Journal of Medicinal Plants Research Vol. 3(13), pp. 1212-1221, December, 2009
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875© 2009 Academic Journals

Review

Traditional practice, bioactivities and commercialization potential of *Elephantopus scaber* Linn.

Wan Yong Ho[1], Huynh Ky[1,2], Swee Keong Yeap[1], Raha Abdul Rahim[1], Abdul Rahman Omar[3], Chai Ling Ho[1] and Noorjahan Banu Alitheen[1,*]

[1]Department of Cell and Molecular Biology, Faculty of Biotechnology and Biomolecular Sciences, University Putra Malaysia, Serdang 43400 Selangor, Malaysia.
[2]Department of Agriculture Genetics and Breeding, College of Agriculture and Applied Biology, Cantho University, 3/2 Street, CanTho City, VietNam.
[3]Institure of Bioscience, University Putra Malaysia, Serdang, 43400 Selangor, Malaysia.

Accepted 16 December, 2009

***Elephantopus scaber* Linn. is known as Prickly-leaves elephant's foot or di dan tou in Chinese. It has been used in traditional medicine to stimulate diuresis, reduce fever and eliminate bladder stones, as well as to treat nephritis, edema, dampness, chest pain, pneumonia, scabies, arthralgia and leukemia. A number of phytochemicals have also been isolated from this plant, such as deoxyelephantopin, 11,13, dihydrodeoxyelephantopin, lupeol, epifriedelinol and stigmasterol. Most of the major studies only involved the bioactivities of the compounds especially deoxyelephantopin. The effects of the plant extract which can benefit a broad mass of people are still lacking. This paper briefly reviews the traditional usage and scientifically proven bioactivities of *E. scaber* which contributed its commercialization potential.**

Key words: *Elephantopus scaber* Linn, deoxyelephantopin, anticancer, antibacterial.

INTRODUCTION

Elephantopus scaber Linn. (Figure 1A), commonly know as Prickly-leaved elephant's foot or di dan tou, is the lectotype species of stiff wiry herb *Elephantopus*, Linn with around 30 species under the family of Compositae (Wang et al., 2004). *E. scaber* is a common wild weed that forms undergrowth in shady places. It can be widely found in Neotropical (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 (Ridley, 1922; Kurokawa and Nakanishi, 1970; Taylor et al., 1995; Manandhar, 2002; Shaw et al., 2002; Panda, 2004; Singh et al., 2005; Than et al., 2005; Wright et al., 2007). It can grow from 3 - 4 inches tall up to over 1 foot where the plant is woolly-tomentose and little branched (Figure 1C). The radical leaves are with sizes of 2 - 4 inches long and 0.5 - 1.25 inches wide, containing hairy nerves beneath and form a spreading rosette on the ground. It contains very short petioles with densely white hair and fruits with average length of 4 mm. The flower with violet homogamous head (the heads collected into a closely packed terminal inflorescence with pappus of 5 spiny bristles) is the identity of this particular species of *Elephantopus* (Figure 1B) (Ridley, 1922; Daniel, 2006). This plant can be easily found in grass plots, grasslands, wasteland and roadsides, along fields and in forest borders of altitude as high as 1500 m and it can be easily cultivated in field (Hammer and Johns, 1993) and *in vitro*. Singh et al. (2004) had successfully established calluses from the leaf of *E. scaber* segments in MS medium fortified with

*Corresponding author: E-mail: noorjahan@biotech.upm.edu.my.

Abbreviations: ESBL, Extended spectrum ß-lactamase; **MRSA,** methicillin resistant *Staphylococcus aureus*; **MSSA,** methicillin sensitive *Staphylococcus aureus*; **LDL,** low density-lipoproteins; **VLDL,** very low density- lipoproteins; **HDL,** high density- lipoproteins; **CADD,** computer –aided drug design; **SGOT,** serum glutamate-oxalate-transaminase; **SGPT,** serum glutamatepyruvate- transaminase.

Figure 1. Photos of *E. scaber*. 1A. *E. scaber* whole plant. 1B. Flower of *E. scaber.* 1C. Stem, leaves and the roots of *E. scaber.* Geographical localisation: Forest Research Institute Malaysia (FRIM), Kepong Selangor. In front of Tropical Forest Biodiversity Centre. 22/12/2008 by Mr. Lim Chung Lu.

0.3 mg/l NAA and 2 mg/l BAP which were then successfully introduced to the soil. This micropropagation has introduced the potential of continuous supply of quality and standard *E. scaber* since long term (6 years or even less) storage of this plant has reported the lost of bioactivities (Griggs et al., 2001). In this review, the tra-

ditional usage and scientifically studied bioactivities were highlighted. With the hope not only to improve public health but also wealth, this review also covers how its traditional practices and bioactivities contribute to patents and commercialization of this plant.

TRADITIONAL PRACTICES

In ancient oriental medicine, root, leaves, aerial part and even the whole plant have been used to treat various diseases. Different countries have different type of practices on this plant for various diseases. In Malaysia, decoction of *E. scaber* root has been used to accelerate contraction of abdominal area and prevent inflammation after childbirth. Besides, whole *E. scaber* was also boiled with red bean to remove flatulence (Hammer and Johns, 1993; Ong and Nordiana, 1999a; Ong and Nordiana, 1999b). People in Thailand have used *E. scaber* to treat cough, tonic (root decoction) (Inta et al., 2008), chapped lips and galactogogue (whole plant decoction) (Hammer and Johns, 1993). It has also been used in Madagascar as an antipyretic agent (decoction of aerial part) (Rasoanaivo et al., 1992); in Taiwan (whole plant decoction) to treat hepatitis; in Nigeria (hot water extract of leaves) to cure arthritis (Hammer and Johns, 1993) and in Mauritius to treat diarrhea, urinary problems (2 pieces of roots and 6 leaves in 1 liter of water) and pimples (root paste) (Gurib-Fakim et al., 1993).

