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Phytochemical Profile and Biological Activities of Ethylacetate Extract of Peanut (*Arachis hypogaea L.*) Stems: In-Vitro and In-Silico Studies with Bibliometric Analysis

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ABSTRACT

The utilization of the stems, leaves, and hulls of peanuts (Arachis hypogea) is not as popular as the seeds. This study aimed to investigate the chemical contents and pharmacological activities of A. hypogaea stems in-vitro and in-silico. This study was also completed with bibliometric analysis. The methanol extract (ME) was reextracted by ethylacetate to get ethyl acetate extract (EAE). The chemical contents of EAE were analyzed by phytochemical screening, Liquid Chromatography-Mass Spectroscopy (LC-MS/MS), TPC (Total Phenolic Content), and TFC (Total Flavonoid Content). In-vitro and in-silico studies evaluated antioxidant potency, toxicity, and cytotoxicity toward MCF-7 cell lines. The results showed that EAE contained terpenoids, flavonoids, alkaloids, and phenolics which were supported by LC-MS/MS data. The EAE was categorized as a very strong antioxidant and moderately active in both cytotoxicity and toxicity.

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1. INTRODUCTION

Peanut (*Arachis hypogaea L*.) is a food crop many consume (Hasid *et al*., 2020). One of the six provinces on the island of Sulawesi is the province of Southeast Sulawesi, located in the eastern part of Indonesia with a total area of 38,140 km2 with various types of soil found (Karimuna *et al*., 2012). Southeast Sulawesi has the potential to develop peanuts. It is caused by sizeable agricultural land for the cultivation of peanuts. Statistical data from the Southeast Sulawesi Provincial Agriculture Service for 2019 shows that harvested area, production levels, and productivity in Southeast Sulawesi over the past 14 years have shown fluctuating developments. Meanwhile, based on Statistics Indonesia data for 2022 shows the average producer price of peanuts in Southeast Sulawesi (in Indonesian Rupiah per 100 Kg) from 2019-2021, respectively 2,144,107, 2,109,916, and 2,212,424. The native peanut to Southeast Sulawesi has a high level of adaptation to environmental pressures due to climate and marginal soils. Another advantage of the local peanut ecotype is its denser seed texture with a savorier taste (Rahni *et al*., 2020). In continuing our group's research on traditional medicinal plants in Southeast Sulawesi, we are interested in studying the peanut plant, which local people use as food and traditional medicine. Several traditional medicinal plants that have been studied previously include Imperata cylindrical (Ruslin *et al*., 2013), Polygonum (Sahidin *et al*., 2014, 2015; Sadino *et al*., 2016, 2017; Megantara *et al*., 2018; Ahmad *et al*., 2018), Persicaria (Sahidin *et al*., 2019) and Etlingera (Sabilu *et al*., 2017; Sahidin *et al*., 2018, 2022, Grashella *et al*., 2019, 2021a, 2021b, 2022; Fristiohady *et al*., 2020a, 2020b, 2021; Yusuf *et al*., 2021a, 2021b; Imran *et al*., 2022).

Arachis hypogaea L. (Leguminosae) is distributed in tropical and subtropical areas. The peanuts consist of four main parts namely leaves, stems, seeds, and hulls. Seeds have important economic and nutritional value. Economically, the use of seeds of this plant is very popular with competitive prices. For nutrition, the seeds have potential biological properties such as anticancer, antioxidant, and anti-inflammatory. It contains organic acids including caffeic acid (2.46%), linoleic acid (58.84%), oleic acid (11.31%), and palmitic acid (8.37%) (Candela *et al*., 2020). In the previous study, methanol extracts from the seeds contained betulinic acid, oleanolic acid, and ursolic acid in a nutraceutical form of a supplement as one of the drugs that prevent breast cancer (Abe *et al*., 2002), some phytosterols identified from this tissue such as b-sitosterol and doucosterol as immunoregulator (Lopes *et al*., 2011), cycloartenol as anticancer (Lee *et al*., 2015), 24-methylene cyclo artenol as antidiabetic (Sadasivan *et al*., 2020). Consumption of the seeds can reduce the risk of obesity, cardiovascular disease, type 2 diabetes, and cancer, and improve memory function (cognitive performance) (Ciftci *et al*., 2022). It shows that A. hypogaea are a potential source of bioactive compounds, including flavonols, and proanthocyanidins, due to the enzymes Leucoanthocyanidin reductase (AhLAR) and Flavonol synthase (AhFLS), which are responsible for their production, have been characterized structurally, transcriptionally, and functionally (Kubra *et al*., 2021). However, until now, the utilization of other plant tissues, such as leaves, stems, and hulls, has yet to be optimal. The hulls are only used as fuel similar to firewood in Indonesia, cellulose source (Sulyman *et al*., 2020), and active carbon adsorbent (Raghunathan *et al*., 2022). The leaves and stems are used as animal and fish feed with nutrient content consisting of ash (3.9%), crude fiber (8%), crude fat (0.8%), crude protein (5.3%), calcium (0.53%) and phosphorus (0.07%). Six compounds were isolated and identified from peanut stems and leaves, namely arahyside A, 4-(2-methoxyethyl) benzene-1,2-diol, (1(R, S),2(R, S))-phenylpropane-1,2-

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diol, tachioside, 1,3-benzendiol, and demethylmedicarpin. All compounds are inactive in four cell cancer lines (including SMMC7721, MCF-7, K562, and A549 with IC50 > 40mM) (Jin *et al*., 2020). Ursolic acid that can be isolated from peanut leaves and stems is known to induce apoptosis through TNF-related apoptosis-inducing ligand (TRAIL-induced apoptosis) in cancer cells and JNK-mediated upregulation of death receptor (DR) and a decrease in decoy receptor-2 (DcR2) so that it can affect cell survival (Prasad *et al*., 2011). Ursolic acid was tested in vitro on MCF-7 breast cancer cells, which showed the cytostatic ability of ursolic acid in the G1 phase. The mechanism influences intracellular Ca2+ signaling to decrease cell proliferatio. It can be concluded that the leaves of *A. hypogaea* can be used as food and herbs or nutraceuticals (Kalra, 2003). However, based on a literature search using ScienceDirect and SpringerLink, studies on the chemical and pharmaceutical aspects of *A. hypogaea* stems which are separated from the leaves are still very limited.

The innovative parts of this article are the chemical composition and pharmacological properties such as antioxidant, toxicity, and cytotoxicity that were examined in-vitro and in-silico on stems of *A. hypogaea L*. To support the analysis, a bibliometric analysis was also completed to understand the trend of this study. Bibliometrics have been used for supporting research analysis in many areas of research (Nandiyanto *et al*., 2021; Nandiyanto & Al Husaeni, 2022a; Wierdartun *et al*., 2022; Al Husaeni & Nandiyanto, 2022a; Nandiyanto *et al*., 2022a; Mubaroq *et al*., 2020; Nandiyanto *et al*., 2022b; Nandiyanto *et al*., 2022c; Nandiyanto *et al*., 2023a; Al Husaeni & Nandiyanto, 2022b; Nandiyanto & Al Husaeni, 2022d; Nandiyanto *et al*., 2022c; Yulifar *et al*., 2021; Al Husaeni & Nandiyanto, 2022e; Nandiyanto & Al Husaeni, 2021; Nandiyanto *et al*., 2023b; Nandiyanto *et al*., 2020; Al Husaeni & Nandiyanto, 2023; Nandiyanto *et al*., 2022d; N'diaye *et al*., 2022; Maryanti *et al*., 2022).

2. METHODS

2.1. Bibliometric Literature review analysis using VOSviewer

The study analyzed the Google Scholar database (998 publications; using Pharmalogical activity and hypogea stems) on 23 December 2022 for articles between 2018 and 2022. Data were downloaded and extracted into formats of *.csv (for Microsoft Excel) and *.ris (for VOSviewer to facilitate data analysis). Detailed information on how to use bibliometric analysis is shown in previous studies (Al Husaeni and Nandiyanto, 2022).

2.2. Materials

Analysis of LC-MS/MS was conducted using water acquity UPLC I-Class aligned with a Xevo G2-X2 Quadropole Time-of-flight (QToF) mass spectrometer. Chemicals including methanol, ethyl acetate, n-hexane, acetone, TLC Chromatography plate: Kieselgel 60 F254 0,25 mm (Merck), Silica gel 60 GF254 p.a (Merck), silica 60 G (Merck), cerium sulfate (CeSO4) (Merck), ascorbic acid (Merck), gallic acid (Merck), doxorubicin (Merck) and MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (Merck). Artemia salina and MCF-7 cells were used for toxicity assay. Arachis hypogaea L. stems were collected from Mekarsari Village, Palangga Sub-District, South Konawe District, Province of Southeast Sulawesi. The plant was determined at the Laboratory of Botany of the Faculty of Teacher Training and Education of Halu Oleo University. The leaves were dried at 40°C and powdered for further analysis.

2.3. Analysis

Several analyses were done:

(i) Extraction and Partition. Dried *A. hypogaea* stems (3.6 Kg) were extracted with methanol 30 L for 3 x 24 h. The extract was concentrated using a vacuum rotary evaporator (Rotavapor (R), RII, Buchi, Switzerland) at 40°C. The

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methanol extract (ME) was partitioned using ethyl acetate to get ethyl acetate extract (EAE) and methanol residue (MR).

