Journal of Medicinal and Chemical Sciences 6 (2023) 1773-1782

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

*Original Article*

# Potential of Bioactive Compound from *Elephantopus scaber* Linn. LEAF as Anti-Cancer through in Silico Test

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**ARTICLE INFO**

**Article history**

Receive: 2022-10-13
Received in revised: 2022-11-15
Accepted: 2022-12-28
Manuscript ID: JMCS-2210-1821
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Ali Delpisheh

**DOI:10.26655/JMCHEMSCI.2023.8.6**

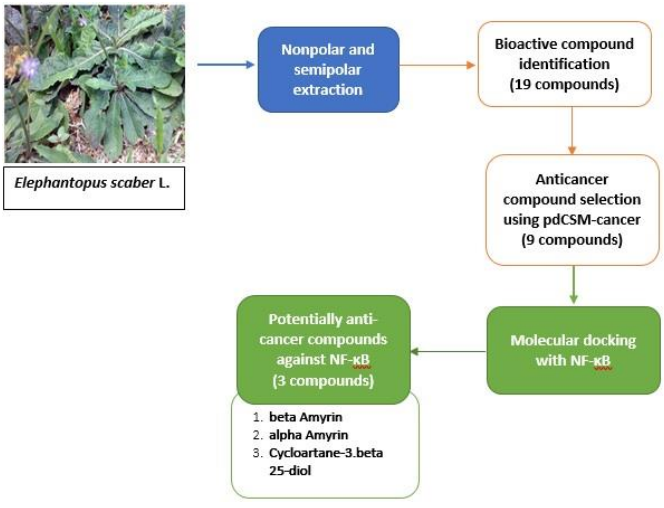
**KEYWORDS**

Bioactive compound
*Elephantopus scaber*
Anticancer
In silico

**ABSTRACT**

*Elephantopus scaber* contains secondary metabolites, such as triterpenoids, sesquiterpene lactones, elephantopin, epifriedelinol, lupeol, stiqmasterol, lupeolacetate, deoxyelephantopin, and isodeoxyelephantopin. The plant can be used for medicinal purposes to treat cancer, diabetes, leukemia, viral and bacterial infections, bronchitis, and hepatitis. Therefore, this research aims to isolate and identify the bio-active compounds in *Elephantopus scaber* leaf extract and to analyze the effectiveness of binding the constituents through molecular docking against NF-kB. The method used included two stages. The first stage was extraction, fractionation, isolation, and identification, while the second was the *in silico* test, including the sample preparation, molecular docking, and visualization. The results showed that 10 bioactive compounds had the potential as anti-cancer compounds. Based on the binding affinity of the molecular docking, the compounds with the lowest values were b-amyrin (-8.0 kcal/mal), a-amyrin (-6.9 kcal/mol), and Cycloartane-3.beta 25-diol (-6.9 kcal/mol). Furthermore, the three compounds have potential as anti-cancer agents.

**GRAPHICAL ABSTRACT**

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## Introduction

Cancer is characterized by continuous cell proliferation, uncontrolled cell replication, and its ability to invade the surrounding tissues. Based on WHO data, in 2018, cancer caused about 9.6 million deaths worldwide and established as a major public health problem [1]. Chemotherapy, chemoradiotherapy, and various anti-cancer medicines are used for local and non-metastatic cancer treatment. However, they become ineffective when cancer has metastasized throughout the body and often causes side effects [2]. Besides using medical treatment, cancer can also be treated with herbal treatment. The high interest in herbal medicines is due to its safety, lower side effects, and less dependence [3, 4].

Herbal medicines developed by the pharmaceutical industry utilize the secondary plant metabolites. One of them from the Asteraceae family, namely *Elephantopus scaber*, is a herb found in the tropical region. *E. scaber* is a medicinal plant with roots, stems, and leaves. The chemical content includes flavonoids, phenol, saponins, steroids, tannins, terpenes, triterpenoids, sesquiterpenes lactone, and elephantopin. It also contains epifriedelinol, lupeol, stiqmasterol, triacontanol-1-ol, dotria-contan-1-ol, lupeolacetate, deoxyelephantopin, isodeoxyelephantopin, and luteolin-7-glucoside [5-7]. Previous research showed that the leaf extract of *E.scaber* contained phenolic and flavonoids. The content of phenol compounds were 0.611 mg/mL, 0.536 mg/mL, and 0.495 mg/mL in methanol, ethyl acetate, and butanol solvents. Meanwhile, flavonoid compounds were 0.83 mg/mL, 0.92 mg/mL, and 0.90 mg/mL in methanol, ethyl acetate, and butanol solvents [8].

