



(REVIEW ARTICLE)



## Utilization of *Elephantopus scaber* as traditional medicine and its bioactivity

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### Abstract

*Elephantopus scaber* has been used various ethnic groups in Indonesia and other countries as traditional medicine. Comprehensive study of the bioactivity of *E. scaber* is still limited, therefore this paper aims to explain the relationship between the use and its bioactivity. The writing of this article is based on a study of literature published online and offline used keywords *E. scaber*, bioactivities of *E. scaber* and uses of *E. scaber*. Ethnobotanically, *E. scaber* used to treat wound, nephritis, edema, chest pain, fever, scabies, sores, coughs, tonics, fever, and bronchitis, and asthma. The local communities in China, *E. scaber* leaves have been developed into "tea" to cure various diseases. The bioactivity of *E. scaber* is anti-bacterial, anti-fungal, anticancer, hepatoprotective, stimulates hair growth, anti-diabetes mellitus, anti-wound, antioxidant, and overcoming kidney disorders. Deoxyelephantopin is one of the main sesquiterpenes lactones derived from *E. scaber* has anti-cancer anticancer development. The development of *E. scaber* tea as an anti-cancer needs to be further investigated because this plant is very easy to find in Indonesia.

**Keywords:** *Elephantopus scaber*; Anti-microbial; Anti-cancer; Deoxyelephantopin

### 1. Introduction

Plants are main sources in the development of medicines. The development of medicinal compounds is based on the use of local communities in various parts of the world. Various facts show that the human need for medicinal substances continues to increase. This is related to the emergence of new diseases that were previously unknown and also the resistance of microorganisms to circulating drugs. Various methods have been used by scientists to obtain new plants or compounds, including through ethnobotany studies and bioactivities tests. Ethnobotany is a study of the use of plants by local communities, including medicinal plants. Purwanto (1) stated that ethnobotany is an efficient and cost-effective way of developing medicinal plants.

*Elephantopus scaber* (ES) is a herb that is very easy in the surrounding environment such as in yards, roadsides, and home gardens and is often considered a weed. By various community groups in Indonesia and other countries, ES used as traditional medicine (2). Silalahi et al (2) stated that the Batak Simalungun sub-ethnic group in North Sumatra, ES leaves have been used to treat wounds. Kabiru and Por (3) stated that the benefits of ES are even wider, namely the treatment of nephritis, edema, chest pain, fever, scabies, wounds, coughs, tonics, febrifuge, and bronchitis, and asthma.

The use of plants as traditional medicines is related to their bioactive compounds, known as phytochemicals. Kabiru and Por (3) stated that ES contains various phytochemical compounds such as flavonoids, terpenoids, saponins, tannins, carbohydrates and proteins. There are many bioactive compounds contained in ES so that Ho et al (4) stated that ES has been developed into "tea" in China to cure various diseases and health drinks. Unlike the case in Indonesia, ES has not

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been developed commercially. The development of ES as a commercial herb in Indonesia has not been widely carried out, it is suspected that it is related to research that has not been done much in Indonesia. To scientifically confirm the bioactivity of plants, bioassays can be done. Comprehensive information regarding the use of plants both ethnobotany and based on bioactivity will help the public's understanding of medicinal plants and their prospects for development.

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## 2. Material and methods

The writing of this article is based on literature review on various scientific articles and books published online and offline. The literature published online, it is obtained from Google Scholar, Scopus and scientific journals using the keyword ES, and bioactivities ES. The articles we obtained were reviewed, but we refer only to those relating to the use and bioactivity of ES. The information obtained was synthesized so that it could explain the benefits and bioactivity of ES.

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## 3. Results and discussion

The articles we obtained were reviewed, but we refer only to those relating to the use and bioactivity of ES. From our search, we found 28 literatures relating to the use and bioactivity of ES. We extract and arrange the studies we obtain so that the information is solid and detailed.

