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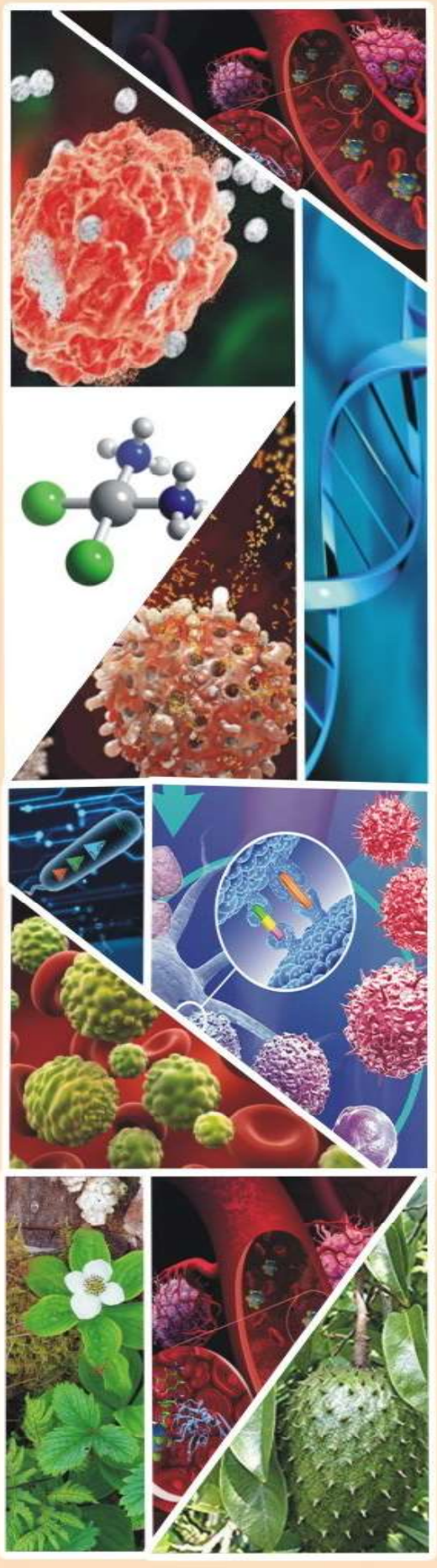

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CONTENT

PHYTOCHEMICAL AND PHARMACOLOGICAL ACTIVITIES OF *Eupatorium adenophorum* SPRENG- *A REVIEW*

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ABSTRACT

Eupatorium adenophorum Spreng belonging to the family Asteraceae have traditionally been used as folklore medicine across the world. In traditional system of medicine, it is regarded as antiinflammatory, antimicrobial, antiseptic, analgesic, antipyretic, blood and coagulant. The present review summarizes the updated information concerning the ethnomedicinal, phytochemical, pharmacological and toxicological aspects of E. adenophorum. The phytochemical and pharmacological studies demonstrated that E. adenophorum possess a wide spectrum of pharmacological activities, such as antitumor, antioxidant, antiseptic and cytotoxic activities which could be attributed to the presence of array of phytochemicals of various groups including terpenoids, phytosterols, alkaloids, flavonoids, phenolic acids, coumarins, phenylpropanoids, sesquiterpene lactones, polysaccharides, and essential oil. Modern phytochemical and pharmacological studies have led to the isolation and characterization of a number of bioactive compounds from different parts of the plant as well as validation of its traditional medicinal uses. This review described the phytoconstituents and pharmacological properties.

Keywords: Eupatorium adenophorum, Traditional uses, Phytochemistry, Pharmacology, Toxicity.

1. INTRODUCTION

Medicinal plants are indispensable natural resource constituting one of the potential sources of bioactive chemical entities for drug development [1]. Traditional medicinal uses of plants offer valuable clue to such drug development. It is estimated that about 60% of the world population and 80% of the population of developing countries rely on traditional medicine for their primary health care needs [2]. Medicinal plants satisfy the need of millions of ethnic and indigenous people living in tribal and rural sector of India. According to the report of the Ministry of Environments and Forest and Climate Change (MOEF&CC), Government of India, tribal communities in India use over 10,000 wild plants for primary health care [3, 4], In recent years, despite incredible development in allopathic medicine, majority of people throughout the globe are opting for herbal healthcare system owing to their efficacy, safety and lesser side effects; as such, herbal medicines are gaining polarity and acceptance than ever before [4]. Medicinal plants related ethno medicinal knowledge has been an important guiding principle for research in the area of new drug development [5]. Persistent research on plants involves a persistent search for new phytochemical molecules with specific pharmacological efficacy and that are non-toxic and efficacious in controlling human diseases. In this respect, various species of Eupatorium hold great potential for in-depth investigation with scientific confirmation of their therapeutic properties thus making them potential sources of safer and more effective treatments.