*Eletophantus scaber* can act as medicinal plant and are used by the community as traditional medicine (ethnomedical) due to its content of various secondary metabolites. This plant has been used as anti-microbial, anti-tumour, antidiabetic, and to treat leukaemia, viral and bacterial infection, bronchitis, and hepatitis [9, 10]. Furthermore, the plant found to have hepatoprotective, analgesic, antioxidant, and anticancer activities [6]. Moreover, its deoxyelephantopin content found to inhibit proliferation of cancer cells [11]. In alcoholic extracts and chloroform, germacranolide (sesquiterpene lactone) was found to be toxic, however in aqueous extracts, it acts as analgesic, diuretic, and anti-inflammatory agent [12]. Sesquiterpene lactones such as deoxyelephantopin, isodeoxyelephantopin, and scabertopin were also prominent anti-cancer agents [13, 14].

Nuclear factor kappa B (NF-kB) is a protein complex involved in DNA transcription, cytokine production, and cell survival signaling. It can be activated by various signals from inside and outside the cell. Activated NF-kB protein will translocate into cell nucleus, and then bind to DNA to induce increased expression of various proteins. Meanwhile, proteins induced by NF-kB have various functions related to physiological processes, including inflammation, cell death, cell immunity, and proliferation [15]. The increased activation of the excessive NF-kB pathway is one of the causes of cancer development. Therefore, one of the novel cancer treatment methods is inhibition of the NF-kB pathway [16].

The potential of the bioactive compounds as anticancer can be tested with an in silico approach, including molecular docking [17, 18]. This test predicts the binding orientation in the form of affinity and activity of drug candidates to their proteins. In silico test speeds up and facilitates identification in the search for drug candidate compounds, optimizes absorption, distribution, metabolism, and toxicity effects, as well as avoids drug side effects [19].

Various research related to cancer drug candidates with in silico test has been conducted, including research on Emodin, a natural compound from *Rheum palmatum* used to treat several types of cancer, such as lung, liver, and pancreas using molecular docking [20]. Vanillin compounds from *Vanilla planifolia* were used as inhibitors of NUDT5 activity in breast cancer [21]. This research adds to similar analysis on developing secondary plant metabolites as medicinal ingredients. The research aimed to isolate and identify bioactive compounds in *Elephantopus scaber* leaf extract and analyze the effectiveness of the bioactive compounds from

the plant as anticancer agent through molecular docking with NF-kB.

## Materials and Methods

*Isolation and identification of bioactive compounds from E scaber leaves*

Leaves of *E. scabra* were taken as much as 5.4 kg, and the samples were then washed and dried at room temperature for 30 days. After drying, the powder was made, and the simplicia obtained was 773 g for extraction. About 350 g of the powder was macerated with 1 liter of methanol as a solvent for 1×24 hours. Thereafter, maceration results were filtered using a buncher funnel and a vacuum pump. The obtained macerate was concentrated with a rotary evaporator.

The extract obtained was partitioned with methanol and n-hexane as a solvent in a ratio of 1:1, and the results of the partitioning of *n*-hexane in a rotary evaporator and extract were obtained. The filtrate that had been partitioned with n-hexane and with ethyl acetate and methanol was carried out in a ratio of 1:1, and the result was then placed in a rotary evaporator. The extracts were weighed 5 g each and impregnated with 60 G silica gel (0.2-0.5 mm) for about 50 g [22].