(ii) Phytochemical Screening. Phytochemical screening was performed using the colorimetric method to detect the presence of secondary metabolites in the samples (ME, EAE, and MR). Tests performed were on phenols and tannins, flavonoids, steroids, terpenoids, and alkaloids using phytochemical screening methods outlined by Harborne (Grashella *et al*., 2019).

(iii) Liquid chromatography-mass spectrometry mass spectrometry (L-CMS/MS). The Standard Operational Procedure of the LC-MS/MS experiment was used to get profile compounds of the sample. A reverse-phase HSS T3 C18 column (2.1×100 mm, 1.8 µm particle size) was used and maintained at 40°C. In addition, The mobile phases: A (0.1% formic acid in water) and B (acetonitrile in 0.1% formic acid). Gradient elution of the mobile phase was performed with a flow rate of 0.3 mL/min, injection volume of 1 µL, data range was from 50-1200 m/z, source temperature, 120°C, desolvation gas flow was at 1000 L/h (500°C), the capillary voltage was at 2.0 kV, and the cone voltage was 30 V. The gradient elution was 5% B (0-8 min), 40% B (8-11 min) and 100% B (11-16 min). Low collision energy (6.00 eV) and high collision energy (10-40 eV) were set to obtain data-independent acquisition (known as MSE mode). All LC-MS data was processed, peak picked, and analyzed using the UNIFI informatics platform (Wahyuni *et al*., 2021a).

(iv) Determination of Total Phenolic Content and Total Flavonoids Content. The TPC of EAE was determined using the Folin and Ciocalteu reagent, following Singleton and Rossi's method with minor adjustments, and the TFC of the samples was determined using Chang methods (Musdalipah *et al*., 2021).

(v) Antioxidant Activity. DPPH and ABTS tests were used to determine the antioxidant capacity of EAE from *A. hypogaea L*. stems (Wahyuni *et al*., 2021a).

(vi) Toxicity Assay. The toxicity of EAE was evaluated using Brine Shrimp Lethal Test (BSLT) with the procedure outlined by Meyer (Musdalipah *et al*., 2021).

(vii) Cytotoxicity test. The EAE from the extract of A. hypogaea L. stems were tested for cytotoxicity in MCF-7 cells by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays (Asasutjarit *et al*., 2021).

(viii) Molecular Docking. RCSB protein database solved crystal structures of xanthine oxidase (XO) (PDB ID 3NRZ) and estrogen receptor alpha (ERα) (PDB ID 3ERT) (Cao *et al*., 2010; Shiau *et al*., 1998). This structure was then prepared by removing water molecules and bound ligands. Then, the protein added polar hydrogen atoms and calculated the Kollman partial charge (Kasmawati *et al*., 2022). The three-dimensional structures of the compounds identified by the LC-MS/MS analysis were collected from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/). The hydrogen atoms were added, and the gasteiger charges were calculated for each compound. All preparation processes utilize the MGLTools v.1.5.6 software. The molecular docking was simulated using AutoDock v.4.2 software to investigate the protein-ligand interactions and their affinity using the Lamarckian genetic algorithm with a population size of 100 individuals (Morris *et al*., 2009). The docking procedure was validated with RMSD criteria (< 2 Å) by redocking the hypoxanthine (HPA) to the XO and 4-hydroxytamoxifen (OHT) to the ERα (Arba *et al*., 2020). The docking process

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occurs at the binding site by following the coordinates of hypoxanthine and 4-hydroxytamoxifen on each protein. All compounds were docked with a cubic conformational search area of 30 x 30 x 30 Å for XO and 40 x 40 x 40 Å for ERα. All affinity energies are summarized, and protein-ligand interactions are visualized with the Discovery Studio Visualizer.

3. RESULTS AND DISCUSSION

3.1. Bibliometric Analysis

In the initial search, the chosen threshold found 2657 terms. There were 378 terms of literacy related to the topic, and 152 terms of articles were determined that are most relevant to the topic.

Figure 1 shows the increase in research published in Google Scholar-indexed journals regarding Pharmacological activity and *A. hypogea* stems. Research on Pharmacological activity and *A. hypogea* stems has increased from 2018 to 2021. There has been a decline in the number of publications in 2022.

The highest publication regarding Pharmalogical activity and *A. hypogea* stems is in 2021, with 152 articles published. In 2018 the number of publications was 90 articles. In 2019 the number of publications was 97 articles. In 2020 there were 117 articles. In 2021 there will be 152 articles, and in 2022 the number of publications regarding Pharmalogical activity and *A. hypogea* stems will only be 131 articles. The increase of research on Pharmalogical activity and *A. hypogea* stems can be used as material for consideration of research on Pharmalogical activity and A. *hypogea* stems which will be carried out in the future. The consideration that can be made is whether the research trend regarding Pharmalogical activity and *A. hypogea* stems is still relevant.

The minimum number of relationships between each term in VOSviewer is two. VOSviewer then evaluates the data. VOSviewer results are grouped into several clusters. In this study, data were obtained from 7 cluster groups. Each cluster describes the relationship between two or more terms.

Cluster number 1 is represented by Red color with 16 items. Cluster 2 is represented by Green color with a total of 16 items, Cluster 3 by Blue color with a total of 14 items, Cluster 4 by Yellow color with a total of 12 items, Cluster 5 is represented by Purple color with a total of 11 items, Cluster 6 by Cyan color with a total of 10 items, and Cluster 7 by orange color with a total of 7 items.

VOSviewer has three different representations for bibliometric mappings. These representations include network visualization (**Figure 2**), overlay visualization (**Figure 3**), and density visualization (**Figure 4**). The colored circles are labels for each keyword. The number of keywords in the title and abstract is closely related to the size of the circle. The size of each circle is closely related to the keyword frequency.

Figure 2 describes the visualization of the net. The results of data analysis show that A. hypogea are found in cluster 6 with the most number. The size of the circle is significantly large. The relationship between terms is depicted in **Figure 2**.

Figure 3 shows the overlay visualization. The newer the research, the brighter the color visualized. From the research data, the color of research under 2019 appears dark or blue, while research over 2021 is bright yellow. Hypogeal research is happening a lot in 2020 to 2021.

Figure 4 describes the density visualization. The results of the analysis show that the research has sufficient density visualization. Hypogeal research occurs significantly. This data analysis can be seen from the size of the circle and the visible light color.

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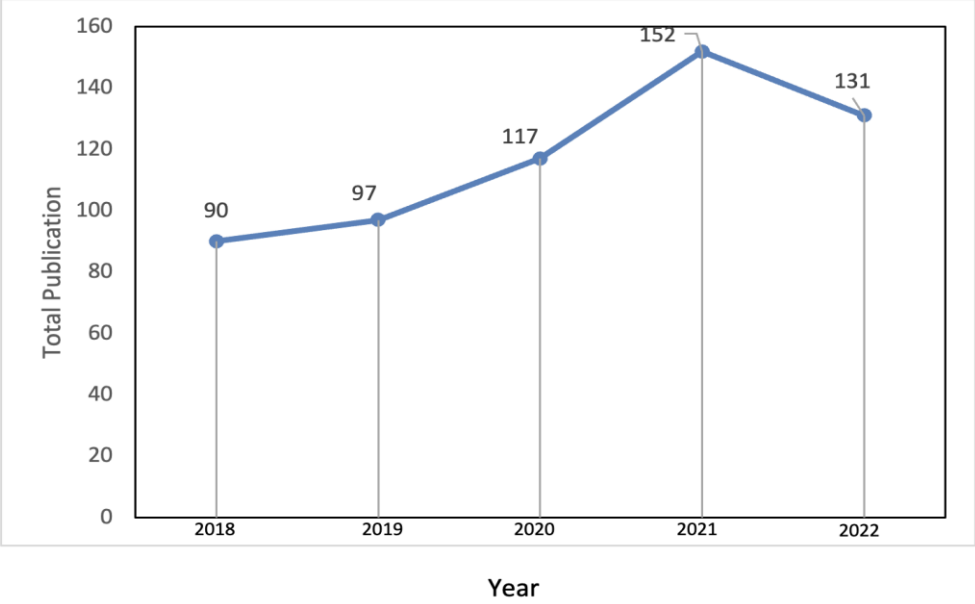

Figure 1. Daily variation in the sedimentation of the sludge at the outlet of the WWTP flocculator.

