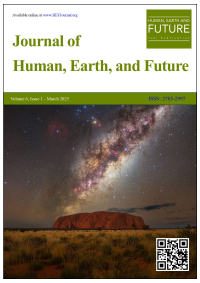
Available online at www.HEFJournal.org

ISSN: 2785-2997

Journal of
Human, Earth, and Future

Vol. 6, No. 1, March, 2025



Phytochemicals and Bioactivities of *Erigeron Sumatrensis* Retz. from Gayo Highlands: Antioxidant, Antidiabetic, Anticancer

Vivera Ruselli Puspa [1, 2], Zumaidar [3*], Nurdin [4], Fitmawati [5]

[1] *Graduate School of Mathematics and Applied Science, Universitas Syiah Kuala, Banda Aceh 23111 Indonesia.*

[2] *Department of Biology Education, Faculty of Teacher Training and Education, Universitas Syiah Kuala, Banda Aceh 23111, Indonesia.*

[3] *Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Banda Aceh 24415, Indonesia.*

[4] *Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Banda Aceh 24415, Indonesia.*

[5] *Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Riau, Pekanbaru 28293, Indonesia.*

Received 16 August 2024; Revised 11 January 2025; Accepted 19 January 2025; Published 01 March 2025

Abstract

The Asteraceae is renowned for its diverse medicinal properties. Among its members, *Erigeron sumatrensis*, locally known as Jelantir, is an ecologically important plant in the Gayo Highlands of Indonesia with unexplored therapeutic potential. This study investigated the methanol leaf extract's phytochemical composition, antioxidant activity, and antidiabetic and anticancer properties. Phytochemical examination revealed the presence of several bioactive components in the methanol extract, including flavonoids, phenolics, terpenoids, steroids, tannins, and alkaloids. Quantification revealed substantial levels of total phenolic content (11854.50 mg GAE/g), total flavonoid content (1056.15 mg QE/g), and total tannin content (442.73 mg TAE/g). The extract exhibited potent antioxidant activity in DPPH, FRAP, and ABTS assays, with IC_{50} values of 48.67 ± 32.38 µg/mL, 35.61 ± 2.05 µg/mL, and 29.60 ± 5.15 µg/mL. GC-MS analysis identified glycidyl palmitate (21.35%) as the most abundant compound in the extract. PASS prediction highlighted several compounds, including glycidyl palmitate, myristic acid glycidyl ester, 9-Octadecenoic acid (Z)-, oxiranylmethyl ester, hexadecanoic acid, estra-1,3,5-trien-17ß-ol, and caryophyllene oxide, as potential antidiabetic and anticancer agents. ADMET analysis further suggested estra-1,3,5-trien-17ß-ol and caryophyllene oxide as promising candidates for oral drug development due to their adherence to Lipinski's rule of five. Molecular docking studies revealed favorable interactions between these compounds and target proteins. In vitro assays confirmed the extract's inability to inhibit α-glucosidase activity but were able to suppress MCF-7 breast cancer cell proliferation. This study gives the first evidence of *E. sumatrensis* therapeutic potential in the Gayo Highlands. Our findings highlight its rich phytochemical profile, potent antioxidant activity, and promising antidiabetic and anticancer properties, warranting further investigation into its clinical applications and optimization for therapeutic use.

Keywords: Asteraceae; *Erigeron sumatrensis* Retz.; α-Glucosidase Inhibitor; MCF-7 Cell; Gayo Highlands.

1. Introduction

Oxidative stress arises from a physiological imbalance between the systemic concentration of antioxidants and free radicals [1]. An imbalance in this context can induce oxidative stress, damaging biomolecules. This phenomenon has been implicated in the pathogenesis of various diseases, including diabetes mellitus and several types of cancer. Diabetes mellitus is a metabolic disorder primarily characterized by chronic hyperglycemia and is closely associated

* Corresponding author: zumaidar@usk.ac.id

http://dx.doi.org/10.28991/HEF-2025-06-01-04

with increased oxidative stress. Elevated glucose levels can overwhelm endogenous antioxidant defense mechanisms by triggering the overproduction of free radicals. This imbalance contributes to pancreatic beta-cell dysfunction, insulin resistance, and vascular complications. Similarly, oxidative stress plays a critical role in cancer development and progression by inducing DNA mutations, promoting uncontrolled cell proliferation, and facilitating tumor invasion and metastasis [2, 3].

Diabetes, a complex metabolic disorder with a multifactorial etiology encompassing genetic predisposition and lifestyle influences, presents a growing global health concern. Projections suggest a staggering increase in global prevalence, with an estimated 643 million cases by 2030, escalating to 783 million by 2045 [4]. Indonesia, in particular, faces a significant public health challenge due to its high diabetes prevalence. Ranked fifth globally, Indonesia reports 19.5 million cases, placing it among heavily burdened nations such as China, India, Pakistan, and the United States. Alarmingly, projections estimate a surge in Indonesian cases, potentially reaching 45 million by 2045. The rising incidence among adolescents and children further underscores the urgent need for effective prevention and management strategies [4]. Acarbose, a commonly prescribed antidiabetic drug, inhibits carbohydrate-digesting enzymes in the small intestine. This mechanism effectively slows sugar absorption, mitigating postprandial blood glucose spikes. Emerging research suggests a potential association between the gut microbiome and acarbose resistance. Studies have identified microbial enzymes capable of degrading acarbose, potentially diminishing its therapeutic efficacy. The economic implications of diabetes are substantial [5]. In 2021 alone, global diabetes treatment expenditures reached an estimated one trillion USD, with projections indicating a significant rise in the future. This significant financial burden highlights the urgent need for the development and implementation of innovative and cost-effective strategies for the management of diabetes [3].

Cancer constitutes a significant global health challenge, ranking as the second leading cause of mortality worldwide. Notably, it represents the seventh leading cause of death in Indonesia. The global cancer burden exhibits a concerning upward trajectory, with an estimated 8.2 million fatalities attributed to the disease in 2012 alone. The World Health Organization states that cancer affects a staggering 1 in 8 men and 1 in 11 women globally. Disturbingly, 70% of cancer-related deaths occur in developing countries [6]. Breast cancer currently stands as the most prevalent cancer worldwide, with 2.3 million cases diagnosed annually, representing 11.7% of all cancer diagnoses. The disease carries a significant mortality rate, accounting for 6.9% of cancer-related deaths [7]. Although tamoxifen remains a critical component of breast cancer treatment regimens, the development of tamoxifen resistance presents a substantial clinical obstacle [8]. The limitations of current cancer treatments, including issues like drug resistance and severe side effects, have prompted a renewed focus on exploring the vast and largely untapped potential of nature's pharmacopeia. Plants, with their intricate biochemical pathways and evolutionary history, offer a rich source of bioactive compounds with diverse mechanisms of action.

The Asteraceae has attracted considerable interest for its potential as a source of novel antidiabetic and anticancer agents. This is attributed to this family's diverse bioactive compounds, including alkaloids, phenolates, terpenoids, flavonoids, saponins, glycosides, xatones, and polysaccharides [9]. Research has established the blood glucose-lowering potential of leaf extracts derived from certain Asteraceae species. Notably, *Vernonia amygdalina* Delile, *Tithonia diversifolia*, *Chromolaena odorata*, *Ageratum conyzoides* L, and *Artemisia absinthium* L. have all exhibited blood glucose-lowering properties in preclinical models [10]. Furthermore, a growing body of research suggests promising anticancer potential within the Asteraceae. Species such as *Artemisia vulgaris* Linn., *Artemisia china* Berg ex Poljakov, *Cosmos caudatus* Kunth, *Vernonia amygdalina*, *Launaea cornuta* (Hochst. Ex Oliv. Hiern) C. Jeffrey, *Microglossa pyrifolia* (Lam.) Kuntze, *Solanecio mannii* (Hook. f.) C. Jeffrey, *Acmella caulirhiza* Delile, *Bidens pilosa* L, and *Galinsoga parviflora* Cav. have shown encouraging results in preclinical cancer models [11-15].

The Gayo Highlands of Aceh Province represent a region of rich biodiversity, particularly within the Asteraceae. These plants are widely distributed throughout the area, along roadsides, and near human settlements. While often perceived as nuisance plants due to their ubiquitous and sometimes invasive nature, wild Asteraceae species possess significant economic and medicinal potential [16]. Local communities have long recognized the value of these plants, incorporating them into traditional medicine practices and utilizing them as biocontrol agents. This conventional knowledge underscores the inherent value of these plants and highlights their potential for further scientific exploration. Previous studies have substantiated the medicinal properties of several Asteraceae species, confirming their potential as valuable sources of pharmaceutical compounds [17-19]. This finding suggests that closely related species within the Gayo Highlands may similarly harbor significant antioxidant properties, and their close relatives are expected to have high antioxidant activity. Therefore, Asteraceae plants in the Gayo Highland have an excellent opportunity to study their benefits scientifically.

The protective effects of antioxidants against oxidative stress are well-documented, particularly in the pathogenesis of diseases such as diabetes and cancer, where oxidative stress is recognized as a significant contributor to their pathogenesis. *Erigeron sumatrensis* Retz. (Synonym: *Conyza sumatrensis*). Locally known as "Jelantir," it is an Asteraceae species abundant in the Gayo Highlands and is regarded by the community as a nuisance plant. Nevertheless, the local population considers *E. sumatrensis* to possess therapeutic properties for diabetes and cancer. This ecological prevalence and its reported phytochemical diversity make it a compelling candidate for further investigation. Previous phytochemical analyses have revealed the presence of various secondary metabolites in *E. sumatrensis*, including anthraquinones, steroid glycosides, phenolics, flavonoids, tannins, saponins, carbohydrates, and terpenoids [20]. Furthermore, water extracts of *E. sumatrensis* leaves have demonstrated promising antioxidant activity

[21]. Considering the diverse range of potential bioactive compounds in *E. sumatrensis* and the proven effectiveness of different solvents in extracting specific phytochemicals, further investigation into the antioxidant potential of *E. sumatrensis* leaf extracts using various solvents is justified.

Previous research has highlighted the potential therapeutic benefits of the *Erigeron* genus. A study conducted in Nigeria demonstrated that a fractionated leaf extract of *E. sumatrensis* exhibited anti-proliferative effects against MCF-7 breast cancer cells, suggesting its potential as an anticancer agent [22]. Nonetheless, studies investigating the potential of E. sumatrensis leaf extract using methanol as a solvent have yet to be undertaken. In comparison, the antidiabetic properties of *E. sumatrensis* remain unexplored. A closely related species, *Erigeron annuus*, has shown promise in mitigating diabetes-related complications. *E. annuus* has demonstrated the ability to mitigate mitochondrial damage and suppress endoplasmic reticulum stress, both of which are implicated in the pathogenesis of diabetes [23]. This finding suggests that *E. sumatrensis* may harbor similar antidiabetic potential due to its close phylogenetic relationship to *E. annuus*.

Despite the potential therapeutic value of *E. sumatrensis*, a comprehensive phytochemical analysis of this species from the Gayo Highlands region has yet to be reported in the scientific literature. This knowledge gap is significant, as geographical factors, including altitude and temperature, can profoundly influence the phytochemical profiles and, consequently, the bioactivity of plant species. The Gayo Highlands have altitudes ranging from 100 to over 2100 meters above sea level and an average temperature of 22.5°C [24]. Present a unique set of environmental conditions that may influence secondary metabolite production [25]. Previous research has shown that high-altitude environments can increase the accumulation of flavonoids and phenolics in plants, enhancing their antioxidant properties. Therefore, a comprehensive investigation encompassing phytochemical analysis, antioxidant assays, and both in silico and in vitro studies is warranted to fully elucidate the potential of *E. sumatrensis* leaf extracts as antioxidant, antidiabetic, and anticancer agents.

2. Material and Methods

2.1. Study Design

The design of this study focuses on three activities: anticancer, antioxidant, and antidiabetic. A flowchart outlining the experimental procedure is presented in Figure 1.

