ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Promising Phytomedicines from *Elephantopus scaber* L: A Review.

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ABSTRACT

Elephantopus scaber L. erect, perennial herb of Asteraceae is a reputed medicinal plant. Tribes across India traditionally employ different preparation of it to treat various ailments. A spectrum of phytochemicals is reported from the organic solvent extracts of the whole plant and their parts mainly leaves and rhizome. Result of phytochemical analyses presents an impressive array of phytomedicines like Elephantopin, Elescaberin, Deoxyelephantopin, Iso-deoxyelephantopin, which show encouraging prospect in treatment of cancer, inflammation, bacterial infection, liver diseases, diabetes and a lot more. This paper presents a comprehensive account of serious investigations that is being conducted globally on this plant, to discover unique drugs with supreme curative properties.

Keywords: *Elephantopus scaber*, Phytomedicines, Elephantopin, Deoxyelephantopin

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ISSN: 0975-8585

INTRODUCTION

Elephantopus scaber L., a scabrescent, erect, perennial herb belongs to the family Asteraceae is a well reputed medicinal plant. The plants vigorously grow in tropical deciduous forest areas [19]. Traditionally the plant is used as folk medicine by tribal communities across India, Reports reveal that different tribal communities regularly depend on this plant in treatment of rheumatism, dysentery, gout, eczema, gummosis, toothache, spider and snake bite [8,82,98,63, 72]. (Fig A and B, Table 1)

Table 1: A detailed list of the community based use of the plant is given below

Name of the ethnic group	District	State	Plant part used	Mode of use	Disease	Ref
	Banaskantha	Gujrat	Root	Used as toothbrush	Gummosis and toothache	Patel and Patel; 2013
Nadar	Kanyakumari	Tamil Nadu	Root	Decoction taken orally	Rheumatism	Kingstone et al.; 2007,
	Rewa	Madhya Pradesh	Whole plant	Used as a tooth brush	Toothache	Yadav and Khan ; 2012
			Leaves	Crushed and mixed with salt. The mixture is taken with curd to check	Dysentery	
	Mayurbhanj district	Odisha	Leaves	Boiled with oil of *Schleichera oleosa* and the prepared paste is applied externally.	On gout affected part of the body.	Singh H. G. et al., 2010
	Kanyakumari	Tamil Nadu	Fresh leaf and rhizome	Pastes are applied externally.	Eczema.	Renuga FB and Bai SMM.; 2013
			Fresh Leaf	Juice	Snake and spider bite.	

Fig: A

Fig. A: Mature plant of *E. scaber* showing rosette leaves with flowering prominent flowering escape

Fig. B: Close up view of flowering escape showing numerous heads.

Fig: B

Phytochemicals

Flavonoids have been shown to be good taxonomic markers for Asteraceae. More than 800 compounds comprising 4700 flavonoid were occurred with some implications of flavonols, flavones and other types as well as structural features of them are discussed for tribes and subtribes of the family Asteraceae [22] apart from that *Elephantopus scaber* has been explored for a large amount of salt such as potassium chloride and minerals especially calcium, magnesium, iron and zinc. Report reveals that the presence of trace elements such as Si, Ca, Cl, Mg, S, K and P in leaf and Al, Fe, Ti, Sr, V in roots whereas, Zn, Cu, As, Rb and Sr availability are less and equally present in roots as well as leaf [78]. The organic solvent like acetone extract of air-dried

powdered seeds is reported to contain terpenoids, flavonoids, steroids, glycosides, alkaloid, quinones, phenols [41]. A number of phytochemical studies have demonstrated the presence of several classes of chemical compounds, the main ones being Phenolic acids, flavonoids, terpenoids, coumarines, quinones, essential oils.

Phenolic acids and flavonoids

Phenolic acids are distributed in nature in their free and bound forms like esters and glycosides. Phenolics range from simple low-molecular weight compounds namely simple phenylpropanoids, coumarins and benzoic acid derivatives, to more complex structures such as flavonoids and tannins. [26] investigated total phenol of hydro-alcoholic, hexane, ethyl acetate and methanolic fractions of leaves and it was found to be 4.49, 3.39, 8.76 and 3.34 mg g-1, respectively. Ethanolic fraction of the plant possess phenolic compounds such as 3,4-dihydroxy benzaldehyde, p-coumaric acid, syringic acid, isovanillic acid, p-hydroxybenzoic acid, ferulic acid, vanillic acid, 3-methoxy-4-hydroxyl cinnamic aldehyde, tricin, syringic acid, E-3-(3-ethoxy-4-hydroxyphenyl) acrylic acid and 2-hydroxybenzolate acid [35,101,10].