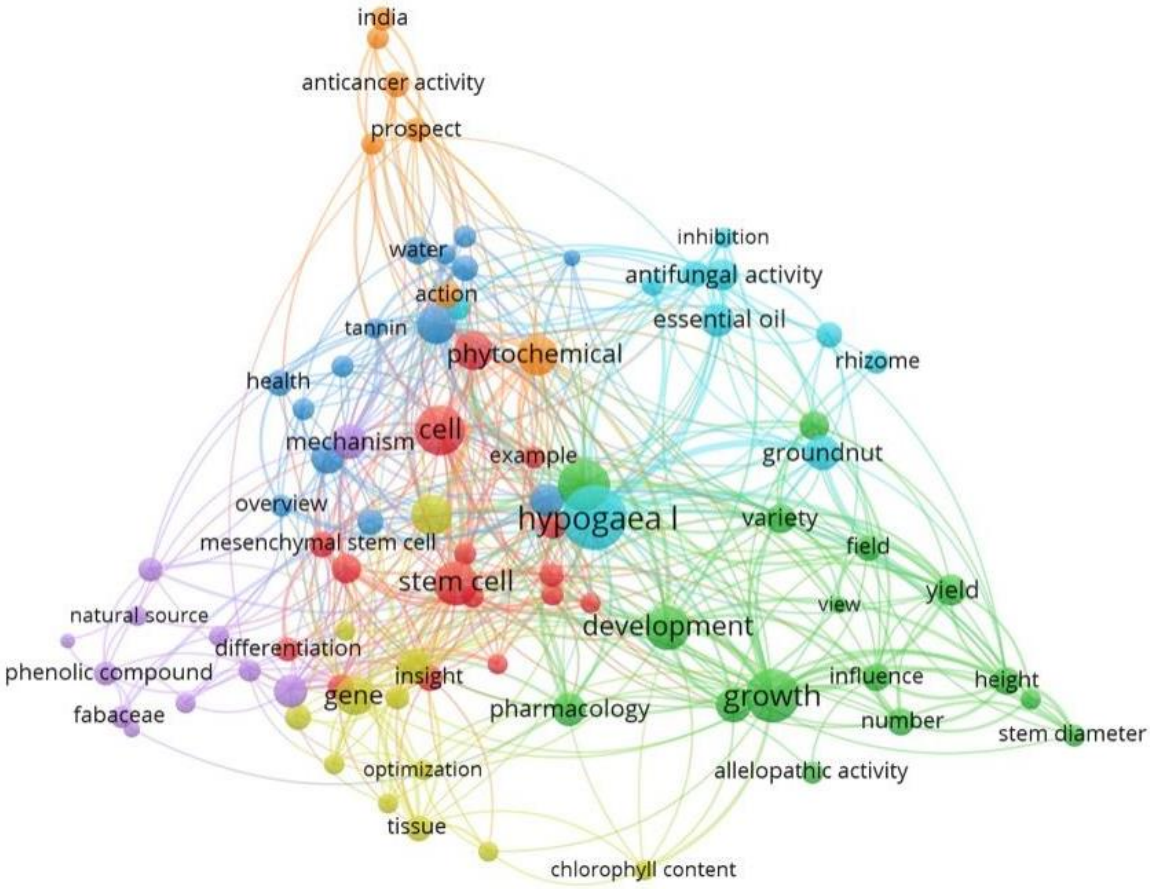

Figure 2. Network visualization of pharmalogival activity and *A. hypogea* stems publication.

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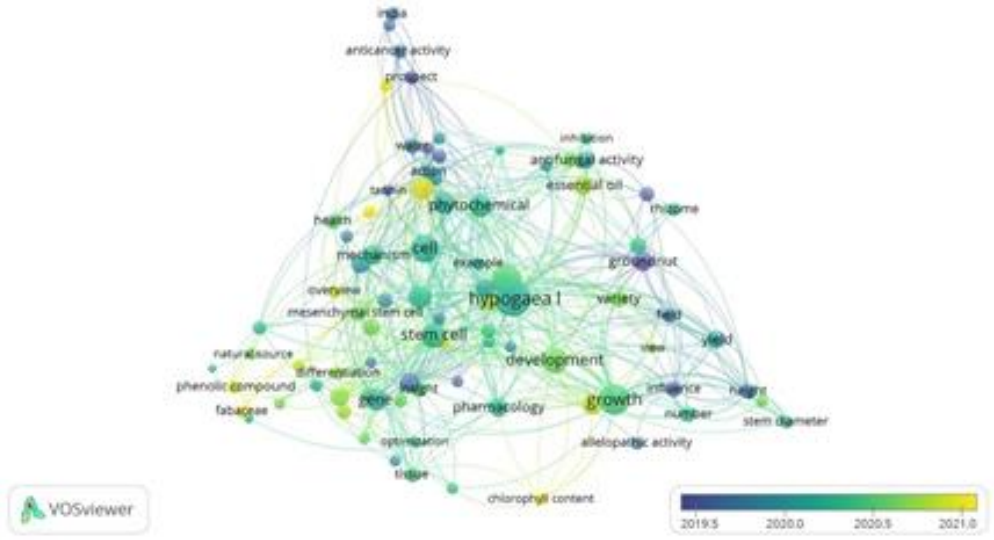

Figure 3. Overlay visualization of pharmalogival activity and *A. Hypogea* stems publication.

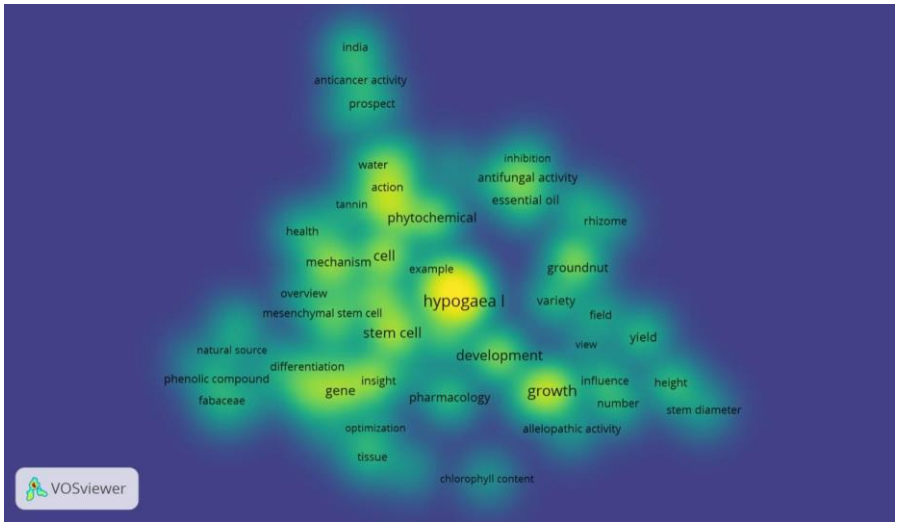

Figure 4. Density visualization of pharmalogival activity and *A. Hypogea* stems publication.

3.2. Phytochemical screening

Results of extraction, partition, and phytochemical screening of ME, EAE, and MR of *A. hypogaea L*. stems were displayed in **Table 1**. The results showed that ME, EAE, and MR samples from *Arachis hypogaea L*. stems contained terpenoids, saponins, tannins/polyphenols, flavonoids, and alkaloids. The results were by several studies showed that *A. hypogaea L*. stems contain polyphenols, flavonoids (Kyei *et al*., 2021), saponins (Kuang *et al*., 2017), terpenoids, tannins, and alkaloids (Prabasheela *et al*., 2015).

Table 1. Phytochemical screening of ME, EAE, and MR of *Arachis hypogaea L*. stems.

Sample (s)	Weight (g)	CHEMICAL CONTENTS				
		terpenoids	saponins	Tannins/ phenolics	Flavonoids	Alkaloids
ME	573	++	++	+++	++	+
EAE	78	++	+	++	+++	+
MR	458	+	++	+++	+	+

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3.3. Total Phenolic Content

The EAE of *A. hypogaea* L. stems has the highest flavonoid content compared to ME and MR. It is a consideration that makes EAE studied further for its biological activities. The TPC, TFC, and biological activities of EAE can be seen in **Table 2**.

3.4. LC-MS Data

Biological activities in EAE of A. hypogaea L. stems cannot be separated from their chemical content. **Table 2** informed that the concentration of TPC is four times that of TFC in EAE. To analyze phenolics compounds and flavonoids and also to support phytochemical screening results, identification of the compounds was done using LS-MS/MS. The results are shown in **Table 3**. Several compounds were successfully identified, including cis-caffeic acid, Baptifoline, Arteamisinine I, Harmol, 1,4-Dihydroxy-2-methyl-anthraquinone, (3R)-5'-Methoxy- vestitol, 5,7-Dihydroxy-3-(4'-hydroxy benzyl) chromone, Aschantin, and 3-(3',4'-Dihydroxybenzyl)-7-hydroxychroman-4-one.

Table 2. Total phenolic content (TPC), total flavonoid content (TFC), and biological activities of EAE of *Arachis hypogaea* L. stems.

Method	Regression Linear	Value
TPC (mgGAE/g ext)	y = 0.0081x + 0.0931 R^2 = 0.9843	88.47 ± 1.2
TFC (mgGAE/g ext)	y = 0.4810x + 17.293 R^2 = 0.9386	21.23 ± 1.3
DPPH (IC_{50} in *mg/L*)	y = 0.9695x + 6.251 R^2 = 0.9955	45.13 ± 1.7
ABTS (IC_{50} in *mg/L*)	y = 1.263 + 9.355 R^2 = 0.9386	33.69 ± 1.1
BSLT (LC_{50} in *mg/L*)	y = 1.5341x + 2.0817 R^2 = 0.9674	79.85 ± 1.3
MTT (IC_{50} in *mg/L*)	y = 0.1609x + 12.711 R^2 = 0.9264	231.75 ± 1.2

Table 3. Compounds of EAE of *Arachis hypogaea* L. stems based on LC-MS/MS data.

