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Metabolite Profiling and Cytotoxicity of Bajakah Tampala (*Uncaria lanosa* var. *ferrea*) Stem Fractions Against Breast Cancer Cells

Profil Metabolit dan Sitotoksisitas Fraksi Batang Bajakah Tampala (*Uncaria lanosa* var. *ferrea*) terhadap Sel Kanker Payudara

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ABSTRACT

Bajakah Tampala (*Uncaria lanosa* var. *ferrea* (Blume) Ridsdale) has been used in traditional medicine, but its cytotoxic activity against breast cancer cells remains insufficiently characterized. This study evaluated the cytotoxicity of *U. lanosa* stem fractions against MCF-7 breast cancer cells and profiled metabolites in the most active fraction. The stem extract was fractionated using hexane, ethyl acetate, and water, and cytotoxicity was assessed using the WST-8 assay. Metabolite profiling was performed using UHPLC-HRMS. Among the plant fractions, the hexane fraction showed the lowest IC_{50} value, 105.37 ± 2.51 µg/mL, followed by the ethyl acetate fraction, 130.58 ± 13.41 µg/mL, and the water fraction, 209.91 ± 16.48 µg/mL. Cisplatin showed a markedly lower IC_{50} value of 4.50 ± 1.92 µg/mL. UHPLC-HRMS tentatively identified ten metabolites in the hexane fraction. These findings indicate that *U. lanosa* var. *ferrea* stem fractions exhibit measurable cytotoxic activity against MCF-7 cells.

Kata kunci:
Bajakah Tampala
Profil metabolit
Sel kanker payudara
Sitotoksisitas
Uncaria lanosa var. *ferrea*

ABSTRAK

Bajakah Tampala (*Uncaria lanosa* var. *ferrea* (Blume) Ridsdale) telah digunakan dalam pengobatan tradisional, tetapi aktivitas sitotoksiknya terhadap sel kanker payudara masih belum banyak dikarakterisasi. Penelitian ini mengevaluasi sitotoksisitas fraksi batang *U. lanosa* terhadap sel kanker payudara MCF-7 dan memprofilkan metabolit pada fraksi paling aktif. Ekstrak batang difraksinasi menggunakan heksana, etil asetat, dan air, sedangkan sitotoksisitas dievaluasi menggunakan uji WST-8. Profil metabolit dianalisis menggunakan UHPLC-HRMS. Di antara fraksi tanaman, fraksi heksana menunjukkan nilai IC_{50} terendah, yaitu 105,37 ± 2,51 µg/mL, diikuti fraksi etil asetat sebesar 130,58 ± 13,41 µg/mL dan fraksi air sebesar 209,91 ± 16,48 µg/mL. Cisplatin menunjukkan nilai IC_{50} yang jauh lebih rendah, yaitu 4,50 ± 1,92 µg/mL. UHPLC-HRMS secara tentatif mengidentifikasi sepuluh metabolit pada fraksi heksana. Temuan ini menunjukkan bahwa fraksi batang *U. lanosa* var. *ferrea* memiliki aktivitas sitotoksik terukur terhadap sel MCF-7.

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1. INTRODUCTION

Breast cancer remains a major global health burden and is one of the most common causes of cancer-related morbidity and mortality among women (Wilkinson & Gathani, 2022). Although advances in diagnosis and therapy have improved patient outcomes, therapeutic resistance, adverse effects, and recurrence remain important challenges in breast cancer management (Nicolini & Ferrari, 2024). These limitations have encouraged continued investigation of natural products as sources of structurally diverse bioactive compounds with potential cytotoxic activity (Cragg & Newman, 2013; Asma et al., 2022).

Medicinal plants contain diverse secondary metabolites, including flavonoids, alkaloids, terpenoids, and phenolic constituents, which have been reported to affect cancer-related biological processes such as cell proliferation, oxidative stress regulation, and inflammatory signaling (Bishayee & Sethi, 2016; Dehelean et al., 2021). However, the cytotoxic activity of plant extracts or fractions depends on solvent polarity, metabolite composition, and the target cell model. Therefore, cytotoxic screening should be supported by metabolite profiling to provide a clearer chemical basis for the observed biological activity.