The Vacuum Liquid Chromatography (VLC) process was carried out with n-hexane and ethyl acetate as eluents. The resulting KCV filtrate was collected in vials per phase. Afterwards, a chromatographic test was performed on a 254 F TLC plate. The samples for each isolate phase were 19 points from the *n*-hexane partition and 20 from the ethyl acetate. Chromatography was carried out using an eluent ratio of hexane and ethyl acetate at 4:1. After the stain on the plate was visible, it was marked, and the Rf value was calculated, ranging from 0.6 to 0.9. In addition, the KCV results in the vial were stored and allowed to evaporate until crystals were formed. Vials containing crystals and the corresponding Rf results were marked. Crystals with different phases were taken for compound analysis using the GC-MS test, with Column specifications: HP-5MS UI. Length: 30 m; I.D.: 0.25 mm; Film: 0.25 µm; and Max Temperature: 325/350 °C.

The compounds identified from the isolation using n-hexane and ethyl acetate as solvents were then determined its potential as anti-cancer agents. The compound was predicted for its potential as an anti-cancer agent using pdCSM-cancer prediction (http://biosig.unimelb.edu.au/pdcsm_cancer/prediction) [23]. After that, compounds with active potential as anti-cancer were carried out by molecular docking of NF-kb.

*Molecular docking with NF-KB*

In-silico technique to analyze the interaction of hypothetical compounds with receptors in 2D and 3D forms. It also predicts the activity of hypothetical compounds, and shows various compounds with low activity values [24]. The biocomputational activity was demonstrated by searching for ligands for the predicted binding affinity match and the site's suitability.

The tools used were laptop with 10$^{th}$ generation Intel Core i3 specifications, 2.10 GHz, 8 GB RAM, and Windows 10 operating system 64-bit, software such as Autodoc, PyRx, Notepad++, and Discovery Studio 2021 Client, Pubchem database (https://pubchem.ncbi.nlm.nih.gov/), the Protein Data Bank (https://www.rcsb.org), and the Swiss Target Prediction web server (www.swisstargetprediction.ch). First, the collection of targeted bioactive compound ligands and their control compounds was downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and saved in 3D format. In addition, the receptor macromolecules were prepared by downloading the protein from the Protein Data Bank (PDB) database (https://www.rcsb.org/). Proteins were downloaded and saved in PDB format, and the macromolecules were sterilized using AutoDock Vina software [25] by removing $H_2O$ molecules. Each macromolecule was separated with an inhibitor to obtain a sterile protein by adding a hydrogen molecule and a partial charge. The sterile protein was then stored in PDBQT format, and the minimization step was carried out to make the ligand more flexible and produce the lowest energy when binding to the target protein region using Pyrex software [27]. The anti-cancer

preparation target compounds from GCMS result were e-continued by downloading *E. scaber* from the PubChem database web (https://pubchem.ncbi.nlm.nih.gov). Compounds are downloaded and saved in SDF format. The molecule is then minimized by converting the format into PDB using PyRx 0.8 software [26]. This makes the sample ligand compound flexible and have the lowest binding energy when molecular docking is performed.

Molecular docking simulations were conducted by tethering the ligands and compounds to the target receptor protein with the coordinates according to the location of the inhibitor (native ligand). Each ligand and compound will interact with the receptor protein under rigid conditions. Meanwhile, the molecular docking was visualized using the Discovery Studio 2016 Client (*Dassault Systèmes Biovia, San Diego, California, USA*) for 2D and 3D visualization. It was performed between potential compounds and Nf-kb protein, and the visualization of the hydrogen bond interaction distance was carried out using Pymol Software. Piecetannol was used as control for NF-kB binding affinity. This visualization clarified the appearance of the hydrogen bond interaction distance in units (Å). The closer the interaction distance, the stronger the hydrogen bonds to maintain the stability of the protein-ligand molecular complex. The obtained data were in the form of binding affinity, type of ligand bond, amino acid on the active site of the binding bond, and visualization of the hydrogen interaction distance. Moreover, the potential compounds were also carried out with potential target based on anti-cancer drugs.

## Results and Discussion

### *Bioactive compounds identification of E. scaber*

*Elephantopus scaber* is still not fully utilized in Indonesia, while it is widely used as traditional herbal medicine in India. The phytochemical content of *E. scaber* has antioxidant, anti-microbial, anti-inflammatory, anti-cancer, antiasthmatic, antidiabetic, nephroprotective, and hepatoprotective properties [27]. The ethyl acetate fraction extract has been investigated to have anti-inflammatory activity because it can suppress the NF-KB translocation [28]. Bioactive compounds identified from *n*-hexane and ethyl acetate extraction are presented in Table 1. Ten bioactive compounds were identified from nonpolar extract, while 9 bioactive compounds were identified from semi-polar extract. Compounds identified then screened using pdCSM-cancer for its potential activity as anticancer. Ten compounds from all compounds identified were found to be potential anticancer agents (Table 2).

