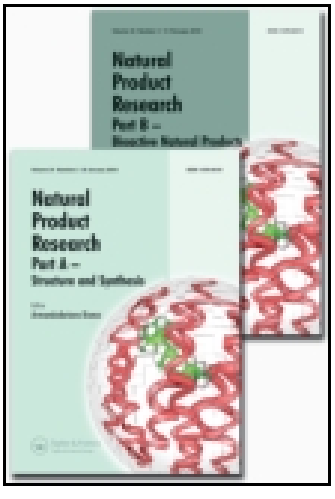

Natural Product Research: Formerly Natural Product Letters
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gnpl20

A review on pharmacology and toxicology of Elephantopus scaber Linn.

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Published online: 05 Feb 2014.

To cite this article: Sachin M. Hiradeve & Vinod D. Rangari (2014) A review on pharmacology and toxicology of Elephantopus scaber Linn., Natural Product Research: Formerly Natural Product Letters, 28:11, 819-830, DOI: 10.1080/14786419.2014.883394

To link to this article: http://dx.doi.org/10.1080/14786419.2014.883394

Natural Product Research, 2014
Vol. 28, No. 11, 819–830, http://dx.doi.org/10.1080/14786419.2014.883394

REVIEW

A review on pharmacology and toxicology of *Elephantopus scaber* Linn.

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(*Received 16 November 2013; final version received 6 January 2014*)

Elephantopus scaber Linn., family Asteraceae, is a small herb found in the Neotropics, Europe, Asia, Africa and Australia. The parts of this plant have been used traditionally for the treatment of number of diseases in many countries. The plant has been extensively screened for anticancer activity. Sesquiterpene lactones such as deoxyelephantopin, isodeoxyelephantopin, scabertopin and isoscabertopin. have been found to be prominent anticancer constituents. Many other biological activities such as antimicrobial, hepatoprotective, antioxidant, antidiabetic, anti-inflammatory, analgesic, antiasthamatic, antiplatelet and wound healing ability have been reported in various research articles. This review has been envisaged with an intention to provide the scientific information about the pharmacological and toxicological profile of *E. scaber*.

Keywords: *Elephantopus scaber*; antitumour; sesquiterpene lactones; deoxyelephantopin; traditional medicine

1. Introduction

The genus *Elephantopus* was included in the Asteraceae family by Linnaeus in 1753. It is a genus with about 32 species centered in the Neotropics (extending from southern Mexico through Central America and northern South America to southern Brazil), Europe, Asia (India, Nepal, Pakistan, Sri Lanka, China, Taiwan, Hong Kong, Japan, Malaysia, Indonesia, Vietnam, Philippines, Thailand and Myanmar), Australia and Africa (Kurokawa & Nakanishi 1970; Kiritikar & Basu 1991; Hammer & Johns 1993; Taylor et al. 1995; Hui & But 1998; Singh et al. 2005; Than et al. 2005; Wright et al. 2007). The lectotype species of *Elephantopus* genus, that is *Elephantopus scaber* Linn., family Asteraceae, is a common wild weed that forms undergrowth in shady places. It is a rather coarse, rigid, erect, hairy herb, 30–60 cm high. Stems are forked and stiff, while leaves are mostly in basal rosette and oblong-ovate to oblong-lance like, 10–25 cm in length and often very much notched on the margins. Purple flowers are 8–10 mm long and each flower head comprises about four flowers. Flowering heads are borne in clusters at the end of the branches and usually enclosed by three leaf-like bracts which are ovate to oblong-ovate, 1–1.5 cm long, and heart-shaped at the base. The flowering heads are crowded in each cluster while the fruits are achenes, ribbed and pappus from 4 to 6 mm long with rigid ristles (Kiritikar & Basu 1991). The image of *E. scaber* has been provided in Figure 1.