No of Compounds	Rt (min)	Observed [M+H] (m/z)	Experimental Neutral Mass (Da)	Theoretical Neutral Mass (Da)	MS^n Fragmentation	Component Name
1	5.92	181.0492	180.04226	180.042252	163.04, 135.04	cis-Caffeic acid
2	6.59	261.1596	260.15248	260.15248	202.09, 160.08, 144.04	Baptifoline
3	7.22	207.1372	206.13068	206.13068	189.13, 149.09	Arteamisinine I
4	7.55	199.0861	198.07931	198.22060	197.12, 179.11, 133.10	Harmol
5	8.63	255.0652	254.05791	254.05791	181.06, 163.07	1,4-Dihydroxy-2-methyl-anthraquinone
6	8.75	303.1074	302.11542	302.11542	137.06	(3R)-5'-Methoxy- vestitol
7	8.83	285.0761	284.06847	286.08412	163.11	5,7-Dihydroxy-3-(4'-hydroxy benzyl) chromone
8	9.1	401.1595	400.15220	400.15220	353.14, 217.09, 205.09, 190.06	Aschantin
9	9.34	287.0914	286.08412	286.08412	137.06	3-(3',4'-Dihydroxybenzyl)-7-hydroxy chroman-4-one

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3.5. Antiradical Activity

The antiradical activity of EAE of *A. hypogaea* L. was simulated against xanthine oxidase. The docking procedure was proper, with an RMSD of 0.514 Å (**Figure 5**). Overall, five compounds have lower binding energies than HPA (-5.73 kcal/mol), namely compounds **4**, **6**, **9**, **7**, and **1**, which are -7.7 kcal/mol, -7.56 kcal/mol, -6.47 kcal/mol, -6.42 kcal/mol, and -6.37 kcal/mol, respectively. On the other hand, compounds **8**, **2**, **5**, and **3** show higher binding energies of -0.22 kcal/mol, -1.47 kcal/mol, -4.56 kcal/mol, and -5.35 kcal/mol.

Generally, hydrogen bond (H-bond) interactions were observed in HPA, **2**, **5, 7**, and **9** with Glu802 and Arg880 residues. Furthermore, almost all compounds formed H-bond interactions with residue Thr1010, except for **4** (Glu802 and Glu1261) and **8** (Ser1008). Uniquely, there are five hydrogen bond interactions in compound **1**, namely Ser876, Thr1010, Val1011, Ala1079, and Glu1261 at the XO binding site. Meanwhile, hydrophobic interactions towards residues Leu873, Phe914, Phe1009, Ala1078, and Ala1079 were observed in all compounds (**Figure 6**).

3.6. Anticancer activity

The anticancer activity of this extract against ERα was experimentally investigated using the molecular docking method with a proper procedure (RMSD of 1.317 Å) (**Figure 7**). The molecular docking results revealed that OHT had a more negative binding energy (-11.5 kcal/mol) than all the compounds identified in the LC-MS/MS results. **7** and **9** are the compounds that have the most potential to inhibit ERα with binding energies of -8.2 and -8.16 kcal/mol, respectively. Meanwhile, compounds **6**, **2**, **8**, **3**, **4**, **5**, and **1** have slightly lower potency than **7** and **9** with binding energies of -6.83 kcal/mol, -6.76, -6.39, -6.21, -5.56, -4.94, and -4.56 kcal/mol.

H-bond interactions were formed with the Glu353 and Arg394 residues of ERα in all compounds except for **5**. Interestingly, no H-bond interaction was observed in these compounds at the ERα binding sites. Meanwhile, the hydrophobic interactions dominated the interactions of the compounds in the *A. hypogaea* L. extract towards Met343, Leu387, Leu391, Met388, and Leu525 residues from ERα (**Figure 8**).

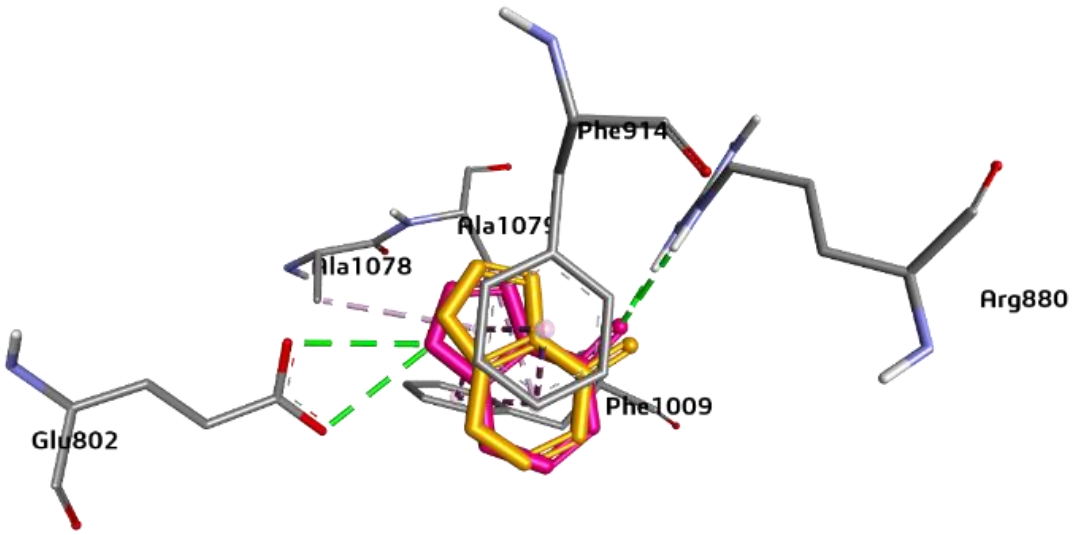

Figure 5. The conformation of HPA after the redocking process (pink) and crystallography conformation (yellow).

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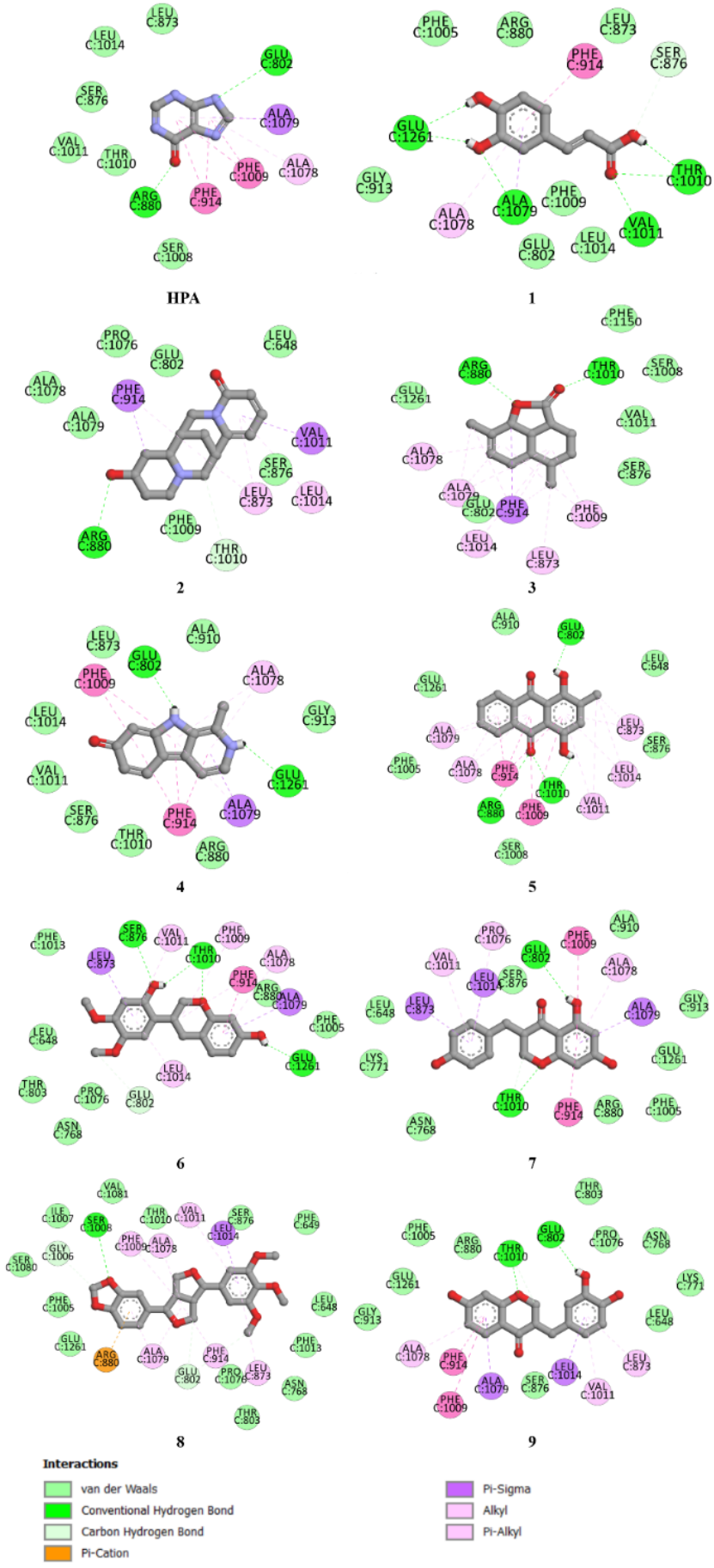

Figure 6. The 2D interaction of each molecule in the active site of xanthine oxidase.

