Phytopharmacological Profile of *Elephantopus scaber*

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**ABSTRACT**

**Background:** Now-a-days, plant based drug discovery has gained a great attention globally to develop new pharmaceuticals. *Elephantopus scaber* is a popular plant that have been traditionally used as medicine for treatment of several ailments including cancer, diabetes, edema, stomach disorder, jaundice, leucorrhoea, rheumatism, fever and scabies. Phytochemical analysis revealed that the plant is a rich source of terpenoids and flavonoids. The isolated compounds have known for diverse biological functions such as antidiabetic, antibacterial, anticancer, antioxidant and hepatoprotective effects. **Aim:** The present review focus on chemical constituents and their potential pharmacological roles isolated from *E. scaber.*

**Key words:** *Elephantopus scaber*, sesquiterpene lactones, deoxylephantopin, antitumor activity, antibacterial, antidiabetic


**INTRODUCTION**

Throughout the history of civilization, plants have played a major role in medication for treatment of various kinds of human diseases. According to World Health Organization, 80% of people in developing countries rely on plant based traditional medicines for their primary health care needs. *Elephantopus scaber* Linn, is a tropical perennial herb that grows widely in many Asian countries such as China, India, Vietnam, Malaysia etc. It has been popular as a medicinal herb in many countries of Southeast Asia, Latin America and Africa for a long time (Hammer and Johns, 1993). The herb is an erect and hairy with a height of 30-60 cm. Leaves are mostly in basal rosette and 10-25 cm in length. Stem usually dichotomously branched and flowering heads are borne in clusters at the ends of the branches. The flowering heads are numerous, sessile and forming a large terminal inflorescence comprising about four violet flowers. The plant is a major part of several traditional medicinal formulations to treat diarrhoea, dysentery, neoplasm and liver diseases (Matos et al., 1991; Behera and Mura, 2005; Singh and Panda, 2005; Reddy et al., 2012). Traditional uses of *E. scaber* are summarized in Fig. 1. Since the 1970s, a number of reports are available regarding the chemical constituents and pharmacological evaluations of *E. scaber.* This review provides information on isolated bioactive principles from *E. scaber* and their different pharmacological applications.

**Major chemical constituents of Elephantopus scaber**

**Sesquiterpene lactones:** The sesquiterpenoids are C_{15} compounds formed by the assembly of three isoprenoid units. 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 carboyclic skeletons, sesquiterpene lactones can be classified into four major groups: Germacranoles, guaianolides, pseudoguaianolides and cudesmanolides. All sesquiterpene lactones contain \(\alpha\)-methylene \(\gamma\)-lactone ring either cis- or trans fused to the \(\mathrm{C}_{3}-\mathrm{C}_{4}\) or \(\mathrm{C}_{3}-\mathrm{C}_{5}\) position of the carboyclic skeleton. Pharmacological activities of sesquiterpene lactones include antimicrobial, antiviral, anti-inflammatory, anti-tumor (Picman, 1986). Most of the research work carried out on this plant, has focused on sesquiterpene lactones. The major sesquiterpene lactones isolated from *E. scaber* are shown in Table 1 and their chemical structures are given in Fig. 2.

**Phenolic acids and flavonoids:** Phenolic acids are distributed in nature in their free and bound forms, as esters and glycosides. Phenolics range from simple low-molecular weight compounds, such as the simple phenylpropanoids, coumarins and benzoic acid derivatives, to more complex structures such as flavonoids, stilbenes and tannins. Phenolic acids and flavonoids were isolated from different fractions of whole plant *E. scaber.* Phenolic compounds 3,4-dihydroxy benzaldehyde, p-coumaric acid, vanillic acid, syringic acid, isovanillic acid, p-hydroxybenzoic acid, ferulic acid,
3-methoxy-4-hydroxyl cinnamic aldehyde, tricin, syringic acid, E-3-(3-ethoxy-4-hydroxyphenyl) acrylic acid, 2-hydroxybenzolact acid were purified from the ethanol fraction of the plant (Hisham et al., 1992; Zhang et al., 2011; Chang et al., 2012). Flavonoid aglycoside luteolin and flavonoid glycosides luteolin-7-O-glucuronide 6"-methyl ester and luteolin-4-O-β-D glucoside were identified along with three polyphenols trans-p-coumaric acid, methyl trans-caffic acid, trans-caffic acid from methanol extract of aerial part of E. saberi (Chang et al., 2012). Bioassay guided isolation of ethanol extract of rhizome leading to obtain dicafeoyl derivatives.
Table 1: Major sesquiterpene lactones isolated from *E. scaber*