Among the 32 species, only one species – namely, *E. scaber* – is known to grow in India (Geetha et al. 2012). The plant has been abundantly found throughout India such as the Western Ghats and widely distributed in the forest of Achanakmar, Chhattisgarh State. It is popularly

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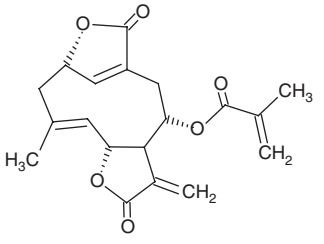
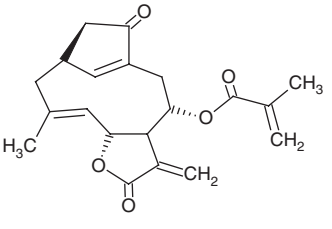
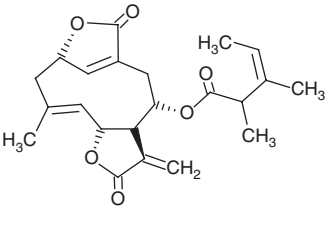
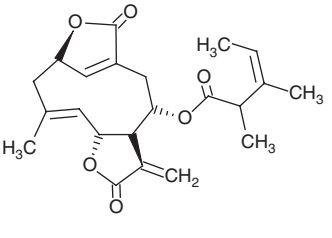
Figure 1. A photograph of *E. scaber.*

known as the prickly leaved elephant foot or elephant's foot (English). In China, the plant is called as Didancao (Hui & But 1998). In India, it has a variety of local names such as Gojivha, Hastipadi or Kharaparnini (Sanskrit), Gobhi (Hindi), Hastipata (Marathi), Eddumalikechettu (Telugu), Yanaiccuvati (Tamil), Nayi nalige (Kannada), Anayatiyan or Anaccuvati (Malayalam) and Hastipod (Bengali) (Kiritikar & Basu 1991).

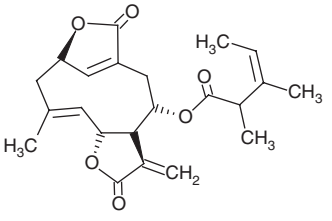
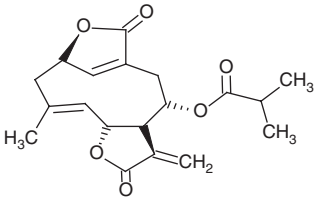
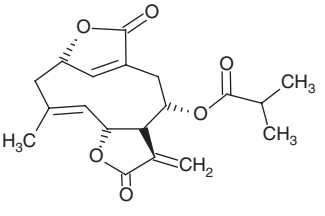
The chemical constituents of *E. scaber* include sesquiterpene lactones, triterpenoids, steroids, flavonoids and phenolic compounds. The sequiterpenoid lactones such as scabertopin, isoscabertopin, deoxyelephantopin, isodeoxyelephantopin, elescaberin, 17,19-dihydrodeoxyelephantopin and iso-17,19-dihydrodeoxyelephantopin are the main therapeutically active constituents reported from the entire plant and also from the roots (Table 1). The triterpenoids reported in *E. scaber* include lupeol acetate, lupeol, betulinic acid, epifriedelanol and ursolic acid (Su et al. 2009). The plant also contains steroidal constituents such as stigmasterol and stigmasterol glucoside (Sim & Lee 1969; Than et al. 2005). The entire plant has exhibited the presence of flavonoids (tricin and luteolin) (Su et al. 2009) and some phenolic compounds (Sim & Lee 1969). A large number of long-chain hydrocarbons and long-chain fatty acids have been reported from the dichloromethane extracts of *E. scaber*

Table 1. Sesquiterpene lactone and extract expressing cytotoxicity against various cell lines.