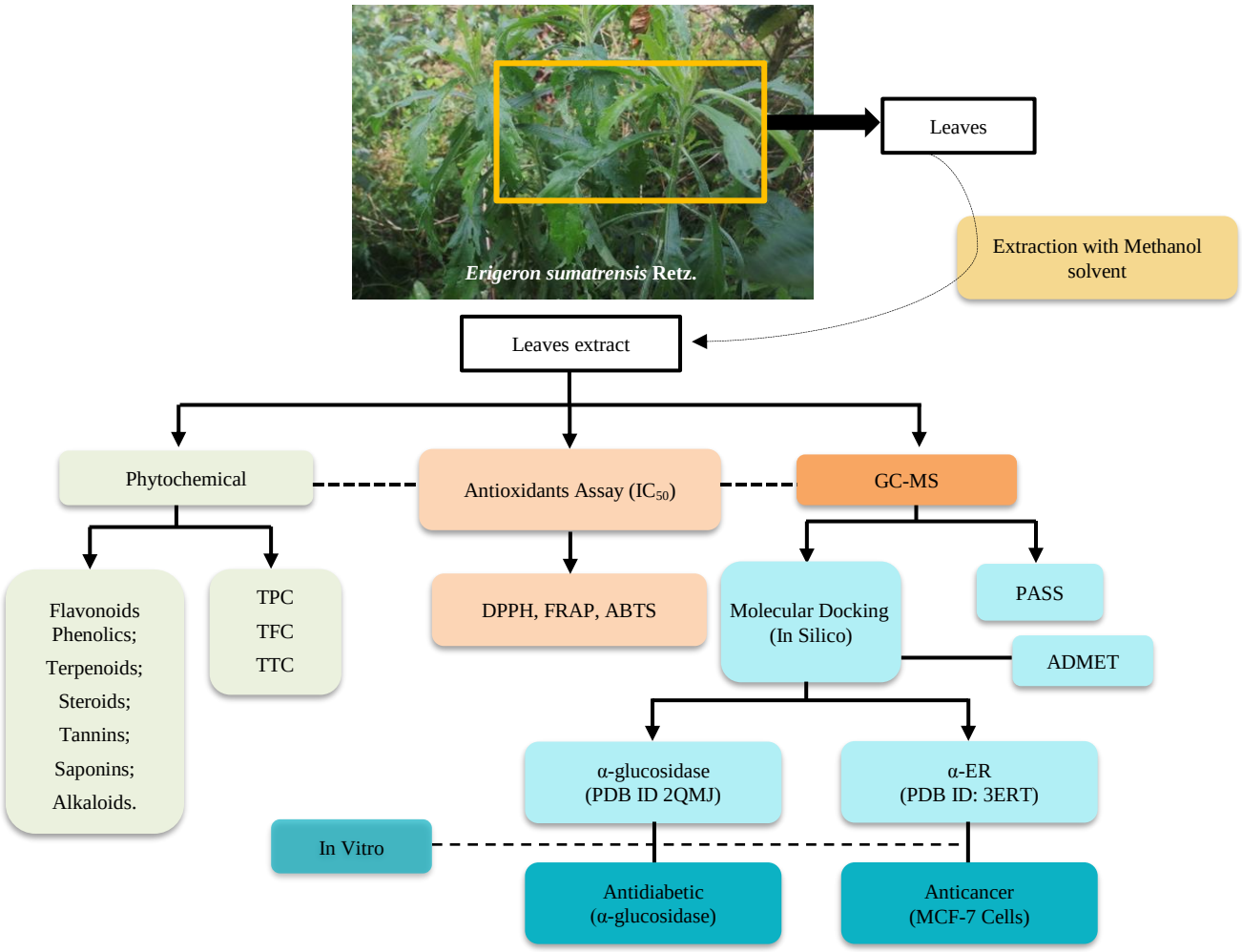


Figure 1. Flowchart of the research methodology

2.2. Plant Material

Erigeron sumatrensis leaves were collected from Wih Pesam District, Bener Meriah Regency. The geographical coordinates of the sampling location are 4°43'37.2"N latitude and 96°44'24"E longitude, at an altitude of 3112 meters above sea level (see Figure 2).

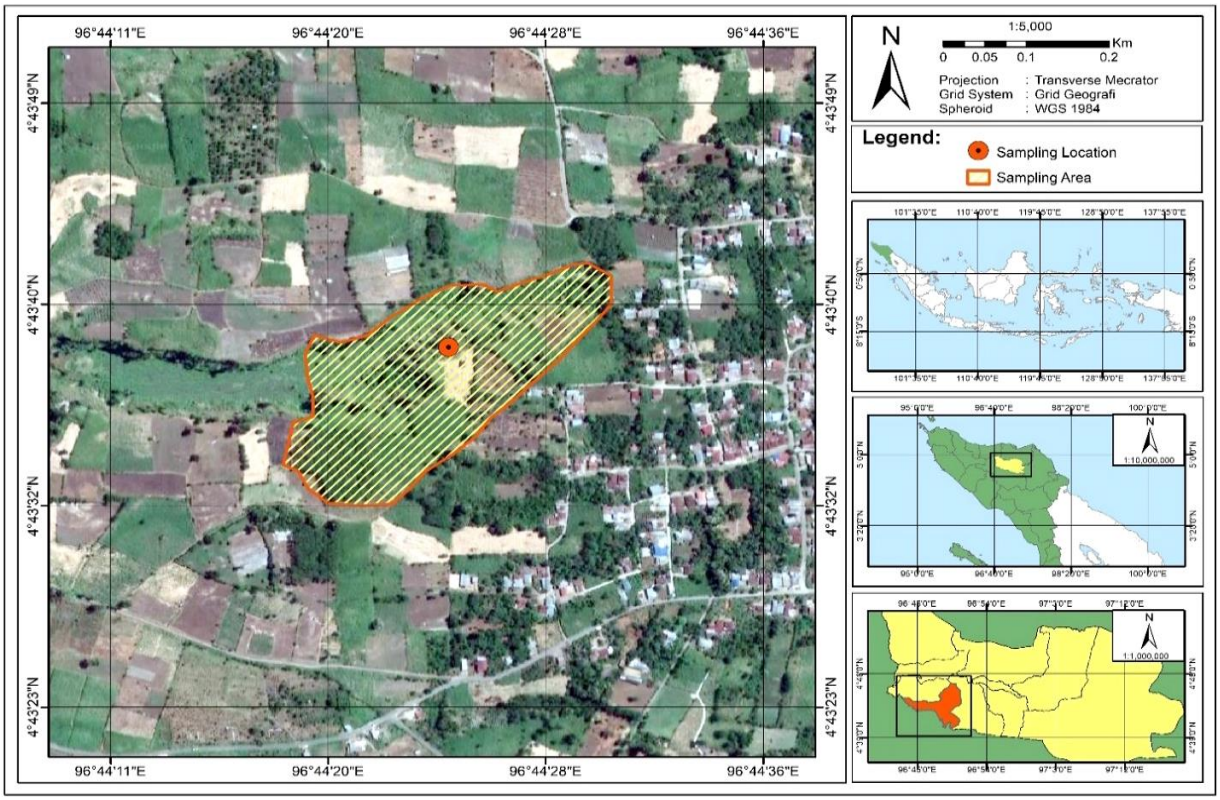


Figure 2. Sampling Location

2.3. Plant Identification

Plant identification was performed at the Biology Education Laboratory, Faculty of Teacher Training and Education, Universitas Syiah Kuala, Aceh Province, Indonesia.

2.4. Sample Preparation and Extraction

Leaves of *E. sumatrensis* were selected for this study due to their year-round availability, ease of collection without specialized tools, and minimal impact on plant survival. 3 kg of fresh leaves were collected, cleaned to remove debris, and thoroughly washed under running water. The leaves were then finely chopped and air-dried for ten days. The resulting 600 grams of dried leaf material was pulverized into a fine powder. Extraction was performed using a maceration method with 96% methanol as the solvent. A 1:10 ratio (w/v) of dried leaf powder to solvent was used, and the maceration process was repeated three times over 72 hours, as described previously [26].

2.5. Phytochemical Analysis

The phytochemical profile of the extract was evaluated using qualitative and quantitative analyses. Qualitative screening, as described in, confirmed the presence of various secondary metabolites, including flavonoids, phenolics, terpenoids, steroids, tannins, saponins, and alkaloids [27]. Quantitative analysis, conducted using a UV-Vis Spectrophotometer (Spectro 20D Plus Spectrophotometer Uvmini-1240 Shimadzu), determined the Total Phenolic Content, Total Flavonoid Content, and Total Tannin Content of the extracts. TPC and TFC were quantified using the Folin-Ciocalteu method, with gallic acid (mg GAE/g) and quercetin (mg QE/g) as standards, respectively. TTC was determined using tannic acid (mg TAE/g) as the standard [28-31].

2.6. Antioxidant Assay

Antioxidants analysed by various methods, i.e. 2,2-diphenyl-1-picrylhydrazyl (DPPH), Ferric reducing antioxidant power (FRAP) and 2,20-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) Assay. Antioxidant activity was assessed using the 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay, adapted from a previously described method [32]. The reducing power of *E. sumatrensis* leaf extracts was determined using a modified ferric-reducing antioxidant power assay, as described previously [33]. The ABTS radical scavenging activity of *E. sumatrensis* leaf extract was determined using the method described [34].

2.7. Gas Chromatography-Mass Spectrometry (GC-MS) Analysis

The chemical composition of the samples was determined using gas chromatography-mass spectrometry analysis, following a previously reported method [35]. A 5 µL aliquot of the methanolic sample was injected into an Agilent Technologies 7890A GC system equipped with an MSD 5975A mass selective detector and an autosampler. Chromatographic separation was achieved using a capillary column with helium as the carrier gas at a flow rate of 1.2 mL/min and a split ratio of 8:1. The injector and detector temperatures were maintained at 250°C and 230°C, respectively. The oven temperature was programmed from an initial temperature of 140°C to a final temperature of 280°C. Compounds were identified by comparing the obtained mass spectra to reference spectra in the National Institute of Standards and Technology Mass Spectral Library.

2.8. Biology Activity Predictions

The detected compounds' biological activity spectra were predicted using the online Prediction of Activity Spectra for Substances tool. PASS analysis predicts various biological activities, representing active and inactive probabilities ranging from 0 to 1. Probabilities closer to 1 indicate a higher likelihood of the compound exhibiting the predicted activity or inactivity [36-38].

2.9. Molecular Docking (In Silico)

Molecular docking studies have evaluated the prospect for binding interactions of the discovered compounds with target proteins associated with antidiabetic and anticancer activities. The crystal structures of α-glucosidase (PDB ID: 2QMJ) and estrogen receptor alpha (PDB ID: 3ERT) originated from the Protein Data Bank of the Research Collaboratory for Structural Bioinformatics. Ligand structures were obtained from the PubChem database. Before docking, water molecules and non-essential atoms were removed from the protein structures using PyMol 2.5.5 software. AutoDockTools 1.5.7 was used to add polar hydrogen atoms, merge non-polar hydrogens, and convert protein and ligand files to the required .pdbqt format [39].

Molecular docking simulations were performed using PyRx 0.8 software. The protein structures were kept rigid during the docking process, while the ligands were allowed to adopt flexible conformations. Grid parameters were generated automatically using the PyRx AutoGrid feature. The docking results were evaluated based on the binding affinity scores, with the most negative value indicating the most favorable binding interaction. The compound exhibiting the lowest binding affinity score was selected as a potential lead compound. Visualization of the protein-ligand complexes was performed using PyMol 2.5.5 software. To analyze the binding interactions between ligands and target protein active site residues, BIOVIA Discovery Studio 2021 generated two-dimensional and three-dimensional interaction diagrams.

2.10. Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Predictions

The compounds identified via GC-MS analysis were evaluated for drug-likeness qualities using the SwissADME online platform, adhering to Lipinski's Rule of Five. Compounds exhibiting favorable docking results were further assessed for their absorption, distribution, metabolism, excretion, and toxicity profiles to estimate their pharmacokinetic characteristics and potential bioavailability. ADMET prediction was conducted using online tools, including SwissADME, Protox II, and pKCSM [40, 41].

2.11. Antidiabetic Test

Testing of α-glucosidase inhibitor activity was conducted at the Biopharmacology Laboratory, Institut Pertanian Bogor (IPB) Bogor, West Java, based on the [42], all experiments were performed in triplicate. The percent inhibition of α-glucosidase activity was calculated using the following formula:

$$\% \text{ inhibition} = [1-(\text{Abs sample}/\text{Abs control})] \times 100 \quad (1)$$

The half-maximal inhibitory concentration (IC_{50}) was calculated by graphing the percentage inhibition with the logarithm of the sample concentration. The regression equation yielded the IC_{50} value, the sample concentration required to inhibit 50% of α-glucosidase activity.

2.12. Anticancer Test

The compounds' antiproliferative activity against MCF-7 breast cancer cells was evaluated using the MTT assay. This colorimetric assay measures cell viability based on the reduction of yellow MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to purple formazan crystals by metabolically active cells. The formation of formazan crystals, indicative of cell viability, is quantified spectrophotometrically. A decrease in formazan formation corresponds to a reduction in cell viability [43].

The antiproliferative efficacy of the *E. sumatrensis* leaf extract against MCF-7 breast cancer cells was assessed utilizing a completely randomized, non-factorial experimental design. Six different extract concentrations were tested, along with an untreated control group. Following a previously reported protocol, the MTT assay assessed cell viability. The experimental procedure involved preparing MCF-7 monolayers, cell suspension preparation, cell counting using a hemocytometer, and evaluating the antiproliferative activity of the extract [44].