In India, decoction of the whole plant has been used to treat gonorrhea and colic pain (Hammer and Johns, 1993) while hot water extract of the root is applied for filariasis. Paste has been made from the either leaves or whole plant to treat menorrhagia (Pattanaik et al., 2008) or rheumatism and tetanus externally and the dry bark has been used to prepare emulsion for wound healing (Hammer and Johns, 1993). Besides, leaves of *E. scaber* has been made into powder and heated with castor, coconut, gingelly oil, *Toddalia asiatica* and *Naravelia zeylanica* to cure rheumatism (Ayyanar and Ignacimuthu, 2005). Fresh root of this plant is employed for treating Spermatorrhea, leucorrhoea, ametrorrhagia, menstrual complaints, menorrhagia and dysmenorrhoea (Behera and Misra, 2005). In Ayurveda medicine, mixture of *E. scaber, Helloborus niger*, *Tinospora cordifolia*, *Clerodendron serratum*, *Aegle marmelos*, *Hoya viridiflora*, *Soymida febrifuga* and *Gynandropis pentaphylla* are used to treat *Vatika granthi* (minor neoplasm). Also, leaves of *E. scaber, Ficus glomerata* and *Tectona grandis* are used together with honey-mixed fine paste of *Aglaja roxburghiana, Caesalpinia sappa, Symplocos racemosa, Terminalia arjuna and Xanthium strumarium* to treat *Pittaja arbuda* (major neoplasm) (Balachandran and Govindarajan, 2005).

In Nepal, root decoction of *E. scaber* is widely used to treat diarrhea, dysentery, stomach troubles and blood vomiting in tuberculosis (Bhattarai, 1989; Taylor et al., 1995). Hot water extract of root has been used to remedy fever (Hammer and Johns, 1993) and bedwetting while its root juice (2 teaspoons three times per day) has been consumed to overcome heart and liver troubles and its leaves juice for wounds and bruises healing. Furthermore, root paste has been used externally as anti venom, antiseptic for cuts and wounds, lesions for chicken pox, antipyresis (2 teaspoonfuls of the root paste three times a day for 2 - 3 day) while its fresh roots are chewed to treat cough, cold and headache (Bhattarai, 1989; Bhandary et al., 1995; Taylor et al., 1995).

Also, the whole plant has been reported to be useful for curing insomnia, diabetes, bronchitis, viral or bacterial infection, leukemia, rheumatism, snake bite, diuresis, antipyresis, to eliminate bladder stones and for filariasis. The root can be used as an antipyretic, cardiotonic and diuretic agent. Moreover, the roots are also useful in reducing fever, cardiac problem and hepatitis. Decoction of the roots and leaves is used as an emollient or to treat dysuria, diarrhea, dysentery and stomach pain while the water extract of the leaves is also applied externally to treat eczema and ulcers (Lin et al., 1995; Mors et al., 2000; Liang et al., 2002; Shaw et al., 2002; Daniel, 2006; Jasmine and Daisy, 2007).

Although plenty of traditional applications of *E. scaber* have been recorded, Poli et al. (1992) have found that aqueous and alcohol extract of whole plant did not possess analgesic, diuretic, antipyretic or anti-inflammatory activities. More scientific studies need to be carried out not only to ascertain these claims but it is also important for the verification of other applications of this plant.

BIOACTIVITIES OF *E. scaber* EXTRACTS AND COMPOUNDS

With the diverse traditional applications of *E. scaber,* United Nations Development Program has recommended *E. scaber* as a potential natural herb which should be further studied (Hammer and Johns, 1993). However, the major barrier in studies of bioactivities for *E. scaber* is the confusion made with *E. tomentosus* Linn (a taller plant with white flowers) (Ridley, 1922) or *E. mollis* Kunth (a taller plant with white or pinkish flower) (Wiart, 2006) which are commonly misused as *E. scaber* in traditional medicine by some botanists and researchers. Thus, plant identification serves as the most important step before any scientific research is carried out.

A number of researches have been performed and the major bioactivities of this plant based on its traditional usages were confirmed. The bioactivities of *E. scaber* were identified using different means of extraction and phytochemical analysis of some of these extracts had led to the discovery and isolation of a few novel compounds that can be potentially used as drugs for a variety of pharmaceutical applications. The bioactivities of the respective extracts will be further discussed in this paper.

Ethanol extract

The ethanolic extract of *E. scaber* had been reported to posses a wide range of bioactivities including wound healing properties on mice models, anti-bacterial activity and treatment for dysuria. Ethanol extract of the leaves promoted wound healing activity in wounded mice as evidenced by histological studies which showed decreased number of chronic inflammatory cells, lesser edema and enhance collagenation. While aqueous extract was found to initiate significant wound contraction effect after day 8, ethanol extract demonstrated an even better effect with promotion of wound healing since day 4 after wound creation (Singh et al., 2005). In addition to this, a more pronounced increase in the rate of wound contraction, skin-breaking strength and weight of the granulation tissue were observed in animals treated by deoxyelephantopin as compared to its crude extract, suggesting that the significant wound healing property of *E. scaber* may be attributed to the presence of deoxyelephantopin (Singh et al., 2005).

In view of the use of *E. scaber* in ethnomedical application for overcoming pain on urination or dysuria, ethanol, hexane and chloroform extracts prepared from this plant were screened for their inhibitory activity on crude enzyme Na^+/K^+-ATPase from rat brain. Among these, only ethanol extract showed moderate diuretic potential with an IC_{50} of 25.4 µg/mL on Na^+/K^+-ATPase in rat brain microsome *in vitro* (Ngamrojanavanich et al., 2006). However, Poli et al. (1992) showed that oral treatment with up to 300 mg/kg of the extract did not influence hydration-induced diuresis in adult rats. On the other hand, despite the abundant ethnopharmaceutical information that reported on the use of *E. scaber* for stimulating diuresis, herbal tea of *E. scaber* given to a group of 10 healthy individuals did not show significant diuretic effect in a clinical trial (Laranja et al., 1991). Hence, the suitability of using ethanol extract as a diuretic could not be concluded as both ethnomedical information and *in vitro* enzymatic inhibitory effect are not sufficient for determining its diuretic potential. As ethanol extract of the whole plant was found to speed up the process of intestinal transition in mice as opposed to the antagonistic effect of aqueous extract (Poli et al., 1992), an evaluation on animal or human models would be a more conclusive evidence in asserting the ability of this extract in promoting diuresis and this is yet to be discovered. Besides, ethanol extracts yielded from both leaves and roots of this plant were also shown to possess antibacterial effect against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* (Valsaraj et al., 1997).

