived medicines which have its own advantages like i.e. low or no adverse effects, poses minimum environmental hazards, easily available and affordable [1-3]. However, infectious diseases remain as world's major problem, accounting for 33% deaths each year and threatening to affect many more millions of people. The undesirable side effects along with the unprecedented upsurge in antibiotic resistance among pathogens upon synthetic drugs exposure have necessitated for looking at alternative therapeutics, particularly the plant based one [4-6].

Parasitic infections are known to lead for the release of free radicals which have severe consequences on functioning of cellular metabolism. Overproduction of ROS (reactive oxygen species) either by normal oxygen metabolic process or by infections, apart from playing a beneficial role, may leads to oxidative stress thereby causing damage to vital components of the cell [7]. Generally, free radicals have been implicated in several disorders (diabetes mellitus, heart diseases, cancer, acquired immunodeficiency syndrome, arthritis, liver disorder, ageing, etc.), and the treatment by antioxidants has gained an utmost importance in the treatment [8]. The presence of both antioxidant and antibacterial compounds in a single medicinal plant extracts, will have the dual therapeutic potential, thus helping in fighting infectious diseases and its further consequences. Although, plants used in the traditional medicine have been identified and their applications well-documented for many, however, the biological efficacy of many plants is yet to be scientifically verified [9-11].

Botanical Description

Clerodendrum colebrookianum Walp is a perennial evergreen flowering shrub or small tree and grows up to 1.5-3 m in height. It is native to South and Southeast Asia [12]. The plant grows generally in moist and waste places. The young

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branch lets of this plant are usually four angled. The leaves are simple, opposite or rarely whorled. Leaf base is wedge-shaped to heart-shaped, margin is entire to slightly wavy, tip long-pointed to point. Flowers are white and borne in 4-6-branched corymbose cymes, at the end of branches. Calyx is campanulate or cup-shaped, densely pubescent, corolla with a slender tube. The Calyx of the flower is campanulate or cup shaped, densely pubescent. Corolla with a slender tube has 5 spreading lobes. Four Stamens are present, ovary 4-locular; ovules are pendulous or laterally attached. The fruit is a drupe with 41-seeded Pyrenees, sometimes separating into 2 2-loculed or 41-locular mericarps. It flowers during post-monsoon from August to December [13].

Table no: 1 Taxonomy Hierarchy:

Kingdom	Plantae
Phylum	Magnoliophyta
Class	Magnoliopsida
Order	Lamiales
Family	Verbenaceae
Genus	Clerodendrum L.
Species	Clerodendrum colebrookianum
Binomial name	Clerodendrum colebrookianum Walp

Phytochemistry

The chemical constituent of Clerodendrum colebrookianum showed the presence of phenols, alkaloids, flavonoids, polyphenols, steroids etc [14]. GCMS analysis of Clerodendrum colebrookianum hexane extract showed the presence of 28 compounds [15]. Five new steroids, colebrin A-E were also isolated from the aerial parts of the species [16]. Moreover, presence of β - sitosterol and sterol compounds in the leaves of Clerodendrum colebrookianum has already been reported [17]. B-sitosterol, a bioactive phytoconstituent that decrease the serum cholesterol and also have cardio protective potentiality which is a valid scientific basis for consuming it for better health in North east region of India [18].

Pharmacological Studies

Hypolipidemic activity

Crude polyphenol fraction obtained from the ethyl acetate extract of Clerodendrum colebrookianum leaves administered in graded oral doses (0.25 g, 0.5 g and 1 g/kg b.w. /day) for a period of 28 days in cholesterol fed rats showed Significant rise in plasma total cholesterol (TC), triglycerides (TG), phospholipids (PL), lowdensity lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and decrease in high-density lipoprotein cholesterol (HDL-C) Increased lipid profile has been depleted and high-density lipoprotein cholesterol (HDL-C) has been increased after chronic feeding of Crude polyphenol Clerodendrum colebrookianum (CPCC). In addition, CPCC leave extract enhanced the excretion of fecal cholesterol (FC) but could not arrest the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase activities in cholesterol fed rats. Histopathological observations showed loss of normal liver architecture in cholesterol fed rats which were retained in CPCC treated groups. The findings of the study suggested that CPCC had a strong hypolipidemic function and could be used as a supplement in healthcare foods and drugs. Ethyl acetate extract of Clerodendrum colebrookianum leaves showed potent hypolipidemic effect in cholesterol fed rats [19].