<table>
<thead>
<tr>
<th>Chemical compound</th>
<th>Chemical type</th>
<th>Part used/extract</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deoxyelephantopin</td>
<td>Germacranolides</td>
<td>Whole plant / ethanol, acetone and</td>
<td>Gorindachari et al. (1976), Bot et al. (1997),</td>
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<td></td>
<td></td>
<td>chloroform</td>
<td>Than et al. (2005), Liang et al. (2008), Su et</td>
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<td>al. (2009), Alamad et al. (2009), Greetha et al.</td>
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<td>(2012), Geetha et al. (2012), Liang et al. (2008)</td>
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<tr>
<td>Isodeoxyelephantopin</td>
<td></td>
<td>Whole plant / ethanol, acetone and</td>
<td>Gorindachari et al. (1976), Bot et al. (1997),</td>
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<td></td>
<td></td>
<td>chloroform</td>
<td>Than et al. (2005), Alamad et al. (2009), Greetha</td>
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<td>et al. (2012), Liang et al. (2008)</td>
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<tr>
<td>Scabertopin</td>
<td></td>
<td>Whole plant / ethanol</td>
<td>Bot et al. (1997), Liang and Mia (2002)</td>
</tr>
<tr>
<td>Isoscabertopin</td>
<td></td>
<td>Whole plant / ethanol</td>
<td>Liang and Mia (2002)</td>
</tr>
<tr>
<td>Scabertopinol</td>
<td>Aerial / Methanol</td>
<td></td>
<td>Chang et al. (2012)</td>
</tr>
<tr>
<td>Iso-17,19-dihydroxyelephantopin</td>
<td></td>
<td>Whole plant / ethanol and acetone</td>
<td>Than et al. (2005)</td>
</tr>
<tr>
<td>11,13-dihydroxyelephantopin</td>
<td></td>
<td>Whole plant / methanol</td>
<td>De Silva et al. (1982)</td>
</tr>
<tr>
<td>Molephantinin</td>
<td>Aerial / Petroleum ether</td>
<td></td>
<td>Murthumani et al. (2009)</td>
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<tr>
<td>Elecanberin</td>
<td>Elemanolide</td>
<td>Whole plant / ethanol</td>
<td>Liang et al. (2008)</td>
</tr>
<tr>
<td>Deacetylcanepicrin</td>
<td>Guianolide</td>
<td></td>
<td>Hisham et al. (1992)</td>
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<tr>
<td>Glucopyranosin-C</td>
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<tr>
<td>Deacetylcanepicrin 3 β-glucopyranoside crepise E</td>
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**Fig. 3:** Some phenolic acids and flavonoids isolated from *E. scaber*

- methyl 3, 4-dicaffeoylquinic (Chang et al., 2012), 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-cyclopentan-3β-ol (Geing et al., 2011) (Fig. 3).
**Other compounds:** A number of triterpenes and steroids have been isolated from *E. sabin* (Table 2 and Fig. 4). An essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants. Other constituents include essential oils, salt and minerals (Table 3 and Fig. 5). Essential oils are primarily composed of terpenes mostly monoterpenes and sesquiterpenes. This plant has been explored for a large amount of salt such as potassium chloride and minerals especially calcium, magnesium, iron and zinc. Santhosh et al. (2012) reported 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.