Methanolic extract aerial part of *E. scaber* possess flavonoid aglycoside luteolin and flavonoid glycosides luteolin-7-Oglucuronide 6"-methyl ester and luteolin-4-O-β-D glucoside were identified along with three polyphenols trans-p-coumari acid, methyl trans-caffeate, trans-caffeic acid [10].

Bioassay guided isolation of ethanol extract of rhizome leading to obtain dicaffeoyl derivatives methyl 3, 4-dicaffeoylquinate [10] 3, 4-di-O-caffeoyl quinic acid, 3, 4-di-O-caffeoyl quinic acid methyl ester, 4, 5-di-O-caffeoyl quinic acid, 4, 5-di-O-caffeoyl quinic acid methyl ester, 1α, 2β-di-O- caffeoyl-cychopentan-3β-ol [30] (Fig 1).

Terpenes or Terpenoides

All terpenoides consist of a combination of one or more isoprene units. Terpenes have not only a variety of roles in mediating antagonistic and beneficial interactions among organisms but also defend many species of plants, animals and microorganisms against predators, pathogens and competitors [31].

Sesquiterpene lactones

Three isoprenoid units form the sesquiterpenoids which are C_{15} compounds. Their structure may be linear, monocyclic or bicyclic. They constitute a very large group of secondary metabolites, the characteristics of the Compositae family. Based on their carbocyclic skeletons, sesquiterpene lactones can be classified into four major groups: these are Germacranolides, guaianolides, pseudoguaianolides and eudesmanolides. Pharmacological activities of sesquiterpene lactones include antimicrobial, antiviral, anti-inflammatory, anti-tumor [64]. The major sesquiterpene lactones and their chemical structures isolated from the whole plant are given in Fig 2.

Other compounds

A number of triterpenes and steroids have been isolated from *E. scaber* these are lupeol, lupeol acetate,ursolic acid, stigmasterol (Fig 3).

An essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants. Other constituents include essential oils, salt and minerals. Essential oils are primarily composed of terpenes mostly monoterpenes and sesquiterpenes (Fig 4).

A General Profile of Phytomedicines: Active Principles and Their Curative Properties

Teng-Khia-U is a Taiwan traditional medicine containing *Elephantopus scaber*, *Elephantopus mollis and Pseudoelephantopus spicatus* is used for treating nephritis, edema, dampness, chest pain, fever, cough of pneumonia and scabies. Evaluation of the anti-inflammatory activities of this crude extract, indicated that pretreatment with 'Teng-Khia-U' significantly inhibited the carrageenan-induced acute arthritis. Moreover, this also suppressed the development of chronic arthritis induced by complete Freund's adjuvant [91].

Anticancer and antitumor activity

The most important bioactive principles isolated from *E. scaber* are sesquiterpene lactones. Among these, extensively studied one is deoxyelephantopin. In vitro and in vivo experiments have demonstrated that deoxyelephantopin possesses cytotoxic activity against a variety of cancer cell lines and malignant tumors. Deoxyelephantopin has shown significant cytotoxicity against human breast cancer cell lines MCF-7, MD-MB 231 and TS/A cells (a murine mammary adenocarcinoma cell line) with IC50 values 1-2 µg mL-1[37] and inhibited colony formation and invasion of TS/A cells and induced G2/M arrest and apoptosis induction. Up regulation of p21Waf1/C1 expression and caspase cascade activation was also observed. Not only that deoxyelephantopin suppressed MMP-9 expression and activation which occur via TNF-α stimulated NF κB activation. NF κB p65 and its binding to consensus DNA elements in TNF-α stimulated TS/A cells was blocked in vivo and in vitro by deoxyelephantopin but also it functioned as a partial agonist of PPARγ and could significantly inhibit the proliferation of HeLa cells and caused cell cycle arrest at G2/M phase [102]. Pre-treatment with deoxyelephantopin by continuous i.p., administration for 14 days was more effective than paclitaxel for suppression of tumor growth and lung metastasis of TS/A cells. Overexpression of VEGF and Cox-2 could significantly inhibited by deoxyelephantopin. Deoxyelephantopin exhibited the strongest effect on the PC-3, CNE and HL-60 cells, with IC50 values of 4.6, 2.6 and 0.9 µg mL-1, respectively. Flow cytometric analysis showed that treatment with deoxyelephantopin caused subG-1 population augmentation in PC-3, CNE and HL-60 cells, suggesting apoptosis was induced in these cells [87].