Antioxidant activity

Aqueous and acetone extract of Clerodendrum colebrookianum leaves showed the highest total phenolic content (2.348 mg/ml), when compared to methanol, ethanol and chloroform extracts, which was 0.549 mg/ml, 0.408 mg/ml and 0.407 mg/ml, respectively. The antioxidant activity

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was more significant for aqueous extract, when compared to other extracts in vitro antioxidant (DPPH) studies [20]. Different concentrations of the water, alcoholic, petroleum ether and ethyl acetate extracts of the dried leaves of Clerodendrum colebrookianum showed a significant inhibition of lipid peroxidation in in vitro lipid peroxidation induced by FeSO4-ascorbate in rat liver homogenate. Water extracts at concentrations (w/v) of 1:30, 1:50, 1:200 and 1:1000 showed the strongest inhibitory activity over the other organic extracts, suggesting maximum antioxidant effect. Chronic feeding of the water extract to Wistar albino rats (both sexes, 150–200g) in 1 or 2g /kg/day doses for 14 days significantly increased the ferric reducing ability of plasma by 19% and 40% on the seventh day, and by 45% and 57% on the fourteenth day of treatment, respectively. Thiobarbituric acid reactive substances (TBARS), as a marker of lipid peroxidation, and some cellular antioxidants (superoxide dismutase, catalase and reduced glutathione) were estimated in heart, liver and kidney showed significant reduction in hepatic and renal TBARS with both the doses, without any change in myocardial TBARS. There was no change in the level of antioxidants in heart, liver and kidney, except for the hepatic superoxide dismutase. Leaves extract of Clerodendrum colebrookianum showed increased antioxidant capacity of blood and had an inhibitory effect on the basal level of lipid peroxidation of liver and kidney [21]. Methanolic leaves extract of Clerodendrum colebrookianum showed potent in vitro antioxidant activity by DPPH radical scavenging assay, Hydroxy radical scavenging assay, Superoxide radical scavenging radical assay, nitric oxide radical scavenging assay, singlet oxygen radical scavenging assay and peroxynitrite radical scavenging assay [22].

Anti-inflammatory activity

Aqueous extracts and its aqueous, n-butanol, ethyl-acetate, and chloroform fractions of Clerodendrum colebrookianum leaves at the dose of 200mg/kg/p.o. showed significant inhibition of carrageenan and histamine-induced inflammation and cotton pallet-induced granuloma formation on acute and chronic inflammation in rats. The test samples, except n-butanol fraction, exhibited inhibitory effect for both COX-1 and COX-2, in in vitro assay but their percentage of inhibition values differs from each other. The test samples (aqueous extracts, aqueous, n-butanol, ethyl-acetate, and chloroform fractions) at 100µg concentration exhibits 54.37%, 33.88%, 62.85%, 56.28%, and 57.48% DPPH radical-scavenging effect respectively in in vitro antioxidant study [23]. Methanolic extract of Clerodendrum colebrookianum leaves showed potent anti-inflammatory effect on carrageenan induced paw edema in Wistar albino rats. It was found that the active anti-inflammatory effect of this plant due to the presence of terpenes, glycosides and sterols [24].Aqueous extract of Clerodendrum colebrookianum leaves showed anti-inflammatory effect in acute and chronic stages of inflammation by free radical scavenging activity and by the inhibition of both the COX-1 and COX-2 enzymes [25].

Antipyretic activity

Hexane extract (HECC) and methanol extract (MECC) of the whole plant of Clerodendrum colebrookianum at doses of 100mg, 300mg and 500mg/kg b.w. showed significant anti-pyretic effect in yeast (10ml/kg b.w.)-induced pyrexia in albino rats and the effect also extended up to 5 hours after the drug administration. The anti-pyretic effect of HECC and MECC was comparable to that of a standard antipyretic agent paracetamol (150 mg /kg, b.w., p.o) [26].

Analgesic activity

The methanolic extract of the Clerodendrum colebrookianum whole plant administered intraperitoneally in the dose of 100mg/kg b.w. and 200 mg/kg b.w. and 200mg/kg b.w. showed potent analgesic effect in acetic acid induced male Swiss albino mice in a dose dependent manner by using hot tail flick test. The leaf extract showed significant analgesic effect in two different doses (100mg/kg b.w. and 200 mg/kg b.w.) by following the hot tail flick method [27].

Antimicrobial activity

Acetone extract of Clerodendrum colebrookianum leaves showed significant antimicrobial activity and exhibited significant zone of inhibition (mm) of 14±0.3, 13±0.3 and 15±0.2 for Escherichia coli, Serratia marcescens and Staphylococcus aureus, respectively [28].