<table>
<thead>
<tr>
<th>Class</th>
<th>Subclass</th>
<th>Compounds</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Triterpenoids</td>
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<td>Friedelin</td>
<td>Liang et al. (2007)</td>
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<td></td>
<td></td>
<td>Epifriedelinol</td>
<td>Sin and Lee (1969), Liang et al. (2007)</td>
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<td></td>
<td></td>
<td>Lupon</td>
<td>Than et al. (2003), Ahamad et al. (2009), Liang et al. (2007), Mors et al. (2000)</td>
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<td></td>
<td></td>
<td>Betulinic acid</td>
<td>Liang et al. (2007)</td>
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<td></td>
<td></td>
<td>30-Hydroxylupone</td>
<td>Liang et al. (2007)</td>
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<td></td>
<td></td>
<td>Lupeol Acetate</td>
<td>Liang et al. (2007), Muthuman et al. (2009)</td>
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<td></td>
<td></td>
<td>Ursolic Acid</td>
<td>Mors et al. (2000), Liang et al. (2007)</td>
</tr>
<tr>
<td>Sterols</td>
<td></td>
<td>ursa-12-ene-3β-heptadecanolate</td>
<td>Liang et al. (2007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stigmastol</td>
<td>Than et al. (2005), Ahamad et al. (2009), Huang et al. (2009)</td>
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<tr>
<td></td>
<td></td>
<td>Stigmastanol-3-O-β-D-glucoside</td>
<td>Finshn et al., 1992, Than et al., 2003, Huang et al. (2009)</td>
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<tr>
<td></td>
<td></td>
<td>β-sitosterol</td>
<td>Zhang et al. (2011)</td>
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<td></td>
<td></td>
<td>Dacosterol</td>
<td>Zhang et al. (2014)</td>
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<td></td>
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<td>28Nor-22(R)-Waha 2,6,23-trienolide</td>
<td>Dassy et al. (2009)</td>
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</table>

Fig. 4: Chemical structures of bioactive triterpenoids and steroids from *E. sabin*
Table 3: Chemical constituents isolated from E. scaber

<table>
<thead>
<tr>
<th>Chemical compounds</th>
<th>Part/extract</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Tetradecane, n-Pentadecane, n-Hexadecane, n-Heptadecane, n-Octadecane, n-Nona decane, Tetramethylethyldecenol, Hexadecanoic acid, Octadecadienoic acid, Dimethyldecane, Trimethyldecane, Methylpropiophenone, Dimethylheptadecane, Methylheptadecane, Myristic acid, Tetramethylethadecene, n-Exosane, Octadecanoic acid Cycloartenol, Copaeol, Isopropylmethylhexahydrodiphenylphene, Zingiberene, Trimethylcyclopenadecahydrodiphenylphene, Caryophyllene, Dimethyl-6-(4-Methyl-3-Pentenyl)2-Norpinen, β-Sequiphellandrene, β-Caryophyllene, Isoeucarophyllene, α-Santolal, Ledol, α-Bisabolol, Caryophyllene oxide, β-Bisabolol, Isopropyl Dimethyl Tetrahydroanthalenol, Hexahydroaromyl acetone, Hexadecanoic acid, Phytol, Octadecadienoic acid Ethyl hexadecanoate, ethyl 9,12-octadecadienoate ethyl- (2)-9-octadecenoate, ethyl octadecanoate 2,3-dimethoxy-4-benzoinone, n-octacosanoic acid Triacont-1-ol (Myricyl alcohol) dotriacont-1-ol (Lacceryl alcohol)</td>
<td>Leaf oil</td>
<td>Wang et al. (2005)</td>
</tr>
<tr>
<td></td>
<td>Whole plant oil</td>
<td>Wang et al. (2004)</td>
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<tr>
<td></td>
<td>Whole plant/ethanol and Acetone</td>
<td>Than et al. (2005)</td>
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<tr>
<td></td>
<td>Whole plant/etherol</td>
<td>Zhang et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Whole plant/petroleum Ether</td>
<td>Sun and Lee (1969), Mathurman et al. (2009)</td>
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<tr>
<td></td>
<td>Whole plant/etherol</td>
<td>Huang et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Aerial/methanol</td>
<td>Chang et al. (2012)</td>
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<tr>
<td></td>
<td>Root/hexane</td>
<td>Ahmad et al. (2009)</td>
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Fig. 5: Chemical structures of selected components of essential oils

PHARMACOLOGICAL ACTIVITIES

Elephantopus scaber exhibits a vast range of pharmacological activities.