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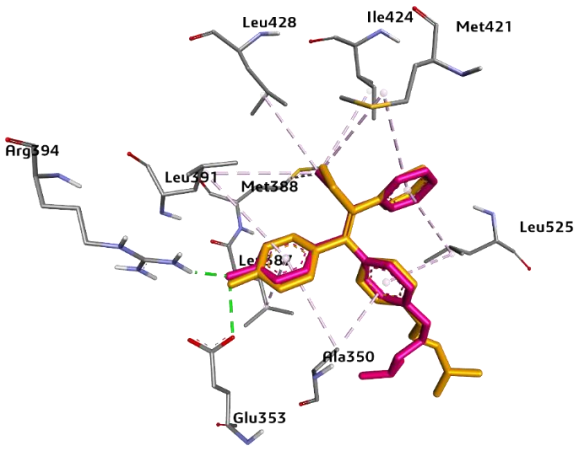

Figure 7. The conformation of OHT after the redocking process (pink) and crystallography conformation (yellow).

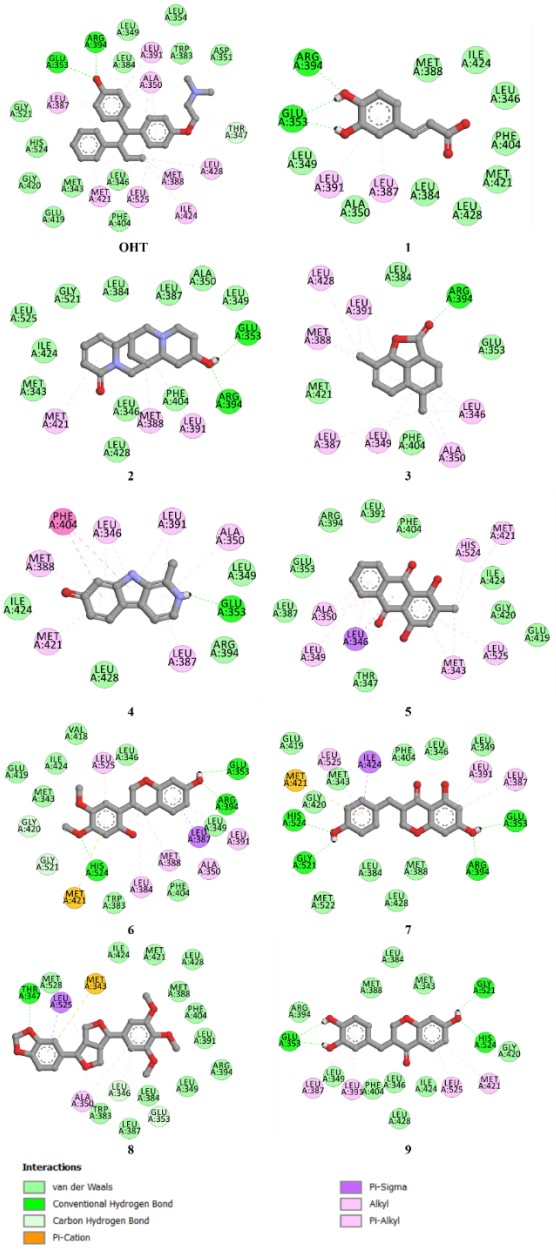

Figure 8. The 2D interaction of each molecule in the active site of estrogen receptor alpha.

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4. DISCUSSION

The study of A. hypogea stems as a pharmaceutical raw material in the future is still interesting as shown by the bibliometric analysis in **Figure 1**. Furthermore, studies of biological activity and its relationship with chemical constituents in-vitro and in-silico are still very limited. Extraction of *A. hypogaea L*. stems using methanol yielded 15.91% methanol extract (ME). Re-extraction of ME using ethyl acetate solvent obtained ethyl acetate extract (EAE) of 13.71% and methanol residue (MR) of 86.29% by weight of ME (**Table 1**). **Table 1** also shows that the major chemical groups of the ME and MR of *A. hypogaea L*. stems are tannins and phenolics compounds. At the same time, flavonoids are the primary component of EAE of *A. hypogaea L.* stems. Based on the flavonoid's contents, the biological activities, including antioxidant, toxicity, and cytotoxicity, were done towards EAE of *A. hypogaea L*. stems.

Data of TPC, TFC, and biological activities of *A. hypogaea L*. stems in **Table 2** will be more detailed and presented in chart form in **Figure 9**. **Table 2** and **Figure 9** reveal that TPC and TFC supported phytochemical screening results about the existence of phenolic compounds and flavonoids. which were 88.47 mgGAE/g ext, and 21.23 mgQE/g ext, respectively. The antioxidant potency of EAE of *A. hypogaea* stems indicated strong antioxidant potency with IC_{50}<50 mg/L based on DPPH and ABTS data, which were 45.13 and 33.69 µg/L), respectively (Sadarun *et al*., 2022). Compared to other plant components, the antioxidant activity of the essential oil of *Arachis hypogea* leaves was screened using the DPPH method. The IC_{50} values for the ethanolic extract of *A. hypogea* were found to be 0.462 µg/mL, while the IC_{50} values obtained for the essential oil extract of *A. hypogea* were absent. Additionally, 15 components from *A. hypogea* oil were extracted and identified using Gas Chromatography-Mass Spectroscopy (GC-MS) analysis. The main compounds are tetradecanoic acid (21.98%), 4,7-dimethyl-1H-isoindol-1,3-yl methyl ether (37.14%), cyclohexanol (4.21%), and O-phenylaniline (3.69%) (Alex *et al*., 2020).

The IC_{50} values of the methanol and ethanol extract from peanut hulls (PH) for radical scavenging were 22.7-76.4 and 38.9-98.6 µg/mL, respectively. The PH extracts' capacity to scavenge free radicals was evaluated using the DPPH test (Hussain *et al*., 2012).

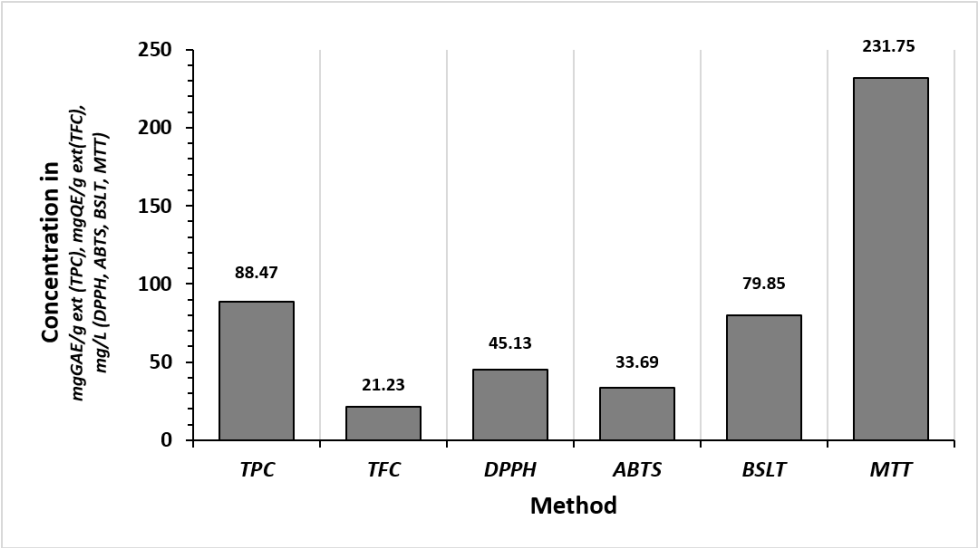

Figure 9. Biological activity of EAE of *A. hypogaea* L stem in various methods.

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The stem was also potentially an antioxidant source, aside from other parts of the plant. Centrifugal partition chromatography (CPC) was used to purify the hairy root cultures of *A. hypogaea*, and the thiobarbituric acid reactive substances (TBARS) assay was used to measure the antioxidant activity of the compounds and the cytotoxicity of the compounds using the MTT assay. According to research findings, the compounds resveratrol, arachidin-1, and arachidin-3 are each 97.1%, 97.0%, and 91.8%. Resveratrol and arachidin-1 doses of 27 and 7 µg each decreased lipid oxidation. However, arachidin-3 doses did not prevent oxidation over 27 µg. Arachidin-1, arachidin-3, and CPC-purified resveratrol all reduced oxidation at 14, 7, and 14 µg, respectively. In RAW 264.7 and HeLa cell lines, arachidin-1 27 µg and arachidin-3 55 µg showed cytotoxicity, although resveratrol showed no cytotoxicity to either cell line (Abbott *et al*., 2010).