The number of viable (unstained) and nonviable (stained) cells was counted in a specific area of the hemocytometer grid, and cell viability was determined using the following formula:

$$\text{Cell per mL} = \text{Average cells counted} \times \text{diluent factor} \times 10^2 \quad (2)$$

The percentage of viable cells (viability) and cell inhibition are calculated. The rate of viability is calculated using the following formula:

$$\text{Viability (\%)} = (1-(\text{OD cells control}-\text{OD of treatment on cells}))/(\text{OD cells control}) \times 100 \quad (3)$$

The percentage of cell inhibition is calculated using the following formula:

$$\text{Inhibition (\%)} = (\text{OD cells control} - \text{OD treatment on cells})/ (\text{OD cells control}) \times 100 \quad (4)$$

The data was evaluated using linear regression. The statistical analyses were carried out with SPSS software version 27.

3. Results and Discussion

3.1. Plant Determination and Extraction Yield

The plant used in this study was identified as *Erigeron sumatrensis* Retz., a member of the Asteraceae family. The extraction process yielded 600 grams of thick leaf extract, resulting in a percentage yield of 11.02%. This yield surpasses the 10% threshold often considered indicative of quality, efficiency, and effectiveness in herbal ingredient processing for final product development [45].

3.2. Phytochemical Profiling

A qualitative phytochemical examination of the methanol extract of *E. sumatrensis* leaves revealed the presence of several bioactive components, including flavonoids, phenolics, terpenoids, steroids, tannins, and alkaloids. These results are consistent with previous research indicating similar phytochemical elements in *E. sumatrensis* leaf extracts [21]. Flavonoids, known for their antioxidant properties, play a crucial role in plant defense mechanisms. Alkaloids, nitrogen-containing compounds, contribute to plant protection against pathogens and herbivores and have been widely utilized for their medicinal properties, including their use as stimulants. Alkaloids and terpenoids have also demonstrated potential as antidiabetic and wound-healing agents [46].

While flavonoids, phenolics, terpenoids, steroids, tannins, and alkaloids were detected, saponins were not found in this study's *E. sumatrensis* leaf extract [20, 47]. This finding contrasts slightly with previous reports, identifying saponins and other phytochemicals in *E. sumatrensis* extracts. Variations in phytochemical profiles can arise from several factors, including differences in geographical origin and the specific plant parts used for extraction. Environmental conditions, known to influence plant growth and development, can also significantly impact the production of secondary metabolites, potentially contributing to the observed discrepancies between studies [25]. Table 1 presents the total phenolic, flavonoid, and tannin content of the *E. sumatrensis* leaf extract. Figure 3 shows standard curves for gallic acid, quercetin, and tannic acid, which are used to quantify TPC, TFC, and TTC, respectively.

Table 1. Total phenolic, total flavonoid and total tannin content

Phytochemicals	Results
TPC	11854.50 mgGAE/g extract
TFC	1056.15 mgQE/g extract
TTC	442.73 mgTAE/g extract

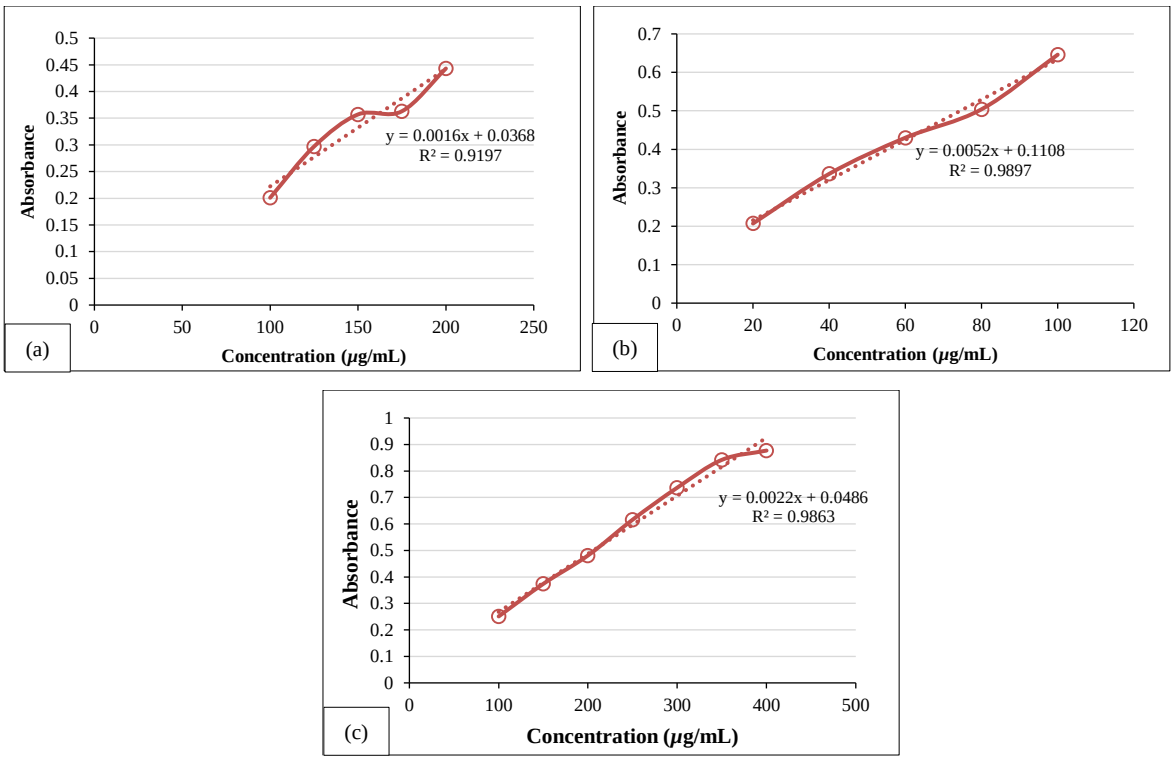


Figure 3. a) Gallic acid standard curve, b) Quercetin standard curve, c) Tannat acid standard curve

The total phenolic content, total flavonoid content, and total tannin content of the *E. sumatrensis* leaf methanol extract were 1185.50 mg GAE/g, 1056.15 mg QE/g, and 442.73 mg TAE/g, respectively. Phenolic compounds and flavonoids are plants' most significant natural antioxidants, contributing to their medicinal properties [48]. The higher TPC value than TFC and TTC suggests phenolics are the predominant bioactive constituents in the *E. sumatrensis* leaf extract. Our previous research work employing a cascading maceration method with n-hexane, ethyl acetate, and methanol yielded a methanol fraction with lower TPC (5945.45 mg GAE/g), TFC (1017.69 mg QE/g), and TTC (274.55 mg TAE/g) values. This discrepancy highlights the influence of extraction methods on the resulting phytochemical profiles. The higher TPC, TFC, and TTC values observed in the methanol extract, compared to the methanol fraction obtained through cascading maceration, may be attributed to the higher yield percentage of the former (11.02% vs. 4.30%) [49]. These findings are consistent with studies on other plant species, such as *Juniperus procera*, where the choice of solvent significantly impacted the extraction efficiency of bioactive compounds. While methanol was the most effective solvent for TPC extraction, ethanol yielded the highest TFC, and acetone was optimal for TTC extraction [50]. Therefore, selecting an appropriate extraction solvent is crucial for maximizing the recovery of desired bioactive compounds from plant materials, and methanol appears to be suitable for extracting phenolic compounds, flavonoids, and tannins from *E. sumatrensis* leaves.

Phenolic compounds and tannins exhibit a wide range of biological activities, including anti-inflammatory, antioxidant, antibacterial, antidiabetic, wound healing, antidiuretic, antiparasitic, cytotoxic, and antineoplastic properties [51]. Phenolic acids, a subclass of phenolic compounds, are aromatic carboxylic acids characterized by at least one carboxylic acid group attached to a phenol ring [52]. These compounds are ubiquitous in the plant kingdom and can be broadly categorized into hydroxybenzoic acids (C7) and hydroxycinnamic acids (C9). Notable examples of phenolic acids include caffeic acid, ferulic acid, p-coumaric acid, and sinapic acid [53]. The number and position of hydroxyl groups influence the antioxidant activity of phenolic compounds. Polyphenols, a diverse class of phenolic compounds, constitute a significant source of dietary antioxidants that are readily absorbed in the gut. In addition to their antioxidant properties, phenolic acids have garnered considerable attention for their potential health benefits, including antibacterial, anticancer, anti-inflammatory, and antimutagenic effects [54]. Significant progress has been made in elucidating the mechanisms of action of numerous phenolic compounds found in medicinal plants, leading to several clinical trials investigating their therapeutic potential [55].

Flavonoids, a widely distributed and extensively studied class of polyphenols encompassing over 4,000 identified compounds, are abundant in various plant parts, including fruits, vegetables, nuts, seeds, stems, and flowers [56]. Structurally, flavonoids are characterized by two phenolic rings (A and B) connected by a three-carbon bridge, forming a central oxygen-containing heterocyclic (C) ring known as a pyran ring. This arrangement results in a C6-C3-C6 skeletal framework [53]. Based on the oxidation state of the core heterocyclic ring, flavonoids are classified into six subclasses: flavanones, isoflavones, flavonols, flavones, flavan-3-ols, and anthocyanidins. These molecules exhibit a diverse range of pharmacological activities, including anticancer, antioxidant, anti-inflammatory, antiviral, neuroprotective, and cardioprotective properties. The specific biological activity of a flavonoid is determined by its chemical structure, mechanism of action, and bioavailability [57]. Similar to flavonoids and phenolic acids, steroids

represent another class of bioactive compounds with significant therapeutic potential, particularly in cancer treatment. The ability of steroids to interact with various receptors makes them attractive targets for drug development, and modifications of steroid structures have led to the discovery of novel anticancer agents [58].

Tannins, a type of naturally occurring phenolic chemical, are widely spread across the plant kingdom, occurring in various plant parts, including fruits, bark, wood, and leaves. Their presence in numerous medicinal plants has led to their traditional use for centuries in treating various infections and diseases, particularly skin ailments. This ethnopharmacological relevance has sparked significant interest among modern researchers, who recognize that tannins have the potential to be excellent sources of bioactive chemicals for pharmaceuticals and medicinal applications [59].

Several species within the Asteraceae family, including *Ageratum conyzoides*, *Acmella oleracea*, *Bidens pilosa*, *Lactuca sativa, and Tithonia diversifolia,* have been reported to possess antidiabetic and anticancer properties [60]. For instance, the ethyl acetate extract of *Santolina chamaecyparissus* leaves exhibited significant α-glucosidase inhibitory activity in vitro, with an IC_{50} =110 ± 4.25 μg/mL, comparable to that of the standard drug acarbose (IC_{50} = 105 ± 3.74 μg/mL). Furthermore, S. chamaecyparissus demonstrated potential anticancer activity, as evidenced by the negative expression of epidermal growth factor receptor protein in human breast cancer cells following treatment [61].

3.3. Antioxidants Activity

The antioxidant capacity of phenolic compounds is attributed to their ability to scavenge reactive oxygen species by donating hydrogen atoms or transferring electrons to free radicals [62]. In the case of *E. sumatrensis* leaf extract, the high total phenolic content, as determined by TPC assay, correlated with its potent antioxidant activity observed in DPPH, FRAP, and ABTS assays. The methanol extract, in particular, exhibited very strong antioxidant activity, with IC_{50} = 48.68 μg/mL, 35.61 μg/mL, and 29.60 μg/mL in the DPPH, FRAP, and ABTS assays, respectively (Table 2). It is worth noting that these results differ slightly from previous findings using a cascading maceration method, where the methanol fraction of *E. sumatrensis* leaf extract showed weak antioxidant activity in the DPPH assay (IC_{50} = 212.84 μg/mL) but relatively strong activity in the FRAP (IC_{50} = 70.19 μg/mL) and ABTS (IC_{50} = 57.67 μg/mL) assays [49]. The enhanced antioxidant activity observed in the methanol maceration extracts suggests a potential synergistic interaction among the extracted compounds. This synergistic effect arises when the combined effect of multiple compounds surpasses the sum of their individual effects. These variations highlight the influence of extraction methods on assessing antioxidant activity, consistent with previous reports [63-65]. For instance, a study on *Tussilago farfara* extracts revealed a strong antioxidant activity for the ethanol extract (IC_{50} = 84.018 μg/mL). Still, weak activity for the ethyl acetate extract (IC_{50} = 311,346 μg/mL), further emphasizing the impact of extraction solvents on antioxidant potential [66].