Anticancer and antitumor activity: The most important bioactive principles isolated from E. scaber are sesquiterpene lactones. Among these, deoxyelephantopin is the extensively studied one. 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 IC_{50} values 1-2 μg mL^{-1} (Huang et al., 2010). The compound has significantly inhibited colony formation and invasion of TS/A cells and induced G2/M arrest and apoptosis induction. Up regulation of p21WAF1 expression and caspase cascade activation was also observed. 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. 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 TSA cells. Overexpression of VEGF and Cox-2 could significantly inhibited by deoxyelephantopin. Deoxyelephantopin exhibited the strongest effect on the IC50 values of 4.6, 2.6 and 0.9 μg mL−1, respectively. Flow cytometric analysis showed that treatment with deoxyelephantopin caused subG1 population augmentation in PC-3, CNE and HL-60 cells, suggesting apoptosis was induced in these cells (Su et al., 2009). Furthermore, deoxyelephantopin 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 (Zou et al., 2008).

In nasopharyngeal carcinoma (CNE) cells, deoxyelephantopin triggered Akt and MAPK signalling pathways (Su et al., 2011). Deoxyelephantopin pronounced activity against melanoma derived cell line MEFX 394NL and mammary cancer cell line MEFX 401NL with IC50 value of 1.1 μg mL−1 (Than et al., 2005). Deoxyelephantopin 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. Xu et al. (2006) also reported the antiproliferative effect of deoxyelephantopin via induction of apoptosis as it was shown by morphological analysis and DNA fragmentation, a hallmark of apoptosis. 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 (Geetha et al., 2012). 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 (Farha et al., 2013a). 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 (Singh, 2005).

The intraperitoneal administration of active fraction of chloroform extract of E. saher 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. saher than the Ehrlich Ascites Carcinoma (EAC) solid tumors. Repeated treatment using E. saher 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 (Geetha et al., 2010). A significant enhancement of mean survival time of DAL tumor bearing Swiss albino mice was noted when treated with aqueous extract of E. saher leaves (Rajkhopo et al., 2002). Geetha et al. (2003) reported that intraperitoneal administration of aqueous extract of whole plant significantly reduced tumor growth and increased the life span of DAL ascitic tumor bearing Swiss albino mice.

Isodeoxyelephantopin showed antiproliferative effect and inhibited the growth of SMMC-7721, HeLa and Caco cell lines in time and concentration dependent manner. After 48 h of treatment, the IC50 values for isodeoxyelephantopin were 18.28, 14.59, 18.28 μM L−1, respectively. It also showed inhibition of viability of Murine fibroblast cell line, L-929 in 72 h culture with an IC50 value of 0.3 μg mL−1 (Geetha et al., 2012). Cytotoxicity towards nasopharyngeal KB cells was apoptosis mediated with an IC50 value of 11.45 μM after 48 h of treatment (Farha et al., 2013b). Isodeoxyelephantopin inhibited NF-κB activation, activation induced by a wide variety of inflammatory agents, including Tumor Necrosis Factor (TNF), interleukin-1β, phosphor 12-miystate 13-acetate and lipopolysaccharide. It mediated the down regulation of NF-κB regulated gene expression that regulates apoptosis (IAP1, IAP2, Bcl-2, Bcl-xl, Bcl-1/A1, TRAF1, FLIP and survivin), proliferation (COX-2, cycin D1 and c-Myc), angiogenesis, invasion (MMP-9 and ICAM-1) and osteoclastogenesis (Ichikawa et al., 2006). 17, 19 dihydrodeoxyelephantopin was highly effective against renal cancer cell line RXF 944L (IC50 value 4 μg mL−1) and iso-17, 19 dihydrodeoxyelephantopin showed marked activity to the large cell lung cancer LXXL 529L (IC50 value 4.3 μg mL−1) (Than et al., 2005). 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 mitochondria-mediated apoptosis mechanism (Yan et al., 2013).

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 (Xu et al., 2006). A new elemanolide sesquiterpene lactone, elescaberin exhibited significant inhibitory activities against human SMMC-7721 liver cancer cells in vitro (IC50 8.18 μM) (Liang et al., 2008). Ethanolic extract of E. saher 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 (Wan et al., 2011).

**Anti inflammatory activity:** Sankar et al. (2001) studied the in vivo anti-inflammatory activity of a compound isolated from the hydroalcoholic extract of aerial part of *E. sauber* in acute, sub acute and chronic experimental models in albino rats and showed that higher dose of compound is highly effective in inhibiting carrageenan induced edema formation in rats. Teng-Khia-U is a Taiwan traditional medicine containing *Elephantopus sauber*, *Elephantopus mollis* and *Pseudoelephantopus spinatus* 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 (Tsai and Lin, 1998).