Deoxyelephantopin in nasopharyngeal carcinoma (CNE) cells triggred Akt and MAPK signalling pathways [86] and showed pronounced activity against melanoma derived cell line MEXF 394NL and mammary cancer cell line MEXF 401NL with IC70 value of 1.1 µg mL-1 [90] where as exhibited significant cytotoxicity against SMMC-7721 liver cancer cells, HeLa and Caco cell lines in vitro with IC50 values of 12.85, 17.40 and 25.85 µM, respectively. Report reveals that the antiproliferative effect of deoxyelephantopin via induction of apoptosis as it was shown by morphological analysis and DNA fragmentation, a hall mark of apoptosis [97]. In addition, deoxyelephantopin can significantly arrest the growth of human sarcoma W256 cells and also showed significant inhibition of tumor growth in a human cervical cancer xenograft model. It also caused a dose dependent reduction in the viability of Murine fibroblast cell line, L-929 in 72 h culture (IC50 value of 2.7 µg mL-1) by the cell viability assay [27]. Deoxyelephantopin inhibited Lung adenocarcinoma A549 cell growth with an IC50 value of 12.287 µg mL-1 via apoptosis induction and G2/M cell cycle arrest [23]. It was reported that elephantopin has inhibitory effect on human nasopharyngeal carcinoma (KB) cells and murine leukaemia (P388) cells with IC50 of 0.28-20 µg mL-1 [81].

The intraperitonial administration of active fraction of chloroform extract of *E. scaber* inhibited the incidence of sarcomas and significantly reduced the tumor diameter in which Dalton's Lymphoma Ascites (DLA) solid tumor responded better to the treatment of *E. scaber* than the Ehrlich Ascites Carcinoma (EAC) solid tumors. Repeated treatment using *E. scaber* showed reduced mean number of skin papillomas induced by DMBA/croton oil and it also showed significant reduction in the tumor volume of 20-methyl cholanthrene (20 MCA) induced soft tissue sarcoma [28]. [29] reported that intraperitoneal administration of aqueous extract of whole plant significantly reduced tumor growth and increased the life span of DLA ascitic tumor beaing swiss albino mice where as significant enhancement of mean survival time of DAL tumor bearing swiss albino mice was noted when treated with aqueous extract of *E. scaber* leaves [70].

Isodeoxyelephantopin showed antiproliferative effect and inhibited the growth of SMMC-7721, HeLa and Caco cell lines in time and concentration dependant manner. Isodeoxyelephantopin inhibited NF κB activation, activation induced by a wide variety of inflammatory agents, including Tumor Necrosis Factor (TNF), interleukin-1β, phorbol 12-myristate 13-acetate and lipopolysaccharide. It mediated the down regulation of NF-κB regulated gene expression that regulates apoptosis (IAP1, IAP2, Bcl-2, Bcl-xL, Bfl-1/A1, TRAF1, FLIP and survivin), proliferation (COX-2, cyclin D1 and c-Myc), angiogenesis, invasion (MMP-9 and ICAM-1) and osteoclastogenesis [40]. 17, 19 dihydrodeoxyelephantopin was highly effective against renal cancer cell line RXF 944L (IC70 value 4 µg mL-1) and iso-17, 19 dihydrodeoxyelephantopin showed marked activity to the large cell lung cancer LXFL 529L (IC70value 4.3 µg mL-1) [90]. Isodeoxyelephantopin upregulated the expression of anti-cancer inflammation factors IL-12a, IFNα and IFNβ through ROS-dependent and independent pathways in nasopharyngeal carcinoma cells and exerts its antitumor effects through ROS-dependent DNA damage and mitochondrial-mediated apoptosis mechanism [99].