Table 2. Antioxidant activity of *E. sumatrensis* leaves

Antioxidant test	IC_{50} (μg/mL)	Standard (μg/mL)
DPPH	48.67 ± 32.38	4.47 ± 11.96
FRAP	35.61 ± 2.05	3.19 ± 3.62
ABTS	29.60 ± 5.15	8.02 ± 18.53

A positive correlation has been observed between phenolic content and antioxidant activity, with higher phenolic compounds generally resulting in more potent antioxidant effects [67, 68]. This trend is supported by several studies demonstrating the superior antioxidant capacity of methanol extracts compared to those obtained using other solvents. For instance, the methanol extract of Leilem leaves (*Clerodendrum minahassae*) exhibited the highest antioxidant activity (IC_{50}: 179.5 μg/mL) among various solvent extracts tested [69]. Similarly, the methanol extract of *Pothomorphe umbellata* L. displayed the most potent antioxidant activity, highlighting the efficacy of methanol, a polar solvent, in extracting antioxidant compounds [70]. This finding aligns with previous reports indicating that polar solvents generally yield extracts with higher antioxidant activity compared to semi-polar and non-polar solvents. Therefore, methanol appears to be a suitable solvent for extracting phenolic compounds with high antioxidant potential.

The observed antioxidant activity in *E. sumatrensis* leaf extract warrants further investigation to explore its therapeutic potential. It is essential to acknowledge that several factors, including geographical location, phytochemical composition, and extraction solvents, can influence the antioxidant capacity of plant extracts [71, 72]. Methanol, a polar and versatile solvent, has demonstrated its efficacy in extracting polar and non-polar constituents from plant materials [73]. Methanol is a polar solvent and a universal solvent because, in addition to being able to focus on polar components, it can also extract non-polar components. Previous studies have reported a correlation between solvent polarity and antioxidant activity, with polar solvents generally yielding extracts with higher phenolic content and, consequently, stronger antioxidant properties [74]. While research on *E. sumatrensis* remains limited, the promising antioxidant activity observed in its methanol extract suggests its potential as a source of bioactive compounds for developing antidiabetic and anticancer agents. This notion is supported by previous studies demonstrating a positive association between high antioxidant activity and therapeutic efficacy in treating diabetes and cancer. Further research is necessary to elucidate the specific bioactive components responsible for the observed antioxidant activity and to evaluate their therapeutic potential in relevant in vivo models [75-77].

3.4. Gas Chromatography-Mass Spectrometry Analysis

Gas chromatography-mass spectrometry analysis was employed to identify the major and minor constituents present in the methanol extract of *E. sumatrensis* leaves. The GC-MS chromatogram revealed numerous peaks, representing a diverse array of compounds (Figure 4). Based on peak area percentage, 18 tentative compounds were initially identified (Table 3), with five compounds exhibiting an area percentage more significant than 5% and 13 compounds showing an area percentage less than 5%. The most abundant compounds included Glycidyl palmitate (21.35%), 9-Octadecenoic acid (Z)-, oxiranylmethyl ester (12.83%), Hexadecanoic acid, methyl ester (7.24%), Methyl stearate (5.60%), and 9-Octadecenoic acid (Z)-, methyl ester (5.54%) (Figure 5). The identified compounds belonged to various chemical classes, including esters, fatty acids, terpenoids, steroids, and hydrocarbons. It is noteworthy that the current GC-MS analysis yielded a slightly different compound profile compared to our previous study on *E. sumatrensis* leaf methanol extract with multiple maceration methods, which reported the presence of triterpenoids, sesquiterpenoids, phenols, sterols, esters, and alcohols [49]. These variations in chemical composition could be attributed to factors such as geographical origin, plant age, and extraction methods employed.

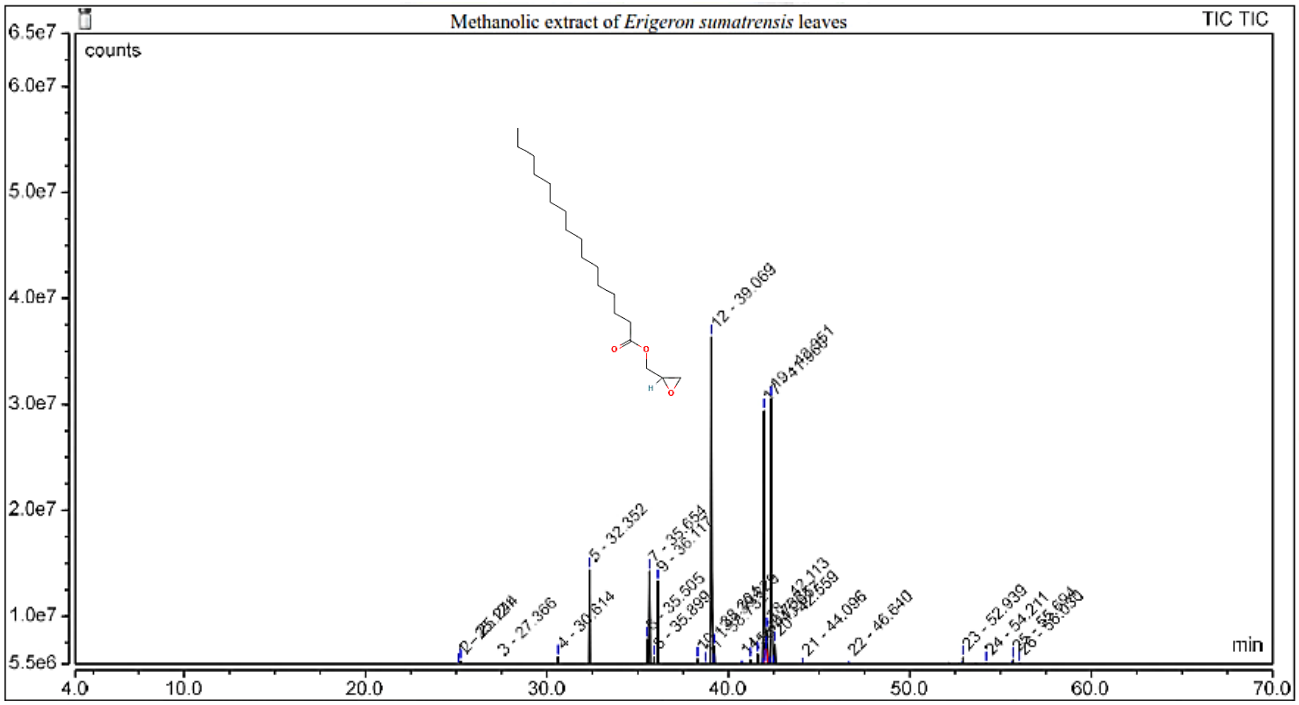


Figure 4. Chromatogram of methanolic extract of *Erigeron sumatrensis* leaves

Table 3. GC-MS Identification compound of methanolic extract

No peak	Retention Time (min)	Compound name	Formula molecule	Area (%)	Similarity Index
1	25.12	1H-Cycloprop[e]azulen-7-ol, decahydro- 1,1,7-trimethyl-4-methylene-, [1ar- (1aa,4aa,7ß,7aß,7ba)]-	$C_{15}H_{24}O$	1.83	100
2	25.24	Caryophyllene oxide	$C_{15}H_{24}O$	2.21	94
3	27.37	Z-3-Hexadecen-7-yne	$C_{16}H_{28}$	0.92	95
4	30.61	Neophytadiene	$C_{20}H_{38}$	2.05	91
5	32.35	Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	7.24	98
6	35.50	Myristic acid glycidyl ester	$C_{17}H_{32}O_3$	3.25	93
7	35.65	9-Octadecenoic acid (Z)-, methyl ester	$C_{19}H_{36}O_2$	5.54	98
8	35.90	Phytol	$C_{20}H_{40}O$	1.57	91
9	36.12	Methyl stearate	$C_{19}H_{38}O_2$	5.6	99
10	38.30	Hexadecanoic acid, 2-hydroxy-1- (hydroxymethyl)ethyl ester	$C_{19}H_{38}O_4$	1.65	99
11	38.73	Glycidyl palmitoleate	$C_{19}H_{34}O_3$	1.31	94
12	39.07	Glycidyl palmitate	$C_{19}H_{36}O_3$	21.35	99
13	41.21	*trans*-9-Octadecenoic acid, pentyl ester	$C_{23}H_{44}O_2$	1.51	96
14	41.62	Octadecanoic acid, 2-hydroxy-1- (hydroxymethyl)ethyl ester	$C_{21}H_{42}O_4$	1.77	99
15	41.96	9-Octadecenoic acid (Z)-, oxiranylmethyl ester	$C_{21}H_{38}O_3$	12.83	100
16	52.94	Estra-1,3,5(10)-trien-17ß-ol	$C_{18}H_{24}O$	0.96	90
17	55.69	Glycidyl (Z)-9-Heptadecenoate	$C_{18}H_{34}O_2$	1.07	97
18	56.03	Hexadecanoic acid, 2-(octadecyloxy)ethyl ester	$C_{36}H_{72}O_3$	1.16	99

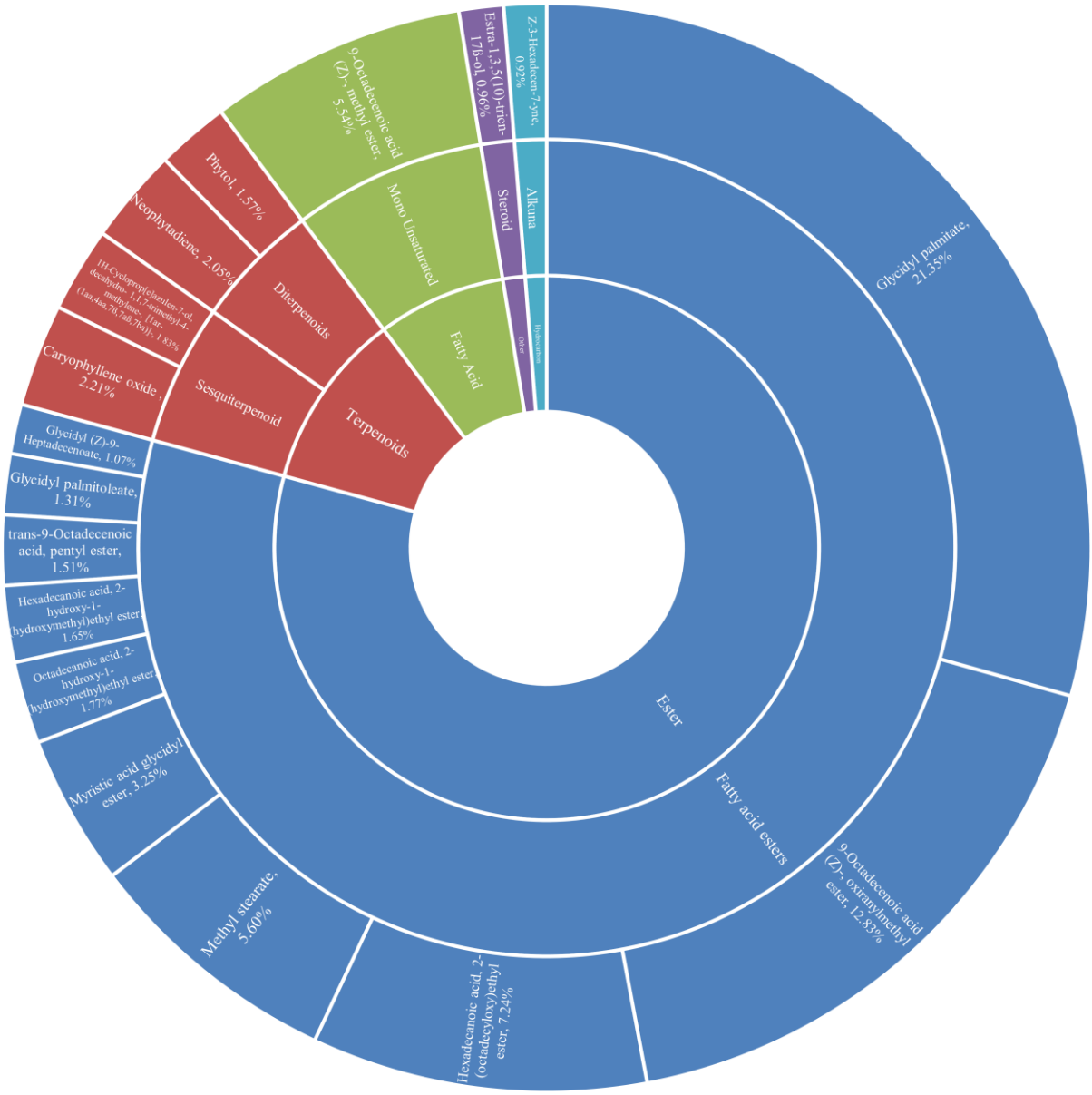


Figure 5. Sunburst chart representing variation in phytoconstituents in *Erigeron sumatrensis* leaves

The GC-MS analysis of *E. sumatrensis* leaf extract revealed glycidyl palmitate as the most prevalent compound. This compound exhibited a high similarity index of 99%, indicating a strong match with the reference standard. It is essential to distinguish between glycidyl palmitate and the broader class of compounds known as glycidyl esters. Glycidyl palmitate is a specific glycidyl ester in which the glycidyl group is esterified with palmitic acid. GEs, conversely, encompass a range of compounds formed during the high-temperature processing of fats and oils [78]. These compounds comprise a glycidyl group bound to various fatty acids, including palmitic acid, oleic acid, and stearic acid [79]. Therefore, glycidyl palmitate represents a specific example within the broader category of glycidyl esters.