Hong et al. (2011) conducted a study to investigate protective mechanism of *E. sauber* using lipopolysaccharide (LPS) induced inflammation of BV-2 microglial cells and acute liver injury in Sprague-Dawley rats. *E. sauber* 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, but not the ethanol extract, of *E. sauber* 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. sauber* involved an antioxidative effect and inhibition of p38 MAP kinase and COX-2 expressions in LPS-stressed acute hepatic injury in rats.

**Antibacterial and antifungal 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* (Thun et al., 2005). The novel terpenoid, 6-[1-(10,13-dimethyl-4,5,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethyl-3-methyl]-3,6-dihydro-2H-2 pyranone isolated from *E. sauber* possessed antibacterial activity against a few multi drug-resistant ESBL producing clinical isolates (Daisy and Priya, 2010). 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* (Daisy et al., 2011a).

The methanolic leaf extract of *E. sauber* 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 (Suresh et al., 2004). The methanolic extract also showed inhibition zones of 19 mm, 18 and 15 mm against *Bacillus megaterium*, *Xanthomonas campestris* and *Escherichia coli*, respectively but showed minimal activity towards *P. vulgaris* (Sunilbabu et al., 2011). Jenny et al. (2012) also showed that 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 sobren*, *Escherichia coli* and *Salmonella typhimurium*. Avani and Neeta (2005) showed 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*. The aqueous leaf extract of *E. sauber* showed not much potential antimicrobial activities against the selected strains *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Leuconostoc latis* and *Salmonella typhi*. Methanolic extract showed the maximum zone of inhibition 28 mm (200 mg disc⁻¹) against *Streptococcus pyogenes* and minimum (18 mm) by the same pathogen at lower concentration of 50 mg (Kamalakannan et al., 2012). Scabertopin, isosacberopin, deoxyelephantopin and isodeoxyelephantopin also inhibited the growth of *Escherichia coli*, *Staphylococcus aureus* and β-streptococcus. 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 chloroform extracts showed the highest zone of inhibition against *Bacillus cereus* (12 mm). The ethanolic extracts of leaves demonstrated the highest zone of inhibition against three pathogens *Entroccoccus faecalis* (18 mm), *Proteus mirabilis* (17 mm), *Salmonella typhi* (14 mm) and *Enterobacter sp.* (11 mm) (Anitha et al., 2012). Aqueous extract exhibited considerable antibacterial activity (MIC = 7.8-25.4 mg mL⁻¹) against serotypes c and d of *Streptococcus mutans* (Chen et al., 1989). Ganga et al. (2012a) 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. Athira and Anisha (2011) showed that ethanol extracts of E. scaber possessed remarkable antibacterial effect against P. aeruginosa, S. aureus and Bacillus megaterium. 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 (Santhosh et al., 2012). There is a synergistic action between the methanol extract of Eugenia jambolana and the acetone extract of Elephantopus scaber against Vancomycin resistant Enterococci bacteria (Jasmine and Selvakumar, 2011). Ethanolic extract of E. scaber was found to be effective against Multi drug resistant S. aureus, Cerebacter freundii and Proteus sp. (Dubey et al., 2012).

Kamalakannan et al. (2012) studied the effect of aqueous and methanolic extract of E. scaber on pathogenic fungal strains 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. Out of four extracts, ethyl acetate fraction showed more inhibition towards fungal species Candida bombii, Candida tropicalis, Candida utilis (Ganga et al., 2012b).

Hepatoprotective activity: Rajesh and Latha (2001) has studied the efficacy of this medicinal plant to prevent carbon tetrachloride (CCL4)-induced chronic liver dysfunction in the rats by determining different biochemical markers such as aspartate aminotransferase (AST), alanine aminotransferase (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 CCI4 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 (CCl₄) induced hepatic damage in rats (Ganga et al., 2012a). 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-oxaloacetate 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’ (Lin et al., 1995). The ethanol extract of E. scaber leaves showed promising hepatoprotection activity in mice with alcohol-induced liver damage (Ho et al., 2012). Methanolic extract of E. scaber dose dependently prevented and reversed nitrosodiethylamine (NDEA) induced hepatotoxicity in experimental animals (Linza et al., 2013). Hot water extract of E. scaber promote cell cycle-induced liver regeneration and suppressed hepatocytes apoptosis after partial heptectomy (Tsai et al., 2013).