2.PHYTOCHEMISTRY

The genus Eupatorium in general and E. adenophorum in particular has been extensively investigated for its phytochemical constituents. Structurally diverse chemicals including (mono-, sesqui-, di-, and tri-) terpenoids, phenylpropanoids, polysaccharides, flavonoids, phenolic acids, coumarins, sterols and alkaloids have been reported from different parts of the plant [6-15]. Xu *et al*., isolated compounds namely n-dotriacontane, βsitosterol, stigmasterol, taraxasterylpalmitate, taraxasteryl acetate from the plant [20]. Ding *et al.,* isolated a new sesquiterpenene lactone, eupqtoranolide and 11 known compounds from the flowers [21]. He *et al.,* isolated four new cadinanesesquiterpenes, including a dimericcadinane derivative and a peroxide cadinane analogue, from the leaves. A novel quinic acid derivative, 5-O-trans-ocoumaroylquinic acid methyl ester (20), together with chlorogenic acid methyl ester (21), macranthoin F (22) and macranthoin G (23) were isolated from the aerial parts of the plant [30]. Essential oils of Eupatorium are richer in sesquiterpenes than in monoterpene compounds. Analysis of the light yellow coloured essential oil from aerial part of *E. adenophorum* showed the presence 45 components and the major compound was found to be torreyol (16.8%) 2-pentanone (7.71%), germacrene (7.49%), bornyl acetate (7.51%), 1-α-bisabolene (6.82%), δ-cadinene (6.4%), α-bisabolol (5.1%) [31]. Another sample of aerial parts essential oil from northern India found to contain 1-naphthalenol (17.5%), α-bisabolol (9.5%), bornyl acetate (8.98%), β-bisabolene (6.16%), germacrene-D (5.74%), α-phellandrene (3.85%) and a di-epi-α-cedrene (2.98%) [19]. Weyerstahl et al. reported the composition of the essential oil from flowers of E. adenophorum as α-phellandrene (15.3%), camphene (12.2%), bornyl acetate (10.6%), p-cymene (8.5%), γ-curcumene (4.5%) and 2-carene. Essential oil from inflorescences is dominated by sesquiterpenes (55.9%) with γcadinene (18.4%), γ-muurolene (11.7%), 3-acetoxyamorpha 4, 7 (11) diene-8-one (7.4%) and bornyl acetate (6.3%) as the major constituents [21].

3.Pharmacology

3.1.Anti-Inflammatory Activity

Ethanolic leaf extract of *E. adenophorum* exerts antiinflammatory activity, likely through inhibition of IL1β, COX2 genes and quenching reactive oxygen species (ROS) such as hydroxyl radical. Intravenous administration of the leaf extract increased the number of CD4 T cells in spleen and tumour necrosis factor (TNF)-α, an established proinflammatory cytokine in serum of delayed DTH mice. The extract also induces TGFβ encoding a cytokine involved in tissue repair mechanism and inhibits expression of another proinflammatory cytokine gene IL1β and down-regulates cycloxygenase 2 (COX2) genes responsible for metabolism of inflammatory mediators like prostaglandins. Furthermore, anti-inflammatory role of ethanolic extract of leaves is also revealed through its property to inhibit hydroxyl radical generation.

3.2.Antipyretic Activity

The anti-pyretic effect of methanol extract of *E. adenophorum* leaves on yeast induced pyrexia at the doses of 300 and 400 mg/kg body weight showed decreased yeast incited rise in body temperature of rats. The standard drug paracetamol significantly reduced the yeast-provoked elevation of body temperature at a dose of 150 mg/kg. The

result suggested a significant antipyretic effect methanol extract of leaves in rats comparable to that of paracetamol (standard drug). The bioactive constituents like triterpenoids, β-sitosterol known to have antipyretic effect might be responsible for the antipyretic efficacy of the plant [6]. The aqueous extract of leaves reported to exhibit significant antipyretic activity in the dosage of 300, 400 and 500 mg/kg body weight as compared to standard drug paracetamol [49]. This validated the tradition medicinal claim on antipyretic efficacy of the plant [11].

3.3.Antioxidant Activity

The ability of ethanolic extract of *E. adenophorum* leaves in quenching the generation of hydroxyl radical has been tested [27]. The quinic acid derivative including 5-O-trans-o-coumaroylquinic acid methyl ester, chlorogenic acid methyl ester, macranthoin F and macranthoin G isolated from the aerial parts of the plant were tested for their antioxidant activity against DPPH radical and found effective [30]. The essential oil and cadinenes from leaves of the plant were evaluated for antioxidant activities using (DPPH) radical scavenging protocol and the (FRAP) which showed antioxidant activity comparable with the standards i.e. ascorbic acid, tert-butyl-4- hydroxy toluene (BHT), and gallic acid, thus suggesting their potent antioxidant activities [20]. *E. adenophorum* oil further tested by DPPH and β-carotene bleaching methods showed potent antioxidant activity with IC_{50} values were 8.3 and 4.2 µl, respectively suggesting it to be a potent antioxidant agent [23].