Glycidyl palmitate has garnered attention for its potential therapeutic properties, particularly in diabetes and cancer. This compound exhibits antidiabetic effects by inhibiting critical enzymes involved in carbohydrate metabolism, namely α-amylase and α-glucosidase. Glycidyl palmitate helps regulate blood sugar levels by inhibiting these enzymes, making it a promising candidate for managing diabetes [80]. Furthermore, glycidyl palmitate possesses anticancer characteristics due to its capacity to alter the PI3K/Akt/mTOR pathway, an important signaling cascade involved in cell growth, survival, and proliferation. Dysregulation of this system is common in various malignancies, making it an appealing therapeutic target. The beneficial effects of glycidyl palmitate in both diabetes and cancer are attributed to its antioxidant properties and its ability to modulate key signaling pathways involved in glucose and lipid metabolism, insulin secretion, and cancer development. Preclinical research in vitro and in vivo has yielded encouraging findings, confirming glycidyl palmitate's potential as a treatment agent for various disorders. However, additional studies, including clinical studies, are required to completely understand its efficacy and safety profile in humans [81].

Comparative analysis of methanol extracts obtained via multiple maceration and methanol maceration extract revealed distinct compound profiles. However, both extracts exhibited the presence of phytol, as confirmed by a 91% similarity index [49]. A prior study employing GC-MS analysis identified 16 compounds within the aerial methanol extract of *E. sumatrensis* sourced from Nigeria. Notably, phytol, a compound previously reported in the *n*-hexane leaf extract of *E. sumatrensis*, was also detected [20]. However, the compound profile differed from the current study's findings on samples collected from the Gayo Highlands, Aceh Province, Indonesia. This discrepancy highlights the influence of geographical location and potentially other factors, such as the plant part analyzed, on the phytochemical composition of *E. sumatrensis*. Given the observed variations in chemical constituents, further investigation is crucial to comprehensively evaluate the therapeutic potential of *E. sumatrensis* from different geographical origins. In silico and in vitro studies would be precious in elucidating the identified compounds' bioactivity and potential mechanisms of action.

3.5. Biology Activity Prediction

Using the PASS platform, the prediction of substance activity spectra yielded outputs categorized as active and inactive, with probabilities ranging from 0 to 1. A probability value of 1 signifies a higher likelihood of the compound exhibiting the predicted activity [36]. The PASS prediction results indicated that the identified secondary metabolite compounds possess potential disease-inhibitory effects in humans. Specifically, glycidyl palmitate and myristic acid glycidyl ester demonstrated a high probability of acting as acrocylindropepsin inhibitors (Pa: 0.970). Similarly, 9-octadecenoic acid (Z)-, oxiranylmethyl ester (Pa: 0.956), and hexadecanoic acid, methyl ester (Pa: 0.962) exhibited a high probability of inhibiting Saccharopepsis. These findings, summarized in Table 4, suggest the potential therapeutic value of these compounds and warrant further investigation.

Table 4. Biological activity of metabolic compounds

Glycidyl palmitate		
Pa	**Pi**	**Activity name**
0.970	0.001	Acrocylindropepsin inhibitor
0.970	0.001	Saccharopepsin inhibitor
0.970	0.001	Chymosin inhibitor
0.956	0.002	Polyporopepsin inhibitor
0.920	0.003	Glucan endo-1,3-beta-D-glucosidase inhibitor
0.908	0.004	Sugar-phosphatase inhibitor
9-Octadecenoic acid (Z)-, oxiranylmethyl ester		
Pa	**Pi**	**Activity name**
0.956	0.002	Saccharopepsin inhibitor
0.956	0.002	Acrocylindropepsin inhibitor
0.956	0.002	Chymosin inhibitor
0.933	0.004	Polyporopepsin inhibitor
0.923	0.002	All-trans-retinyl-palmitate hydrolase inhibitor
0.890	0.005	Antieczematic
Hexadecanoic acid, methyl ester		
Pa	**Pi**	**Activity name**
0.962	0.002	Saccharopepsin inhibitor
0.962	0.002	Acrocylindropepsin inhibitor
0.962	0.002	Chymosin inhibitor
0.942	0.003	Acylcarnitine hydrolase inhibitor
0.942	0.003	Polyporopepsin inhibitor
0.926	0.003	Pro-opiomelanocortin converting enzyme inhibitor
Myristic acid glycidyl ester		
Pa	**Pi**	**Activity name**
0.970	0.001	Acrocylindropepsin inhibitor
0.970	0.001	Saccharopepsin inhibitor
0.970	0.001	Chymosin inhibitor
0.956	0.002	Polyporopepsin inhibitor
0.920	0.003	Glucan endo-1,3-beta-D-glucosidase inhibitor
0.908	0.004	Sugar-phosphatase inhibitor

Estra-1,3,5(10)-trien-17ß-ol		
Pa	**Pi**	**Activity name**
0.979	0.001	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0.978	0.001	JAK2 expression inhibitor
0.973	0.002	CYP2C12 substrate
0.966	0.002	CYP2J substrate
0.964	0.001	CYP2J2 substrate
0.958	0.002	Antiseborrheic
Caryophyllene oxide		
Pa	**Pi**	**Activity name**
0.950	0.004	Antineoplastic
0.836	0.006	Apoptosis agonist
0.810	0.011	HIF1A expression inhibitor
0.812	0.016	Antieczematic
0.791	0.004	Antineoplastic (lung cancer)
0.950	0.004	Antineoplastic

PASS predictions indicated glycidyl palmitate and myristic acid glycidyl ester exhibit potential as sugar phosphatase inhibitors (Pa: 0.908). Sugar phosphatases play a considerable part in controlling sugar metabolism by catalyzing the dephosphorylation of sugar phosphates. Consequently, inhibiting these enzymes can impact various metabolic pathways. The inhibition of sugar phosphatases can influence the balance between glycolysis, the breakdown of glucose for energy production, and gluconeogenesis, the synthesis of glucose from non-carbohydrate sources. This modulation of glucose metabolism can contribute to regulating blood sugar levels. Moreover, sugar phosphatase inhibition can impact glycogen metabolism, affecting both the synthesis and breakdown of glycogen, a crucial energy storage molecule. This regulation is essential for maintaining cellular energy balance. Sugar phosphatases are also implicated in various signaling pathways that govern critical cellular processes, including cell growth, differentiation, and apoptosis. Inhibiting these enzymes can disrupt signal transduction, potentially offering therapeutic benefits for diseases such as cancer and diabetes. Indeed, sugar phosphatase inhibitors are currently being explored as potential treatments for metabolic disorders like diabetes, aiming to improve insulin sensitivity and lower blood glucose levels. Furthermore, their potential in cancer therapy is under investigation due to their ability to disrupt the metabolic pathways crucial for cancer cell survival and proliferation [82].

Peak compounds, including glycidyl palmitate, 9-octadecenoic acid (Z)-, oxiranylmethyl ester, hexadecanoic acid, methyl ester, and myristic acid glycidyl ester, exhibit inhibitory effects on acrocylindropepsin. Acrocylindropepsin inhibitors function by suppressing the activity of this enzyme. These inhibitors are valuable tools for investigating the mechanisms of acid protease enzymes and their therapeutic potential in treating acid protease-related diseases. Notably, acrocylindropepsin inhibitors have shown promise in anticancer therapy due to the role of acid proteases in protein degradation during cancer cell proliferation [83].

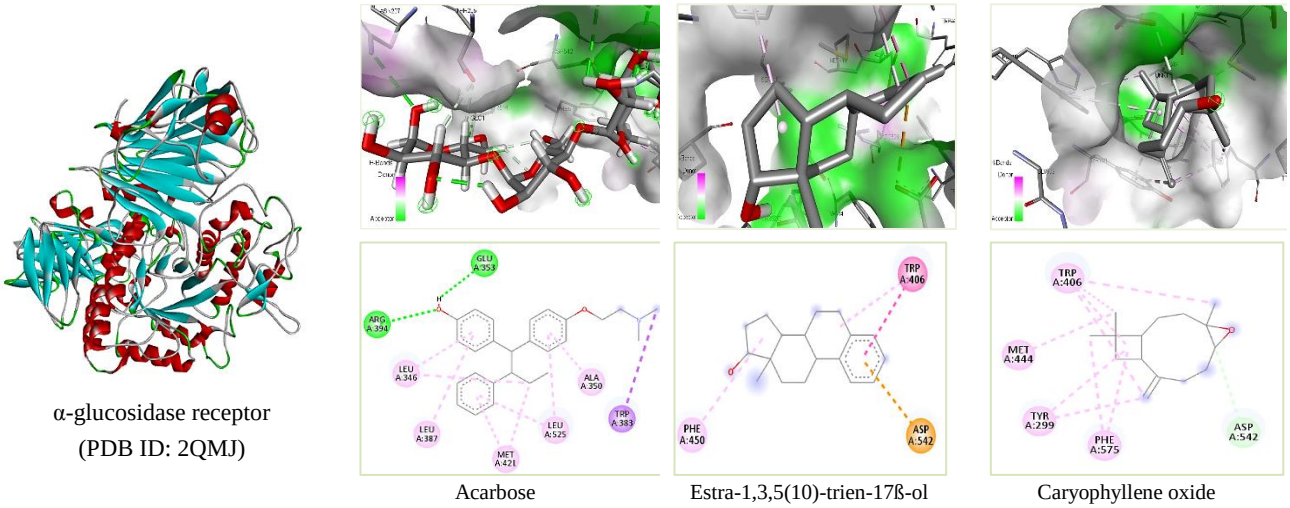
3.6. Molecular Docking (In Silico)

Molecular docking simulations estimated the binding interactions of α-glucosidase (target) and ligands identified through GC-MS analysis (Table 3). In silico techniques, leveraging computational power and structural biology, are crucial in drug discovery. Our study focused on identifying compounds with a high affinity for α-glucosidase. A lower docking score, represented by a higher negative value, indicates stronger binding energy. Estra-1,3,5-trien-17ß-ol (-6.6 kcal/mol) and caryophyllene oxide (-6.2 kcal/mol) exhibited the highest binding affinities to α-glucosidase. Acarbose, used as a positive control, showed a binding affinity of -7.8 kcal/mol (Table 5). While these compounds demonstrated notable binding potential, their affinities did not surpass the positive controls. The docking simulations were performed using a grid box centered at X:12.9984, Y:47.0405, Z:25.5006 on the 2QMJ receptor structure, with dimensions of X: 23.4628 Å, Y: 20.4467 Å, and Z: 21.3274 Å.receptor 2QMJ X:12.9984, Y:47.0405, Z:25.5006, dimension (Angstrom) X: 23.4628, Y: 20.4467, Z: 21.3274.