Antihypertensive activity

100 µg/mL of aqueous extract (AECc), its aqueous, n-butanol (nBFCc), Ethyl-acetate (EtFCc) and Chloroform fractions of Clerodendrum colebrookianum leaves showed calcium antagonism in rat ileum and at 50 µg/mL and 75

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µg/mL doses exhibited Rho-associated coiled-coil protein kinase (ROCK–II), phosphodiesterase-5 (PDE-5) inhibition respectively where, EtFCc was caused maximum 68.62% (ROCK-II) and 52.28% (PDE-5) inhibition, but none of the test sample was exhibit effect in angiotension converting enzyme (ACE) at 100 µg/mL. The test samples also showed negative inotropic and chronotropic effect on isolated frog heart and significant ($P<0.001$) reduction in systolic blood pressure and heart rate in hypertensive rats compared to control [29]. Docking studies showed that three chemical constituents (acteoside, martinoside, and osmanthuside β6) out of 21 reported from the Clerodendrum colebrookianum to interact with the anti-hypertensive drug targets with good glide score. In addition, they formed H-bond interactions with the key residues Met156/Met157 of ROCK I/ROCK II and Gln817 of PDE5. Further, molecular dynamics (MD) simulation of protein–ligand complexes suggest that H-bond interactions between acteoside/osmanthuside β6 and Met156/Met157 (ROCK I/ROCK II), acteoside and Gln817 (PDE5) were stable. The present investigation suggests that the anti-hypertensive activity of the plant is due to the interaction of acteoside and osmanthuside β6 with ROCK and PDE5 drug targets. The identified molecular mode of binding of the plant constituents could help to design new drugs to treat hypertension [30].

Hepatoprotective and oxidative stress activity

Post oral administration of different doses of Clerodendrum colebrookianum leaves extract (50,100 and 200 mg/kg b.w.) showed significant decrease in different biochemical oxidation and collagen content in Iron overload induced liver injury by intraperitoneal administration of iron dextran into mice. The extract effectively enhanced the antioxidant enzyme levels and also exhibited the potential activity of the reductive release of ferritin iron. The protective effect of the plant extract on injured liver was furthermore supported by the histopathological studies that showed improvement histologically. The study revealed that the plant extract has hepatoprotective efficiency for iron overload diseases in mice and possess potential in vitro iron chelation effect and protection of Fenton reaction induced DNA damage [31].

CNS depressant activity

Clerodendrum colebrookianum leaves extract at the dose of 20mg/kg and 40 mg/kg showed marginal reduction of awareness and motor activity whereas at the dose of 80 mg/kg, the extract showed marked inhibition of awareness and motor activity in mice. The extract prolonged the effect of mepobamate, diazepam, chlorpromazine and pentobarbitone significantly in a dose dependent manner. Pretreatment of the extract caused significant protection of strychnine and leptazol induced convulsion and mortality [32].

Anti-stress activity

Administration of aqueous leaves extract of Clerodendrum colebrookianum at the dose of 100mg/kg prevented the cold restraint stress and showed anti-stress property in induced cold restraint stress in Swiss albino mice by significant reduction in the WBC count, eosinophil, basophil level and spleen weight while the level of ALT, neutrophills, blood glucose and plasma corticosterone along with the liver weight was found to be increase significantly on stress treatment. The studies reported that such cold restraint stress induced apoptotic cell death including alterations in the leukocyte numbers, blood glucose level, ALT activity, liver and spleen weight could be prevented by using this plant extract [33].

Anthelmintic activity

Leaves extract of Clerodendrum colebrookianum at three different doses, i.e. 200, 400 and 800 mg/kg b.w. given singly for 5 days in experimentally induced Hymenolepis diminuta (a zoonotic tapeworm) infections in Wistar rats showed that the leaves extract possesses a dose-dependent efficacy against the larval, immature and adult stages of Hymenolepis diminuta. However, the efficacy of the extract was found to be considerably high only against the adult stages of the parasite. A single 800 mg/kg dose of extract, given for 5 days, resulted into 68.42% reduction in the eggs per gram of feces (EPG) counts and 62.50% reduction in the worm counts. The study suggested that leaves of this plant possess significant anthelmintic properties and supports their use against intestinal tapeworm infections in traditional medicine [34].

DISCUSSION AND CONCLUSION

Keeping in view the above literature, Clerodendrum colebrookianum has excellent therapeutic effect for treatment of a wide spectrum of health disorders in traditional and folk medicine. Further, it needs to biochemical studies, isolation,

characterize the active component of toxicities and elucidate more insight on the mechanism of action of different active compound and their bioavailability which may lead to discover the potential lead compounds or molecules against life threatening diseases of human life such as hypertension, diabetes. Development of database, proper harvesting and cultivation techniques and also awareness programs in the state as well as region level for the conservation and management of potential species are utmost important.

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