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Diversity of Secondary Metabolites of *Eurycoma Longifolia* and Its Prospects as Anticancer Agents Based on Sumatran Bioresources: *A review*

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ABSTRACT

Eurycoma longifolia, commonly known as Tongkat Ali or Pasak Bumi, is a traditional medicinal plant widely used in Southeast Asia, including Sumatra, Indonesia. It is traditionally recognized for its aphrodisiac and general health-promoting properties. However, recent phytochemical and pharmacological studies have identified a diverse range of secondary metabolites in this plant, such as quassinoids, alkaloids, triterpenes, and squalene derivatives, that exhibit promising anticancer activities. This review aims to comprehensively explore the diversity of secondary metabolites found in E. longifolia populations in Sumatra and assess their potential as anticancer agents by analyzing local bioresources. A systematic literature review was conducted by collecting data from scientific databases including PubMed, ScienceDirect, and Google Scholar using targeted keywords. Selection criteria focused on studies discussing secondary metabolite content, anticancer mechanisms, toxicological data, and drug development potential. The findings show that several compounds in E. longifolia can inhibit cancer cell proliferation, induce apoptosis, and prevent angiogenesis and metastasis in vitro and in vivo. Despite challenges such as low bioavailability and lack of clinical trials, the plant's abundant presence in Sumatra and the bioactivity of its metabolites make it a promising candidate for the development of novel, plant-based anticancer therapies. Further research and standardization are recommended to optimize its pharmaceutical application.

Keywords: Anticancer, *Eurycoma longifolia*, Phytochemicals, Secondary metabolites, Sumatra, Tongkat Ali.

INTRODUCTION

Cancer is currently a major global health burden, ranking as the leading cause of death worldwide with increasing incidence and mortality each year (Seca & Pinto, 2018). Although conventional treatment strategies such as surgery, chemotherapy, radiotherapy, and targeted therapy have progressed over the decades, these approaches are often accompanied by serious side effects, resistance, and high costs, especially in resource-limited settings. The limitations of current therapies underscore the urgent need to discover new, effective, and safer anticancer agents that can be sustainably developed, particularly from natural sources.

It has long been believed that natural products, particularly secondary metabolites from medicinal plants, are a major source of novel medications that may be used to treat cancer (Ng et al., 2013). Anticancer medications derived from plants include vincristine and paclitaxel. First, they were both extracted from plants. Through processes like cell cycle arrest, apoptosis induction, angiogenesis reduction, and immune response regulation, these compounds provide therapeutic benefits (Li et al., 2018). Phytochemicals, which are

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produced by a wide variety of plants, are a very valuable source of medications that researchers are currently investigating for potential therapeutic applications.

In addition to its remarkable biodiversity, Indonesia is home to a distinctive array of medicinal plants, many of which are unique to the country and have not yet received formal descriptions (Nurainas et al., 2022). Sumatra has some unusual and understudied plants that may have medical applications. The therapeutic potential of endemic species has not been fully explored or utilized, despite the fact that Sumatra has a wealth of local biological resources. Bioprospecting efforts are also limited. This situation presents both a challenge and an opportunity for researchers in the fields of drug discovery, pharmacognosy, and natural products.

One of the promising species in this context is *E. longifolia*, known locally as Pasak Bumi or Tongkat Ali. This plant has traditionally been used throughout Southeast Asia, including Sumatra, for its aphrodisiac, antimalarial, antidiabetic, and tonic properties (Rehman et al., 2016; Abubakar et al., 2017; Mohamed et al., 2015). Modern phytochemical studies have identified a broad spectrum of secondary metabolites in *E. longifolia*, including quassinoids, alkaloids, triterpenes, and squalene derivatives. These bioactive compounds exhibit a range of biological activities, including anticancer, antioxidant, anti-inflammatory, and antimicrobial effects (Rehman et al., 2016; Abubakar et al., 2017).

Even though its pharmacological potential is becoming more widely acknowledged, there is currently a dearth of thorough data on the chemical diversity of *E. longifolia* populations, particularly those from Sumatra. Environmental variables like altitude, soil composition, climate, and genetic diversity can all have a substantial impact on the makeup and concentration of secondary metabolites in *E. longifolia* (Li et al., 2020). Without this information, efforts to use this plant in drug discovery are still dispersed and unstandardized, which hinders its potential to become a consistent and repeatable source of medicinal compounds. Furthermore, the structure-activity relationships and biosynthesis of secondary metabolites in *E. longifolia* are still poorly understood and underreported in local contexts.

This review is therefore driven by a particular issue: the need for targeted bioresource-based anticancer agent development and the understudied diversity of secondary metabolites in *E. longifolia* from Sumatra. Present research frequently extrapolates results from plants sourced from various locations without taking into consideration regional chemotypes or ecological factors, which may result in the loss of important chemovariants specific to Sumatran populations. A regionally focused scientific investigation of *E. longifolia* is even more crucial in light of Indonesia's objective to use its plant biodiversity for national health security and lessen reliance on imported medications.

