QUALITY IMPROVEMENT IN DENTAL AND MEDICAL KNOWLEDGE, RESEARCH, SKILLS AND ETHICS FACING GLOBAL CHALLENGES

Edited by
Armelia Sari Widyarman, Muhammad Ihsan Rizal,
Moehammad Orliando Roeslan & Carolina Damayanti Marpaung

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Preface

Faculty of Dentistry Universitas Trisakti (Usakti) presents FORIL XIII 2022 Scientific Forum Usakti conjunction with International Conference on Technology of Dental and Medical Sciences (ICTDMS) on December 8th–10th 2022. The theme of the conference is "Quality Improvement in Dental and Medical Knowledge, Research, Skills and Ethics Facing Global Challenges".

The triennial conference has served as a meeting place for technical and clinical studies on health, ethical, and social issues in field medical and dentistry. It is organized around 12 major themes, including behavioral, epidemiologic, and health services, conservative dentistry, dental materials, dento-maxillofacial radiology, medical sciences and technology, oral and maxillofacial surgery, oral biology, oral medicine and pathology, orthodontics, pediatrics dentistry, periodontology, and prosthodontics.

The most recent findings in fundamental and clinical sciences related to medical and dental research will be presented in the conference that will be published as part of the conference proceeding. This proceeding will be useful for keeping dental and medical professionals up to date on the latest scientific developments.

Dr. Aryadi Subrata
Chairman FORIL XIII conjunction with ICTDMS

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Elephantopus scaber Linn.: Potential candidate against oral squamous cell carcinoma

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ABSTRACT: The sixteenth leading cause of mortality worldwide is oral cancer. Based on the type, location, and stage, there are several treatment options for oral cancer, including chemotherapy, radiotherapy, surgery, or a combination of these. However, it is important to take into account the possibility of adverse effects brought on by high medicine dosages and uneconomical costs. As research indicates, plants have been a significant source of anticancer chemicals. A plant named *Elephantopus scaber* Linn is said to have anticancer properties. This review aims to discover the potentials of *E. scaber* L. as a candidate against oral squamous cell carcinomas (SCC). References were discovered by searching PubMed for the terms "anticancer" and "Elephantopus scaber" between 2000 and 2022. For this review, only English references were taken into account. *E. scaber* L. has been used traditionally as a treatment in many countries. Additional pharmacological activity associated with *E. scaber* includes anticancer, antioxidant, antidiabetic, antibacterial, and anti-inflammatory characteristics. Despite the fact that there is still much to understand about *E. scaber* and its therapeutic potential as an anticancer agent, it has tremendous potential against cancer. To investigate its potential as a candidate against oral cancer, more research on *E. scaber*'s anticancer activities against oral squamous cell carcinomas (SCC) is needed.

1 INTRODUCTION

Oral cancer is a kind of malignant tumor that appears in the mouth. Squamous cell carcinomas (SCC) make up more than 90% of all oral cancers. It has various levels of differentiation as well as a tendency for lymph node metastasis (Rivera 2015). The main risk factors are smoking and alcohol drinking, but several other factors such as human papillomavirus (HPV), nutritional deficiencies, and genetic predisposition have also been linked (Pires et al. 2013). There are many approaches to oral cancer treatment, such as chemotherapy, radiotherapy, surgery, or a combination of these, depending on the type, location, and stage of cancer. However, the potential for side effects caused by large doses of drugs and uneconomical prices has to be taken into consideration (Singh et al. 2016).

There are numerous plant species that have been utilized to treat or stop the growth of cancer. By concentrating on plants used in traditional medicine in developing nations, some researchers have discovered plant species that have exhibited anticancer effects (Greenwell & Rahman 2015). One of the plants reported to have anticancer effects is *Elephantopus scaber* Linn. The reported anticancer potential is that the isolates of *E. scaber* L. extract could induce apoptosis in the human colon tumor cell line (HCT-116) (Geetha et al. 2012). Therefore, this review was to explore *E. scaber* L. potential against oral SCC.

2 METHODS

References were found by searching the phrases "anticancer," and "*Elephantopus scaber*" from 2000 to 2022 on PubMed. Only English references were taken into account.

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The total initial articles search results as a whole on PubMed totaled 12 journals. Then three article that did not meet the criteria was excluded. As many as 9nine journals that match the criteria were read in their entirety and none were excluded.

3 RESULTS

Data obtained from articles that comply with the criteria are listed below in Table 1.

Table 1. Anticancer potentials of *Elephantopus scaber* against various cancer cells.