Phytochemical analysis of the whole plant ethanol extract of *E. scaber* revealed a number of secondary metabolites including some triterpenoids such as lupeol, sesquiterpene lactones (deoxyelephantopin, isodeoxyelephantopin, 17,19-dihydrodeoxyelephantopin, scabertopin, isoscabertopin and elescaberin), fatty acid esters (ethyl hexadecanoate, ethyl-9,12-octadecadienoate, ethyl-(Z)-9-octadecenoate, and ethyl octadecanoate), stigmasterol, stigmasterol glucoside, alkaloids, aurones, chalcones and a small amount of a phenolic compound (Sim and Lee, 1969; Liang et al., 2002; Singh et al., 2005; Than et al., 2005; Xu et al., 2006; Liang et al., 2008). Interestingly, all of the identified sesquiterpene lactones had been screened for their anti-cancer effect *in vitro* while deoxyelephantopin had also been examined for its anti-tumour effect *in vivo* (Table 1). Astonishing cytotoxic effects of the sesquiterpene lactones were depicted by their anti proliferative activity against a variety of cancer cell lines. In addition to its cytotoxicity towards various cancer cell lines and human cervical cancer xenograft model, deoxyelephantopin also promoted significant wound healing activity in mice (Singh et al., 2005).

Methanol extract

Another alcoholic solvent which is frequently used for extraction of secondary metabolites from *E. scaber* is methanol. In literature, methanol extract of this plant were shown to possess antimicrobial, anti-inflammatory and hypoglycemic activities. Only a few compounds isolated from this extract had been characterized, namely lupeol, stigmasterol and 11,13 dihydrodeoxyelephantopin (Silva et al., 1982) but no bioactivities of these compounds were further studied.

Diabetes mellitus is a major health threat to people all around the world and no satisfactory effective therapy has been discovered so far (Daisy et al., 2009). Adverse effects brought about by the commercially available therapeutic agents for treating diabetes such as insulin has gain an interest for the search of more effective therapeutic options from medicinal plants. Methanol extract of *E. scaber* had been reported as an effective hypoglycemic agent. Although its activity was reported to be low in a study comparing the hypoglycemic activity against STZ-induced diabetic rats treated by methanol, hexane and acetone extracts from the whole plant of *E. scaber* (Daisy et al., 2007), a comparison made between different leaf extracts showed that methanol leaf extract has the highest capacity of restoring hyperglycemic conditions of the diabetic rats back to near normal in comparison to the hexane and ethyl acetate extracts of *E. scaber* (Daisy et al., 2009). However, extraction from the root part was claimed to exert the best hypoglycemic effect among all methanolic extracts from *E. scaber* (Daisy and Jasmine, 2008).

In STZ-induced diabetic rats, hyperglycemic characteristics such as elevation of plasma glucose level and decline in serum insulin level and body weight were observed. In addition, lipid profile of the diabetic rats was also altered with increased level of triglycerides, LDL and VLDL and a decreased amount of HDL (Daisy and

Table 1. Sesquiterpene lactones from ethanol extract of *E. scaber* and their cytotoxic effect against various cancer cell lines *in vitro.*

Sesquiterpene lactones	Empirical formula	Cell lines	References
Elescaberin	$C_{20}H_{24}O_7$	Human hepatocarcinoma, SMMC7721	Liang et al., 2008
Isodeoxyelephantopin	$C_{19}H_{20}O_6$	Human hepatocarcinoma, SMMC7721, human cervical carcinoma, HeLa and human colon carcinoma Caco-2.	Liang et al., 2008; Xu et al., 2006
Deoxyelephantopin	$C_{19}H_{20}O_6$	Human hepatocarcinoma SMMC7721, human cervical carcinoma, HeLa, human colon carcinoma, Caco-2, melanoma derived cell line MEXF 394NL, mammary cancer cell line MAXF 401NL, human sarcoma W256 cells and human cervical cancer xenograft model*	Liang et al., 2008; Than et al., 2005; Xu et al., 2006
Isoscabertopin	$C_{20}H_{22}O_6$	Human cervical carcinoma, HeLa and human colon carcinoma Caco-2	Xu et al., 2006
Scabertopin	$C_{20}H_{22}O_6$	Human hepatocarcinoma SMMC7721, human cervical carcinoma, HeLa and human colon carcinoma Caco-2	Xu et al., 2006
17,19-dihydro deoxyelephantopin	$C_{19}H_{22}O_6$	Melanoma derived cell line MEXF 394NL and renal cell carcinoma RXF 944L.	Than et al., 2005

*Anti-tumour effect in mice model *in vivo.*

Jasmine, 2008; Daisy et al., 2009). The methanol extract from leaves and roots of *E. scaber* could significantly restore back these adverse effects to normal (Daisy and Jasmine, 2008). In addition, diabetes is always followed by occurrence of renal disease. The methanolic leaf extract of *E. scaber* significantly increased the reduced serum protein level and decreased the elevated urea, uric acid and creatinine levels of STZ-induced diabetic rats which corresponded to kidney dysfunction (Daisy et al., 2009).

Other than these parameters which are normally assessed in the discovery of antidiabetic function, Daisy and Jasmine (2008) also reported that insulin deficiency demonstrated adverse effect on glucose oxidation in liver and skeletal muscles of STZ-induced diabetic rats which could be related in part to a decrease in insulin secretion during diabetes. Methanol extract significantly decreased the rate of glucose oxidation and production of glycogen by the liver and muscles (Daisy and Jasmine, 2008; Daisy et al., 2009). These findings had showed that methanol extract of *E. scaber* does not only possess hypoglycemic activity but is also effective in reverting hypercholesterolemia and hypertriglyceridemia in diabetic rats.

The methanol extract of *E. scaber* exerted high inhibitory effect on the nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages but caused cytotoxicity when a high concentration (200 ug/mL) was tested. NO is produced by inducible nitric oxide synthase (iNOS) in macrophages during inflammatory reaction but can damage functional normal tissues or react with superoxide anion radical to form the even stronger oxidant peroxynitrite when produced excessively. Therefore, effective inhibition of NO by methanol extract of *E. scaber* represents a beneficial therapeutic strategy for anti inflammatory activity (Choi and Hwang, 2005).

Besides, methanol extract of *E. scaber* also showed antimicrobial activity. The extract was active against acid-fast bacterium *Mycobacter phlei* and Gram-positive bacteria such as *Bacillus subtilis*, *Bacillus cereus* and *Staphylococcus aureus* (Taylor et al., 1995; Wiart et al., 2004). It also showed inhibitory activity against dermatophytic fungi like *Microsporum gypseum* and *Trichophyton mentagrophytes* (Taylor et al., 1995). However, it could only partially inactivate Sindbis virus at the concentration of 100 g/ml in dark while active against human poliovirus-I, POLIO only in the presence of UV-A radiation (Taylor et al., 1996).