Scabertopin had notable inhibitory effect on SMMC-7721, HeLa and Caco cell lines at 48 h with IC50 values of 18.20, 14.08, 9.53 µM L-1, respectively. Human colon carcinoma Caco-2 cells are more sensitive to the scabertopin and isoscabertopin [97].A new elemanolide sesquiterpene lactone, elescaberin exhibited significant inhibitory activities against human SMMC-7721 liver cancer cells in vitro (IC50 8.18 µM) [51]. Ethanolic extract of *E. scaber* showed cytotoxic effect towards MCF-7 cells with an IC50 value of 15 µg mL-1. In comparison to the untreated control, the extract triggered cell death with increased phosphatidylserine externalization, DNA breaks and significant morphological apoptotic characteristics in the MCF-cells. Furthermore, expression of the tumor suppressor p53 protein was up-regulated in response to the treatment [93]. Lupeol has the ability to downregulate the expression of Bcl-2 and Bcl-xL anti-apoptotic protein elucidates the mechanism of action of the compound on the key cancer targets as a result it induce apoptosis and act against breast cancer [13]. Deoxyelephantopin exhibited cytotoxicity to A549 cells (IC50 = 12.287 µg/mL), however, there was no toxicity towards normal human lymphocytes, it suppressed the colony-forming ability of A549 cells in a dose-dependent manner [43].

Anti-inflammatory activity/Analgesic

Studied the in vivo anti-inflammatory activity of a compound isolated from the hydroalcoholic extract of aerial part of *E. scaber* in acute, sub acute and chronic experimental models in albino rats and showed that higher dose of compound is highly effective in inhibiting carragenan induced edema formation in rats [76].

A study to investigate protective [39] mechanism of *E. scaber* using lipopolysaccharide (LPS) induced inflammation of BV-2 microglial cells and acute liver injury in Sprague-Dawley rats. *E. scaber* reduced LPS-induced nitric oxide, interleukin (IL)-1, IL-6, reactive oxygen species and prostaglandin production in BV-2 cells. It significantly decreased serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in LPS-treated rats. Furthermore, the water extract of E. scaber dose-dependently inhibited LPS-induced JNK, p38 mitogen-activated protein kinases (MAPK) and slightly inhibited cyclooxygenase (COX-2) in BV-2 cells but decreased p38 MAPK and COX-2 expressions in the liver of LPS-treated rats. These results suggested that the protective mechanism of E. scaber involved an antioxidant effect and inhibition of p38 MAP kinase and COX-2 expressions in LPS-stressed acute hepatic injury in rats.

Antimicrobial activity

The antibiotic activity of 17, 19 dihydrodeoxyelephantopin and iso-17, 19 dihydrodeoxyelephantopin were negligible, showing an inhibition zone of 11 mm diameter against *Staphylococcus aureus* and no activity was observed against *Bacillus subtilis* and *Candida albicans* [90]. The novel terpenoid, 6-[1-(10,13-dimethyl-4, 5, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-dodecahydro-1H-cyclopenta[α] phenanthren-17-yl)ethyl-3-methyl]-3,6-dihydro-2H-2 pyranone isolated from E. scaber possessed antibacterial activity against a few multi drug-resistant ESBL producing clinical isolates [12]. Molecular docking studies revealed that lupeol, a pharmacologically active triterpenoid isolated from the plant can inhibit the activity of autolysin by forming a strong interaction with the active site residues for treating *Staphylococcus aureus* [15].
The methanolic leaf extract of E. scaber showed significant antibacterial activity against *Staphylococcus aureus* (29 mm), Escherichia coli (27 mm), *Pseudomonas aeruginosa* (23 mm), *Bacillus subtilis* (29 mm) and *proteus vulgaris* (25 mm) at 100 µg disc-1 [89] and showed inhibition activity against *Bacillus megaterium*, *Xanthomonas campestris* and *Escherichia coli*, respectively but showed minimal activity towards *P. vulgaris* [88]. Out of all extracts, methanol extract was found to be the most effective as compared to chloroform extract and petroleum ether extract against bacteria such as *Staphylococcus aureus, Salmonella paratyphi A, K. pneumonia, P. aeruginosa, Salmonella sonnei, Escherichia coli* and *Salmonella typhimurium* [42]. The inhibitory effect of ethyl acetate extract of whole plant against *Streptococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus epidermis, Staphylococcus aureus, Bacillus cereus, Bacillus pumilus, Bacillus subtilis, Bordetella bronchiseptica* and *Micrococcus luteus*. Scabertopin, isoscabertopin, deoxyelephantopin and isodeoxyelephantopin also inhibited the growth of *Escherichia coli, Staphyloccocus aureus* and *β-streptococcus* [4]. The ethanolic extracts of root have shown the highest zone of inhibition against three pathogens *Staphylococcus aureus* (24 mm), *Escherichia coli* (16 mm) and *Pseudomonas aeruginosa* (13 mm) while the chlorofrom extracts showed the highest zone of inhibition against *Bacillus cereus* (12 mm). Aqueous extract exhibited considerable antibacterial activity (MIC = 7.8-23.4 mg mL-1) against serotypes c and d of *Strptococcus mutans* [11]. It is reported that all the fractions (hexane, ethyl acetate, methanol and hydro alcoholic fractions showed highly significant activity at a concentration of 1 mg 100 µL-1 in which ethyl acetate