Taxonomically, ES belongs to the Asteraceae, but its flower character is very different from other Asteraceae which is characterized by the presence of ray and tube flowers. In Indonesia, those plants are easily found in the environment along roadsides, yards, home gardens and on the edges of rice fields. *Elephantopus scaber* is a herbaceous with leaves that form a rosette (Figure 1), with a white corolla.



**Figure 1** Habitus of *Elephantopus scaber* with inflorescence (personal documentation)

*Elephantopus scaber* has long been used by local people in Indonesia and in other countries and has also been traded as "tea" especially in China. Ethnobotany ES is used as an antipyretic, cardiotonic, dysuria, diarrhea, dysentery, abdominal pain, and diuretic (5), fever medicine, chest pain medication, pneumonia, scabies, and leukemia (6). In Taiwan ES is used in the treatment of fever, diarrhea, dysentery, and abdominal pain, and is a diuretic (7), while in China it is used to treat headaches, colds, diarrhea, hepatitis, and bronchitis (8). ES has long been used as a medicine to treat various diseases such as cancer, diabetes mellitus, edema, gastric disorders, leucorrhea, rheumatism, fever, and scabies (9).

The use of plants as medicine is related to the presence of bioactive compounds produced by plants, including ES. Deoxyelephantopin (DET) and isodeoxyelephantopin (isoDET) can be isolated from the ethyl acetate fraction of ES leaves (10). Several compounds that have also been isolated from ES, such as deoxyelephantopin, 11,13, dihydrodeoxy-

elephantopin, lupeol, epifriedelinol and stigmasterol (6). Deoxyelephantopin (DET) is one of the main sesquiterpene lactones derived from ES which has anti-cancer properties (10). Compounds isolated from ES have bioactivity as anti-bacterial, anti-fungal, anti-cancer, hepatoprotective, stimulate hair growth, anti-diabetes mellitus, anti-wound, anti-oxidant, anti-neuroinflammatory and treat kidney disorders.

### 3.1. Antibacterial

Various types of microbes are pathogenic to humans so that they can cause various types of diseases. Compounds that inhibit microbial growth are called anti-microbial compounds. The use of ES as an anti-microbial has been widely reported in both bacteria and fungi (11-13). In laboratory experiments, the anti-microbial activity can be measured using the minimum inhibitory concentration (MIC).

The ES extract has been shown to be able to inhibit the growth of Gram positive and Gram negative bacteria (11). ES extracts inhibit growth of Gram-positive bacteria {*Staphylococcus aureus* (11,14), *Bacillus subtilis* (11,12), *Micrococcus luteus* and *Bacillus cereus* (11)} and Gram negative {*Escherichia coli* (11,12,14), *Pseudomonas aeruginosa* (11,14), *Proteus vulgaris* and *Salmonella typhi* (11), *Salmonella paratyphi*, *Klebsiella pneumoniae*, *Shigella sonnei*, *Salmonella typhimurium* (14), *Pseudomonas aeruginosa*, *Proteus vulgaris* (12)}.

The anti-bacterial activity of ES varies and is strongly influenced by concentration (11). MIC values for Gram-positive bacteria range from 50 to 500 µg/mL and for Gram-negative bacteria from 100 to 500 µg/mL (11). At a concentration of 100 µg / disc using the disk diffusion method showed significant antibacterial activity and was compared with chloramphenicol (30 µg / disc) (12). ES plant fractions have steroids, triterpenoids, saponins, flavonoids, carbohydrates, glycosides, and essential oils.

### 3.2. Antifungal

Various microscopic fungi cause disease in humans. The bioactivity of ES as an anti-fungal has been reported by Kamalakannan et al (14). ES leaf extract inhibits the growth of *Aspergillus niger* (12,14), *Aspergillus flavus*, *Rhizopus indicus*, *Mucor indicus*, *Mucor* sp. (13), *Candida albicans*, and *Aspergillus clavatus* (11).