On the other hand, methanol extract of *E. scaber* also possess moderate antioxidant. The antioxidant property of leaf methanolic extract from *E. scaber* was evaluated by investigating on its free radical scavenging activity and reducing power. The extract showed medial antioxidant capacity with moderate electron donating activity and reducing capacity (Choi and Hwang, 2005).

Acetone extract

Other than ethanol extract, the acetone extract of *E. scaber* contains the highest number of compounds with studied bioactivities. Many of these compounds were discovered through fractionation of extract from their bio-

activity screening. For instance, the crude acetone extract of *E. scaber* was found to bring about a significant reduction in blood glucose levels and increased the lowered insulin concentrations in the STZ-induced hyperglycemic rats (Jasmine and Daisy, 2007; Daisy et al., 2009). In search of the functional compound that potentiates this satisfactory hypoglycemic activity, a new steroid–with anolide was identified. Unsurprisingly, the isolated compound yielded a more pronounced hypoglycemic and anti-diabetic effect than its crude extract (Jasmine and Daisy, 2007) which rendered it as a potential treatment for diabetes.

Likewise, screening of anti-bacterial effect against a variety of bacterial strains by using the acetone extract of *E. scaber* had shown that the extract demonstrated a broad-spectrum of activity against all the Extended Spectrum ß-Lactamase (ESBL) -producing multidrug-resistant strains tested. These include *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Citrobacter-freundii, Acinetobacter banumanii, Aeromonas hydrophila, Enterobacter aerogenes, Proteus mirabilis* and *Morganella morganii* (Jasmine et al., 2007b). ESBL production renders multiresistance to a wide range of bacteria. This is especially unfavourable to hospital outpatients who are more susceptible to infection by ESBL-producing bacteria (Jain et al., 2003). Bacteria conferring multiresistance imparts a serious threat to individuals by limiting therapeutic options as they are highly resistant towards many of the conventional antibiotics (Jasmine et al., 2007b). The acetone extract of *E. scaber* which showed noble inhibition against Methicillin resistant *Staphylococcus aureus* (MRSA) and Methicillin sensitive *S. aureus* (MSSA) had lead to the identification of a terpenoid, 6-[l-(10,13-dimethyl-4,5,8,9,10,ll,12,13,14,15,16,17-dodecahydro-lH-cyclopenta[a] phenanthren -17-yl)-ethyl]-3-methyl-3,6-dihydro-2 H-2- pyranone which contributed to the anti-bacteria activity against these two strains of ESBL-producing bacteria (Jasmine et al., 2007a). Further characterization of the novel terpenoid predicted that this compound imparts its antibacterial activity through inhibition of autolysin (Daisy et al., 2009). This was carried out through simulation of drug – receptor interactions using Computer –Aided Drug Design (CADD). The docking software deduced that the terpenoid can inhibit the activity of autolysin, a bacteriolytic enzyme that digest the cell wall peptidoglycon by forming a strong atomic interaction with the active site residues (Daisy et al., 2009). Identification of this compound would be advantageous in the discovery of a new drug against multidrug-resistance bacteria.

Moreover, phytochemical analysis had revealed that this extract also contains alkaloids, tannins, phenols, proteins, glycosides, saponins and other terpenoids and steroids (Jasmine et al., 2007a; Jasmine et al., 2007b). However, reports on detailed characterization of these phytoconstituents had been scarce thus far. Two sesquiterpene lactones, namely deoxyelephantopin and iso-17,19 dihydrodeoxyelephantopin were identified from chromatographic separation of the acetone extract of *E. scaber.* Both of these compounds showed cytotoxicity against melanoma derived cell line MEXF394NL (Than et al., 2005). Deoxyelephantopin exerted marked cytotoxicity towards the mammary cancer cell line MAXF 401NL while the activity of iso-17,19 dihydrodeoxyelephantopin was more pronounced in large cell lung cancer LXFL 529L (Than et al., 2005).

Aqueous extract

Aqueous extract is the most common orally taken extract regardless of plant species in folk medicine. As discussed above, water extract of *E. scaber* had also been used traditionally as emulsion or in a paste form for topical applications. In parallel to the traditional practices of using *E. scaber* for wound healing, anti-venom, anti-diabetic and anti-inflammation purposes, researches carried out on mice models had also proved these bioactivities in its water extract.

The aqueous extracts of roots and leaves from *E. scaber* portrayed excellent hypoglycemic effect in diabetic rats by lowering the blood glucose level and serum insulin level. A decrease in the elevated levels of glycosylated hemoglobin, liver glycogen, triglycerides and serum cholesterol in alloxan-induced hyperglycemic rats was also reported by Daisy et al. (2007). On the other hand, HDL level was enhanced and an improvement of kidney function in these rats was also observed (with reduction in the increased serum urea and creatinine production which is commonly associated with diabetes) (Daisy et al., 2007). On top of these, a remarkable unique feature shown by root and leaf aqueous extracts of *E. scaber* is worth noted where treatment with these extracts stimulated rejuvenation and regeneration of beta islet cells in pancreas of the hyperglycemic rats, prevailing over the treatment by insulin, a commercial diabetic drug, which showed no effect on the beta islet cells (Daisy et al., 2007).

Besides hypoglycemic activity in mice models, aqueous extract of *E. scaber* also showed significant anti-inflammatory effect in both experimental acute and chronic arthritis rat models. The aqueous extract from the whole plant significantly inhibited the development of pad swelling in the acute experimental arthritis rats at a dose of 300 mg/kg while higher concentration of the extract (500 mg/kg) was required to inhibit the development of chronic joint swelling in the chronic inflammatory model (Tsai and Lin, 1999). Also, hepatoprotective effect of this extract had also been examined. The administration of this extract decreased the serum glutamate-oxalate-transaminase (SGOT) and serum glutamatepyruvate-transaminase (SGPT) levels in the rats with β-D-galactosamine (D-Ga1N)- and acetaminophen (APAP)-

induced acute hepatic damage. Pathological changes of hepatic lesions were also recovered following treatment with the extract (Lin et al., 1995).

The aqueous extract of *E. scaber* is not only applicable for oral administration but is also useful when applied externally. The extract induced wound healing effect in excision, incision and dead space wound models in rats when applied topically (Singh et al., 2005). Besides, the water extract was also scientifically proved to posses anti venom effect against snake from the species *Bothrops jaracaca* (Houghton and Osibogun, 1993) which could be due to the presence of lupeol and epifriedelinol in the extract that are capable of interacting with the target receptors and enzymes to neutralize the effects of snake venoms of the jararaca (Walter et al., 2000).