In addition, the toxicity of EAE of *A. hypogaea* stems towards *A. salina* larvae has toxic category with LC_{50}<1000 mg/L, and moderately active against breast cancer cells lines MCF-7 with IC_{50}<500 mg/L (Sadarun *et al*., 2022). The LC_{50} in *A. salina* was 79.85 µg/L, while the IC_{50} against MCF-7 cell line was 231.75 µg/L. Extract activity is inseparable from its chemical content. LC-MS/MS analysis results in support compound groups resulting from phytochemical screening. The data from LC-MS/MS consists of Retention time (Rt) (min), Observed [M+H] (m/z), Experimental Neutral Mass (Da), Theoretical Neutral Mass (Da), MS^n Fragmentation, and Component Name. Interpreting all data and comparing them with references resulted in compound structures like the names obtained from LC-MS/MS (**Table 3**) and the fragmentation patterns in **Figures 10-19**. Compound **1** is cis-Caffeic acid (Santos *et al*., 2013), **2** (Baptifoline) (Chang *et al*., 2016), **3** (Arteamisinine I) (Oke *et al*., 2022), **4** (Harmol) (Fahmy *et al*., 2021), **5** (1,4-Dihydroxy-2-methyl-anthraquinone) (Saha *et al*., 2015), **6** (3R)-5'-Methoxy-vestitol (Bankova *et al*., 2016), **7** (5,7-Dihydroxy-3-(4'-hydroxybenzyl) chromone (Robbani *et al*., 2022), **8** (Aschantin) (Patyra *et al*., 2022), and **9** (3-(3',4'-Dihydroxybenzyl)-7-hydroxychroman-4-one) (Yodha *et al*., 2021). The identified compounds are nine of fifteen major compounds from the EAE of *A. hypogaea* stems. The unidentified compounds have molecular formulas $C_{34}H_{40}O_9$, $C_{12}H_{18}O_4$, $C_{13}H_{15}NO_5$, $C_{10}H_{17}NO_5$, $C_{31}H_{53}NO_3$, and $C_{25}H_{26}N_2O_3$). The structure of identified compounds from EAE of *A. hypogaea* L. stems can be seen in **Figure 10.**

Figure 10 interprets the fragmentation pattern of peak one in Table 3 with a retention time of 5.92 minutes which is relevant to the structure of cis-caffeic acid (Santos *et al*., 2013). The fragments consist of m/z 181.0492 (observed, $[M+H]^+$) and MS^n fragmentation (m/z 163.04, 135.04). Fragment of m/z 181.0492 comes from the molecular weight of cis-caffeic acid plus the atomic weight of H or $[M+H]^+$, m/z 163.04 is the result of releasing one OH group (m/z 17) from the molecular weight of cis-caffeic acid (m/z 180.04226) or Experimental Neutral Mass (Da) or $[M-OH]^+$. A fragment of m/z 163.04 is the most stable fragment shown by the highest intensity. The fragment with m/z 135.04 originates from the fragmentation m/z 163.04 by removing CO units (m/z 28) or $[M-CO]^+$.

Peak no 2 in **Table 3** has a retention time of 6.59 minutes and molecular weight or neutral mass m/z 260.15248 are similar to Baptifoline (Chang *et al*., 2016). The suitability of the chemical structure is supported by the fragmentation pattern of Baptifoline in **Figure 11**. Fragment of m/z 261.1596 comes from $[M+H]^+$, m/z 202.09 $[M-C_3H_6O]^+$, m/z 160.08 $[M- C_3H_6O-C_2H_4N]^+$ and m/z 144.04 $[M- C_3H_6O-C_2H_4N-CH_4]^+$.

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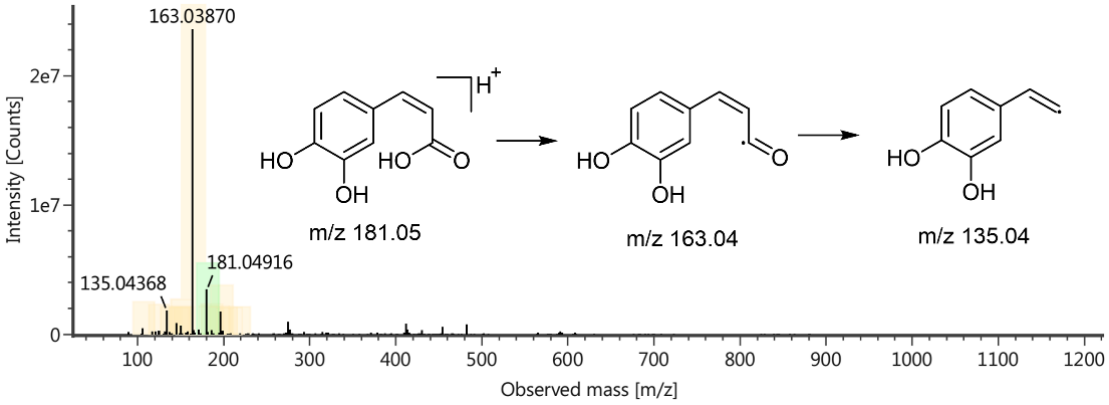

Figure 10. Fragmentation of ESI-MSn pattern of identified compound cis-Caffeic acid of ethyl acetate extract of *A. hypogaea L*. stem.

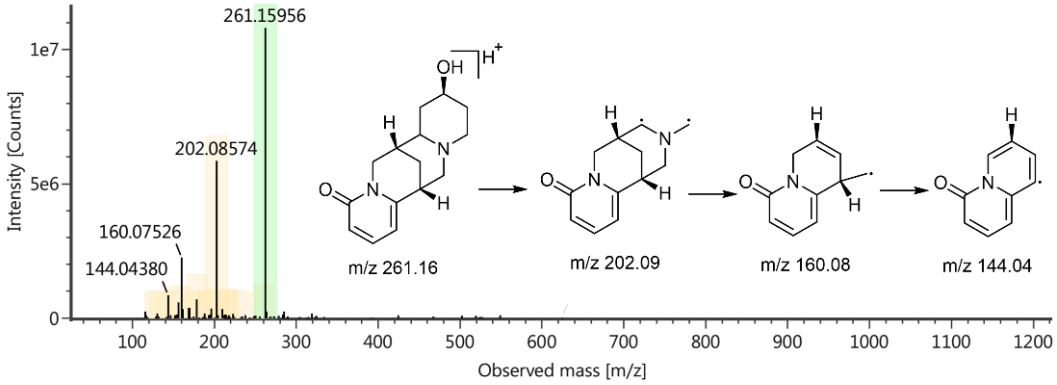

Figure 11. Fragmentation of ESI-MS^n pattern of identified compound Baptifoline of ethyl acetate extract of *A. hypogaea* L. stem.

Peak no 3 in **Table 3** has a retention time of 7.22 minutes and molecular weight or neutral mass m/z 206.13068 are similar to Arteamisinine I (Oke *et al*., 2022). The suitability of the chemical structure is supported by the fragmentation pattern of Arteamisinine I in **Figure 12**. Fragment of m/z 207.1372 comes from $[M+H]^+$, m/z 189.13 $[M-CH_3-H_2]^+$, and m/z 149.09 $[M-CH_3-H_2-C_3H_4]^+$.

Peak no 4 in **Table 3** has a retention time of 7.55 minutes and molecular weight or neutral mass m/z 198.07931are similar to Harmol (Fahmy *et al*., 2021). The suitability of the chemical structure is supported by the fragmentation pattern of Harmol in **Figure 13**. Fragment of m/z 199.0861 comes from $[M+H]^+$, m/z 197.12 $[M-H]^+$, m/z 179.11 $[M-OH-H_2]^+$ and m/z 133.10 $[M-H-C_4H_4N]^+$.

Peak no 5 in **Table 3** has a retention time of 8.63 minutes and molecular weight or neutral mass m/z 254.05791 are similar to 1,4-Dihydroxy-2-methyl-anthraquinone (Saha *et al*., 2015). The suitability of the chemical structure is supported by the fragmentation pattern of 1,4-Dihydroxy-2-methyl-anthraquinon in **Figure 14**. Fragment of m/z 255.0652 comes from [M+H], m/z 181.06 $[M+H-C_6H_2]^+$, and m/z 163.07 $[M-C_6H_2-OH]^+$.

Peak no 6 in **Table 3** has a retention time of 8.75 minutes and molecular weight or neutral mass m/z 302.11542 are similar to (3R)-5'-Methoxy-vestitol (Bankova *et al*., 2016). The suitability of the chemical structure is supported by the fragmentation pattern of (3R)-5'-Methoxy-vestitol in **Figure 15**. Fragment of m/z 303.1074 comes from $[M+H]^+$ and m/z 137.06 is for $[M+H-C_9H_{10}O_3]^+$.

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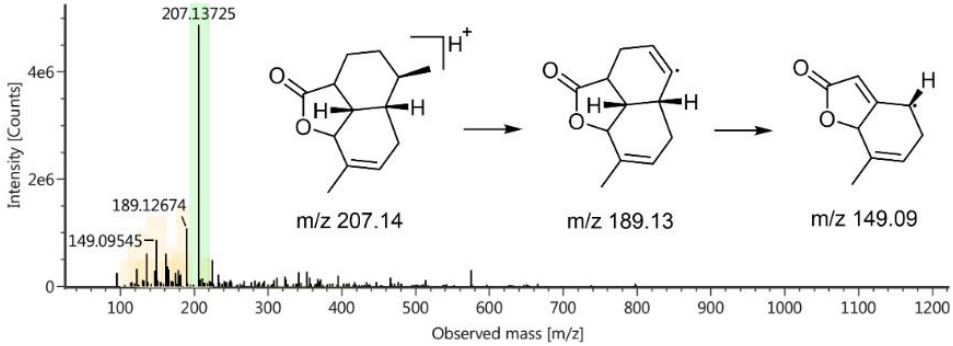

Figure 12. Fragmentation of ESI-MS^n pattern of identified compound Arteamisinine I of ethyl acetate extract of *A. hypogaea* L. stem.