For the antimicrobial test, a well diffusion technique was used and the zone of inhibition of microorganisms was measured in mm (14). The ES methanolic extract showed maximum antifungal activity of 32 mm inhibition zone recorded from 200 mg of extract against *Mucor indicus* and a minimum of 14 mm with 50 mg of extract against *Rhizopus indicus* (14). The antifungal activity of *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* with concentrations ranging from 200-1000 µg/mL (11). Phytochemical analysis revealed the presence of alkaloids, flavonoids, saponins, tannins, phenols, proteins and carbohydrates in various concentrations (13). In the study of anti-microbial activity all fractions showed a good zone of inhibition of *Candida* spp.

### 3.3. Anticancer

The search for new anticancer drugs continues in the hope of finding compounds that cause fewer cancer cells, without causing damage to non-cancerous cells. Natural compounds from plants are believed to have relatively minor side effects (15,16). Cancer is one of the main causes of death in humans. Until now, the compounds used as anti-cancer agents are compounds that have a very complex structure and most of them are extracted directly from plants. Although there have been many commercial anti-cancer compounds such as taxol, vinblastine, and vincristine, the search for new compounds is still underway. Cancer is a disease caused by uncontrolled cell growth that is thought to be caused by gene mutations and is widely associated with free radicals, therefore compounds that are anti-free radicals are compounds that have the potential to act as anti-cancer.

In laboratory experiments, N-Nitrosodiethylamine used to induce hepatocellular carcinoma in mice (17). ES is a type of plant as an anti-cancer. The use of ES as an anti-cancer has been widely reported, among others (6,8,16,17). Histopathological and immunohistochemical studies for cancer markers namely Proliferating Cell Nuclear Antigen (PCNA), vascular endothelial growth factor (VEGF) and Cyclin D1 were performed on liver tissue to confirm the anti-cancer properties of ES extract. Methanol extract ES with doses (100 mg/kg and 200 mg/kg) given to mice that have been induced by NDEA (0.02% in water) or liver cancer in male Wistar rats showed activity as anti-cancer (16).

The deoxyelephantopin and isodeoxyelephantopin compounds from the ES extract caused a reduction in the viability of L-929 tumor cells in 72 h culture (IC<sub>50</sub> values 2.7 µg/mL and 3.3 µg/mL) and activity was influenced by concentration. These two compounds act selectively on silent and stimulated human lymphocytes and inhibit the tritiated incorporation of thymidine into the cellular DNA of DLA tumor cells. The deoxyelephantopin compound at a

concentration of 3 µg/mL caused maximum apoptotic cells. It also demonstrated significant *in vivo* antitumor efficacy against DLA tumor cells. ES shows the antiproliferative properties of deoxyelephantopin and isodeoxy-elephantopin can be used to treat tumors with broad proliferative potential (16).

Deoxyelephantopin (DET) is one of the main sesquiterpene lactones derived from ES which has anti-cancer properties. Deoxyelephantopin induces apoptosis and cell cycle cessation followed by cell death in HCT116 cells (10). DET induces a dose- and time-dependent significant inhibition of HCT116 cell growth. Some of the characteristics of apoptosis including changes in core morphology and externalization of phosphatidylserine are seen in DET-treated cells. DET also significantly results in activation of caspase-3 and PARP cleavage. In addition, DET induces cell cycle termination in the S phase along with upregulation of p21 dose and expression of phosphorylated p53 protein. DET induces apoptosis and cell cycle termination in HCT116 colorectal carcinoma, suggesting that DET has potential as an anticancer agent for colorectal carcinoma (18).

Isodeoxyelephantopin (IDOE) isolated from ES is used in the treatment of several types of cancer. IDOE antiproliferative activity on T47D cells of breast carcinoma and lung cancer cells A549 (19). IDOE inhibited the growth of A549 and T47D cells depending on the dose and time depending on IC<sub>50</sub> values of 10.46 and 1.3 µg / mL, respectively. IDOE is not significantly toxic to normal lymphocytes. IDOE-induced cell death was associated with activation of caspase-3 expression followed by cell cycle arrest in the G<sub>2</sub> / M phase. IDOE inhibits the proliferation of breast cancer cells and lung carcinoma cells and induces caspase-3 mediated apoptosis and cell cycle cessation (19).