In Taiwan, hot water extract from the whole plant of *E. scaber* was studied for its anti-bacterial effect against serotypes c and d of *Streptococcus mutans*, a group of bacteria which causes dental caries in humans (Grossi et al., 1983). The extract showed strong antibacterial effect towards type c while intermediate inhibitory effect was observed against type d. The difference in susceptibility to treatment was said to be due to the individual characteristics of the glucan that are synthesized by these serotypes. Unlike the water-insoluble glucan produced by type d of *S. mutans*, dextransucrase synthesized by type c of *S. mutans* is water-soluble in the presence of sucrose and may diffuse into the surrounding environment thereby reducing its protective activity.

Other extracts

Both hexane extract and ethyl acetate extract of the *E. scaber* showed hypoglycemic effect towards STZ-induced hyperglycemic rats. Both these extract increased body weight of the rats after treatment and successfully restored plasma glucose and serum insulin levels to near normal. Besides, other parameters such as the elevated total cholesterol, triglycerides, LDL, VLDL, glycosylated hemoglobin, urea, uric acid and creatinine content that were increased as a consequence of hyperglycemia were effectively reduced while the decline in HDL, liver glycogen and muscle glycogen content were reverted back to normal level (Daisy et al., 2009).

In addition to hypoglycemic effect, ethyl acetate extract of the plant also showed activity against a range of bacteria including *Bacillus cereus*, *Bacillus pumilus*, *Bacillus subtilis*, *Bordetella bronchiseptica*, *Escherichia coli*, *Klebsiella pneumonia*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermis* and *Streptococcus faecalis* at 4 mg/ml concentration. However, lower concentrations of the extract showed concentration-dependent inhibition and no activity against all these bacteria was observed at a concentration of 1 mg/ml (Avani and Neeta, 2005). In addition, petroleum ether extract of this plant was also used for screening the same array of bacteria but the extract showed a very weak antibacterial activity where only *Micrococcus luteus* showed susceptibility to its inhibitory effect when a concentration of higher than 2 mg/ml was applied (Avani and Neeta, 2005).

Although chloroform extract of *E. scaber* had not been assayed for its bioactivities, two compounds, namely deoxyelephantopin and isodeoxyelephantopin, which were isolated from the extract, were shown to portray anti-inflammatory activity. Isodeoxyelephantopin was found to down-regulate the expression of a number of NF-κB regulated gene products including those involved in cell proliferation (COX-2, cyclin D1 and c-Myc), invasion (MMP-9 and ICAM-1) and antiapoptosis (IAP1, IAP2, Bcl-2, Bcl-xL, Bfl-1/A1, TRAF1, FLIP and survivin) as well as enhancing the apoptotic effects of tumor necrosis factor(TNF). As isodeoxyelephantopin could inhibit the activation of NF-κB by a variety of inflammatory agents and in a wide range of cell lines, it is likely that isodeoxyelephantopin potentiates apoptosis through the suppression of antiapoptotic gene products regulated by NF- κB. Hence, isodeoxyelephantopin is not only applicable for effective chemoprevention purposes but can also be used as a therapeutic agent for healing a variety of NF-κB-linked proinflammatory diseases (Ichikawa et al., 2006).

Essential oil and light petroleum extract of *E. scaber* had also been subjected to chemical constituent analysis. Chromatography analysis revealed that light petroleum extract contains epifriedelinol, lupeol, stigmasterol and a mixture of triacontan-l-01 and dotriacontan-l-01 (Sim and Lee, 1969) while the essential oil of the whole plant of *E. scaber* yielded cyclosativene, copaene, isopropyl dimethyl hexahydronaphthalene, trimethyl dimethylene-decahydronaphthalene, zingiberene, β-Caryophyllene, caryophyllene, dimethyl-6-(4-methyl-3-pentenyl)-2-norpinene, β-Sesquiphellandrene, isocaryophyllene, α-Santalol, ledol, α-Bisabolol, caryophyllene β-Bisabolol, isopropyl dimethyl tetrahydronaphthalenol, cadinol, oxide, hexahydrofarnesyl acetone, hexadecanoic acid, phytol, octadecadienoic acid, n-tetradecane, n-pentadecane, n-hexadecane, n-heptadecane, n-octadecane and tetramethylhexadecenol (Wang et al., 2004, 2005).

PRECAUTION, SAFETY AND TOXICITY OF *Elephantopus scaber*

In the practice of traditional medicine, *E. scaber* should not be prescribed for pregnant women and should be prescribed at low concentration for children (Bhattarai, 1989). This was supported by Poli et al. (1992) who reported that no LD_{50} was obtained for p.o. of both ethanolic and water extracts of *E. scaber* up to 6 g/kg. However, intraperitoneal injection of water, ethanolic and acetone extracts induced writhing, loss of muscle tone, ataxia, prostration, mild liver central venous congestion

and death with LD_{50} approximate 2 g/kg (Poli et al., 1992; Lin et al., 2005; Daisy et al., 2009). *In vitro* studies showed that *E. scaber* was toxic to African green monkey kidney cell line, Vero (Taylor et al., 1996) and on RAW264.7 cells (Choi and Hwang, 2005) at 200 µg/ml and did not contribute to the recovery of acetaminophen-induced nephrotoxocity on transformed primary embryonal kidney cell line, HEK 293. However, all of the above *in vitro* studies utilized the transformed cell line rather than normal primary cultured cell. Thus, cytotoxicity effect of various extract of *E. scaber* should be further tested with normal and primary cultured cell to confirm the possible mode of toxicity. Chen and Deng (2005) found that ethanol extract of *E. scaber* did not lead to irritation on rabbit's eyes. However, no detailed information of the concentration was stated in their study. To validate this result, we have tested the acute irritation potential of *E. scaber* ethanol extract on human, dog, rabbit and chicken red blood cell lysis assay. The extract can be classified as non-irritated since no red blood cells lysis was observed up to 300 µg/ml of extract (unpublished data).

PATENTS AND COMMERCIALIZATION POTENTIAL

The objectives for natural product research and development not only contribute to the global awareness of safety and bioactivities of herbs which are widely used in certain ethnic but also can contribute to the buildup of personal or national wealth for those who put effort to study, patent, commercialize and market that particular natural product.

In Chinese traditional medicine, 3 products were formulated with *E. scaber* work as one of the important active ingredients.