Extract/sesquiterpene lactones with structure	Cell lines	Reference
Aqueous extract	DAL	Rajkapoor et al. (2002)
Ethanolic extract	Breast cancer cell line (MCF-7)	Ho et al. (2011)
Deoxyelephantopin 	*In vitro* study: human hepatocarcinoma cell line (SMMC-7721), human cervical carcinoma (HeLa), human colon carcinoma (Caco-2), melanoma-derived cell line (MEXF 394NL), mammary cancer cell line (MAXF 401NL), human prostate carcinoma cell (PC-3), human nasopharyngeal carcinoma epithelial cell (CNE), human acute promyelocytic leukaemia cell (HL-60) *In vivo* study: DAL human cervical cancer xenograft model, murine mammary adenocarcinoma cell line (TS/A), human breast adenocarcinoma cell line (MCF-7), human breast skin fibroblast cell line (CCD966SK), metastatic human breast cancer cell line (MDA-MB-231)	Xu et al. (2006), Geetha et al. (2012), Than et al. (2005), Su et al. (2009, 2011), Huang et al. (2010)
Isodeoxyelephantopin 	Human hepatocarcinoma cell line (SMMC-7721), human cervical carcinoma (HeLa), human colon carcinoma (Caco-2) DAL, human chronic myeloid leukaemia (KBM-5), lung adenocarcinoma (H1299), human promyelocytic leukaemia (HL60), human embryonic kidney carcinoma (A293), human breast adenocarcinoma (MCF-7), human multiple myeloma (MM.1S), and human multiple myeloma cell lines (U266)	Xu et al. (2006), Geetha et al. (2012), Ichikawa et al. (2006)
Scabertopin 	Human hepatocarcinoma cell line (SMMC-7721), human cervical carcinoma (HeLa) and human colon carcinoma (Caco-2)	Xu et al. (2006)
Isoscabertopin 	Human hepatocarcinoma cell line (SMMC-7721), human cervical carcinoma (HeLa), and human colon carcinoma (Caco-2)	Xu et al. (2006).

(*continued*)

Table 1. (*continued*)

Extract/sesquiterpene lactones with structure	Cell lines	Reference
Elescaberin 	Human hepatocarcinoma cell line (SMMC-7721)	Liang et al. (2008)
17,19-dihydro-deoxyelephantopin 	Melanoma-derived cell line (MEXF 394NL) and renal cancer cell line (RXF 944L)	Than et al. (2005)
Iso-17,19-dihydro deoxyelephantopin 	Melanoma-derived cell line (MEXF 394NL), lung cancer (LXFL 529L)	Than et al. (2005)

(Wang et al. 2005). The essential oil (0.05%) and about 21 of its constituents have been reported by Wang et al. (2004).

In folk medicinal practices, various parts of the plant and even the whole plant of *E. scaber* have been used in many countries for the treatment of a number of diseases. Detailed pharmacological review of *E. scaber* is provided in Section 2.

2. Pharmacological activities

The review of ethnomedical history of *E. scaber* clearly indicates its use in various parts of the world for the treatment of a variety of disease conditions. Many of these ethnomedical uses have been scientifically validated by the results of biological activity studies. A review of these biological activity studies is presented in the later sections.

2.1. *Antitumour activity*

The antitumour activity study of *E. scaber* supersedes all other activities as evident from the studies of various researchers.

Sesquiterpene lactones are the characteristic constituent of the Asteraceae family and responsible for the antitumour effect. Several sesquiterpenoids (scabertopin, isoscabertopin, deoxyelephantopin, isodeoxyelephantopin, elescaberin, 17,19-dihydrodeoxyelephantopin and iso-17,19-dihydrodeoxyelephantopin) have been isolated from *E. scaber* and almost all of them have indicated significant antitumour activity (But et al. 1997; Than et al. 2005; Ichikawa et al. 2006; Xu et al. 2006; Liang et al. 2008; Su et al. 2009, 2011; Huang et al. 2010; Geetha et al. 2012; Lee & Shyur 2012). Among these constituents, deoxyelephantopin appears to be a very promising compound for the treatment of cancer.

Deoxyelephantopin exhibited strong effect against the PC-3 (human prostate carcinoma cell), CNE (human nasopharyngeal carcinoma epithelial cell) and HL-60 (human acute promyelocytic leukaemia cell) cell lines. In CNE cell lines, it inhibited the CNE cell proliferation by arresting the cell cycle in S and G2/M phases and also triggered apoptosis in the CNE cells. Dysfunction in mitochondria was found to be associated with the deoxyelephantopin-induced apoptosis as evidenced by the loss of mitochondrial membrane potential, the translocation of cytochrome *c* and the regulation of Bcl-2 family proteins (Su et al. 2009, 2011). Against murine mammary adenocarcinoma (TS/A), human breast adenocarcinoma (MCF-7), human breast skin fibroblast (CCD966SK), metastatic human breast cancer (MDA-MB-231) and non-cancerous human mammary epithelial cell lines, deoxyelephantopin has potential as a chemopreventive agent for breast cancer and suppresses mammary adenocarcinoma and lung metastasis and double survival time in mice by several mechanisms (Huang et al. 2010).