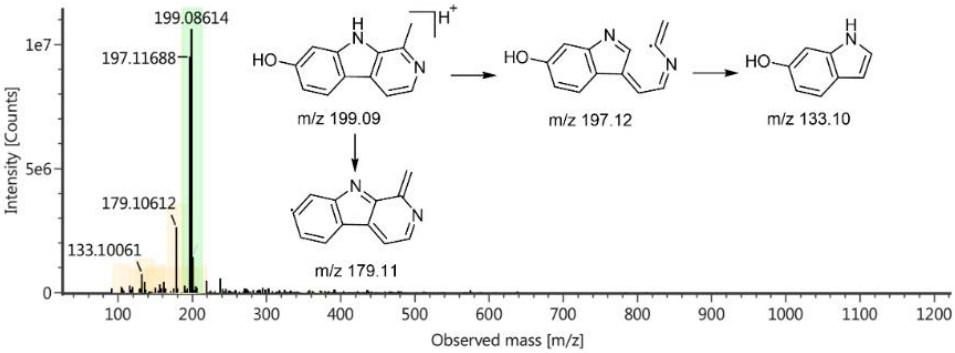

Figure 13. Fragmentation of ESI-MS^n pattern of identified compound Harmol of ethyl acetate extract of *A. hypogaea* L. stem.

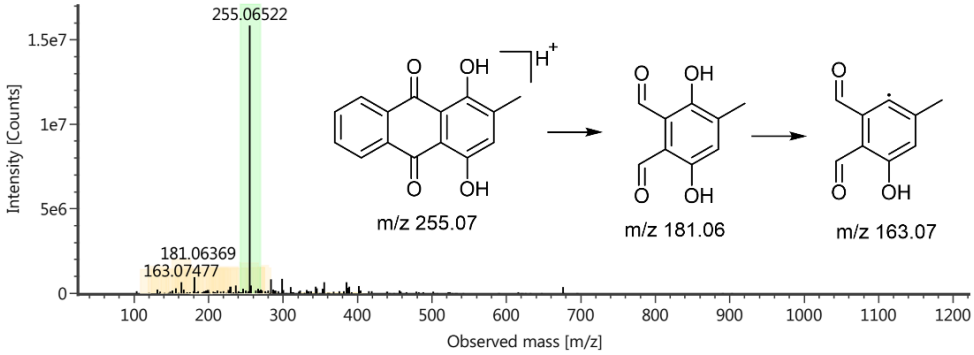

Figure 14. Fragmentation of ESI-MS^n pattern of identified compound 1,4-dihydroxy-2-methyl-anthraquinone of ethyl acetate extract of *A. hypogaea* L. stem.

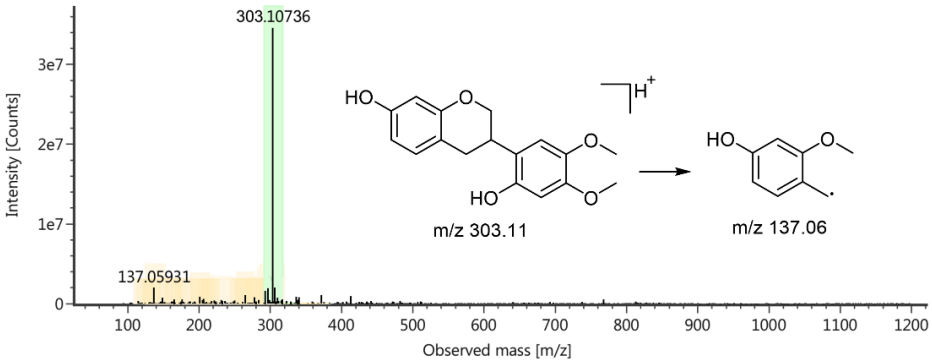

Figure 15. Fragmentation of ESI-MS^n pattern of identified compound (3R)-5'-methoxy-vestitol of ethyl acetate extract of *A. hypogaea* L. stem.

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Peak no 7 in **Table 3** has a retention time of 8.83 minutes and molecular weight or neutral mass m/z 284.06847 are similar to 5,7-Dihydroxy-3-(4'-hydroxybenzyl) chromone (Robbani *et al.*, 2022). The suitability of the chemical structure is supported by the fragmentation pattern of 5,7-Dihydroxy-3-(4'-hydroxybenzyl) chromone in **Figure 16**. Fragment of m/z 285.0761 comes from [M+H] and m/z 163.11 is for $[M+H-C_7H_6O_2]^+$.

Peak no 8 in **Table 3** has a retention time of 9.1 minutes and molecular weight or neutral mass m/z 400.15220 are similar to Aschantin (Patyra *et al.*, 2022). The suitability of the chemical structure is supported by the fragmentation pattern of Aschantin in **Figure 17**. Fragment of m/z 401.1595 comes from $[M+H]^+$, m/z 353.14 $[M-CH_4O_2]^+$, m/z 217.09 $[M-CH_4O_2-C_8H_8O_2]^+$, m/z 205.09$[M-C_{10}H_{12}O_4]^+$ and m/z 190.06 $[M-C_{10}H_{12}O_4-O+H]^+$.

Peak no 9 in **Table 3** has a retention time of 9.34 minutes and molecular weight or neutral mass m/z 286.08412 are similar to 3-(3',4'-Dihydroxybenzyl)-7-hydroxychroman-4-one (Yodha *et al.*, 2021). The suitability of the chemical structure is supported by the fragmentation pattern of 3-(3',4'-Dihydroxybenzyl)-7-hydroxychroman-4-one in **Figure 18**. Fragment of m/z 287.0914 comes from $[M+H]^+$ and m/z 137.06 is for $[M+H-C_9H_{10}O_2]^+$.

Based on the analysis of the LC-MS/MS data above, the structures of the compounds contained in the EAE are shown in **Figure 19**.

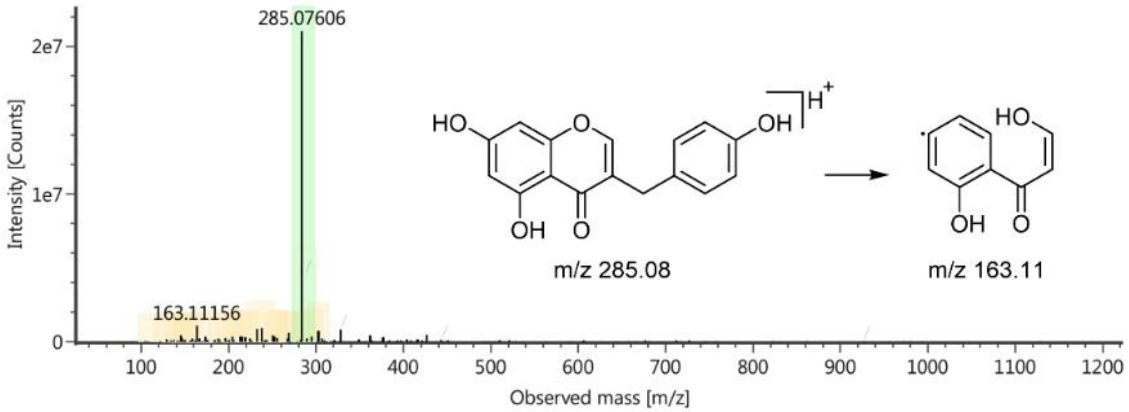

Figure 16. Fragmentation of ESI-MS^n pattern of identified compound 5,7-dihydroxy-3-(4'-hydroxybenzyl) chromone of ethyl acetate extract of *A. hypogaea* L. stem.

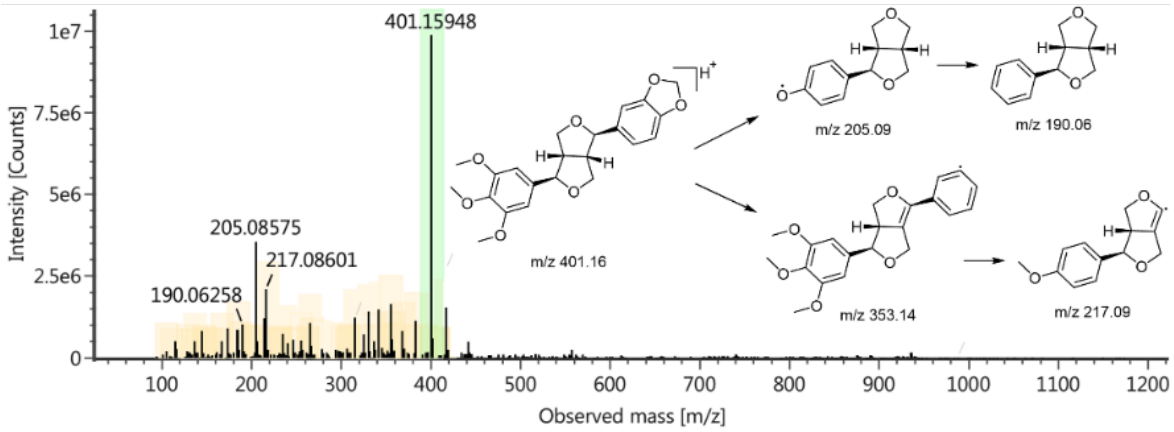

Figure 17. Fragmentation of ESI-MS^n pattern of identified compound Aschantin of ethyl acetate extract of *A. hypogaea* L. stem.