ES extract has a cytotoxic effect on breast cancer cells, MCF-7 with an IC<sub>50</sub> value of 15 µg/mL. When compared with control, the ES extract triggered cell death with increased phosphatidylserine externalization, DNA damage and significant apoptotic characteristics in MCF cells. Administration of ES also showed increased tumor suppressor p53 protein expression (6). The anti-cancer and anti-oxidant activity of ES has scientifically validated its use as a source of potential anti-cancer drugs (17).

### 3.4. Hepatoprotective

The liver is an organ in the body that functions as an antidote to toxins. Various chemical compounds that enter the body can cause liver damage or damage. On the other hand, various natural products from plants are believed to have the effect of restoring or protecting the liver which is known as hepatoprotective (20). Research on plants as hepatoprotective is ongoing, including ES (21).

Various chemical compounds that enter the body can cause disruptive effects on the liver, but on the other hand there are various compounds produced by plants that can improve liver function or are known as hepatoprotective (20). ES has traditionally been used as a liver tonic (6,22). In laboratory studies, liver damage can be induced with alcohol (6). Accelerated serum biochemical profiles (including AST, ALT, ALP, triglycerides, and total bilirubin) associated with reduced necrotic fat and body fat in the liver were observed in ethanol-treated mice. Low ES concentrations can reduce the serum biochemical profile (including AST, ALT, ALP, triglycerides, and total bilirubin) and fat accumulation in the liver. The high concentration of ES was able to reverse liver damage, which was comparable to normal controls. ES has no acute oral toxicity in mice. These results suggest a potential effect of this extract as a hepatoprotective agent towards ethanol-induced liver damage without acute oral toxicity effects. These activities may contribute to, or at least in part, to the high total phenolic and flavonoid content (6).

ES has traditionally been used as a liver tonic. Liver regeneration after partial hepatectomy is a physiological response to maintain homeostasis (21). In laboratory experiments, liver damage can be induced with alcohol or ethanol (6). Serum biochemical profiles such as AST, ALT, ALP, triglycerides, and total bilirubin can be used as hepatoprotective indicators. At low concentrations, the ES extract was able to reduce the serum biochemical profile and fat accumulation in the liver and at high concentrations it was able to reverse liver damage, which was comparable to normal controls. *E. scaber* has no acute oral toxicity in mice. The bioactivity of ES as hepatoprotective is associated with high total phenolic and flavonoid content (6) (Ho et al 2012). ES has the effect of liver regeneration through increasing levels of HGF and IGF-1 protein expression which leads to the cell cycle. ES shows that it plays an important role in the liver that induces cell cycle regeneration and suppressed hepatocyte apoptosis (21).

Aqueous ES extract had activity on lipopolysaccharide (LPS) induced inflammation of BV-2 microglial cells and acute liver injury in Sprague-Dawley (SD) mice. ES reduces LPS-induced nitric oxide (NO), interleukin (IL) -1, IL-6, reactive oxygen species (ROS), and prostaglandin production (PGE<sub>2</sub>) in BV-2 cells. ES significantly decreased serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in LPS in mice (23).

Methanol ES extract administered to mice exposed to N-nitrosodiethylamine (NDEA) induced hepatotoxicity (0.02% NDEA in water five days per week, orally) in a preventive and curative model. Mice given NDEA for six weeks then given n-hexane methanol ES extract (200 and 100 mg / kg) for ten days showed a significant reduction ( $P \leq 0.05$ ) levels of AST, ALT, and MDA. The ES extract also increased antioxidant enzymes and protein levels in mice treated with NDEA. The hepatotoxicity caused by NDEA can be reversed by administering the ES extract (22).