Against Dalton's ascitic lymphoma (DAL) tumour cells, deoxyelephantopin and isodeoxyelephantopin act selectively on quiescent and phytohaemagglutinin-stimulated proliferating human lymphocytes and inhibited tritiated thymidine incorporation into cellular DNA of DAL tumour cells and cause apoptosis. Therefore, the results indicated that deoxyelephantopin and isodeoxyelephantopin are not cytotoxic to normal human lymphocytes, and only the proliferating cells were affected and hence could be used in regimens for treating tumours with extensive proliferative potencies (Geetha et al. 2012). Later, Lee and Shyur (2012) observed that deoxyelephantopin significantly deregulated adhesion formation in TS/A cells (a murine mammary adenocarcinoma cell line), probably through inhibition of m-calpain activity. Epithelial growth factor (EGF)-mediated activation of Rho GTPase Rac1 and formation of lamellipodia in TS/A cells were remarkably suppressed by deoxyelephantopin treatment. Further, deoxyelephantopin impaired the vesicular trafficking of EGF and induced protein carbonylation and formation of centrosomal aggregates in TS/A cells. Deoxyelephantopin-induced reactive oxygen species were observed to be the upstream stimulus for the formation of centrosomal ubiquitinated protein aggregates that might subsequently restrict cancer cell motility.

Isodeoxyelephantopin mediated its effects by suppressing nuclear factor-κB (NF-κB) activation and potentiating apoptosis. It inhibited the activation of NF-κB by a variety of inflammatory agents and in a variety of cell lines such as KBM-5 (human chronic myeloid leukaemia), H1299 (lungadenocarcinoma), HL60 (human promyelocytic leukaemia), A293 (human embryonic kidney carcinoma), MCF-7 (human breast adenocarcinoma), MM.1S (human multiple myeloma), U266 (human multiple myeloma cell lines) and RAW 264.7. Specifically, NF-κB activity was inhibited because isodeoxyelephantopin suppressed IKK (IκB kinase) activation, resulting in the inhibition of IκBα phosphorylation and degradation. Consequently, isodeoxyelephantopin also blocked p65 phosphorylation and p65 nuclear translocation. Furthermore, it suppressed the expression of gene products involved in cell proliferation, antiapoptosis and invasion. Suppression of NF-κB by isodeoxyelephantopin enhanced the apoptosis induced by tumour necrosis factor (TNF) and inhibited TNF-induced cellular invasion and osteoclastogenesis (Ichikawa et al. 2006).

The details of anticancer activity studies of crude extract and sesquiterpene lactones isolated from the different extracts of *E. scaber* against various cell lines along with structures are provided in Table 1.

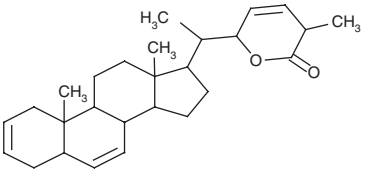
2.2. *Antibacterial activity*

Petroleum ether, chloroform and methanol extracts from the aerial parts of *E. scaber* investigated for antibacterial potential against *Staphylococcus aureus*, *Salmonella paratyphi* A, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Shigella sonnei*, *Escherichia coli* and *Salmonella typhimurium* expressed significant antibacterial activity; however, the methanolic extract was found to be the most effective against the tested organisms (Jenny et al. 2012). The antibacterial activity of the methanolic extract of *E. scaber* was reported to be significant against Gram-positive bacterium *Streptococcus pyogenes* but insignificant against Gram-negative bacteria. The aqueous extract of *E. scaber* leaf was also tested on selected bacterial strains such as *E. coli*, *S. aureus*, *S. pyogenes*, *P. aeruginosa*, *Leuconostoc lactis*, *Bacillus subtilis*, *Proteus vulgaris* and *S. typhi*. However, it has not indicated marked activity against both Gram-positive and Gram-negative bacteria (Sureshkumar et al. 2004; Kamalakannan et al. 2012). In addition, the ethanolic extracts from the leaves of *E. scaber* demonstrated the highest zone of inhibition against pathogens, namely, *Enterococcus faecalis*, *Proteus mirabilis*, *S. typhi* and *Enterobacter* spp. The ethanolic extracts from the roots of *E. scaber* illustrated the highest zone of inhibition against three pathogens, namely, *S. aureus*, *E. coli* and *P. aeruginosa*. The chloroform extracts of the *E. scaber* roots expressed the highest zone of inhibition against *Bacillus cereus* (Anitha et al. 2012).