Bajakah Tampala, identified as *Uncaria lanosa* var. *ferrea* (Blume) Ridsdale, is a medicinal plant traditionally used by local communities in Kalimantan, Indonesia. Previous studies have reported that Bajakah Tampala contains several secondary metabolites, including flavonoids, phenolic compounds, and saponins (Mahfudh et al., 2024; Rikhaturhohmah et al., 2024; Yusuf et al., 2023). Nevertheless, the cytotoxic activity of different stem fractions of *U. lanosa* against breast cancer cells remains insufficiently characterized, and the metabolite profile of the active fraction has not been clearly described.

Ultra-high-performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-HRMS) is useful for profiling complex plant metabolites because of its sensitivity, resolution, and mass accuracy (Aydoğan, 2020; Deschamps et al., 2023). Therefore, this study aimed to evaluate the cytotoxic activity of hexane, ethyl acetate, and water fractions of *U. lanosa* var. *ferrea* stems against MCF-7 breast cancer cells using the WST-8 assay and to characterize the metabolite profile of the selected fraction using UHPLC-HRMS.

2. METHODS

2.1. Plant authentication, extraction, and fractionation

Stems of Bajakah Tampala (*U. lanosa*) were collected from the Tabakai River forest, located in Saka Kajang Village, Jabiren Raya District, Pulang Pisau Regency, Central Kalimantan, Indonesia. The plant material was authenticated at the InaCC-BRIN Characterization Laboratory (Cibinong, Bogor, Indonesia). This identification was based on the morphological evaluation of relevant plant parts, followed by a comparative analysis against established taxonomic data and the existing InaCC-BRIN herbarium collection (Determination Letter No. B-493/II.6.2/IR.01.02/3/2023).

The dried stems of *U. lanosa* were pulverized (Herman et al., 2022), and 4,000 g of the resulting powder was macerated in 96% ethanol for 24 h (Rudiana et al., 2023). The crude ethanolic extract (15 g) underwent liquid-liquid fractionation utilizing 400 mL each of n-hexane (non-polar), ethyl acetate (semi-polar), and water (polar) (Safithri et al., 2022). Following filtration, each fraction was concentrated under reduced pressure via rotary evaporation. This process yielded 6.9540 g (0.51%) of the n-hexane fraction, 14.2749 g (1.08%) of the ethyl acetate fraction, and 71.5258 g (5.37%) of the water fraction. The n-hexane fraction was subsequently subjected to UHPLC-HRMS for metabolite profiling.

2.2. Cell culture

MCF-7 breast cancer cells (catalogue no. 86012803, batch no. 18F024, passage +3) were obtained from the European Collection of Authenticated Cell Cultures (ECACC; Public Health England). The cells possessed a certified viability of 96.7% (total count of 5.45×10^6 cells) and were confirmed free of mycoplasma contamination via ECACC quality control testing.

Cryopreserved MCF-7 cell stocks were thawed from −80°C storage at 37°C. The cells were centrifuged to discard the cryopreservation medium, resuspended in fresh growth medium, and transferred into culture flasks. The cells were maintained in Minimum Essential Medium (MEM; Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS; Sigma-Aldrich), 1% L-glutamine (Sigma-Aldrich), and 1% penicillin–streptomycin (Sigma-Aldrich). Cultivation was performed at 37°C in a humidified incubator containing 5% CO_2 until approximately 80% confluency was achieved. The cells were then washed with phosphate-buffered saline (PBS) and harvested using trypsin–EDTA. Following centrifugation, the cell pellet was resuspended in fresh medium. Cell concentration and viability were assessed via trypan blue exclusion using a hemocytometer, calculated as follows: cells/mL = counted cells × dilution factor × 10^4 (Rostinawati et al., 2024).