No.	Author	Topic	Year Published	Results
1.	(Huang et al. 2010)	Deoxyelephantopin, antimammary tumor, mammary adenocarcinoma	2010	Deoxyelephantopin's antimammary tumor properties, which result from its targeting of several important factors in angiogenesis, inflammation, and cell death, indicate that deoxyelephantopin has a lot of potential for further research as a breast cancer treatment.
2.	(Kabeer et al. 2014)	Isodeoxyelephantopin, cell cycle arrest, caspase-3-mediated apoptosis, breast carcinoma T47D cells, lung carcinoma A549 cells	2014	Breast and lung carcinoma cells were both prevented from proliferating by *Elephantopus scaber*'s isodeoxyelephantopin, resulting in cell cycle arrest and caspase-3-mediated death in the treated cells.
3.	(Pitchai et al. 2014)	Anticancer potentials, lupeol, MCF-7 cell line	2014	When applied to normal breast cells, lupeol is harmless but has an effect on the survival and proliferation of ER- α positive MCF-7 cells.
4.	(Beeran et al. 2015)	Enriched fraction of *E scaber*, apoptosis, multi-drug resistance, human epithelial cancer cells	2015	The current study found that *Elephantopus scaber*, an indigenous medicinal herb, had cytotoxic, apoptosis-inducing, genotoxic, and MDR-reversing effects on multiple human epithelial cancer cell lines.
5.	(Chan et al. 2016)	Deoxyelephantopin, HCT116, apoptosis, cell cycle arrest	2016	Deoxyelephantopin has been shown in their study to have the capacity to induce apoptosis and cell cycle arrest in HCT116 cells via regulating the proteins p53, cyclins, and cyclin-dependent kinases.
6.	(Wang et al. 2017)	Isodeoxyelephantopin, protective autophagy, lung cancer cells	2017	Their findings demonstrated that blocking autophagy, Nrf2, or p62 could considerably increase the anticancer activity of isodeoxyelephantopin, which was derived from the *Elephantopus scaber*.
7.	(Kabeer et al. 2017)	Molecular mechanisms, anticancer, deoxyelephantopin, cancer cells	2017	Deoxyelephantopin extracted from *E. scaber* possesses considerable apoptotic, anticancer, and antimetastatic potential, according to their findings.
8.	(Hong et al. 2020)	Isodeoxyelephantopin, thioredoxin reductase 1, ROS-mediated JNK signaling pathway, human colon cancer cells	2020	They discovered a novel small molecule inhibitor of TrxR1 and reported that isodeoxyelephantopin, which was derived from E. scaber, caused cell death in colon cancer cells via the ROS-mediated JNK signaling pathway. Their results amply proved that isodeoxyelephantopin is a unique anticancer medication that can be developed for the treatment of colon cancer. They also discovered that both in vitro and in vivo, isodeoxyelephantopin dramatically improved cisplatin's anticancer efficacy.

(*continued*)

Table 1. Continued

No.	Author	Topic	Year Published	Results
9.	(Ji et al. 2022)	Deoxyelephantopin, apoptosis, colon cancer, miR-205/Bcl2 axis	2022	Deoxyelephantopin from *E. scaber* is confirmed to have antihuman colon cancer activity in their study. Deoxyelephantopin induces apoptosis by the miR-205-Bcl2 axis. It also heightened the chemosensitivity of 5FU to colon cancer, offering a promising future in the treatment of patients with colon cancer.

4 DISCUSSION

The sixth most frequent malignancy worldwide is oral cancer (Dhanuthai et al. 2018). Ninety percent of all oral malignant neoplasms are SCC. Any area of the oral cavity can be affected by SCC, one of the most common is head and neck malignancies; however, it most frequently affects the tongue (30% of the time) (Soudry et al. 2010; Turner et al. 2013). SCC has a fair prognosis if identified early, but the majority of cases are discovered late, with a less than 50% 5-year survival rate. Patients with untreated metastatic disease have a four-month survival rate (Rivera 2015). Due to multifactorial causes, the cause of oral SCC is unknown with certainty (Sirait 2013). Tobacco usage, alcohol consumption, betel nut chewing, and poor diet have all been identified as major risk factors (Amtha et al. 2009). Human papillomavirus (HPV) and ultraviolet radiation are also risk factors (UV) (Rivera 2015).