### 3.5. Stimulates Hair Growth

Hair is one of the enhancements to human appearance and several diseases in the hair can cause baldness. Candlenut oil is one of the well-known herbs that humans use to stimulate hair growth. Sahoo et al (24) stated that the methanol extract of ES leaves was able to play a role in stimulating rat hair growth. The administration of leaf extract with a concentration of 2-3% for 30 days was able to significantly increase the hair growth of rats compared to the standard Minoxidil compound. In vitro dissolved follicles grew significantly ( $p < 0.05$ ) and also increased initiation of new hair follicles.

### 3.6. Anti-diabetes Mellitus

Diabetes mellitus is a chronic disease characterized by hyperglycemia, alteration in fat and protein metabolism. Injection of chemical drugs used to treat hyperglycemia can cause side effects such as hypoglycemia, coma and liver and kidney damage (25). The antidiabetic activity of the aqueous extract of ES roots and leaves given at a concentration of 0.3 / kg body weight for 12 weeks resulted in a decrease in blood glucose. Administration of extract with a concentration of 0.6 / kg body weight is effective for returning blood sugar to normal levels and regenerating  $\beta$ -islet cells (25).

### 3.7. Anti-wounds

*Elephantopus scaber* is traditionally used as a wound healing herb. *In vivo* wound healing activities using excision wound model, incision wound model, and burn model were seen in mice treated with the ES extract. The ES crude extract had a much faster EC50 action (15.67  $\mu\text{g} / \text{mL}$ ) but less inhibition (87.66%) compared to the combination polyherbal formulation (30  $\mu\text{g} / \text{mL}$ ). Polyherbal formulation had the highest inhibition (89.49%) at the same dose compared to only ES (87.66%). Ethyl acetate fraction ES polyherbal formulation had the fastest activity (EC50 14.83  $\mu\text{g} / \text{mL}$ ) with inhibition (89.28%). Bioactivity as an anti-wound is thought to be related to the content of flavonoids which work synergistically with lactone sesquiterpenes and other bioactive compounds (26).

### 3.8. Anti-kidney Disorders

Lipid profile abnormalities are one of the most common complications found in people with diabetes mellitus. STZ-induced diabetic rats showed elevated blood glucose levels accompanied by impaired lipid profiles. Impaired kidney function can be detected by looking at abnormalities in serum urea, protein and creatinine levels. Crude extract of ES root hexane was given to white albino rats at a dose of 0.15 g / Kg bwt for 30 days to prove to have a long-term hypolipidemic effect which proved to be irreversible because the plant was reported to have regenerative properties. The ES root extract resulted in a significant ( $p < 0.001$ ) dose-dependent reduction in levels of total cholesterol, triacylglycerol, low-density lipoprotein cholesterol, with a significant increase in high-density lipoprotein cholesterol levels and restoring kidney function back to near normal (27).

### 3.9. Improve Memory

ES ethanol extract has activity to increase memory in mice. Memory enhancing activity can be measured by transfer latency (TL) in the height plus maze test; step-down latency (SDL) in tests of passive avoidance, cholinesterase, and caspase levels of rat brain homogenates. ES leaf extracts at doses of 150, 300, and 600 mg / kg body weight were administered orally for 15 days to groups of mice ( $n = 6$ ) of different ages and found a dose-dependent increase in memory scores after the cessation point. In old mice, ES leaf ethanol extract reversed significant amnesia potential in TL and SDL, reduced cholinesterase levels significantly, and significantly increased caspase levels compared to the control group (28).

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## 4. Conclusion

- Ethnobotany *Elephantopus scaber* is used as wound medicine, treatment of nephritis, edema, moisture, chest pain, fever, scabies, wounds, cough, tonic, febrifuge, and bronchitis, and asthma.
- The bioactivity of *Elephantopus scaber* is anti-bacterial, anti-fungal, anti-cancer, hepatoprotective, stimulates hair growth, anti-diabetes mellitus, anti-wound, and renal disruption.

- Deoxyelephantopin is one of the main sesquiterpen lactones derived from *Elephantopus scaber* which has anti-cancer properties.

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## Compliance with ethical standards

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### Disclosure of conflict of interest

I declare the article there is no conflict of interest.

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