2.3. Cytotoxicity assay

The cytotoxic activity of the fractions was evaluated in vitro using the WST-8 assay. MCF-7 cells were seeded into 96-well plates at a density of 8,000 cells/well and incubated for 24 h in Minimum Essential Medium to allow cell attachment (Chamchoy et al., 2019). The cells were then treated with *U. lanosa* var. *ferrea* stem fractions at concentrations of 15.625, 31.25, 62.5, 125, 250, 500, and 1,000 μg/mL. Cisplatin was used as the positive control at concentrations of 1.25, 2.5, 5, and 10 μg/mL. After treatment, the cells were incubated for 24 h at 37°C in a humidified atmosphere containing 5% CO_2 (Zhang et al., 2020).

After incubation, 10 μL of WST-8 reagent was added to each well, and the plates were further incubated for 2–4 h. Absorbance was measured using a microplate reader at 450 nm, with correction at 620 nm. Absorbance values from three replicate wells were converted into percentage cell viability, and the results are presented as mean ± standard deviation. IC_{50} values were determined using nonlinear regression analysis in GraphPad Prism version 10.4.0 (527) (Chou, 2010).

2.4. Metabolite profiling using UHPLC-HRMS

Metabolite profiling of the *U. lanosa* stem n-hexane fraction was performed using a Thermo Scientific™ Vanquish™ UHPLC system coupled to a Q Exactive™ Hybrid Quadrupole-Orbitrap™ High-Resolution Mass Spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Chromatographic separation was achieved on an Accucore™ Phenyl-Hexyl column (100 mm × 2.1 mm i.d., 2.6 μm; Thermo Fisher Scientific) maintained at 40 °C. The mobile phase consisted of MS-grade water (A) and MS-grade methanol (B), both containing 0.1% formic acid. The flow rate was set to 0.3 mL/min with an injection volume of 3 μL. The gradient elution program was programmed as follows: 0–16 min, 5% to 90% B; 16–20 min, isocratic at 90% B; and 20–25 min, return to 5% B for column re-equilibration.

Mass spectrometric analysis was conducted using positive electrospray ionization (ESI+). Nitrogen was utilized as both the sheath and auxiliary gas at flow rates of 45 and 25 arbitrary units, respectively. The optimized source parameters included a spray voltage of 3.30 kV, an S-lens RF level of 55.00, a capillary temperature of 320 °C, and a probe heater temperature of 30 °C. Mass spectra were acquired over a scan range of *m/z* 66.7–1000. Metabolites were tentatively identified by evaluating accurate mass data against reference literature and the ChemSpider database.

2.5. Statistical analysis

Cytotoxicity data were summarized as mean ± standard deviation. Cell viability was calculated from replicate wells for each treatment concentration. IC_{50} values were determined independently for each replicate using log-concentration interpolation at 50% cell viability between the two concentration points surrounding the 50% survival level. Final IC_{50} values were expressed as mean ± standard deviation from three independent replicate calculations. Statistical comparison among groups was performed using one-way analysis of variance followed by Tukey's honestly significant difference post hoc test. A p-value below 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Cytotoxic activity of *Uncaria lanosa* var. ferrea stem fractions

The cytotoxic activity of *U. lanosa* stem fractions against MCF-7 breast cancer cells was evaluated using the WST-8 assay. The dose–response curves showed that all fractions reduced MCF-7 cell viability as the concentration increased, although the magnitude of response differed among fractions and remained lower than that of cisplatin as the positive control (**Figure 1**). This result indicates that the stem fractions produced measurable cytotoxic effects in this in vitro model, but their activity should be interpreted as preliminary screening evidence rather than proof of anticancer efficacy.