**Table 1:** Bioactive compounds identified from *Eletophantopus scabra* extraction

| No. | Compound | CID | Extraction type |
|---|---|---|---|
| 1 | Hydroperoxide, 1-methylpentyl | 141084 | Nonpolar |
| 2 | Furan,2,3-dihydro-2,2-dimethyl-3-(1-methylethenyl)-5-(1-methylethyl) | 596568 | Nonpolar |
| 3 | 2-Pentadecanone, 6,10,14-trimethyl | 10408 | Nonpolar |
| 4 | 2-Piperidinone, *N*-[4-bromo-n-butyl] | 536377 | Nonpolar |
| 5 | Octadecane, 6-methyl | 93065 | Nonpolar |
| 6 | Silane, trichlorodocosyl | 81761 | Nonpolar |
| 7 | Oxalic acid, allyl hexadecyl ester | 6420236 | Nonpolar |
| 8 | Valeric acid, 4-pentadecyl ester | 559043 | Nonpolar |
| 9 | 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione | 545303 | Nonpolar |
| 10 | 4-Trifluoroacetoxytridecane | 543275 | Nonpolar |
| 11 | 2-Octanone, 1-nitro | 27670 | Semipolar |
| 12 | 3-Trifluoroacetoxydodecane | 534402 | Semipolar |
| 13 | ß-Amyrin | 73145 | Semipolar |
| 14 | a-Amyrin | 73170 | Semipolar |
| 15 | Lupeol | 259846 | Semipolar |
| 16 | Methanesulfonic acid, 2-(3-hydroxy-4,4,10,13,14-pentamethyl-2,3,4 | 556214 | Semipolar |
| 17 | 1,6,10,14,18,22-Tetracosahexaen-3-ol, 2,6,10,15,19,23-hexamethyl | 5366014 | Semipolar |
| 18 | 3beta-Cycloartane-3,25-diol | 565447 | Semipolar |
| 19 | a-Tocospiro A | 21674156 | Semipolar |

**Table 2.** Potential anti-cancer compounds from hexane and ethyl acetate solvents based on predictions of pdCSM-cancer

| No. | Compound name | Extraction type |
|---|---|---|
| 1 | Silane, trichlorodocosyl | Nonpolar |
| 2 | Oxalic acid, allyl hexadecyl ester | Nonpolar |
| 3 | 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione | Nonpolar |
| 4 | 4-Trifluoroacetoxytridecane | Nonpolar |
| 5 | ß-Amyrin | Nonpolar |
| 6 | a-Amyrin | Semipolar |
| 7 | a-Tocospiro A | Semipolar |
| 8 | 1,6,10,14,18,22-Tetracosahexaen-3-ol, 2,6,10,15,19,23-hexamethyl | Semipolar |
| 9 | 3beta-Cycloartane-3,25-diol | Semipolar |

In this research, a number of compounds were identified from nonpolar (hexane) and semi-polar (ethyl acetate) extracts. Hydroperoxide, 1-methylpenthyl; Furan, 2,3-dihydro-2,2-dimethyl-3-(1-methylethenyl)-5-(1-methylethyl); 2-Pentadecanone, 6,10,14-trimethyl; 2-Piperidinone, N-[4-bromo-n-butyl]; Octadecane, 6-methyl; and various other compounds are the polar extracts identified (Table 1). Meanwhile, the nonpolar extracts identified are 2-Octanone, 1-nitro; 3-Trifluoroacetoxydodecane; b-Amyrin; a-Amyrin; Lupeol and Methanesulfonic acid (Table 2). Based on the prediction results with pdCSM-cancer, there are 5 compounds with active anticancer activity from the two extractions, namely 2-Piperidinone, N-[4-bromo-n-butyl]; Silane, trichlorodocosyl; Oxalic acid, allyl hexadecyl ester; 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione; and 4-Trifluoroacetoxytridecane from hexane and ß-Amyrin solvents; a-Amyrin; a-Tocospiro A; 1,6,10,14,18,22-Tetracosahexaen-3-ol,2,6,10,15,19,23-hexamethyl; and 9,19-Cyclo-9ß-lanostane-3ß,25-diol from ethyl acetate solvent (Table 2).