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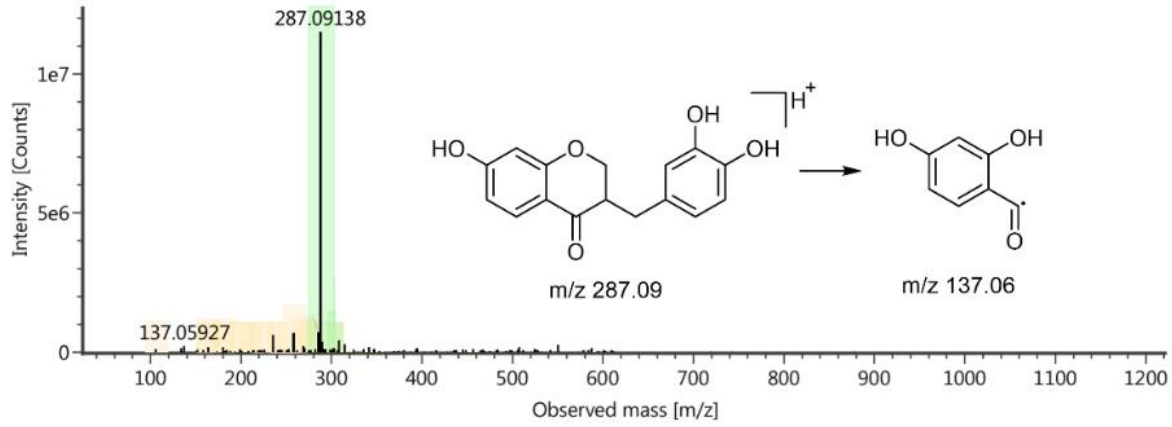

Figure 18. Fragmentation of ESI-MS^n pattern of identified compound 3-(3',4'-Dihydroxybenzyl)-7-hydroxychroman-4-one of ethyl acetate extract of *A. hypogaea* L. stem.

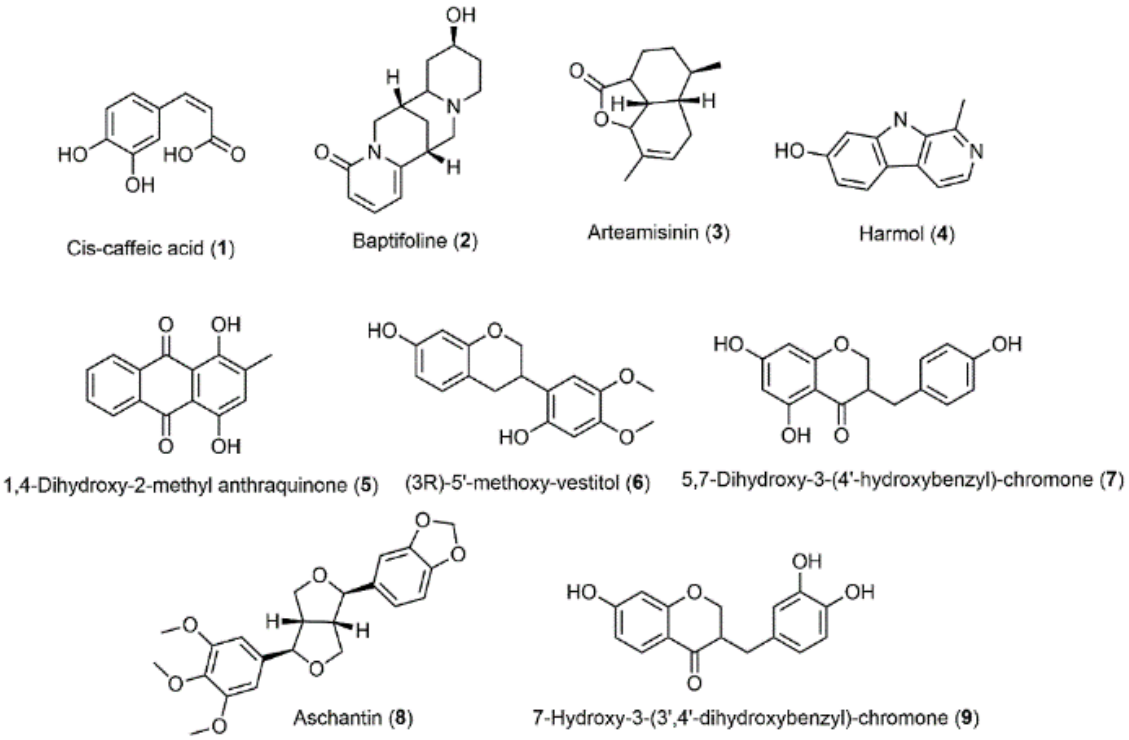

Figure 19. Compound structures of ethyl acetate extract of *Arachis hypogaea* stems.

Compound **1** and chromones (**7** & **9**) are a phenylpropanoids derivate, compounds **2** and **4** are alkaloids, compounds **3** (terpenoids), **5** (anthraquinone), **6** (isoflavonoids), and **7** are lignans. The presence of isoflavonoids and other phenolic compounds influences the antioxidant properties of EAE. Some compounds reported to have antioxidant potency, including vestitol, have intense activity as an antioxidant (Morais *et al.*, 2021; Yu *et al.*, 2007) which can reduce free radical formation and scavenge free radicals (Pietta, 2000), and caffeic acid also an active antioxidant compound (Gulcin, 2006).

Toxicity of EAE of peanut stems towards *Artemia salina* and anticancer potential against breast cancer were supported by presenting of harmol, which was active against Human Non-small Cell Lung Cancer A549 cells by autophagy mechanism (Abe *et al.*, 2011), baptifoline was active towards HL-60 and NoVo cells lines (Innocenti *et al.*, 2006), and cytotoxic property against HeLa

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cells lines displayed by vestitol (Forma & Brys, 2021). Compared to HFF normal cells, the viability of A549 lung cancer cells was dramatically reduced by the 50.3 nm Arachis hypogaea oil nanoemulsion (AHO-NE).

The rising SubG1 peaks and the overexpression of Caspase 3 show that AHO-NE causes apoptosis in A549 cells. Additionally, it has antioxidant action (ABTS IC50: 270.42 lg/mL; DPPH IC50: 208.51 lg/mL) (Fazelifar *et al*., 2021). Another research discovered that Resveratrol (RV) in peanut stem extract (PSE) showed that both RV and PSE dose-dependently induced cell death in DOC-2/DAB2 interactive protein (DAB2IP) deficient prostate cancer (PCa) cells with the radioresistant phenotype. Furthermore, either RV or PSE alone or in combination led to a delayed repair of radiation-induced DNA double-strand breaks (DSB) and a protracted G2/M arrest, which led to apoptosis, ultimately leading to the death of PCa cells (Chen *et al*., 2017).

The presence of two identified alkaloids (harmol and baptifoline) and an unidentified alkaloid ($C_{13}H_{15}NO_5$, $C_{10}H_{17}NO_5$, $C_{31}H_{53}NO_3$, and $C_{25}H_{26}N_2O_3$) are thought to cause EAE of *A. hypogaea* stems from being toxic and has potential as anticancer, especially breast cancer. It follows the breast cancer drug that has been traded, tamoxifen, which includes alkaloids. To provide a quick solution, we performed an *in-silico* study using molecular docking to estimate the antiradical and anticancer activity of the chemical components in *A. hypogaea* L. extract. The LC-MS/MS analysis revealed that nine compounds were successfully docked to XO and ERα. Five compounds from EAE *A. hypogaea* L., namely compounds **4**, **6**, **9**, **7**, and **1**, demonstrated antiradical activity by targeting XO. Three of these compounds are flavonoids (**6**, **7**, and **9**), alkaloids (**4**), and phenylpropanoid derivatives (**1**). Flavonoids, generally, are known to have antioxidant properties, which is in line with our findings.

The five compounds interacted with XO's active site residues (Glu802 and Arg880) and the conserved residue Glu1261. Meanwhile, anticancer activity targeting ERα revealed the potential of two compounds from this extract (**7** and **9**). These two compounds interacted with conserved residues Glu353 and Arg394 from ERα. Based on the ligand binding mode, it was revealed that compounds **7** and **9** could act as antiradical and anticancer and achieve a similar interaction with the native ligands (HPA and OHT) more effectively while obtaining the highest binding energy than the other compounds.

5. CONCLUSION

Based on the chemical profile, in-vitro, and in-silico studies, the EAE of *Arachis hypogaea* L. stems reveal antioxidant and cytotoxic potencies. Also, they have an outstanding possibility of becoming nutraceutical. The presence of vestitol and caffeic acid supported the antioxidant potency. In addition, toxicity against *Artemia salina* and cytotoxic toward MCF-7 cell lines were thought to be caused by the chemical content consisting of baptifolin, harmol, and several unidentified alkaloi.

6. ACKNOWLEDGMENT

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7. AUTHORS' NOTE

The authors declare that there is no conflict of interest regarding the publication of this article. Authors confirmed that the paper was free of plagiarism.

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