Teng-Khia-U (*E. scaber, E. mollis* and *Pseudoelephantopus spicatus*) is a Taiwan traditional medicine formulated for treating nephritis, edema, dampness, chest pain, fever/cough of pneumonia and scabies/ arthralgia that was caused by wound. Researches have showed that Teng-Khia-U possessed hepatoprotective and anti-inflammatory activity (Lin et al., 1995; Tsai and Lin, 1999).

Yi-Gan-Yin (15 g of *E. scaber; Hedyotis diffusa* Willd. 20 g, *Scutellariae Barbatae* 15 g, *Rabdosia serra* (Maxim) Hara 15 g, *Polygonum cuspidatum* Sieb. et Zucc. 12 g, *Radix Sophorae Tonkinensis* 15 g, *Ganoderma lucidum* (Leyss. ex. Fr.) Karst. 12 g, *Panax notoginseng* (Burk.) F. H. Chen, 5 g, *Astragalus henryi* 20 g, *Pseudostellaria heterophylla* 30 g, *Salvia miltiorrhiza* Bge. 12 g, *Curcuma longa* 12 g, *Radix Paeoniae Alba* 15 g, *Rhizoma Sparganii* 6 g, *Rhizoma Curcumae* 6 g, *Concha Ostreae* 20 g, *Carapax Trionycis* 15 g, *Radix Glycyrrhizae* 5 g, *Opsithoplatia orientalis* Burmeiter 8 g, *Bupleuri Radix* 9 g) is a formulated herb which was antihepatitis B, immunomodulator, antiinflammatioon, liver protection (prevent or treat liver cancer, liver hemangioma, fatty liver and cirrhosis) (Li, 2006).

Dang Gui Lu Hui Wan (*E. scaber, Angelica sinensis* (Oliv.) Diels, *Aloe vera* L., *Saussurea lappe* Clarke, *Scutellaria baicalensis* Georgi, *Phillodendron chinensis* Schneid., *Coptis chinensis* Franch, *Gardenia jasminoides* Ellis, *Rheum palmatum* L., *indigofera tinctoria* L. and *Moschus moschiferus*. L.) which has entered into phase I and II clinical trials was able to improve the chemotherapy on patients with Chronic Myeloid Leukemia (CML) (Han, 1988).

Plenty of herbal formulation with the presence of *E. scaber* as an important active ingredient has been patented for different therapeutic purpose. Solanki (2003, 2004) has patented 2 different herbal formulations with 5% of root and stem of *E. scaber* which benefit the cancer patients. The first formulation which comprises *Tinospora cordifolia* (40%), *Chlorphyton borivilianum* (15%), *Curcuma longa* (10%), *Asparagus racemosus* (10%), *Hygrophila auriculata* (10%), Achyranthus aspera (10%) and *E. scaber* (5%) was claimed to be beneficial to patients with myeloma through prevention of development of drug resistance to cancer, promote patient's health and reduce side effect after chemotherapy and radiotherapy (Solanki, 2003). The second formulation which comprises *Withania somnifera* (10%), *Chlorphyton borivilianum* (5%), *Boerhavia diffusa* (10%), *E. scaber* (5%), *Moringa oleifera* (10%), *Tecoma undulata* (10%), *Bauhinia purpurea* (10%), *Ficus racemosa* (5%), *Cyperus rotundus* (10%), *Sphaeranthus acmella* (5%) and *Tinospora cordifolia* (20%) was claimed to be beneficial to lung cancer patients with metastasis through maintain or reduce of tumor size, promote patient's health and reduce side effect after chemotherapy and radiotherapy at 450 mg three times per day (Solanki, 2004).

Besides as major ingredient in anticancer remedy, *E. scaber* has also been formulated and patented with other herbs to treat acne. Lee (2005) has formulated an anti-inflammatory and anti-infection water extract of herbal solution which comprise dandelion (0.5 - 5%), Seneca (0.1 - 6%), *E. scaber* (0.1 - 5%), *Lonicerae japanicae* (0.1-4%), *Fragrant angelica* (0.1 - 5%), *Scutellariae baicalensis* radix (0.1 - 5%) and *Hamamelis virginiana* L. (0.1 - 6%) with the present of three transdermal agents: benzyl alcohol (0.1 - 5%), propylene glycol (0.1 - 10%) and ethyl alcohol (1 - 20%). This herbal formulation was able to cure acne through killing the bacteria in hair follicle and sebaceous glands and reduced the inflammation from pilosebaceous unit within 3 to 5 days. Other than that, Hozumi et al. (1995) have also patented the antiviral activity of leaves water extract of *E. scaber* against polio and measles virus at the concentration range from 100 to 500 µg/mL.

Although plenty of researches and patents have been filed, until today, no product (either crude extract of *E. scaber* or the compounds isolated from the plant can be found in the international market. Thus, inventors who are

interested in this plant should focus on optimizing the plantation, product formulation base on the current available scientific information and more importantly educate the market about the value of this plant.

CONCLUSION

For centuries, natural products had been used as remedies in traditional medicine worldwide. Other than the ability to cure common injuries such as for wound healing and inflammation prevention, herbal medicine is also applied for treating acute and chronic diseases in some nations. The use of herbs as medicine which can be traced back as early as a few centuries ago had given it a token of credibility in their safety, efficacy and cultural acceptability (Kamboj, 2000). Besides, the mass media also plays an important role in publicizing the putative healing effects of herbs to the public as well as in increasing their awareness towards these products (Chang, 2000). Nevertheless, many commercial drugs used for treating various diseases have their origins from the higher plants. Ethnopharmacological knowledge serves as an important tool for the discovery of medicinal property of natural products. However, bioactivity screening and clinical toxicity tests are also equally valuable for proving the efficacy and suitability of these products for medicinal principle in humans. Hence, this paper focuses on the review of numerous applications of *E. scaber* in folk medicine as well as the bioactivities shown by the varied extracts and respective compounds of this plant. Bioactivity screening of the extracts and their compounds had shown that *E. scaber* possess wound healing, anti-venom, anti-microbial, anti-inflammatory, anti-diabetic, cytotoxic and anti-tumour activities. These studies had also successfully identified some compounds like deoxyelephantopin, isodeoxyelephantopin, scabertopin, isoscabertopin, elescaberin, 17, 19-dihydrodeoxyelephantopin and a terpenoid which showed a broad range of biological functions. Besides, the commercialization potential of *E. scaber* is also witnessed in its embracement in a number of patents and traditional medicine. As evidenced by the biological activities of *E. scaber* that have been revised in this review, it is certain that this plant is an invaluable source for medicinal applications in a broad spectrum of health disorders. Further pharmacological evaluation as well as compound isolation and characterization from this herb would serve as an interesting focus for future studies and in product commercialization.