The whole-plant extracts of *E. scaber* were screened against extended-spectrum β-lactamase-producing methicillin-resistant *S. aureus* (MRSA) bacterial strain. Fractionation of the plant extracts revealed that the acetone fraction exhibited significant activity, while less activity was found in the methanol and hexane fractions (Jasmine et al. 2007a). Although acetone extract exhibited higher inhibitory activity against MRSA bacterial strain, no inhibitory zones were observed against *Pseudomonas* spp., while the methanol and hexane extracts of *E. scaber* were effective against *Pseudomonas* spp. The plant exhibited similar activity against Gram-positive and Gram-negative bacteria, which may be indicative of the presence of broad-spectrum antibiotic compounds in *E. scaber* (Jasmine et al. 2007b). The petroleum ether and ethyl acetate extracts of the whole plant were tested against 11 American Type Culture Collection bacterial isolates. Concentrations of 1, 2 and 4 mg/mL of ethyl acetate and petroleum ether extract were used. The ethyl acetate extract of the plant exhibited growth inhibitory effect at 4 mg/mL concentration in all the bacterial isolates tested except *K. pneumoniae* where it expressed 75% inhibition. Lower concentrations of the extract indicated concentration-dependent inhibitory effect. At 2 mg/mL, 50% inhibition was observed, whereas at 1 mg/mL it was completely ineffective. The inhibitory effect of petroleum ether extract at all three concentrations was not found on any of the cultures except *Micrococcus luteus* where it exhibited 50% inhibition at 2 mg/mL and complete inhibition at 4 mg/mL. Hence, the study confirmed that the ethyl acetate extracts of *E. scaber* possess antimicrobial potential (Avani & Neeta 2005). Whereas hydro-alcoholic, hexane, ethyl acetate and methanol extracts of the whole plant of *E. scaber* were tested for antibacterial potential against *S. aureus*, *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *S. typhimurium*. This study observed that the highly significant zone of inhibition was exhibited by the ethyl acetate and hexane fractions of *E. scaber* against all tested organisms (Gangarao et al. 2012). The aqueous extract of *E. scaber* has also been reported to possess considerable antibacterial activity against the cariogenic bacterium, *Streptococcus mutans* (Chen et al. 1989).

The novel terpenoid, {6-[1-(10,13-dimethyl-4,5,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-17-yl)ethyl]-3-methyl-3,6-dihydro-2*H*-2 pyranone}, isolated

from the acetone extract of the whole plant of *E. scaber* has expressed significant antibacterial activity against *S. aureus*. This terpenoid acted through the inhibition of autolysin which is a bacteriolytic enzyme that digests the cell wall peptidoglycan. It is involved in numerous cellular processes including cell growth, cell-wall turnover, peptidoglycan maturation, cell division, separation, motility, chemotaxis, genetic competence, protein secretion, differentiation and pathogenicity. The terpenoid inhibits the activity of autolysin by forming a strong atomic interaction with the active-site residues (Daisy et al. 2008).



6-[1-(10,13-Dimethyl-4,5,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α] phenanthren-17-yl) ethyl]-3-methyl-3,6-dihydro-2*H*-2pyranone

2.3. *Antifungal activity*

Duraipandiyan and Ignacimuthu (2011) used hexane, ethyl acetate and methanol extracts of the root of *E. scaber* for the evaluation of antifungal activity. The fungal strains used were *Trichophyton rubrum* MTCC 296, *T. rubrum* 57/01, *Trichophyton mentagrophytes* 66/01, *Trichophyton simii* 110/02, *Epidermophyton floccosum* 73/01, *Scopulariopsis* sp. 101/01, *Aspergillus niger* MTCC1344, *Botrytis cinerea*, *Curvularia lunata* 46/01, *Magnaporthe grisea* and *Candida albicans* MTCC 227. Hexane extract did not exhibit antifungal properties against the tested fungi, while ethyl acetate and methanol extracts inhibited only few tested fungi such as *T. mentagrophytes*, *E. floccosum* and *T. simii*.