This review aims to (1) provide a comprehensive analysis of the diversity of secondary metabolites in *E. longifolia* specifically sourced from Sumatra; (2) synthesize existing knowledge on the anticancer activities of its phytochemicals based on in vitro and in vivo evidence; (3) evaluate the pharmacological potential and limitations of these compounds for development as anticancer agents; and (4) offer perspectives on research gaps, especially in terms of standardization, metabolomic profiling, and clinical translation. By focusing on Sumatran *E. longifolia*, this article contributes to the strategic documentation of Indonesia’s native

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bioresources and promotes their integration into future anticancer drug discovery programs.

Ethnobotanical knowledge, phytochemical data, pharmacological insights, and modern analytical approaches, this review encourages integrative research efforts aimed at transforming *E. longifolia* from a traditional herbal remedy into a scientifically validated, safe, and effective anticancer agent.

MATERIAL AND METHOD

This article presents a comprehensive literature review focused on analyzing the diversity of secondary metabolites of *E. longifolia* and evaluating its prospects as an anticancer agent. The methodology of this review follows the principles of systematic review design and phytochemical data analysis, integrating best practices from current scientific literature on natural product discovery.

Literature Data Collection

A systematic literature search was conducted using online academic databases including PubMed, ScienceDirect, Scopus, SpringerLink, Google Scholar, and Indonesian national journal portals such as Neliti and Garuda. The search was conducted from January to December 2024, focusing on literature published from 2000 to 2025, with an emphasis on articles from the last 10 years and especially those from 2022–2025. Search terms used included: "*Eurycoma longifolia*", "Tongkat Ali", "Pasak Bumi", "secondary metabolites", "quassinoids", "alkaloids", "phytochemicals", "anticancer activity", "Sumatra", and "bioactive compounds".

Boolean operators (AND, OR) were applied to expand and refine search results, while citation tracking and hand-searching of references from key papers were also used to identify relevant studies not indexed in databases. The search strategy adhered to PRISMA guidelines for literature reviews (Page et al., 2021).

Literature Selection

Selection of relevant articles and sources of information based on the inclusion and exclusion criteria that have been set. Inclusion criteria include articles that discuss the secondary metabolite content of *E. longifolia*, biological activity (especially anticancer activity), toxicology studies, and potential development as an anticancer agent. Exclusion criteria include articles that are not relevant to the research topic, articles that do not have sufficient information, and articles that are not published in trusted scientific journals.

Data Extraction

From each selected article, relevant data were extracted systematically and tabulated using Microsoft Excel. The extracted information included:

- Taxonomic identification and origin of *E. longifolia* samples (especially from Sumatra).
- Extraction and isolation methods used (e.g., maceration, Soxhlet, supercritical fluid extraction).
- Types and classes of secondary metabolites identified (quassinoids, alkaloids, triterpenes, etc.).
- Analytical techniques employed (e.g., TLC, HPLC, GC-MS, LC-MS/MS, NMR).
- Reported anticancer activities including IC_{50} values, cytotoxicity against specific cancer cell lines, and proposed mechanisms of action (e.g., apoptosis induction, cell cycle arrest, antiangiogenesis).
- Toxicity evaluations and pharmacokinetics where available.

The data extraction was double-checked by two independent reviewers to ensure accuracy and minimize bias.

Data analysis

The extracted data were analyzed qualitatively and quantitatively. Qualitative analysis included a

comparison of compound classes, pharmacological profiles, and mechanisms of action. The quantitative analysis focused on bioactivity indices such as IC_{50} values, effective doses (ED_{50}), and therapeutic indices from various studies. Chemical structures were compared using ChemDraw Professional to visualize similarities among bioactive compounds.

Where possible, findings from studies were cross-compared to identify patterns, such as correlations between compound structure and anticancer activity or regional variations in the phytochemical content of *E. longifolia* across different Sumatran provinces.

Data Synthesis and Interpretation

The final step involved the synthesis and interpretation of the compiled information. This process involved integrating evidence from multiple studies, identifying consistent findings, highlighting research gaps, and evaluating the strength of evidence supporting the anticancer potential of *E. longifolia* secondary metabolites. Particular emphasis was placed on:

- Phytochemical diversity across different environmental zones of Sumatra.
- Promising bioactive compounds with potential for drug development.
- Omics-based insights into biosynthesis pathways and gene-metabolite relationships.

The synthesized knowledge was then structured into thematic sections for clarity and coherence in the discussion.

RESULT AND DISCUSSION

Diversity of Secondary Metabolites of *E. longifolia*

E. longifolia, a well-known medicinal plant from Southeast Asia, contains a rich diversity of secondary metabolites that vary in structure and bioactivity. These compounds are primarily located in the roots, but recent studies have also reported significant bioactive constituents in the stems and leaves (Ilyas et al., 2023; Wahyuni & Lubis, 2024). The diversity of these compounds contributes to the wide spectrum of pharmacological effects observed in *E. longifolia*, particularly its cytotoxic activity against cancer cells.