ACKNOWLEDGEMENT

We would like to thank Mr. Lim Chung Lu for his kindness in the preparation of plant photo, plant identification and herbarium deposition.

REFERENCES

Avani K, Neeta S (2005). A study of the antimicrobial activity of *Elephantopus scaber*. Indian J. Pharmacol. 37: 126-128.

Ayyanar M, Ignacimuthu S (2005). Traditional knowledge of Kani tribals in Kouthalai of Tirunelveli hills, Tamil Nadu, India. Indian J. Pharmacol. 102: 246-255.

Balachandran P, Govindarajan R (2005). Cancer: An ayurvedic perspective. Pharmacol. Res. 51: 19-30.

Behera SK, Misra MK (2005). Indigenous phytotherapy for genitor-urinary diseases used by the Kandha tribe of Orissa. Indian J. Pharmacol. 102: 319-325.

Bhandary MJ, Chandrashekar KR, Kaveriappa KM (1995). Medical ethnobotany of the Siddis of Uttara Kannada district, Karnataka, India. Indian J. Pharmacol. 47: 149-158.

Bhattarai NK (1989). Traditional phytotherapy among the sherpas of Helambu, central Nepal. J. Ethnopharmacol. 27: 45-54.

Chang J (2000). Medicinal herbs: Drugs or dietary supplements? Biochem. Pharmacol. 59: 211–219

Chen JJ, Deng XJ (2005). Distribution and utilisation of Chinese herb *Elephantopus scaber* in Guang Dong. J Zhanjiang Ocean Univ 25(3): Available from: http://scholar.ilib.cn/A-zjhydxxb200503023.html

Choi EM, Hwang JK (2005). Screening of Indonesian medicinal plants for inhibitor activity on nitric oxide production of RAW264.7 cells and antioxidant activity. Fitoterapia 76: 194-203.

Daisy P, Jasmine R (2008). Role of *Elephantous scaber* on the glucose oxidation in liver and skeletal muscles of streptozotocin (STZ) induced diabetic adult male rats. Res. J. Med. Plants 2: 22-27.

Daisy P, Jasmine R, Ignacimuthu S, Murugan E (2009). A novel steroid from *Elephantopus scaber* L. an ethnomedicinal plant with antidiabetic activity. Phytomedicine 16: 252-257.

Daisy P, Rayan NA, Rajathi D (2007). Hypoglycemic and other related effects of *Elephantopus scaber* extracts on alloxan induced diabetic rats. J. Biol. Sci. 7: 433-437.

Daniel M (2006). Medicinal plants: chemistry and properties. Science Publishers Enfield, New Hampshire 03748, pp: 85-86.

Griggs JK, Manandhar NP, Towers GHN, Taylor RSL (2001). The effects of storage on the biological activity of medicinal plants from Nepal. J. Ethnopharmacol. 77: 247-252.

Grossi S, Prakobphol A, Linzer R, Campell LK, Knox KW (1983).Characterization of serological cross-reactivity between polysaccharide antigens of *Streptococcus mutans* serotypes C and D. Infect. Immun. 39: 1473-1476.

Gurib-Fakim A, Sewraj M, Guehoh J, Dulloo E (1993). Medicalethnobotany of some weeds of Mauritius and Rodrigues. J. Ethnopharmacol. 39: 175-185.

Hammer MLA, Johns EA (1993). Tapping an Amazonian plethora: four medicinal plants of Marajo Island, Para (Brazil). J. Ethnopharmacol. 40: 53-75.

Han J (1988). Traditional Chinese medicine and the search for new antineoplastic drugs. J. Ethnopharmacol. 24: 1-17.

Houghton PJ, Osibogun IM (1993). Flowering plants used against snakebite. J. Ethnopharmacol. 39: 1-29.

Hozumi T, Matsumoto T, Ooyama H, Mamba T, Shiraki K, Hattori M, Kurokawa M, Kadota S (1995). Antivaral agent containing crude drug., Antivaral agent containing crude drug. United State Patent No. US 5,411,733.

Ichikawa H, Nair MS, Takada Y, Sheeja DBA, Kumar MAS, Oommen OV, Aggarwal BB (2006). Isodeoxyelephantopin, a novel sesquiterpene lactone, potentiates apoptosis, inhibits invasion and abolishes osteoclastogenesis through suppression of nuclear factor-kB (NF-kB) activation and NF-kB-regulated gene expression. Clin. Cancer Res. 12: 5910-5918.

Inta A, Shengji P, Balslev H, Wangpakapattanawong P, Trisonthi C (2008). A comparative study on medicinal plants used in Akha's traditional medicine in China and Thailand, cultural coherence or ecological divergence? J. Ethnopharmacol. 116: 508-517.

Jagadeesh Singh SD, Krishna V, Vidya SM, Manjunath BK, Mankani KL, Shankarmurthy K (2004). Micropropagation of *Elephantopus scaber* through leaf segments. J. Trop. Med. Plants. 5(2): Avilable from: http://www.tropmedplants.com/article.php?aid=192