and hexane fraction showed more activity towards *Klebsiella pneumoniae* and *P. aeruginosa* than the other test organisms *Escherichia coli, Staphylococcus aureus, Salmonella typhi* [25]. Ethanol extracts of E. scaber possessed remarkable antibacterial effect against [3] *P. aeruginosa, Streptococcus, S. aureus* and *Bacillus megatterium*, a zone of inhibition was found against Chloroform extract of E. scaber bearing disc at 4 mg mL-1 concentration by *Bacillus subtilis, Staphylococcus aureus* and *Escherichia coli* [78] and found to be effective against Multi drug resistant *S. aureus, Citrobacter freundii* and *Proteus sp.* [21]. The ethanolic extracts of leaves demonstrated the highest zone of inhibition against three pathogens *Enterococcus faecalis* (18 mm), *Proteus mirabilis* (17 mm), *Salmonella typhi* (14 mm) and *Enterobacter sp.* (11 mm) [2]. There is a synergistic action between the methanol extract of *Eugenia jambolana* and the acetone extract of *Elephantopus scaber* against Vancomycin resistant *Enterococci* bacteria [41].

The effect of aqueous and methanolic extract of E. scaber on pathogenic fungal strains [44] *Aspergillus niger, Aspergillus flavus, Rhizopus indicus* and *Mucor indicus* and found that there was a dose dependent increase in antifungal activity and maximum activity was observed with methanolic extract against *Mucor indicus* (32 mm) and minimum activity against *Rhizopus indicus* (14 mm). There was no activity observed in aqueous extract against the tested fungus. Among the four extracts, ethyl acetate fraction showed more inhibition towards fungal species namely *Candida bombii, Candida tropicalis, Candida utilis* [26]. *Elephantopus scaber* is a potential resource of β sesquiphellandrene, one of the important sesquiterpene compounds showing antirhinoviral activity [94]. A new dicaffeoyl derivative, 1α, 2β-O-dicaffeoylcyclopentan-3β-ol showed in vitro antiviral activity against Respiratory Syncytial Virus i.e RSV. Four dicaffeoylquinic acids 4, 5 di-O-caffeoylquinic acid, 3, 4, di-O-caffeoylquinic acid and their methyl esters also possessed strong anti – RSV activity with IC50 lower than that of ribavirin, a positive control drug [30].

Hepatoprotective activity

Studies shows that it can prevent [69] carbon tetrachloride (CCl_4)-induced chronic liver dysfunction in the rats by determining different biochemical markers such as aspartate aminotrasferase (AST), alanine aminotrasferase (ALT), alkaline phosphatase (ALP) and also protein in serum and total lipid, cholesterol and phospholipids in tissues. The results showed that the biochemical changes induced by CCl_4 in different tissues particularly in the liver tissue were improved significantly following treatment with the plant extract. Oral administration of different fractions (hexane, methyl acetate, methanol and ethanol) of E. scaber in different doses (125, 250 and 500 mg kg-1) showed anti hepatotoxic activities against carbon tetrachloride (CCl_4) induced hepatic damage in rats [25]. The hepatoprotective effects of water extract of Teng-Khia-U' (a folk medicine containing E. scaber from Taiwan) against β-D-galactosamine (D-GalN)-and acetaminophen (APAP)-induced acute hepatic damage were studied in rats. The results indicated that the serum glutamate-oxalate-transaminase (sGOT) and the serum glutamate-pyruvate-transaminase (sGPT) levels caused by D-Gal N and APAP decreased along with hepatic lesions improvement after treatment with crude extracts of 'Teng-Khia-U' [53]. The ethanol extract and methanolic extract of leaves shows hepatoprotection activity in mice with alcohol-induced liver damage [36] and prevented and reversed nitrosodiethylamine (NDEA) induced hepatotoxicity in experimental animals [54] repectively where as hot water extract promote cell cycle-induced liver regeneration and suppressed hepatocytes apoptosis after partial hepatectomy [92]. Hexane extract show not only a better hypolipidemic potential and a similar trend in renal functions stating the efficiency of the plant as an efficient source of reducing coronary risk and renal failures but also the ability to reduce blood glucose levels [14]. The serum cholesterol and triglycerides decreased, whereas HDL-cholesterol increased. Serum protein increased whereas serum urea and creatinine decreased. Hexane extract brought about a better antihyperglycemic effect.