The methanol and aqueous extracts of *E. scaber* leaf was tested on selected four fungal strains: *A. niger*, *Aspergillus flavus*, *Rhizopus indicus* and *Mucor indicus*. The antifungal activity was observed in a dose-dependent manner, and the highest activity was observed with methanolic extract against *M. indicus* (32 mm) and minimum activity was recorded against *R. indicus* (14 mm). There was no activity observed in aqueous extract against the tested fungal strains (Kamalakannan et al. 2012). Gangarao et al. (2012) have reported antifungal activity studies of the hexane, ethyl acetate and methanol and hydroalcoholic extracts of the whole plant of *E. scaber* against *Candida bombii*, *Candida tropicalis* and *Candida utilis.* Highly significant antifungal activity was indicated by hexane and ethyl acetate extracts. However, the probable mechanism of action responsible for the antifungal activity has not been reported in these studies.

2.4. *Hepatoprotective activity*

The aqueous extract of *E. scaber* has been tested against three experimental models such as lipopolysaccharide (LPS)-, D-galactosamine (D-GalN)- and acetaminophen-induced hepatic damage in rats. The serum glutamate-oxalate-transaminase and the serum glutamate-pyruvate-transaminase levels have been decreased so that the hepatic lesions and leucocyte infiltration were prominently reduced by *E. scaber* treatment. The mechanism of the hepatoprotective effect by *E. scaber* was mainly due to the suppression of p38 MAPK and to a lesser degree of COX-2 pathway (Lin et al. 1995; Hung et al. 2011). The methanol extract of *E. scaber* root against carbon tetrachloride (CCl_4)-induced hepatic necrosis expressed significant hepatoprotective activity. CCl_4 causes decrease in the level of antioxidant enzymes such as superoxide dismutase

and catalase, which has been prevented by the administration of methanolic extract of *E. scaber* roots (Sheeba et al. 2012).

Battu et al. (2012) evaluated the hexane, ethyl acetate and ethanol fractions of the whole plant of *E. scaber* against CCl_4-induced hepatic damage in rats and expressed significant hepatoprotection by ethanol fraction as compared with other fractions. In addition, the ethanolic leaf extract of *E. scaber* against alcohol-induced liver damage in mice indicated promising hepatoprotection activity. The ability of *E. scaber*-treated mice to cope with the oxidative stress induced by alcohol could be accountable to the antioxidant capacity of the herb and most effectively restore the liver damage to near normal (Ho et al. 2012).

A sesquiterpene lactone, deoxyelephantopin, isolated from *E. scaber* plant also demonstrated potential hepatoprotective effect against LPS/D-GalN-induced fulminant hepatitis. Deoxyelephantopin acts by modulating multiple molecular targets or signalling pathways that counteract inflammation during the progression of fulminant hepatitis and may serve as a novel lead compound for future development of anti-inflammatory or hepatoprotective agents (Huang et al. 2013).