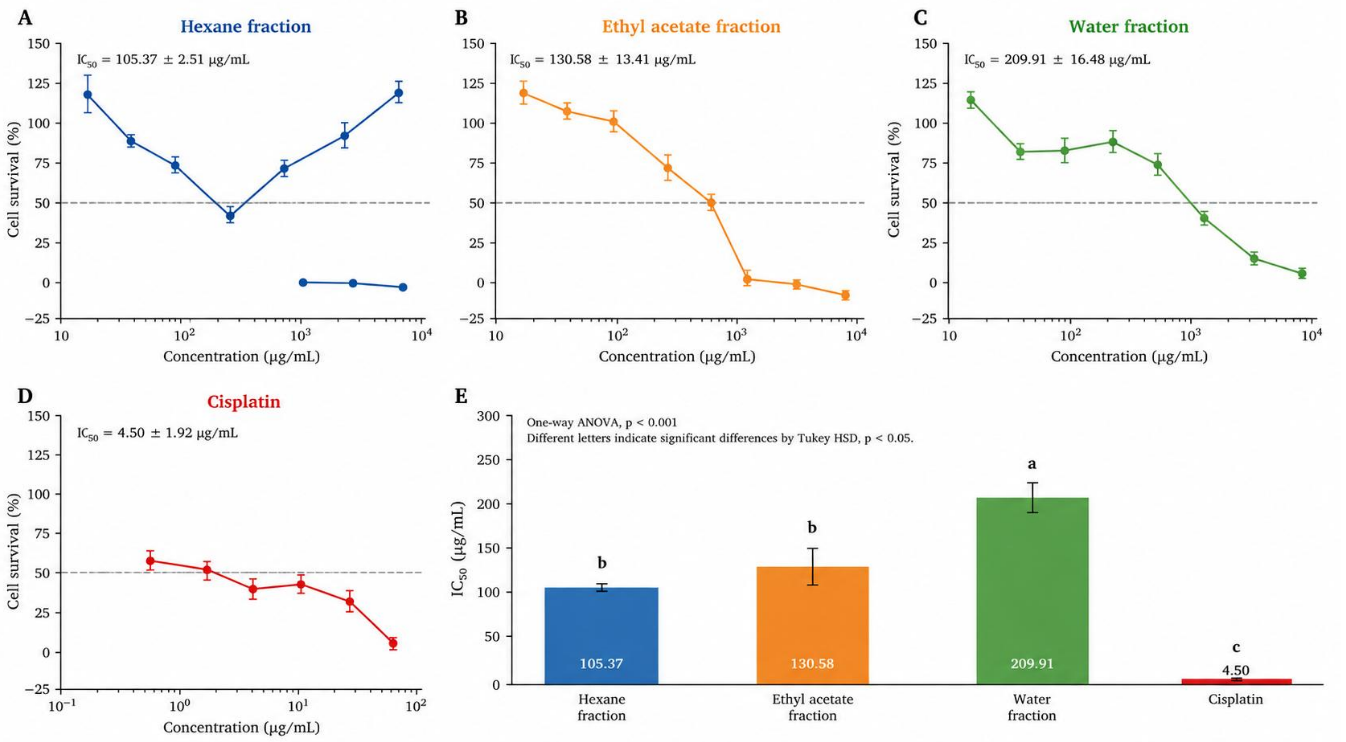

Figure 1. Dose–response curves and IC_{50} values of *Uncaria lanosa* var. *ferrea* stem fractions and cisplatin against MCF-7 cells. Panels A–D show cell survival following treatment with the hexane fraction, ethyl acetate fraction, water fraction, and cisplatin, respectively. Panel E summarizes IC_{50} values calculated from replicate dose–response data. Data are presented as mean ± SD; different letters indicate significant differences by Tukey's HSD test ($p < 0.05$).

Among the plant fractions, the hexane fraction showed the lowest IC_{50} value, 105.37 ± 2.51 μg/mL, followed by the ethyl acetate fraction at 130.58 ± 13.41 μg/mL. Both fractions were assigned to the same Tukey group, indicating that their cytotoxic activities were not significantly different under the tested conditions. The water fraction showed a higher IC_{50} value of 209.91 ± 16.48 μg/mL and was statistically separated from the hexane and ethyl acetate fractions, indicating lower cytotoxic activity. Cisplatin showed the lowest IC_{50} value, 4.50 ± 1.92 μg/mL, and was significantly different from all plant fractions. These results demonstrate that fraction type influenced the cytotoxic response, with the hexane and ethyl acetate fractions showing stronger activity than the water fraction, while cisplatin remained markedly more potent than all fractions.