Table 5. Molecular docking results of active compounds of *E. sumatrensis* leaves extract against α-glucosidase (2QMJ) and ERα (3ERT)

Ligand	Compound ID	Binding Free Energy (Kcal/mol)	
		2QMJ	3ERT
Acarbose		**-7.8**	-
Tamoxifen		-	**-9.8**
Estra-1,3,5(10)-trien-17ß-ol	537293	**-6.6**	**-9.4**
Caryophyllene oxide	1742210	**-6.2**	**-8.4**
Neophytadiene	10446	-5.8	-6.8
1H-Cycloprop[e]azulen-7-ol, decahydro- 1,1,7-trimethyl-4-methylene-, [1ar- (1aa,4aa,7ß,7aß,7ba)]-	91747864	-5.7	-8.1
Phytol	5280435	-5.7	-6.7
9-Octadecenoic acid (Z)-, methyl ester	5364509	-5.5	-6.2
Glycidyl palmitate	347736	-5.5	-6.2
9-Octadecenoic acid (Z)-, oxiranylmethyl ester	5354568	-5.5	-6.1
Glycidyl palmitoleate	23624909	-5.4	-6.5
Myristic acid glycidyl ester	346148	-5.3	-6.1
Glycidyl (Z)-9-Heptadecenoate	10902087	-5.3	-6.3
Octadecanoic acid, 2-hydroxy-1- (hydroxymethyl)ethyl ester	79075	-5.2	-5.8
Hexadecanoic acid, methyl ester	8181	-5.1	-5.9
Hexadecanoic acid, 2-(octadecyloxy)ethyl ester	545613	-5.1	-5.3
Hexadecanoic acid, 2-hydroxy-1- (hydroxymethyl)ethyl ester	123409	-5	-6.1
Z-3-Hexadecen-7-yne	5362886	-5	-6.1
Methyl stearate	8201	-5	-6.1
trans-9-Octadecenoic acid, pentyl ester	5462694	-4.9	-6.3

Analysis of the protein-ligand interactions revealed that hydrophobic interactions dominate binding, while hydrogen bonding contributes somewhat (Figure 6). The binding efficacy of the ligands can be attributed to the specific interactions formed between the ligand molecules and the amino acid residues within the receptor's active site [84]. Various types of bonds contribute to receptor-ligand interactions, including hydrogen bonds, carbon-hydrogen bonds, van der Waals forces, alkyl and Pi-alkyl interactions, sulfur bonds, Pi-Anion interactions, and Pi-Pi T-shaped interactions. For instance, acarbose binds to the active site of α-glucosidase (PDB ID: 2QMJ) through multiple hydrogen bonds with residues ASP327, ASP542, and ARG526, as well as carbon-hydrogen bonds with HIS600 and ASP327. Other residues lining the sugar-binding pocket include ASP443, TYR299, ILE238, ILE364, TRP441, and MET444 [85, 86]. Interestingly, the identified ligands, estra-1,3,5-trien-17ß-ol and caryophyllene oxide, primarily engage in carbon-hydrogen bonds and alkyl/Pi-alkyl interactions, similar to acarbose. Notably, acarbose and estra-1,3,5-trien-17ß-ol form a hydrogen bond with the ASP542 residue. Additionally, estra-1,3,5-trien-17ß-ol participates in a Pi-Anion interaction, while caryophyllene oxide forms a carbon-hydrogen bond within the active site.



α-glucosidase receptor (PDB ID: 2QMJ)

Acarbose | Estra-1,3,5(10)-trien-17ß-ol | Caryophyllene oxide

Figure 6. α-glucosidase receptor docking visualization (PDB ID: 2QMJ) with Acarbose, Estra-1,3,5(10)-trien-17ß-ol and Caryophyllene oxide (Pose prediction by BIOAVIA Discovery Studio)

Analysis of amino acid residue interactions suggests that caryophyllene oxide holds significant potential as an α-glucosidase inhibitor. It exhibits the most favorable binding affinity, indicated by the lowest docking score, and demonstrates extensive interactions with the α-glucosidase protein. Specifically, caryophyllene oxide forms fundamental interactions with residues ASP542, TRP406, MET444, TYR299, and PHE575. While caryophyllene oxide displays a strong binding affinity and interacts with crucial residues within the active site, its binding mode differs from that of the positive control acarbose (Table 6). This difference in binding interactions may influence the overall effectiveness of the extract in inhibiting α-glucosidase activity. Further investigation is warranted to elucidate the specific implications of these distinct binding modes on enzyme inhibition.

Table 6. Description of 2QMJ amino acid residues

Ligand	Amino Acid Residue
Acarbose	Hydrogen Bond: **ASP203, ARG526, ASP542** Carbon Hydrogen Bond: **HIS600, ASP327**, ASP443 Van der Waals: PHE450, SER448, GLY541 TRP539, ARG598, ASP571, TRP441, ILE364, ILE328, ALA576, THR544, THR205, ASN207 Sulphur: MET444 Pi-Alkyl: TYR299, PHE575, TRP406
Estra-1,3,5(10)-trien-17ß-ol	Pi-Anion: **ASP542** Pi-Pi T-shaped: TRP406 Pi-Alkyl: PHE450
Caryophyllene oxide	Carbon Hydrogen: **ASP542** Alkyl and Pi-Alkyl: TRP406, MET444, TYR299, PHE575

Molecular docking studies were conducted using the 3ERT crystal structure (Human Estrogen Receptor Alpha in MCF-7 breast cancer cells) to investigate potential interactions with the estrogen receptor alpha. Two compounds identified through GC-MS analysis, estra-1,3,5-trien-17ß-ol and caryophyllene oxide, exhibited notable binding affinities for ERα, with docking scores of -9.4 kcal/mol and -8.4 kcal/mol, respectively. Tamoxifen, a known ER antagonist, was employed as a positive control and yielded a docking score of -9.8 kcal/mol. Although the identified compounds demonstrated considerable binding potential, their affinities did not surpass that of the positive control, tamoxifen. The docking simulations were performed using a grid box centred at X: 30.2822, Y: -2.0799, Z: 25.2104 on the 3ERT receptor structure, with dimensions of X: 15.3768 Å, Y: 14.6191 Å, and Z: 13.1393 Å.

Analysis of the protein-ligand interactions for ERα revealed a predominance of hydrophobic interactions, with a relatively minor contribution from hydrogen bonding (Figure 7). Several bonds were observed between the receptor and ligands, including hydrogen bonds, alkyl and Pi-alkyl interactions, Pi-sulfur interactions, and Pi-Sigma interactions. Tamoxifen, the positive control, binds to the active site of ERα (PDB ID: 3ERT) primarily through hydrogen bonds with residues GLU353 and ARG394. Other residues lining the binding pocket include TRP383, LEU346, LEU387, MET421, LEU525, and ALA350. Interestingly, the identified ligand, estra-1,3,5-trien-17ß-ol, exhibited a similar interaction pattern to tamoxifen, forming a hydrogen bond with the ARG394 residue. This suggests that estra-1,3,5-trien-17ß-ol may exert its effects similarly to tamoxifen despite the overall lower binding affinity observed in the docking studies.

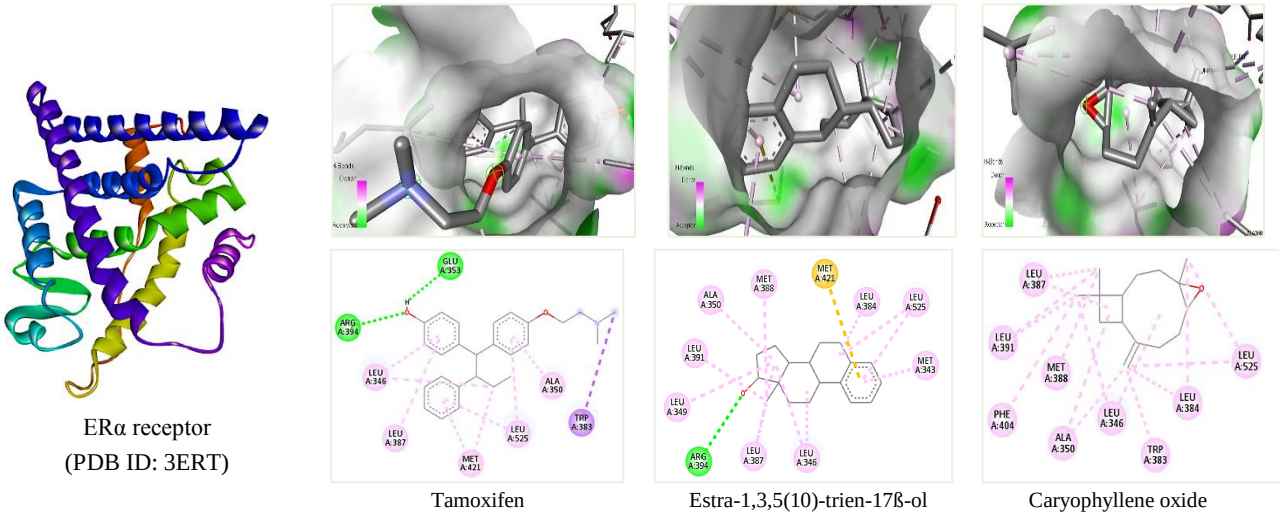


Figure 7. ERα receptor docking visualization (PDB ID: 3ERT) with Tamoxifen, Estra-1,3,5(10)-trien-17ß-ol and Caryophyllene oxide (Pose prediction by BIOAVIA Discovery Studio)

Amino acid residue analysis highlights estra-1,3,5-trien-17ß-ol as a promising compound for ERα inhibition. It exhibits the most favorable binding affinity, indicated by the lowest docking score, and forms extensive interactions with the ERα protein. Notably, estra-1,3,5-trien-17ß-ol interacts with key residues GLU353 and ARG394, similar to the positive control tamoxifen, and engages additional residues, including TRP383, LEU346, LEU387, MET421, LEU525, and ALA350 (Table 7). The shared hydrogen bonding interaction with ARG394, observed in both estra-1,3,5-trien-17ß-ol and tamoxifen, suggests a potentially similar mechanism of action for ERα inhibition. This similarity in binding mode strengthens the potential of estra-1,3,5-trien-17ß-ol as an effective ERα inhibitor. Furthermore, PASS prediction analysis suggests that estra-1,3,5-trien-17ß-ol may also act as a JAK2 inhibitor (Pa: 0.978). This prediction, coupled with the promising ERα binding data, warrants further investigation into the therapeutic potential of estra-1,3,5-trien-17ß-ol. However, it is crucial to acknowledge the lack of existing research data on this compound. Further experimental validation is necessary to confirm its efficacy and explore its potential as a therapeutic agent.

Table 7. Description of 3ERT amino acid residues

Ligand	Amino Acid Residue
Tamoxifen	Hydrogen Bond: **GLU353, ARG394** Pi-Sigma: TRP383 Alkyl and Pi-Alkyl: LEU346, LEU387, MET421, LEU525, ALA350
Estra-1,3,5(10)-trien-17ß-ol	Hydrogen Bond: **ARG394** Pi-Sulphur: MET421 Alkyl and Pi-Alkyl: LEU349, LEU391, ALA350, MET388, LEU384, LEU525, MET343, LEU346, LEU387
Caryophyllene oxide	Alkyl and Pi-Alkyl: LEU525, LEU384, TRP383, LEU346, ALA350, MET388, PHE404, LEU391, LEU387

Janus kinase 2 inhibitors have emerged as crucial agents in managing conditions driven by JAK2 mutations, particularly myeloproliferative neoplasms. Key inhibitors in this class include ruxolitinib, fedratinib, and momelotinib. These drugs exert their therapeutic effects by inhibiting the proliferation of aberrant cells and disrupting critical signaling pathways involved in disease pathogenesis. Beyond myeloproliferative neoplasms, ongoing research efforts are exploring the potential of JAK2 inhibitors in treating autoimmune diseases and various cancers. However, the emergence of resistance to these inhibitors poses a significant challenge. To address this, clinical trials investigate the efficacy of combination therapies involving JAK2 inhibitors to overcome resistance mechanisms and improve treatment outcomes [87, 88].

According to PASS prediction analysis, caryophyllene oxide, a natural compound found in various essential oils, has demonstrated promising antineoplastic activity (Pa: 0.950). Antineoplastic agents, broadly defined as substances that inhibit or prevent the growth and spread of cancerous cells, encompass a diverse group of drugs with various mechanisms of action. These mechanisms include interfering with DNA replication and repair, inhibiting cell division, and inducing programmed cell death (apoptosis) [89]. Recent research has highlighted the potential of caryophyllene oxide as an antidiabetic agent. Studies suggest that this compound may inhibit key enzymes involved in glucose metabolism, such as α-glucosidase, crucial in carbohydrate digestion and glucose absorption. This inhibitory effect on α-glucosidase could contribute to improved glycemic control in individuals with diabetes [90, 91]. Beyond its potential in diabetes management, caryophyllene oxide exhibits other beneficial biological activities, including anti-inflammatory and antioxidant effects. These properties are particularly relevant in the context of diabetes, as chronic inflammation and oxidative stress are recognized as significant contributors to the development and progression of diabetic complications [92].

Caryophyllene oxide, a naturally occurring compound, has garnered significant attention for its anticancer properties. Studies have demonstrated its ability to induce apoptosis and inhibit the proliferation of cancer cells, particularly in breast cancer models. A study investigating the effects of CPO on the MCF-7 breast cancer cell line revealed concentration-dependent cytotoxicity. CPO induced cell cycle arrest at the G2/M phase, increased apoptosis, and promoted DNA fragmentation, indicating its potential as a chemopreventive agent against breast cancer [93]. These findings suggest that *E. sumatrensis*, specifically from the Gayo Highlands of Aceh Province, Indonesia, could be a valuable source of natural compounds with antidiabetic and anticancer properties. Two promising candidates identified from this plant include estra-1,3,5-trien-17ß-ol and caryophyllene oxide. Further investigation into these compounds is warranted to explore their therapeutic potential fully.