*In-silico visualization of anti-cancer potential against NF-kB*

NF-kappa-B is a homo or heterodimeric complex formed by proteins containing the Rel-like domains RELA/p65, RELB, NFKB1/p105, NFKB1/p50, REL, NFKB2/p52, and a heterodimeric p65-p50 complex. The results of compounds with the highest chromatogram picked after analysis using http://biosig.unimelb.edu.au/pdcsm_cancer/ obtained 4 active compounds as anti-cancer candidates. The four compounds were continued in silico using NF-KB1 protein, and the results showed the highest binding affinity value of -5.8 compared with the other three for *n*-hexane. For the ethyl acetate solvent, 5 active compounds were obtained as anti-cancer candidates, with the highest binding affinity value of -8.0, as seen in Tables 3.

**Table 3:** Results of binding affinity and interaction of amino acid solvent *n*-hexane

| No. | Compound Name | CID | Binding Affinity |
|---|---|---|---|
| 1 | 7,9-Di-tert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione | 545303 | -5.8 |
| 2 | (Z)-tridec-4-ene | 5362712 | -4.2 |
| 3 | Oxalic Acid, Allyl Hexadecyl Ester | 6420236 | -4.9 |
| 4 | b-amyrin | 73145 | -8.0 |
| 5 | a-amyrin | 73170 | -6.9 |
| 6 | a-Tocospiro A | 21674156 | -5.2 |
| 7 | 3beta-Cycloartane-3,25-diol | 565447 | -6.9 |
| 8 | (6E,10E,14E,18E)-2,6,10,15,19,23-hexamethyltetracosa-1,6,10,14,18,22-hexaen-3-ol | 5366014 | -5.1 |

The molecular docking test showed that of the 9 compounds in the *Elephantopus scraper* extract, 3 had a lower binding affinity value than the control drug, namely Piceatannol. The NF-KB1 protein in cancer cells will form a complex with 3 compounds resulting in bond stability. The binding affinity is negative and lower than the control compound Piceatannol, which has a binding affinity value of -6.1 kcal/mol.

Formation of complex with a binding affinity value that is more negative than the Piceatannol compound showed an optimal inhibition than the drug. These three compounds will inhibit NF-KB1 and transduction. Binding affinity is the strength of the protein-ligand bond complex, which is more stable at lower value. The three compounds were b-amyrin, a-amyrin and 15-(6-hydroxy-6-methylheptan-2-yl)-7,7,12,16-tetramethyl-pentacyclo-[9.7.0.01,3.03,8.012,16]octadecan-6-ol or 9,19-Cyclo-9ß-lanostane-3ß,25-diol.

The protein and ligand complexes were visualized with PyMol and Discovery Studio to determine the type and position of the interaction and the number of amino acid residues. The most potent compound is the b-amyrin compound with the lowest binding affinity value of -8 kcal.mol. Hence, this compound will form a complex with NK-KB1, which is more stable than other compounds. The interactions formed from these compounds are hydrogen bonds, Pi interactions, and Van der Waals interactions. Compound b-amyrin forms a complex with 13 amino acid residues, and the protein-hydrogen ligand interaction is at the amino acid positions Asp-121 and Gly-121. The Pi interaction was formed at the amino acid positions THR-153, Lys-149, ARG-157, and Ser-123. Meanwhile, the Van der Waals interaction was formed at the amino acid positions Val 145, Leu 143, HIS 144, Tyr 60, THr 146, and Lys 149 as indicated in Figure 1A, where the more amino acid binding residues is directly proportional to the negativity of the binding and complex stability.