3.4.Wound Healing Activity

Wound healing potential of *E. adenophorum* ethanolic extract formulated as gel was estimated by excision and incision wound models. Ethanolic extract gel showed highly significant activity as compared to pure gel control. The plant exhibited moderately significant wound healing potential in both excision as well as incision wounds as evident from the tensile strength, epithelialization time and wound index data. The plant showed strongly significant ($p<0.01$) wound healingpotential in excision as 90.98% wound contraction and 36.16% reduction in epithelialization time. In incision model,significant increase (37.86%) in tensile strength was recordedas compared to pure gel control. Wound index data clearly showed that quality of healing was much better in plant extrac ttreated animals as compared to pure gel control [20]

3.5.Antibacterial Activity

Essential oil from aerial parts exhibited antibacterial activity against Arthrobacterprotophormiae, Escherichia coli, Micrococcus luteus, Rhodococcusrhodochrous, and Staphylococcus aureus [9]. Arvind et al. reported the antibacterial activity of petroleum ether extract of *E. adenophorum* leaves against *Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Escherichia coli, Klebsiellaaerogenes and Pseudomonas aeruginosa* [27]. In another study, the essential oil showed significant antibacterial activity against both gram positive (*Klebsiella pneumoniae* and *Staphylococcus aureus*) and gram negative (*Escherichia coli* and *Proteus vulgaris*) bacteria. However, gram-positive bacterial strains showed greater susceptibility than gram-negative bacteria, suggesting that the essential oil is more active against gram positive bacteria [31]. The bioactive compounds 5-O-trans-

ocoumaroylquinic acid methyl ester, chlorogenic acid methyl ester, macranthoin F and macranthoin G isolated from the aerial parts of *E. adenophorum* showed in vitro antibacterial activity toward bacterial strains, Salmonella enterica with MIC values of 7.4 and 14.7 μM, respectively [30]. The inflorescence oil showed higher antibacterial activity against *K.pneumoniae*, while the root oil was more effective against *S. aureus* [32].

3.6.Antifungal Activity

Extracts of *E. adenophorum* leaves and stems have been reported to inhibit fungal strains including *F. moniliformae*, *F. eroliferum*, *F. proliferatum* and *F. oxysporum* [3]. further the volatile oil extracted from E. adenophorum inhibited four types of fungal pathogens [23]. Petroleum ether extract of E. adenophorum leaves showed antifungal activity against Aspergilusniger, Aspergiluscandidus and Candida albicans [27]. Antifungal activity of cadinenesesquiterpenes including cadinan-3-ene-2, 7-dione, 7-hydroxycadinan-3-ene-2-one, 5, 6- dihydroxycadinan-3-ene-2, 7-dione, cadinan-3, 6-diene-2, 7- dione and 2-acetyl-cadinan-3, 6-diene-7-one isolated from leaves of the plant were evaluated against four phytopathogenic fungi. These compounds were found to be selective against pathogenic fungi and the compound cadinan-3-ene-2, 7-dione showed the highest inhibitory action towards *S. rolfsii* (ED50 181.60 ± 0.58 μg/mL) and *R. solani* (ED50 189.74 ± 1.03 μg/mL) thus indicating significant antifungal activity of the plant [24]. In another study, the essential oil from aerial parts exhibited moderate antifungal activity against Fusariumoxysporum by disk diffusion method [25].

3.7.Antitumour Activity

The cadenine sesquiterpene 9-oxo10, 11-dehydroageraphorone (euptox A) isolated from *E. adenophorum* was tested for cytotoxicity to human lung cancer A549 cells, Hela cells and Hep-2 cells in vitro. The results suggest that euptox A had significant antitumor activity against the three tumor cell lines in vitro in a dose-dependent manner. The percent inhibition of human lung cancer A549 cells, Hela cells and Hep-2 cells were 76.42, 68.30 and 79.05 %, respectively at concentration of 500 μg/mL.

3.8. Cytotoxic Activity

The cytotoxicity of *E. adenophorum* in relation to the cell cycle and apoptosis of splenocytes in Saanen goats was studied which demonstrated that the plant significantly inhibits the growth of splenocytes through G0/ G1phase cell cycle arrest and the induction of apoptosis. *E. adenophorum* induced apoptosis and spleen impairment through the induction of mitochondrial dysfunction in splenocytes [27]. The cytotoxicity of ethanol extract of E. adenophorum leaf was tested against human breast adenocarcinoma cell line (MCF 7), human hepatocarcinoma cell line (HepG) and human cervix adenocarcinoma cell line (HeLa) by MTT assay, trypan blue exclusion assay. The leaf extract was found to inhibit the growth of HeLa cells by ~61%. An IC value of 32 μg/ml for HeLa cells and 50 μg/ml for HepG was obtained with the extract [28].

4.Conclusion

The interest in phytomedicine has been renewed over the few last decades and consequently, a number of plant species with traditional medicinal significance have been

phytochemically and pharmacologically investigated in the quest of effective and safe herbal remedies. In recent years, *E adenophorum* has received considerable attention and phytochemical and pharmacological studies of the plant have led to the isolation and characterization of a number of bioactive compounds as well as validation of its traditional medicinal uses. Phytochemical and pharmacological studies of extracts of different parts of *E. adenophorum* and compounds isolated from the plant have received much interest and reviwed in this article.

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