3.7. Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Predictions

To further evaluate the drug-likeness of the identified compounds, those exhibiting the most favorable binding affinities underwent in silico analysis using online prediction tools. These tools assess various parameters related to pharmacokinetics, physiochemical behavior, and drug similarity. Lipinski's rule of five, a widely employed rule of thumb for estimating oral bioavailability, was applied to the compounds identified in the *E. sumatrensis* leaf extract. Ten out of eleven compounds satisfied Lipinski's rule of five, indicating potential for oral administration. However, hexadecanoic acid, 2-(octadecyloxy)ethyl ester violated two criteria, suggesting potential limitations as an orally bioavailable drug. Compounds that adhere to Lipinski's rule of five generally exhibit favorable characteristics for oral administration, which is often preferred due to patient convenience and ease of administration. Oral medications offer advantages such as pain-free delivery and simplified dosing regimens [63]. Further in silico analysis focused on predicting the Absorption, Distribution, Metabolism, Excretion, and Toxicity profiles of the compounds with the best binding affinities (Table 8).

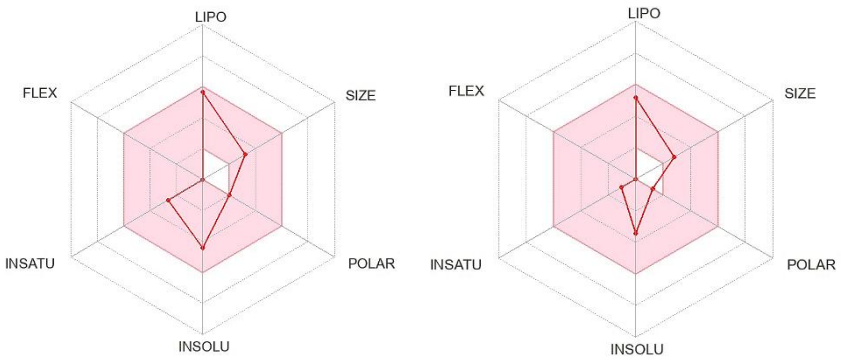
Table 8. ADMET prediction of the best docking compounds

	Parameter	Estra-1,3,5(10)-trien-17ß-ol **LD_{50}: 5010 mg/kg Toxicity class: 6**	Caryophyllene oxide **LD_{50}: 5000mg/kg Toxicity class: 5**
Absorption	Water solubility	Moderately soluble	Soluble
	Log Kp (Skip Permeation)	-4.76 cm/s	-5.12 cm/s
	GI absorption[1]	High	High
Distribution	BBB[2]	Yes	Yes
	P-gp substrate[3]	Yes	No
	VDss[4] (human) log L/kg	0.739	0.586
Metabolism	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	Yes
	CYP2C9 inhibitor	No	Yes
	CYP2D6 inhibitor	Yes	No
	CYP3A4 inhibitor	No	No
Excretion	Excretion Total Clearance (log mL/min/kg)	1.074	0.905
	Renal OCT2 substrate	No	No
Toxicity	Hepatotoxicity	0.72	0.80
	Carcinogenicity	0.85	0.57
	Immunotoxicity	0.95(active)	0.83(active)
	Mutagenicity	0.95	0.88
	Cytotoxicity	0.86	0.79
	Estrogen Receptor Alpha	0.90 (active)	0.96

[1] gastrointestinal absorbance; [2] blood bran barriers; [3] P-glycoprotein; [4] vol of distributions.

* Predict as "active for toxicity", Class 5; may be harmful if swallowed (2000 mg/kg < LD_{50} ≤ 5000 mg/kg), Class 6; non-toxic (LD_{50}> 5000).

Solubility, a crucial factor influencing the pharmacokinetic profile of a drug, directly impacts its absorption, distribution, metabolism, and, ultimately, its therapeutic efficacy. Caryophyllene oxide exhibits favorable solubility, while Estra-1,3,5-trien-17ß-ol demonstrates moderate solubility. Drug solubility correlates with its absorption rate and the onset of therapeutic effects. Highly soluble drugs tend to be absorbed more rapidly, leading to a faster onset of action. Additionally, solubility plays a crucial role in drug disposition within the body. Lipophilic drugs, characterized by low solubility, tend to bind to plasma proteins, undergo rapid distribution, and are primarily metabolized by the liver. Conversely, hydrophilic drugs exhibit wider distribution with their high solubility and are predominantly metabolized by the kidneys [94]. The bioavailability radar of the best compound (best binding affinity) is presented in Figure 8.



Estra-1,3,5(10)-trien-17ß-ol **Caryophyllene oxide**

Figure 8. Bioavailability RADAR of best-docked compounds Estra-1,3,5(10)-trien-17ß-ol and Caryophyllene oxide

3.8. Antidiabetic Test

This study investigated the antidiabetic potential of *E. sumatrensis* leaf extract through in vitro inhibition of α-glucosidase enzyme activity. Acarbose, a commercially available antidiabetic drug known for its α-glucosidase inhibitory action, was a positive control. The methanol extract of *E. sumatrensis* leaves exhibited an IC_{50} = 4194.58 µg/mL against α-glucosidase, categorizing its inhibitory activity as very weak. In contrast, acarbose demonstrated significantly greater potency with an IC_{50} = 0.143 µg/mL. These results indicate that the extract's ability to inhibit α-glucosidase is substantially lower than acarbose. Acarbose, a commonly prescribed medication for managing type 2 diabetes, exerts its therapeutic effect by inhibiting α-glucosidase in the small intestine. This inhibition delays the breakdown of complex carbohydrates into simpler sugars, slowing glucose absorption and mitigating postprandial hyperglycemia. However, acarbose use is associated with potential side effects, including bloating, diarrhea, abdominal pain, hypoglycemia, and elevated liver enzymes [95].

The composition of secondary metabolites within the *E. sumatrensis* leaf extract is crucial in determining its α-glucosidase inhibitory activity. The observed inability of the extract to significantly inhibit α-glucosidase aligns with the in silico predictions, which indicated a lack of favorable binding affinity and ligand interactions compared to acarbose. However, PASS prediction analysis highlighted several compounds within the extract, notably glycidyl palmitate and myristic acid glycidyl ester, possessing potential glucose-lowering properties. This discrepancy between the overall extract activity and the predicted potential of specific compounds underscores the need for further investigation. Isolating and characterizing the individual compounds in the *E. sumatrensis* leaf extract is essential to reconcile these findings.

In vitro analysis revealed that the extract did not exhibit inhibitory activity against the α-glucosidase enzyme. This observation aligns with the molecular docking results, which indicated that the identified compounds did not surpass the positive control regarding binding affinity. This lack of inhibitory activity against α-glucosidase warrants further investigation, particularly in light of our previous in silico studies. These studies demonstrated the antidiabetic potential of leaf methanol extracts obtained through multilevel maceration, specifically highlighting their inhibitory effects against both α-glucosidase and α-amylase enzymes. Molecular docking simulations from these prior studies revealed that cucurbitacin compound b, 25-desacetoxy (-8.3 kcal/mol), and β-sitosterol (-8.3 kcal/mol) exhibited higher binding affinities to α-glucosidase compared to the control, acarbose (-7.8 kcal/mol). Similarly, for α-amylase, cucurbitacin b, 25-desacetoxy (-10.6 kcal/mol), and α-amyrin (-10.9 kcal/mol) demonstrated superior binding affinities compared to acarbose (-9.2 kcal/mol). The discrepancy between these previous in silico findings and the current in vitro results suggests that the extraction method employed may significantly influence the bioactivity of the extracted compounds. This highlights the need for further research exploring the impact of different extraction techniques on the antidiabetic properties of *E. sumatrensis* leaf extracts. A comprehensive investigation encompassing various enzymes involved in diabetes pathogenesis will enable a more precise evaluation of the bioactivity of individual constituents within the extract and facilitate the identification of promising candidates for antidiabetic drug development. This is particularly crucial given the limited research on the antidiabetic properties of *E. sumatrensis* species, which represents a significant gap in our current understanding. The stem of other species has been reported to exhibit potential antidiabetic properties [96]. Therefore, further research investigating the extract of *E. sumatrensis* stems is warranted to explore its therapeutic potential and underlying mechanisms.

3.9. Anticancer Test

The anticancer activities of *E. sumatrensis* leaf extract were examined using the MCF-7 breast cancer cell line. Tamoxifen, a widely used chemotherapeutic agent inhibiting cancer cell division, was a positive control. Untreated MCF-7 cells and breast cancer cells were included as controls to assess the extract's selectivity towards MCF-7 cells [97]. The study employed the MTT assay to evaluate the cytotoxicity of the extract against MCF-7 cells. Cytotoxicity

testing is crucial for evaluating the safety profile of novel extracts against target cells. This study employed the MTT assay to determine the cytotoxic potential of *E. sumatrensis* leaf methanol extract against the MCF-7 breast cancer cell line. The U.S. National Cancer Institute provides guidelines for classifying cytotoxic activity based on IC_{50} values: no cytotoxic effect (IC_{50} > 501 µg/mL), weak cytotoxic (200-500 µg/mL), moderate cytotoxic (21-200 µg/mL), and high cytotoxic (<20 µg/mL) [98]. The *E. sumatrensis* leaf methanol extract exhibited an IC_{50} value of 288.329 µg/mL against MCF-7 cells, placing it within the weak cytotoxic category. It is important to note that lower IC_{50} values indicate greater cytotoxicity and, consequently, higher potential for anticancer activity [99].

Figure 9 shows that the concentrations of 500 µg/mL and 1000 µg/mL resulted in the highest inhibition percentages of cell proliferation. At a concentration of 500 µg/mL, the test results showed that the methanol extract of *E. sumatrensis* leaves had the best inhibitory effect compared to other concent rations. The percentage of inhibition of cell proliferation was 98.72±0.26. This shows that the extract contains bioactive compounds that can suppress the activity of cancer cells. At this concentration, the antiproliferation effectiveness indicates that compounds such as flavonoids, terpenoids, and phenolic compounds in the extract begin showing their biological activity.

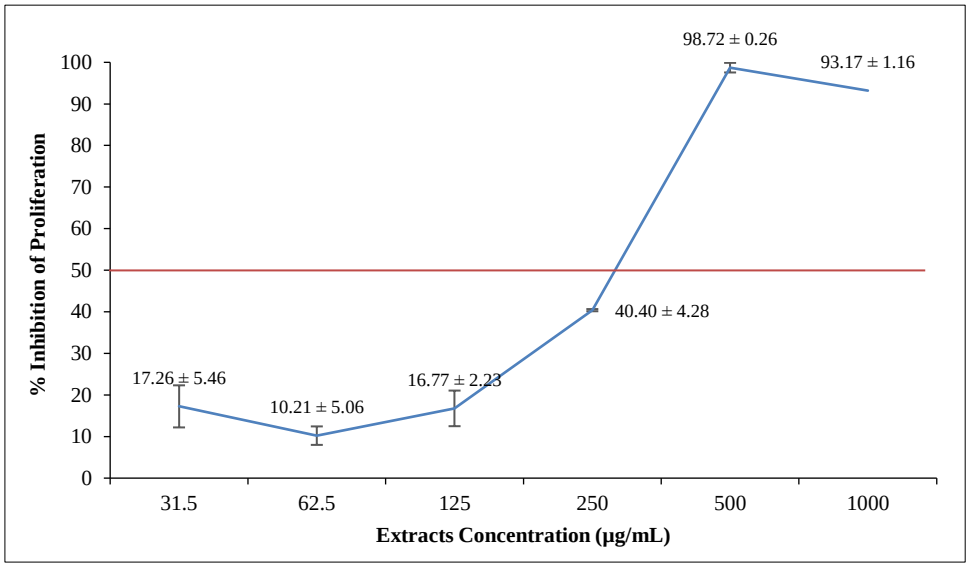


Figure 9. Percent inhibition of proliferation in different extract concentrations

Meanwhile, at a concentration of 1000 µg/mL, the percentage of inhibition of MCF-7 cell proliferation was slightly reduced, 93.17±1.16. A decrease in the percentage of proliferase inhibitors of cancer cells indicates that methanol extract has dose-responsive properties, where the inhibitory activity increases with increasing dose but decreases at a concentration of 1000 µg/mL. This aligns with other studies that report that higher concentrations indicate the potential drug's ability to apoptotic and autophagy in MCF-7 cells [100]. This reinforces the hypothesis that the active compounds in the extract work more effectively at concentrations of 500 µg/mL in inducing apoptosis or inhibiting the division of MCF-7 cancer cells, which reduces the number of live cancer cells.

The mechanism behind this inhibition may involve the interaction of active compounds with cellular signaling pathways involved in the proliferation of cancer cells. Some potential pathways that can be affected by the compounds in *E. sumatrensis* methanol extract are PI3K/AKT and MAPK pathways, which are known to play a role in the growth and survival of cancer cells. Inhibition of these pathways can cause disruption in the process of cell replication and trigger apoptosis, which is a programmed process of cell death that helps reduce the growth of cancer cells [81].