The higher cytotoxicity of the hexane and ethyl acetate fractions suggests that non-polar to semi-polar constituents may contribute more strongly to the reduction of MCF-7 cell survival than polar constituents extracted in the water fraction. The hexane fraction is expected to contain more lipophilic compounds, whereas the ethyl acetate fraction may contain semi-polar metabolites that also contribute to cytotoxic activity. In contrast, the weaker activity of the water fraction suggests that the polar constituents recovered under these conditions had lower cytotoxic effects against MCF-7 cells. This pattern supports the importance of solvent-based fractionation in separating bioactive constituents and prioritizing fractions for further chemical profiling.

The interpretation of these results should remain conservative because the study was limited to a single in vitro cancer cell model. MCF-7 cells are widely used as an estrogen receptor-positive breast cancer model for preliminary evaluation of bioactive compounds, but results from one cancer cell line cannot establish selectivity, mechanism of action, or therapeutic relevance (Lee et al., 2015; Elkaeed et al., 2021). Further studies using normal cell controls, additional breast cancer subtypes, and mechanism-specific assays are required to determine whether the observed cytotoxicity is selective and biologically meaningful across broader experimental conditions.

3.2. Metabolite profile of the hexane fraction

The hexane fraction was selected for metabolite profiling because it showed measurable cytotoxic activity and represented the non-polar fraction of *U. lanosa* stem extract. UHPLC-HRMS analysis indicated the presence of multiple metabolites in this fraction. The metabolite profiling data are presented in **Table 1**.

The metabolite profile showed that the hexane fraction contained chemically diverse constituents, including terpenoid-, fatty acid-, alkaloid-, and aromatic ketone-related compounds. The largest peak area was observed for 4,4a-dimethyl-6-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, followed by piperine and 9-(non-1′,3′-dienoxy)non-8-enoic acid. These data indicate that the hexane fraction was not dominated by a single compound but contained several detectable metabolites with different retention times and relative abundances.

The detected metabolite groups provide a plausible chemical basis for the cytotoxic response observed in the WST-8 assay. Terpenoid-related compounds and alkaloid-type metabolites have been reported to influence cancer-related cellular processes in previous studies, while fatty acid derivatives may contribute to biological activity through membrane-associated or metabolic effects (Rezk et al., 2015; Dumontet & Jordan, 2010; Yang et al., 2022). However, these mechanisms were not directly tested in the present study. Therefore, the detected compounds should be considered candidate contributors to the observed cytotoxicity, not confirmed active principles.

Several annotated compounds in the hexane fraction have been associated with biological activities in previous reports. Caryophyllene oxide has been linked to anti-inflammatory and antimicrobial activities, cis-eleostearic acid has been reported to show antioxidant and anticancer-related activities, and piperine has been investigated for several pharmacological properties (Shrinet et al., 2021; Tripathi et al., 2022; Ramírez-Santos et al., 2024). These reports support the biological relevance of the detected metabolites, but they do not confirm that each compound contributed directly to the activity of the hexane fraction in MCF-7 cells. Further isolation and activity-guided testing are required to clarify their individual roles.

3.3. Chromatographic profile of the hexane fraction

The total ion chromatogram of the hexane fraction showed several detectable peaks over the analysis time, reflecting the chemical complexity of the fraction (**Figure 2**). In UHPLC-HRMS analysis, retention time provides information on chromatographic behavior, whereas peak intensity reflects the relative ion abundance of detected compounds under the analytical conditions (Núñez et al., 2020; Zang et al., 2023). The chromatogram showed a prominent peak around 12.01 min, consistent with the high peak area recorded for the major annotated metabolite in **Table 1**.

The chromatographic pattern supports the interpretation that the hexane fraction contains a mixture of non-polar and moderately non-polar constituents. Peaks detected between approximately 7 and 13 min corresponded to several annotated compounds listed in the metabolite profiling table. This distribution is consistent with the use of hexane as a non-polar fractionation solvent and supports the selection of UHPLC-HRMS for chemical profiling of this fraction.