Jain A, Roy I, Gupta MK, Kumar M, Agarwal SK (2003). Prevalence of

extended-spectrum {beta}-lactamase-producing Gram-negative bacteria in septicaemic neonates in a tertiary care hospital. J. Med. Microbiol. 52: 421-425.
Jasmine R, Daisy P (2007). Effect of crude extract and fraction from *Elephantopus scaber* on hyperglycemia in Streptozotocin-diabetic rats. . Int. J. Biol. Chem. 1: 111-116.
Jasmine R, Daisy P, Selvakumar BN (2007). Evaluating the antibacterial activity of *Elephantopus scaber* extracts on clinical isolates of a-lactamase producing methicillin resistant *Staphylococcus aureus* from UTI patients. Int. J. Pharmcol. 3: 165-169.
Jasmine R, Daisy P, Selvakumar BN (2007). A novel terpenoid from *Elephantopus scaber* with antibacterial activity against beta-lactamase-producing clinical isolates. Res. J. Microbiol. 2: 770-775.
Kamboj VP (2000) Herbal medicine. Current Science 78: 35-39.
Kurokawa T, Nakanishi K (1970). Deoxyelephantopin and its interrelation with elephantopin. Tetrahedron Let. 33: 2863-2866.
Laranja SM, Bergamaschi CM, Schor N (1991). Evaluation of acute administration of natural products with potential diuretic effects, in humans. Mem. Inst. Oswaldo Cruz. 86: 237-240.
Lee W (2005). Treatment of acne by topical herbal extract solution. United State Patent No. US 2005/0084473 A1.
Li YY (2006). 321 cases clinical observation of chronic hepatitis B and liver cirrhosis treated with "Yi Gan Yin". Med. Magaz. China 3: 92-93.
Liang QL, Min ZD, Cheng L (2002). Studies on the two dipepetides from *Elephantopus scaber*. J. Chinese Pharmacol. Univ. 33: 178.
Liang QL, Min ZD, Tang YP (2008). A new elemanolide sesquiterpene lactone from *Elephantopus scaber*. J. Asian Nat. Prod. Res. 10: 403-407.
Lin CC, Tsai CC, Yen MH (1995). The evaluation of hepatoprotective effects of Taiwan folk medicine 'Teng-Khai-U'. J. Ethnopharmacol. 45: 113-123.
Lin HY, Chen JJ, Wu QX, Chen HX (2005). Study on acute and subacute toxicities of extract from *Elephantopus scaber*. Prog. Vet. Med. 26: 69-91.
Manandhar NP (2002) Plants and people of Nepal. Timber Press, Inc. Portland, Oregon
Mors WB, Nascimento MC, Pereira BMR, Pereira NA (2000). Plant natural products active against snake bite-the molecular approach. Phytochemistry 55: 627-642.
Ngamrojanavanich N, Manakit S, Pornpakakul S, Petsom A (2006). Inhibitory effects of selected Thai medicinal plants on Na^+K^+ATPase. Fitoterapia 70: 10-14.
Ong HC, Nordiana M (1999). Malay ethno-medico botany in Machang, Kelantan, Malaysia. Fitoterapia 70: 502-513.
Ong HC, Nordiana M (1999). Malay herbal medicine in Gemencheh, Negeri Sembilan, Malaysia. Fitoterapia 70: 10-14.
Panda H (2004). Handbook on Medicinal Herbs with uses. Asia Pacific Business Press, Delhi, India. Pp. 510.
Pattanaik C, Reddy CS, Murthy MSR (2008). An ethnobotanical survey of medicinal plants used by the Didayi tribe of Malkangiri district of Orissa, India. Fitoterapia 79: 67-71.
Poli A, Nicolau M, Simoes CMO, Nicolau RMR, Zanin M (1992). Preliminary pharmacologic evaluation of crude whole plant extracts of *Elephantopus scaber*. Part I: *in vivo* studies. J. Ethnopharmacol. 37: 71-76.
Rasoanaivo P, Petitjean A, Ratsimamanga-Urverg S, Rakoto-Ratsimamanga A (1992). Medicinal plants used to treat malaria in Madagascar. J .Ethnopharmacol. 37: 117-127.
Ridley HN (1922). Flora of Malay Peninsula Ed, Published under the Authority of the Government of the Straits Settlements and Federated Malay states, London.
Shaw PC, Wang J, But PPH (2002). Authentication of Chinese medicinal material by DNA technology.World Scientific Publishing Co. Pte. Ltd., Farrer Road, Singapore. Pp. 244.
Silva LBD, Herath WHMW, Jennings RC, Mahendran M, Wannigama GE (1982)A new sesquiterpene lactone from *Elephantopus scaber*. Phytochemistry 21: 1173-1175.
Sim KY, Lee HT (1969). Constituents of *Elephantopus scaber* (*Compositae*). Phytochemistry 8: 933-934.
Singh SDJ, Krishna V, Mankani KL, Manjunatha BK, Vidya SM, Manohara YN (2005). Wound healing activity of the leaf extracts and deoxyelephantopin isolated from *Elephantopus scaber* Linn. Indian J. Pharmacol. 37: 238-242.
Solanki R (2003). Herbal Formalation, United State Patent No. US 2003/0147896 A1.
Solanki R (2004). Herbal formalation, United State Patent No. US 2004/0009240 A1.
Taylor RS, Manandhar NP, Towers GHN (1995). Screening of selected medicinal plants of Nepal for antimicrobial activities. J. Ethnopharmacol. 46: 153-159.
Taylor RSL, Manandhar NP, Hudson JB, Towers GHN (1996). Antiviral activities of Nepalese medicinal plants. J. Ethnopharmacol. 52: 157-163.
Than NN, Fotso S, Sevvana M, Sheldrick GM, Fiebig HH, Kelter G, Laatsch H (2005). Sesquiterpene lactones from *Elephantopus scaber*. Z. Naturforsch. 60: 200-204.
Tsai CC, Lin CC (1999). Anti-inflammatory effects of Taiwan folk medicine 'Teng-Khia-U' on carrageenan-and adjuvant-induced paw edema in rats. J. Ethnopharmacol. 64: 85-89.
Valsaraj R, Pushpangadan P, Smitt UW, Adsersen A, Nyman U (1997). Antimicrobial screening of selected medicinal plants from India. J. Ethnopharmacol. 58: 75-83.
Walter BM, Maria CN, Bettina MRP, Nuno AP (2000). Plant natural products active against snake bite - the molecular approach. Phytochemistry 55: 627-642.
Wang L, Jian S, Nan P, Liu J, Zhong Y (2004). Chemical composition of the essential oil of *Elephantopus scaber* from southern China. Z. Naturforsch. 59: 327-329.
Wang L, Jian S, Nan P, Liu J, Zhong Y (2005). Chemotypical variability of leaf oils in *Elephantopus scaber* from 12 locations in China. Chem. Nat. Compd. 41: 491-493.
Wiart C (2006). Ethnopharmacology of medicinal plants: Asia and the Pacific Humana Press, Totowa, New Jersey. Pp. 228.
Wiart C, Mogana S, Khalifah S, Mahan M, Ismail S, Buckle M, Narayana AK, Sulaiman M (2004). Antimicrobial screening of plants used for traditional medicine in the state of Perak Peninsular Malaysia. Fitoterapia 75: 68-73.
Wright CI, Buren LV, Kroner CI, Koning MMG (2007). Herbal medicines as diuretics: a review of the scientific evidence. J. Ethnopharmacol. 114: 1-31.
Xu G, Liang Q, Gong Z, Yu W, He S, Xi L (2006). Antitumor activities of the four sesquiterpene lactones from *Elephantopus scaber* L. Exp. Oncol. 28: 106-109.