Previous studies have explored the anticancer properties of *E. sumatrensis* extracts. However, these studies employed different extraction methods, such as chloroform solvents. The current study investigated the antiproliferative effects of *E. sumatrensis* leaf methanol extract against MCF-7 breast cancer cells. Results demonstrated the extract's potential to inhibit MCF-7 cell proliferation, supporting its traditional use for tumor treatment in certain Nigerian regions [22]. Further research is necessary to elucidate the specific mechanisms of action, optimize extract formulations for enhanced efficacy, and identify the bioactive compounds responsible for the observed anticancer activity. Other studies have explored the anticancer potential of other Asteraceae species against MCF-7 breast cancer cells. For instance, research on *A. conyzoides* demonstrated the cytotoxic activity of its *n*-hexane extract fraction against MCF-7 cells, with an IC_{50} value of 148.5 µg/mL. This highlights the potential of the Asteraceae as a source of novel anticancer agents [101]. Molecular docking simulations identified estra-1,3,5-trien-17ß-ol and caryophyllene oxide as potential anticancer compounds within the *E. sumatrensis* leaf extract. This prediction aligns with the observed anti-proliferative activity of the extract against MCF-7 cells at concentrations of 500 µg/mL and 1000 µg/mL.

Although in vitro testing has shown promising results, further development is needed to ensure these extracts are safe and effective for clinical applications. Further research, including in vivo studies and toxicity testing of non-cancerous cells, is important for evaluating the selectivity and safety of the extract. In addition, the isolation and characterization of the main bioactive compounds from the extracts need to be carried out to understand the mechanism of action and the synergistic potential between the compounds. Overall, methanol extracts of *E. sumatrensis* leaves showed promising antiproliferation activity at 500 and 1000 µg/mL concentrations. However, more in-depth research is needed to develop anticancer therapeutic agents to ensure the effectiveness, safety, and potential clinical application of the bioactive compounds they contain. It was reported that the seed extract of *Ammi mariana*, one of the Asteraceae species, showed better cytotoxicity, namely IC_{50} of 87.35 ± 2.44, compared to the root extract IC_{50} of 92.45± 2.14 [102]. This shows there is also potential for *E. sumatrensis* to be further studied on other organs.

Microscopic examination revealed distinct morphological alterations in MCF-7 cells following treatment with *E. sumatrensis* leaf extract (Figure 10). Untreated MCF-7 cells exhibited a normal morphology, adhering to the growth surface. In contrast, treated cells displayed signs of damage, characterized by a darkened appearance and irregular shape. The extent of morphological changes correlated with the degree of growth inhibition. Cells with less than 50% inhibition retained a morphology similar to control cells, while those exceeding 50% inhibition exhibited pronounced changes. These changes included a loss of colony formation, irregular shape, and detachment from the growth surface. The observed cell detachment can be attributed to the disruption of intercellular bonds, potentially mediated by enzymatic factors such as trypsin, proteases, and collagenases. Cell death, evidenced by the inability to reduce MTT reagent to formazan crystals, was characterized by decreased cell volume, morphological alterations, and irregular shape. These findings are consistent with previous reports describing morphological hallmarks of MCF-7 cell death [103].

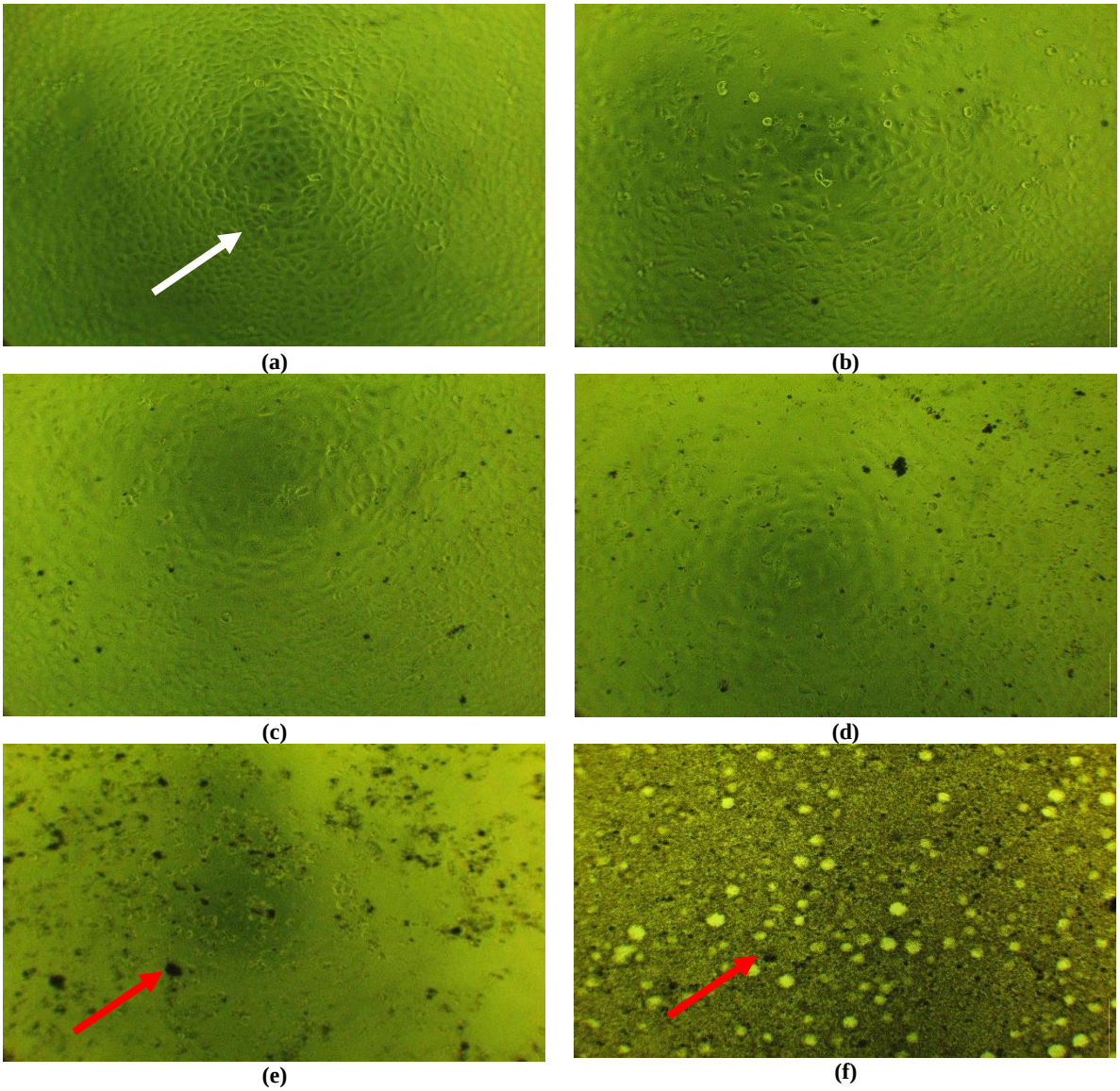


Figure 10. Morphology of MCF-7 cells under a microscope in (a) control cells; (b) a concentration of 62.5 µg/mL; (c) a concentration of 125 µg/mL; (d) a concentration of 250 µg/mL; (e) a concentration of 500 µg/mL; (f) a concentration of 1000µg/mL. Description: live cells (white arrow), dead cells (red arrow).

Microscopic examination is an important method to assess the anticancer activity of *E. sumatrensis* leaf extract against MCF-7 cancer cells. After treatment with this extract, the morphological changes in MCF-7 cells indicated antiproliferative and pro-apoptotic activity. Some of these changes included cell shrinkage, loss of normal shape, and the appearance of cytoplasmic vacuoles, indicating the potential of this extract to trigger cancer cell death. MCF-7 cells treated with the extract at certain concentrations showed different morphology than control cells (untreated). Signs of apoptosis, such as cytoplasmic shrinkage and cell nucleus fragmentation, indicate the main mechanism in inhibiting cancer cell growth. This apoptotic process is important because it can eliminate cancer cells without triggering excessive inflammation in surrounding tissues, an advantage of plant extract-based treatment methods [104].

Other morphological changes observed included chromatin clumping and cell detachment from the culture substrate, signaling disruption in cellular adhesion, and membrane integrity. This loss of adhesion and increased membrane fragility suggest that the extract may disrupt the structure of the cell cytoskeleton, induce autophagy, or damage mitochondrial membranes, all of which play a role in cell death pathways [100]. These findings indicate that *E. sumatrensis* leaf extracts contain active compounds with anticancer therapeutic potential. The compounds may interact with specific biochemical pathways that trigger apoptosis and autophagy. Flavonoids and terpenoids, often found in plant extracts, are known to have these activities, and the presence of these compounds in the extract may contribute to the observed morphological changes.

Microscopic observations revealed that treatment with *E. sumatrensis* leaf extract caused morphological changes in MCF-7 cells typical of apoptotic processes and cell death. This study confirms the need for further research to isolate and identify specific active compounds and verify the molecular mechanisms involved. In addition, further in vivo tests and toxicity evaluations are required to validate the clinical potential of this extract as an effective anticancer agent. These findings suggest that *E. sumatrensis* holds promise as a potential source of novel anticancer agents, particularly for breast cancer. Further investigations using different extraction solvents and another part of E. mathesis are warranted to explore the full spectrum of its anticancer properties.

4. Conclusion

This comprehensive study investigated methanol extract's antioxidant, antidiabetic, and anticancer properties from *E. sumatrensis* leaves collected from the Gayo Highlands of Aceh Province. A multi-faceted approach was employed, encompassing plant identification, extraction, phytochemical profiling (total phenolic, flavonoid, and tannin content), antioxidant activity assessment, GC-MS analysis, biological activity prediction, ADMET analysis, molecular docking studies targeting antidiabetic (PDB ID: 2QMJ) and anticancer (PDB ID: 3ERT) proteins, and in vitro evaluation of α-glucosidase inhibition and antiproliferative effects against MCF-7 breast cancer cells. Phytochemical analysis revealed a rich profile of bioactive compounds, including flavonoids, phenolics, terpenoids, steroids, tannins, and alkaloids. Notably, the extract exhibited high levels of total phenolic content, total flavonoid content, and total tannin content. The *E. sumatrensis* leaf extract demonstrated potent antioxidant activity across all assays employed, with IC_{50} values of 48.67 ± 32.38 µg/mL, 35.61 ± 2.05 µg/mL, and 29.60 ± 5.15 µg/mL. PASS prediction identified several compounds within the extract, including glycidyl palmitate, myristic acid glycidyl ester, 9-Octadecenoic acid (Z)-, oxiranylmethyl ester, hexadecanoic acid, estra-1,3,5-trien-17ß-ol, and caryophyllene oxide, as potential antidiabetic and anticancer agents. ADMET analysis highlighted estra-1,3,5-trien-17ß-ol and caryophyllene oxide as promising candidates for oral drug development due to their compliance with Lipinski's rule of five. Molecular docking studies confirmed ligand interactions with target proteins, with estra-1,3,5-trien-17ß-ol and caryophyllene oxide exhibiting favorable binding energies. While these energies were not superior to the control, interactions were observed at key active sites. In vitro assays demonstrated that the extract could not inhibit α-glucosidase activity but suppress MCF-7 cell proliferation best in 500 µg/mL and 1000 µg/mL extract concentrations. This study provides compelling evidence for the therapeutic potential of *E. sumatrensis* leaf extract as a natural source of antioxidants, antidiabetic, and anticancer agents. Further research is warranted to explore its clinical applications and optimize its therapeutic efficacy.

5. Declarations

5.1. Author Contributions

Conceptualization, V.R.P., Z., and N.; methodology, Z., N., and F.; software, V.R.P.; validation, Z., N., and F.; formal analysis, V.R.P. and Z.; investigation, V.R.P. and Z.; data curation, V.R.P. and N.; writing—original draft preparations, V.R.P, Z., N., and F.; writing—review and editing V.R.P. and Z.; visualization, V.R.P.; supervision, Z., N., and F.; project administrations, V.R.P. and Z.; funding acquisition, V.R.P. All authors have read and agreed to the published version of the manuscript.

5.2. Data Availability Statement

The data presented in this study are available in the article.

5.3. Funding

This research was supported by Indonesia's Ministry of Education, Culture, Research, and Technology for funding this study through Beasiswa Pendidikan Indonesia (BPI), the Indonesian Education Scholarship for the Penyelesaian Studi S3 Scheme.

5.4. Acknowledgments

The authors thank Indonesia's Ministry of Education, Culture, Research, and Technology for funding this study through Beasiswa Pendidikan Indonesia (BPI) for supporting this research in collecting and analyzing data.

5.5. Institutional Review Board Statement

Not applicable.

5.6. Informed Consent Statement

Not applicable.

5.7. Declaration of Competing Interest

The authors declare that there are no conflicts of interest concerning the publication of this manuscript. Furthermore, all ethical considerations, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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