2.5. *Antidiabetic activity*

In streptozotocin-induced diabetic rats, methanol, hexane and ethyl acetate extracts of *E. scaber* leaves were tested and proved to possess significant hypoglycaemic properties. The effective dosage of various extracts was fixed to be 250 mg/kg body weight (b.w.)/day. These extracts improved the biochemical parameter assessed, and also brought about regeneration of β-cells of pancreas with increasing insulin levels (Daisy, Vargese, et al. 2009), while in the same experimental model, hexane extract of *E. scaber* root brought about a better hypolipidaemic potential and a re-establishment of renal functions. The extract produced a significant dose-dependent decrease in the levels of total cholesterol, triacylglycerol, low-density lipoprotein-cholesterol, with a significant increase in the level of high-density lipoprotein-cholesterol and reported the restoration in renal functions back to near normal (Daisy & Priya 2010). The acetone extract of *E. scaber* plant reduced the blood glucose levels in streptozotocin-induced diabetic rats significantly by potentiating the insulin effect of plasma by increasing either the pancreatic secretion of insulin from the β cells of islets of Langerhans or its release from bound insulin. Further fractionation of the acetone extract yielded a new steroid, 28Nor-22(*R*)-witha-2,6,23-trienolide which demonstrated a significant antidiabetic activity by reducing the elevated blood glucose levels and restoring the insulin levels in the same experimental model (Jasmine & Daisy 2007; Daisy, Jasmine, et al. 2009). However, the methanol extract of *E. scaber* root was more effective than *E. scaber* leaf in correcting the metabolic disorders. The insulin deficiency had adverse effect on glucose oxidation in liver and skeleton muscles of diabetic rats and this metabolic disorder was corrected by *E. scaber* (Daisy & Jasmine 2008).

Daisy et al. (2007) reported the comparative study between the aqueous extract of *E. scaber* root and leaf against alloxan-induced hyperglycaemic rats and observed that the aqueous root extract of *E. scaber* demonstrated better hypoglycaemic action by reducing the blood glucose level when compared with the leaf extract.

2.6. *Antioxidant activity*

The methanolic extract of *E. scaber* root has proved to be an efficient antioxidant in the *in vitro* model. The superoxide generation by the reaction of photo-reduced riboflavin and oxygen is inhibited by the methanolic extract of *E. scaber* root. The generation of malondialdehyde and the reaction of related substances from the lipid extract with thiobarbituric acid were found to be inhibited by the methanolic extract of *E. scaber* root. The degradation of deoxyribose to

thiobarbituric acid reactive substances by the hydroxyl radicals generated from Fe^{3+}–ascorbate–EDTA–H_2O_2 system was markedly decreased by the methanolic extract of *E. scaber* root (Sheeba et al. 2012). However, the hydroalcoholic, hexane, ethyl acetate and methanol extracts of the whole plant of *E. scaber* were tested for antioxidant potential and were found to possess concentration-dependent inhibition using 2,2-diphenyl-1-picrylhydrazyl, superoxide and hydroxyl radical-scavenging activity (Gangarao et al. 2012).

2.7. *Anti-inflammatory and analgesic activities*

The aqueous extract of *E. scaber* leaves possesses significant analgesic activity and weaker anti-inflammatory activity (Ruppelt et al. 1991). In another study, Poli et al. (1992) reported that the aqueous and hydroalcoholic extracts of the whole plant did not possess analgesic, diuretic, antipyretic or anti-inflammatory activities. However, these extracts when administered intravenously reduced blood pressure and heart rate in rats. The aqueous extract decreased the intestinal transit time in mice while the hydroalcoholic extract increased it. Later, in contradiction to the report of Poli et al., Tsai and Lin (1999) reported that the aqueous extracts of *E. scaber* whole plant exhibited significant anti-inflammatory effects by inhibiting the development of chronic joint swelling induced by complete Freund's adjuvant and also significantly inhibited the carrageenan-induced acute arthritis. The hydroalcoholic extract of the aerial parts of *E. scaber* expressed significant anti-inflammatory activity by reducing carrageenan-induced pedal oedema (57%) and formalin-induced pedal oedema in rats (58%) which is comparable to diclofenac (Sankar et al. 2001).

2.8. *Other activities*

Ethanolic extract of *E. scaber* leaves has exhibited significant antiasthmatic, wound-healing and nephroprotective activities along with its prominent antiplatelet activity (Sankaranarayanan et al. 2010). Deoxyelephantopin isolated from the ethanolic extract of *E. scaber* leaves promotes significant wound-healing activity by increasing cellular proliferation, formation of granulation tissue, synthesis of collagen and by increasing the rate of wound contraction (Singh et al. 2005).

In spite of this, the ethanol extract of *E. scaber* leaves (250 and 500 mg/kg) also significantly decreased the bronchospasm induced by histamine, acetylcholine and protected mast cell degranulation as compared with the control groups. It also decreased the histamine-induced constriction on isolated guinea pig trachea in a dose-dependent manner. Antiasthmatic action of the *E. scaber* could be due to its antihistaminic, anticholinergic and mast-cell-stabilising property (Sagar & Sahoo 2012). In addition, it also restored the elevated serum urea and creatinine level, indicating its significant nephroprotective effect (Bhusan et al. 2012).