Anti coagulant activity: The triterpenoid lupeol (C₂₉H₄₆O) isolated from E. scaber 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 (Sankaranarayanan et al., 2010).

Anti Snake venom activity: Pentacyclic triterpenes lupeol and urosolic acids from E. scaber have shown anti-snake venom activity. Lupeol showed 72% protection against snake venom (Mors et al., 2000).

Anti diarrhoeal activity: Methanolic extract of roots showed significant antidiarrheal activity against castor oil induced diarrhoea in rats. The presence of tannins, alkaloids, sterols and reducing sugar, the constituents responsible for antidiarrheal activity also present in methanolic extract (Reddy et al., 2008). Muthumani et al. (2010) revealed the significant antidiarrheal activity of ethyl acetate extract.

Antiviral activity: Elephantopus scaber is a potential resource of β sesquiphellandrene, one of the important sesquiterpene compounds showing antiviral activity (Wang et al., 2004). A new dicafeoyl derivative, 1α, 2β-D-dicafeoylcycoptan-3β-ol showed in vitro antiviral activity against Respiratory Syncytial Virus (RSV). Four dicafeoylquinic acids 4, 5-di-O-cafeoylquinic acid, 3, 4, di-O-cafeoylquinic acid and their methyl esters also possessed strong anti -RSV activity with IC₅₀ lower than that of ribavirin, a positive control drug (Geng et al., 2011).

Antidiabetic activity: 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) Witha 2, 6, 23-trienolide, a major steroid isolated from the acetone extract of the E. scaber decreased blood level glucose in STZ diabetic rats. This may be due to a stimulating effect on insulin release from regenerated β-cells of the pancreas or increased cellularity of the islet tissues (Daisy et al., 2009). 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 (Daisy et al., 2008). Ethyl acetate root extract and methanol leaf extract of E. suaber showed anti-hyperglycemic 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 (Daisy et al., 2011b). 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 enzyme glucokinase (Modilal and Daisy, 2011).

**Antioxidant and free radical scavenging activity:**
Sheeba et al. (2012) has investigated in vitro antioxidant activity by determining superoxide scavenging, hydroxyl scavenging and Fe²⁺-ascorbate induced lipid peroxidation inhibiting activity of methanolic extract of E. suaber root. The methanolic extract of root was found to be a scavenger of superoxide with an IC₅₀ of 48±5 μg mL⁻¹ and inhibited hydroxyl radicals generated by Fe²⁺/ascorbate/EDTA/H₂O₂ system with an IC₅₀ of 72±12 μg mL⁻¹. There was lipid peroxidation inhibiting activity with an IC₅₀ of 103±18 μg mL⁻¹. In vivo experiments showed that administration of methanolic extract of E. suaber 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. Koppula and Amman (2011) have studied the total phenolic content and antioxidant activity of methanol extract of several concentrations of E. suaber ranging from (100-500 μg mL⁻¹). The extracts showed significant antioxidant activity. The antioxidant activity increased with increasing concentration of extract. Ganja et al. (2012b) investigated the phenolic content in 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. Among the selected fractions ethyl acetate fraction showed high phenolic content. The four extracts also possessed concentration dependent inhibition using DPPH, superoxide and hydroxyl radicals scavenging activity. It was found that the ethanolic extract of E. suaber 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 (Pongpiriyadacha et al., 2009).

**Anthemintic activity:** The alcoholic extract of leaves of E. suaber showed the significant anthemintic effect against Pheretima posthuma at concentrations (20, 40, 60, 80 and 100 mg mL⁻¹). Aqueous extract also showed significant inhibition (Khan et al., 2011).

**Anti-ulcer activity:** Aqueous root extract of E. suaber possessed significant anti-ulcer 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 (Reddy et al., 2008).