Visualization of a-amyrin also shows complex protein-ligand interactions, such as hydrogen, Pi, and Van der Waals. The protein-hydrogen ligand is at the amino acid position SER 249. The Pi interaction is formed at the amino acid position LEU 272; HIS 307; ALA 311, and PHE 310, while the Van der Waals is formed at the amino acid position CYS 273; VAL 254, ASP 274, and ASN 250, as displayed in Figure 1B. Another potential is also shown by the compound Cycloartane-3.beta 25-diol. The protein-hydrogen ligand interaction is at the amino acid position SER 249, the Pi interaction is formed at LYS 275, PHE 310, and LYS 244, while the Van der Waals interaction is at LYS 252; ASP 274, GLY 55, and ARG 57.

Based on the prediction of cancer activity, the compound with higher anti-cancer activity is conducted by molecular docking of the NF-KB target. Three compounds from the ethyl acetate extract had a lower binding affinity than the piceatannol control (-6.1 kcal/mol), namely b-amyrin (-8.0 kcal/mal), a-amyrin (-6.9 kcal/mol), and Cycloartane-3.beta 25-diol (-6.9 kcal/mol) (Tables 3).

Binding affinity is influenced by the many variations of interactions formed and the number of interacting amino acid residues. Determination of the position and the type of interaction requires visualization. The lowest binding affinity value was visualized to determine the position and type of interaction as well as amino acid residues with the compound's ligands. The visualization results show hydrogen, Van der Waals, and pi interactions. Protein-ligand complexes can be formed in the presence of hydrogen, alkyl, Van der Waals, and hydrophobic interactions [29]. Furthermore, the interaction between the NF-KB complex and b-amyryl has 13 amino acid residues. The interaction of hydrogen formed with residue VAL 145 and Lys 147 has a distance of 3.42 Å and 3.98 Å. The shorter the interaction distance, the stronger the interaction; hence, the formed complex will be more stable [30].

Piceatannol is a stilbene compound of a phenol group analogue of resveratrol. According to the previous studies, piceatannol is indicated to have strong anti-cancer abilities. It interferes with cancer progression in different signalling pathways [31], one of which is by suppressing the expression of the NF-KB [32]. In this research,

piceatannol had a fairly low binding affinity for NF-KB, namely -6.1 kcal/mol.