Anti-coagulant activity

The triterpenoid lupeol ($C_{30}H_{50}O$) isolated from leaves act as antagonist to platelet aggregation in vitro by blocking calcium channel blocking, since the release of Ca2+ activates the ERK2 for signalling in platelets [77].

Anti-Snake venom activity

Pentacyclic triterpenes lupeol and urosolic acids from the plant have shown anti-snake venom activity among them Lupeol showed 72% protection against snake venom [57].

Diarrhoeal treatment

Methanolic extract of roots showed significant antidiarrhoeal activity against castor oil induced diarrhoea in rats [71] and ethyl acetate extract also possess antidiarroheal activity [58].

Controlling diabetes

Diabetes mellitus is one of the common metabolic disorders and 2.8% of the population suffers from this disease throughout the world. 28Nor-22(R) with a 2, 6, 23-trienolide, a major steroid isolated from the acetone extract of the *E. scaber* decreased blood level glucose in STZ diabetic rats which may be due to a stimulating effect on insulin release from regenerated β-cells of the pancreas or increased cellularity of the islet tissues [16]. Diabetes induces increased level of cholesterols, triacylglycerols, VLDL and LDL. The hexane, methanol and aqueous extract of the plant showed a significant dose dependent decrease in the levels of total cholesterol, triacylglycerol, LDL cholesterol with a significant increase in the level of HDL cholesterol [18]. Ethyl acetate root extract and methanol leaf extract of E. scaber showed antihyperglycemic effect by reducing the blood glucose level, glycosylated hemoglobin, a change in the lipid profile and kidney functions, liver and muscle glycogen, serum insulin levels and histopathological studies [17]. Oral administration of aqueous extract of leaves and roots into alloxan induced diabetic rats significantly reduced serum glucose, glycosylated hemoglobin and the activity of gluconeogenic enzyme glucose-6-phosphatase, but increased serum insulin, liver and skeletal muscle glycogen content and the activity of glycolytic enzsssyme glucokinase [56]. Report reveals that Terpenoid and 2,6,23 - trienolide isolated from whole plant act as anti diabetic agent [73].

Antioxidant and free radical scavenging activity

Investigation shows that vitro antioxidant activity by determining superoxide scavenging, hydroxyl scavenging and Fe2+-ascorbate induced lipid peroxidation inhibiting activity of methanolic extract of E. scaber root, which was found to be a scavenger of superoxide with an IC50 of 48±5 µg mL-1 and inhibited hydroxyl radicals generated by Fe3+/ascorbate/EDTA/H2O2 system with an IC50 of 72±12 µg mL-1 [79]. There was lipid peroxidation inhibiting activity was with an IC50 of 103±18 µg mL-1. In vivo experiments showed that administration of methanolic extract of E. scaber root significantly ($p = 0.05$) restored the activities of the antioxidant enzymes SOD, catalase and peroxidases and the level of glutathione to near normal compared with the corresponding CCl4 intoxicated group. Studies shows that the antioxidant activity of methanol extract of several concentrations of E. scaber ranging from (100-500 µg mL-1) [47] and hydro-alcoholic, hexane, ethyl acetate and methanolic fractions of leaves possessed concentration dependent inhibition using DPPH, superoxide and hydroxyl radicals scavenging activity [26]. It was found that the ethanolic extract of *E. scaber* showed high DPPH scavenging activity with SC50=12.4 µg mL-1. Furthermore, the extract also strongly inhibited xanthine oxidase activity with IC50 value of 93.1 µg mL-1, since XOD catalyses the oxidation of hypoxanthine and xanthine to uric acid which play a crucial role of gout [67].

Antihelmintic activity

Aqueous extract showed significant inhibition against Pheritima posthuma at concentrations [46]. Report reveals that n-hexane, chloroform and methanolic extracts show concentration dependent and significant anthelmintic activity [45].

Ulcer treatment

Aqueous root extract of E. scaber possessed significant antiulcer property which could be either due to cytoprotective action of the drug or by strengthening of gastric and duodenal mucosa and thus enhancing mucosal defence [71].