**Diuretic activity:** Poli et al. (1992) has examined the diuretic potential of aqueous and hydroalcoholic extracts of whole plants on rat. Both extracts failed to modify diuresis. A clinical trial was carried out in ten healthy volunteers and their effects compared to placebo in order to evaluate the potential diuretic effect of E. suaber. There was no effect on electrolytes or renal function parameters such as urinary and plasma sodium, potassium, uric acid, calcium, phosphate, urea, creatinine and this probably excludes any renal tubular or glomerular effect from these substances (Laranja et al., 1991). Both these two reports didn’t support the traditional use of E. suaber as a diuretic. Ethanolic extract of whole plant of E. suaber 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⁺-ATPase inhibitor (Ngamrojanavanich et al., 2006).

**Wound healing activity:** Singh et al. (2005) has studied the effect of three extracts, aqueous and ethanolic extract of aerial parts, deoxyxylephantopin, on wound healing on Swiss wistar strain rats. Three wound models, the excision, the incision and dead space were used for the study. As compared to the ethanolic extract, deoxyxylephantopin showed more significant wound healing activity by increasing cellular proliferation, formation of granulation tissue, synthesis of collagen and increase in the rate of wound contraction. The wound healing property of deoxyxylephantopin may be due to the presence of active moiety, α-methylene γ lactone. Aqueous extract of E. suaber is taken orally to heal wounds (Basha et al., 2013).

**Anti asthmatic activity:** The ethanolic, chloroform and ethyl acetate fraction of E. suaber was used to inhibit mast cell degranulation by compound 48/80 in which the chloroform fraction was more effective than the other fractions (Padmaswinata, 1994). The ethanolic extract of
leaves of E. saher significantly increased the preconvulsive dyspnoea time following exposure to histamine and acetylcholine aerosols induced bronchospasms in guinea pigs. It also inhibited in vitro rat peritoneal mast cell degranulation significantly induced by compound 48/80. Histamine induced muscle contraction of trachea was significantly inhibited by the ethanolic extract. So, it suggested that the extract had antianaphylactic, anticholinergic an antihistaminic activity (Sagar and Sahoo, 2012).

Other pharmacological activities: Tetrahydrodron phthalalene showed hypocholesterolemic effect and antioxidant activity (Wang et al., 2004). Methanolic extract of E. saher hair oil formulation on topical application stimulate the hair growth initiation and completion time and direct impact on hair follicles (Sahoo et al., 2015). The petroleum ether extract of dried aerial parts showed significant cardio tonic activity on the hypodynamic frog heart (Muthumani et al., 2011). Administrations of E. saher water and ethanolic extracts into adult male rats markedly enhanced the libido and sperm counts. There was an increase in ischiocavernous muscle weight and bulbospongiosus muscular weight. Female/male offspring sex ratios were higher in water and alcohol extract feeding groups than those of control (Chaidichoey and Srihako, 2008). The ethanolic extract of E. saher at low dose showed oxytocin effect and enhanced spermatogenesis and increased sperm density (Pinnongkholgul et al., 2012). Singh et al. (2013) performed an in vitro test to study the effect of E. saher, 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. The following compounds-deoxyelephantopin, iso-deoxyelephantopin, lupeol, lupeol acetate, stigmasterol and diadinoxanthine derivative-isolated from the chloroform extract of air dried leaves of E. saher possessed antimotogenic activity (Ragasa et al., 1995). Gout, a heading joint disease was treated by applying the paste of E. Safer leaves and oil of Schleicheria oleosa externally on gout affected part of the body (Singh et al., 2010). Gentamicin-drug induced nephrotoxicity increased the serum urea level and total creatinine which can be restored by ethanolic extract of E. saher (Bhusan et al., 2012). Deoxyelephantopin showed antiprotozoal activity against Trypanosoma brucei rhodesiens (Zahari et al., 2013).

CONCLUSION AND FUTURE PROSPECTIVE

Plants used in folk medicine have provided a rich source of drugs for many diseases, including cancer. In traditional system of medicines such as Chinese medicine and Ayurveda, the use of E. saher for treating various illness have been well documented. Using the ethnomedical approach and bioassay-guided fractionation, several compounds with biological activity were isolated and identified from the plant. Many of these isolations were based on the uses of the agents in traditional medicine which showed pharmacological activities including antiviral, anti-cancer and anti-tumour, anti-diabetic, anti-microbial, anti-inflammatory, anti-oxidant and hepatoprotective effects. The present review provides a preliminary data about the chemical constituents isolated from E. saher and its pharmacological effects. In this context, further investigations are necessary to validate its traditional use and establish it as chemotherapeutic drugs.

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