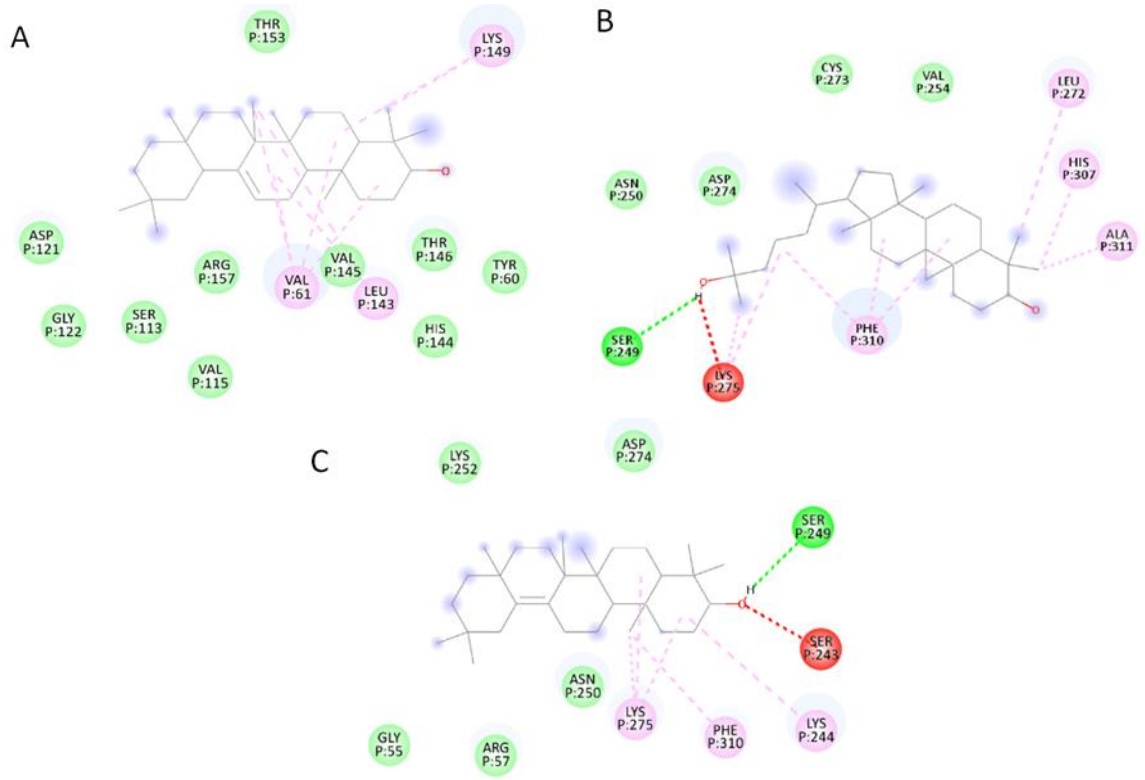


**Figure 1:** Interaction of potential compounds with NF-KB1. A. b-amyrin, B. a-amyrin, and C. Cycloartane-3.beta 25-diol

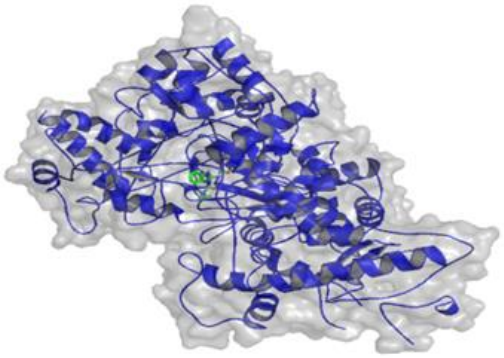

**Figure 2:** Surface area interaction of b-amyrin with NK-KB1

Alpha and beta amyrin are pentacyclic triterpenoid compounds with many potential biological activities. They have anti-tumour activity and can suppress NF-KB activity [33]. Beta amyrin has the highest binding affinity with NF-KB1 in this research (-8.0 kcal/mol. Hence, it has implications for anti-cancer activity. Beta amyrin has been investigated to suppress inflammation by reducing the expression of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, PGE-2, and COX-2 in previous research [34]. An increase in proinflammatory cytokines is one of the factors that will activate the NF-KB pathway and lead to cancer formation [35]. Alpha amyrin has been studied virtually as an inhibitor of Cyclooxygenase-2 ($COX_2$) and 5-Lipooxygenase (5-LOX). COX and LOX enzyme pathways develop

several types of cancer, including colon, lung, and breast [36].

Research on the potential bioactivity of cyclobutane is still limited. Cycloartane is a small molecule studied to have cytotoxic activity against cancer cells MDA-MB48 and MCF-7 [37]. Furthermore, cycloartane-3,24,25-triol can suppress MRCKα kinase activity associated with cancer progression through cytoskeleton control [38]. This compound possibly possesses anticancer activity in several different pathways, one of them to potentially suppress level of NF-KB, preventing further cancer development.

One of the disadvantages of alpha and beta amyrin is their low bioavailability, characterized by a low absorption rate and fast metabolism [39]. Piceatannol, which has the great potential for bioactivity, also has low bioavailability [31]. Therefore, future studies should develop various methods related to drug delivery for increasing the absorption and stability of bioactive compounds with high potential in metabolism.

Based on the obtained results, there are three secondary metabolites of *Elephantopus scaber* that have potential as anti-cancer agents through the binding of NF-KB. They are b-Amyrin (binding affinity -8 kcal/mol), a-Amyrin (binding affinity -6.9 kcal /mol), and Cycloartane-3.beta 25-diol with binding affinity of -8 kcal/mol, -6.9 kcal /mol and -6.9 kcal/mol, respectively. Further research can be conducted to determine the effectiveness of these compounds as anti-cancer agents *in vivo*.

## Acknowledgements

The authors would like to thank Universitas Negeri Surabaya for funding this research through Basic Research Fund scheme year 2022.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

## Conflict of Interest

The author declared that they have no conflict of interest.

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**HOW TO CITE THIS ARTICLE**
Yuliani, Firas Khaleyla, Dwi Anggorowati. Potential of Bioactive Compound from *Elephantopus scaber* Linn. LEAF as Anti-Cancer through in Silico Test. *J. Med. Chem. Sci*., 2023, 6(8) 1773-1782
https://doi.org/10.26655/JMCHEMSCI.2023.8.6
URL: http://www.jmchemsci.com/article_163593.html