The metabolite annotations should be interpreted with caution because accurate mass-based profiling alone is insufficient for definitive structural confirmation. Although UHPLC-HRMS can support tentative annotation of plant metabolites, confirmation requires authentic standards, MS/MS fragmentation matching, or additional spectroscopic evidence. Previous metabolite profiling studies of *Uncaria* species have also emphasized the usefulness of mass spectrometry for characterizing complex extracts while still requiring careful validation of compound identity (Mangurana et al., 2019). Thus, the present metabolite list should be regarded as a preliminary chemical profile.

Table 1. Metabolite profiling of the active hexane fraction

No.	Tentatively identified metabolite	Formula	Calculated molecular weight	Retention time (min)	Area (max)
1	4,4a-Dimethyl-6-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one	$C_{15}H_{22}O$	218.16642	12.002	19166841908
2	Piperine (1-piperoylpiperidine)	$C_{17}H_{19}NO_3$	285.13573	10.968	8484187513
3	9-(Non-1′,3′-dienoxy)non-8-enoic acid	$C_{18}H_{30}O_3$	294.21894	13.001	5170797568
4	(2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trienoic acid	$C_{15}H_{24}O_2$	236.17703	10.570	3530057175
5	2-Ethylamino-3-phenylbicyclo[2.2.1]heptane	$C_{15}H_{21}N$	215.16689	7.283	1946656649
6	cis-Eleostearic acid	$C_{18}H_{30}O_2$	278.22416	12.650	1878246485
7	1-(5-Acetyl-2-hydroxyphenyl)-3-methyl-1-butanone	$C_{13}H_{16}O_3$	220.10938	13.108	1520635265
8	Caryophyllene oxide	$C_{15}H_{24}O$	220.18223	13.264	1441319334
9	4,5-Epoxy-4,11,11-trimethyl-8-methylenebicyclo[7.2.0]undecane	$C_{15}H_{24}O$	220.18223	12.462	1441319334
10	1-Methyl-4-(6-methylhept-5-en-2-yl)benzene	$C_{15}H_{22}$	202.17166	12.738	1163063160

Note: Metabolites were annotated tentatively based on UHPLC-HRMS data. Definitive identification requires comparison with authentic standards, MS/MS spectral matching, or additional structural analysis.