Diuretic activity

Ethanolic extract of whole plant of E. scaber showed more than 50% inhibition of Na+-K+ ATPase activity, isolated from rat brain microsome as compared to ouabain which is the known Na+-K+-ATP ase inhibitor [60].

Wound healing activity

Deoxyelephantopin, may be due to the presence of active moiety, α methylene γ lactone showed more significant effect than ethanolic extract towards wound healing activity by increasing cellular proliferation, formation of granulation tissue, synthesis of collagen and increase in the rate of wound contraction [81]. Aqueous extract of E. scaber is taken orally to heal wounds [5].

Asthma management

The ethanolic, chloroform and ethyl acetate fraction of E. scaber was used to inhibit mast cell degranulation in which the chloroform fraction was more effective than the other fractions [62]. The ethanolic extract of leaves of E. scaber had antianaphylactic, anticholinergic an antihistaminic activity [74] and not only that it significantly increased the preconvulsive dyspnoea time following exposure to histamine and acetylcholine aerosols induced bronchospasm in guinea pigs but also inhibits histamine induced muscle contraction of trachea.

Miscellaneous application

Methanolic extract of *E. scaber* hair oil formulation on topical application stimulate the hair growth initiation and completion time and direct impact on hair follicles [75]. The petroleum ether extract of dried aerial parts showed significant cardio tonic activity on the hypodyanamic frog heart [58]. Administrations of aqueous and ethanolic extracts into adult male rats markedly enhanced the libido and sperm counts. There was an increase in ischiocavernosus muscle weight and bulbospongiosus muscular weight. Female/male offspring sex ratios were higher in water and alcohol extract feeding groups than those of control [9]. The ethanolic extract of *E. scaber* not only at low dose showed oxytocin effect and enhanced spermatogenesis and increased sperm density [65] but also effective against gentamicin-drug induced nephrotoxicity increased the serum urea level and total creatinine which can be restored [7]. Performance an in vitro test to study the effect of *E. scaber*, which is widely used due to the belief that it can promote good sexual activity but found that it reduced the spermatic count and motility rate [84]. The following compounds-deoxyelephantopin, isodeoxyelephantopin, lupeol, lupeol acetate, stigmasterol and diadinoxanthine derivative-isolated from the chloroform extract of air dried leaves of *E. scaber* possessed antimutagenic activity [68].Gout, a heading joint disease was treated by applying the paste of *E. Scaber* leaves and oil of *Schleichera oleosa* externally on gout affected part of the body [82]. Deoxyelephantopin showed antiprotozoal activity against Trypanosome brucei rhodesience [100].

List of isolated bioactive compounds and their specific application are given in Table 2.

Table 2: list of isolated bioactive compounds and their specific application are detailed below

Name of bioactive compound	Application
Tetrahydrona phthalenol	Antioxidant
β sesquiphellandrene	Antirhinoviral
dicaffeoylquinic acids 4, 5 –di-O-caffeoylquinic acid, 3, 4, di-O-caffeoylquinic acid and their methyl esters	Antiviral
1α, 2β-O-dicaffeoylcyclopentan-3β-ol	
lupeol	Anti snake venom, Anti coagulant, antibacterial, Anti cancer.
Terpenoid and 2,6,23 - Trienolide	Antidiabetic
Isoscabertopin	Anti bacterial
Deoxyelephantopin	
Urosolic acids	Anti snake venom
Elephantopin	Anticancer and antitumor
Isodeoxyelephantopin	
17, 19 dihydrooxyelephantopin	
Scabertopin	
Elescaberin	
Deoxyelephantopin	

CONCLUSION

E. scaber is one of such plants which have tremendous reputation in indigenous traditional system of medicine in India, by virtue of which it has drawn the attention and concern of scientists for exploration of its medicinal properties through phytochemical and pharmacological evaluation. The plant is well known for its huge medicinal properties namely, anticancerous, hepatoprotective, antidiabetic and antimicrobial considered to be important aspects. Research findings confirm the presence of some promising phytochemicals like Elephantopin, Elescaberin, Deoxyelephantopin, Isodeoxyelephantopin which will be great source of phytomedicines in near future. In this era of herbal science, frenzied research activity is being seen throughout the world to discover drugs that can be panacea not only to cure chronic problems but also may be administered to tackle new diseases including some deadly viral epidemics.

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