3. Toxicological studies

Oral administration of either aqueous or hydroalcoholic extracts of the whole plant of *E. scaber* up to 6 g/kg, p.o. neither produced any abnormal effect nor any mortality (Poli et al. 1992; Sankar et al. 2001). However, intraperitoneal injections of the aqueous (0.03–3 g/kg) or of hydro-alcoholic extract (0.1–3 g/kg) induced writhing, loss of muscle tone, ataxia, prostration and death. Hence, the acute toxicity tests indicated that the LD_{50} values for the extracts were higher than 2 and 6 g/kg when administered i.p. and p.o., respectively, thus revealing a low acute toxicity (Poli et al. 1992).

Singh et al. (2005) reported that the maximum-tolerated dose for the aqueous and ethanol extracts of *E. scaber* was 3 g/kg, b.w. and for the isolated compound deoxyelephantopin it was 40 mg/kg b.w. Hence, 1/10 of these doses, that is 300 mg/kg, b.w. of aqueous or ethanol extract

and 4 mg/kg b.w. of the compound, were selected for the topical evaluation of wound-healing efficacy. However, the acute toxicity studies revealed that the ethanol and acetone extracts of the whole plant of *E. scaber* did not show mortality and any sign of toxicity at higher doses (2000 and 6000 mg/kg). The result clearly indicated the non-toxicity of the plant extract (Daisy, Jasmine, et al. 2009; Battu et al. 2012; Sagar & Sahoo 2012). Ho et al. (2012) observed no mortality after 14 days of treatment with a limited dose of 5000 mg/kg b.w. of ethanolic extract of leaves of *E. scaber*. Oral administration of ethanolic extract produces no signs of abnormalities or gross lesions in necropsy findings. It has revealed no statistically significant difference in the body weight of the treated and untreated control group. Thus, LD_{50} of *E. scaber* could not be determined and the extract could be regarded as non-toxic for oral consumption up to a concentration of 5000 mg/kg b.w. in mice.

During the literature survey, no reports were found on the chronic toxicity studies, clinical studies and reproductive toxic effects of *E. scaber*. Further studies of the extract and the active constituents of *E. scaber* need to be carried out for its evaluation as a potential therapeutic agent.

4. Conclusion

E. scaber Linn., family Asteraceae, is a small herb spread all over the world. It has been used as a medicine since a long period of time in almost all countries where it grows, and many ethnomedical claims have been scientifically proved by conducting extensive research on this plant. About a dozen of multifarious activities ranging from anticancer, antibacterial, antifungal, hepatoprotective, antidiabetic, antioxidant, anti-inflammatory, analgesic, antiplatelet, antiasthamatic and nephroprotective to that of wound-healing activity have been reported in the literature.

E. scaber has been reported to contain novel sesquiterpene lactones in the specific extracts such as chloroform, acetone, methanol, ethanol and aqueous extracts (Ho et al. 2009). The major sesquiterpenoids that contribute to the above-mentioned biological activities have been identified as deoxyelephatopin, isodeoxyelephantopin, scabertopin, isoscabertopin and few others. However, the plant contains other constituents such as triterpenoids such as lupeol, betulinic acid, ursolic acid and epifridelanol. Steroidal constituents may also have a role in certain specific pharmacological activities.

The most prominent activity for which *E. scaber* has attracted the attention of drug researchers is its anticancer activity. The major sesquiterpenoids of *E. scaber* have been subjected to a variety of anticancer activity studies and highly significant results have been reported. Certain patents related to anticancer activity have already been granted. The therapeutic effectiveness of *E. scaber* and its sesquiterpene lactones may possibly develop it as a potential anticancer drug in future.

Acknowledgements

The authors acknowledge with thanks the financial support as JRF from the H'ble Vice Chancellor, Guru Ghasidas Vishwavidyalaya, Bilaspur, India and the technical support from the Head, School of Pharmaceutical Sciences, Bilaspur for the provision of laboratory and library facilities.

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