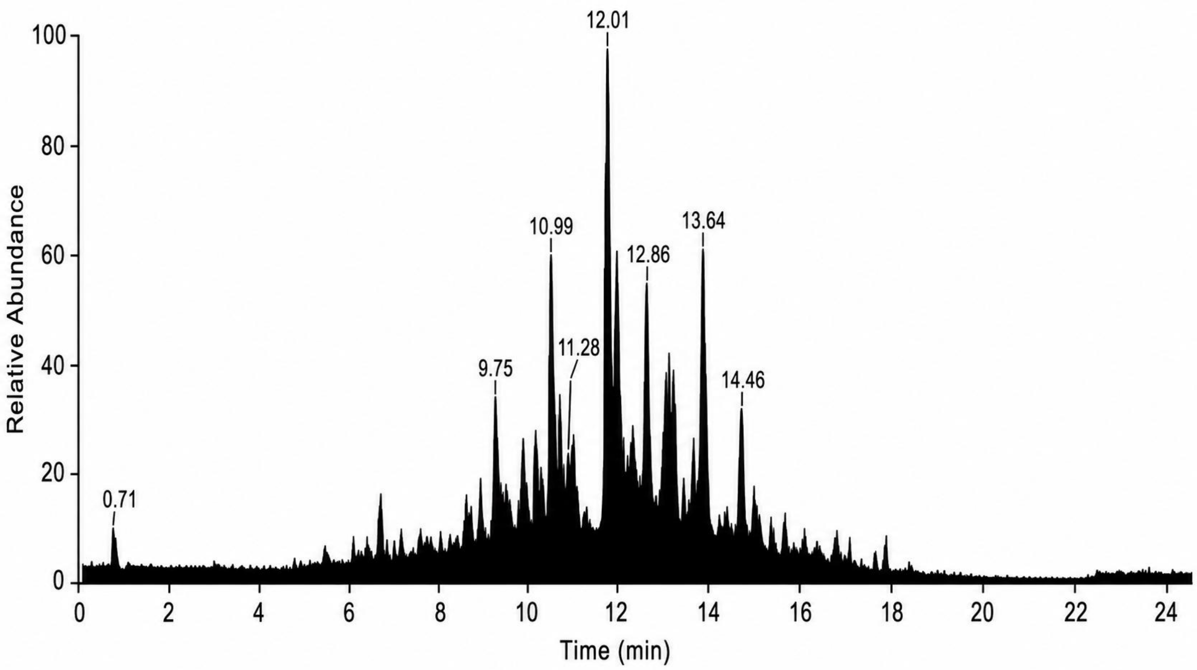

Figure 2. Total ion chromatogram of the hexane fraction of *Uncaria lanosa* var. *ferrea* stem

3.4. Integrated interpretation

The combined cytotoxicity and metabolite profiling results indicate that *U. lanosa* stem fractions showed measurable cytotoxic activity against MCF-7 breast cancer cells. The hexane fraction showed the strongest cytotoxicity among the plant fractions, followed by the ethyl acetate and water fractions, whereas cisplatin remained markedly more potent than all plant fractions. Cisplatin remained markedly more potent than all plant fractions, indicating that the fractions should not be presented as alternatives to standard chemotherapy. Instead, the results provide an initial basis for identifying bioactive fractions and candidate metabolites for further investigation.

The findings also show that the hexane fraction contains several tentatively annotated metabolites that may be relevant to its biological activity. However, the current study does not establish selectivity, mechanism of action, or definitive compound identity. The absence of normal cell controls, apoptosis-specific assays, and confirmatory metabolite identification limits the interpretation of the cytotoxic findings. Future studies should include selectivity testing, compound isolation, validation using authentic standards, and mechanistic assays to clarify the pharmacological relevance of *U. lanosa* stem fractions.

4. CONCLUSION

This study showed that stem fractions of *Uncaria lanosa* var. *ferrea* exhibited measurable cytotoxic activity against MCF-7 breast cancer cells. Among the plant fractions, the hexane fraction showed the strongest cytotoxicity, followed by the ethyl acetate and water fractions, although all fractions were substantially less potent than cisplatin. UHPLC-HRMS analysis of the hexane fraction tentatively identified ten metabolites, including terpenoid-, fatty acid-, and alkaloid-related compounds, which may provide an initial chemical basis for the observed cytotoxic response. These findings contribute preliminary evidence on the cytotoxic profile and metabolite composition of Bajakah Tampala stem fractions and may serve as a useful reference for future studies on bioactive constituents from *U. lanosa* var. *ferrea*. Further research involving normal cell controls, compound isolation, structural confirmation, and mechanism-specific assays is needed to clarify the selectivity and pharmacological relevance of the active fraction.

AUTHOR CONTRIBUTIONS

Conceptualization, M.Y. and M.M.; methodology, M.Y., M.M., and R.A.; validation, M.Y., M.M., R.A., and I.Y.; formal analysis, M.Y.; investigation, M.Y.; resources, M.M. and R.A.; data curation, M.Y.; writing—original draft preparation, M.Y.; writing—review and editing, M.M., R.A., and I.Y.; visualization, M.Y.; supervision, M.M., R.A., and I.Y. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable. This study did not involve humans or animals, and all experiments were conducted using established cell lines under standard laboratory conditions.

INFORMED CONSENT STATEMENT

Not applicable. This study did not involve human participants or identifiable human data.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ROLE OF FUNDERS

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DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist in improving the clarity, structure, grammar, and readability of the text. After using this tool, the authors carefully reviewed, edited, and verified the entire content to ensure that it accurately represents their own data, analysis, and interpretation. The authors take full responsibility for the integrity, accuracy, and originality of the manuscript.

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