Surgery, radiation, chemotherapy, or a combination of the three are frequently used to treat oral SCC (Huang & O'Sullivan 2013). The patient's comorbidities, nutritional state, ability to tolerate treatment, and willingness to undergo therapy are taken into account when determining the best course of action in addition to the primary tumor's size, stage, and location (Rivera 2015). If the tumor is sufficiently tiny and has a good chance of providing positive results, surgery is conducted. Chemoradiotherapy is frequently used during surgery, particularly when the tumor is inoperable. Many oral cancer patients experience long-term side effects such as fatigue, speech difficulties, difficulty swallowing, hair loss, loss of taste, and dry mouth. Numerous investigations have been done as a result to discover alternative therapies with less negative effects. One of them is the use of natural agents derived from plants, which have been shown to attack cancer cells while leaving normal cells alone (Scully & Bagan 2009; Zhang et al. 2018).

E. scaber L. can be found in Europe, Australia, Asia, and Neotropics (Hiradeve & Rangari 2014b). This plant is also called Elephant's Foot in English, Tapak Liman in Indonesia, and Didancao in China. It is a 30 to 60-cm tall, coarse, upright, and rather rigid herb (Hiradeve & Rangari 2014a). This plant has the taxonomic classification of the kingdom of Plantae, division of Magnoliophyta, class of Magnoliopsida, order of Asterales, the family of Asteraceae, a genus of Elephantopus, and species of *Elephantopus scaber* Linn (Schoch et al. 2020). Traditional medicine utilizes *E. scaber* L. to cure bronchitis, headaches, diarrhea, hepatitis, and fever (Wang et al. 2014). There are various ways of processing *E. scaber* L. plants, one of which is a fairly simple way, namely by boiling it directly (Ho et al. 2009). Additional pharmacological activity associated with *E. scaber* L. includes anticancer, antioxidant, antidiabetic, antibacterial, and anti-inflammatory characteristics. Several phytochemical studies have reported *E. scaber* L. contains sesquiterpene lactones, flavonoids, triterpenoids, phenolic compounds, and essential oils (Hiradeve & Rangari 2014a; Mohan et al. 2010).

When the cytotoxicity of *E. scaber* L's enriched ethanol extract was evaluated against human epithelial cancer cells, it was discovered to possess strong, dose-dependent cytotoxicity. Additionally, the enriched extract activated apoptosis in HeLa, A549, MCF-7, and

Caco-2 cells by causing nuclear condensation and other apoptosis-related traits, such as membrane blebbing. The multidrug-resistant transporters ABC B1 and ABC G2 present in cancer cells were likewise inhibited by the enriched fraction (Beeran et al. 2015).

Deoxyelephantopin, a compound derived from *E. scaber* L, significantly inhibited the development and spread of mammary adenocarcinoma TS/A cells both *in vitro* and *in vivo*, indicating that it might be an effective breast cancer treatment (Huang et al. 2010). Deoxyelephantopin can trigger apoptosis by triggering caspase-3 and cleaving PARP, according to a different study. Eventually, DNA damage induced p53 and p21 activation, which led to apoptosis and S-phase cell cycle arrest (Kabeer et al. 2014). In HCT116 cells, deoxyelephantopin also reduces the expression of the proteins CDK2, CDK4, cyclin B1, cyclin E2, cyclin D1, and cyclin A2 (Chan et al. 2016). Another study revealed that deoxyelephantopin can increase the chemosensitivity of 5FU to colon cancer and cause colon cancer apoptosis by the miR-205-Bcl2 axis, offering a promising future in the treatment of patients with colon cancer (Ji et al. 2022). Isodeoxyelephantopin caused cell cycle arrest and caspase-3-mediated apoptosis, which prevented the growth of lung carcinoma and breast cancer cells. According to a different study (Hong et al. 2020), isodeoxyelephantopin caused the death of colon cancer cells via the ROS-mediated JNK signaling pathway. Growth of MCF-7 cells was suppressed, and their viability was markedly decreased, by lupeol, a compound derived from *E. scaber* L. It can inhibit the antiapoptotic proteins Bcl-2 and Bcl-xL, which then release apoptogenic substances such as cytochrome c, allowing cells to start the apoptotic process by activating caspases (Pitchai et al. 2014).

5 CONCLUSION

Side effects of cancer treatments encourage us to look for alternative drugs that have minimal side effects. Among them is to use the active substances contained in traditional plants, which are reported to have anticancer potential. *E. scaber* L. and its phytochemical have shown promising results against different types of cancer cell lines. Therefore, *E. scaber* L. and its phytochemical are potential candidates against oral SCC and require further research in the future.

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