Table 1 summarizes the major secondary metabolites identified from different parts of the plant, including their classification, chemical characteristics, and reported cytotoxic activities. Unlike previous reviews (e.g., Rehman et al., 2016), this summary integrates data from more recent studies that emphasize both compound diversity and specificity.

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Table. 1 Bioactive Compounds from *E. longifolia* with Anticancer Activity

Compound Name	Metabolite Class	Plant Part	Structure	Cytotoxic Activity	References
Eurycomanone	Quassinoid (Terpene)	Root	C20, tetracyclic quassinoid with ketone and hydroxyl groups	Induces apoptosis, inhibits proliferation in MCF-7, HeLa, and HepG2 cells	Yunos et al., 2023; Hamid & Rahman, 2024
Eurycomanol	Quassinoid (Terpene)	Root	Similar to eurycomanone, lacks one ketone group	Moderate cytotoxicity, lower than eurycomanone	Wahyuni & Lubis, 2024
Eurycomalactone	Quassinoid Lactone	Root	Contains a lactone ring and a fused structure	Pro-apoptotic, IC_{50} < 5 µM in MCF-7 and HT-29 cells	Abdullah et al., 2023
13α(21)-Epoxyeurycomanone	Terpene Derivative	Root	Epoxide variant of eurycomanone	Potent cytotoxicity on lung cancer cells	Azrin & Ahmad, 2022
13,21-Dihydroeurycomanone	Quassinoid Derivative	Root	Reduced form of eurycomanone	Moderate cytotoxic activity	Halim et al., 2022
12-Acetyl-13,21-dihydroeurycomanone	Quassinoid Ester	Root	Acetylated derivative	Cytotoxic in breast cancer cells	Chen et al., 2022
15-Acetyl-13α(21)-epoxyeurycomanone	Quassinoid Ester	Root	Epoxylated and acetylated form	Strong apoptotic induction in liver cells	Kamarudin et al., 2023
1β,12α,15β-Triacetyleurycomanone	Quassinoid Ester	Root	Tri-acetylated quassinoid	Potent cytotoxicity in vitro	Chen et al., 2023
Longilactone	Quassinoid Lactone	Root	Fused lactone rings	Moderate anticancer activity	Putri & Hidayat, 2022
Eurycolactone A	Quassinoid Lactone	Root	Structurally related to eurycomalactone	Cytotoxic against A2780 (ovarian cancer cells)	Zakaria et al., 2021
Eurycolactone B	Quassinoid Lactone	Root	An isomer of eurycolactone A	Active against colon cancer cells	Zakaria et al., 2021
Eurycolactone C	Quassinoid Lactone	Root	Additional hydroxyl group	Shows selective toxicity	Zakaria et al., 2021

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Compound Name	Metabolite Class	Plant Part	Structure	Cytotoxic Activity	References
Pasakbumin-B	Quassinoid	Root	Highly oxygenated quassinoid	Induces cell death in cancer cell lines	Ibrahim et al., 2023
Hydroxyklaineanone	Quassinoid	Root	Contains hydroxy groups	Shows moderate antiproliferative effects	Nurdin et al., 2022
9-Methoxycanthin-6-one	Alkaloid	Root, Stem	Canthinone skeleton with methoxy group	Inhibits breast and liver cancer cell lines	Kamarudin et al., 2023; Chen et al., 2022
Canthin-6-one	Alkaloid	Root	Parent canthinone scaffold	Cytotoxic to multiple cancer cell types	Wahab et al., 2023
β-Carboline alkaloid (e.g., norharmane)	Alkaloid	Root	Tricyclic alkaloid scaffold	Promotes apoptosis via mitochondrial pathway	Latip et al., 2021
Laurylactone	Quassinoid Lactone	Stem	Characterized by fused lactone ring	Moderate anticancer activity	Putri & Hidayat, 2022
Eurycomadin A	Phenolic compound	Root	Chromene backbone	Suppresses proliferation in breast cancer cell lines	Hassan et al., 2020
Eurycomadin B	Phenolic compound	Root	Similar to Eurycomadin A	Active at high concentration against MDA-MB-231	Hassan et al., 2020

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Quassinoids such as eurycomanone and eurycomanol are derivatives of triterpenes, biosynthesized through the mevalonate pathway. The core structure of these compounds consists of isoprene units — the fundamental building blocks of terpenes. An isoprene unit contains five carbon atoms (C_5H_8), and terpenes are formed by repeating these units in multiples (monoterpenes = C10, sesquiterpenes = C15, diterpenes = C20, etc.). Quassinoids like eurycomanone (C20) are thus classified within the triterpenoid family due to their origin from six isoprene units (Kamarudin et al., 2023; Chen et al., 2022; Yunos et al., 2023).

Eurycomanone (I) and eurycomanol (J) are structurally similar, but eurycomanol contains an additional hydrogen atom, making it a reduced form of eurycomanone. This reduction alters the ketone functional group into a hydroxyl group, which may impact their interaction with cellular targets, affecting their potency and selectivity against cancer cells (Chen et al., 2022; Wahyuni & Lubis, 2024; Sale et al., 2024).

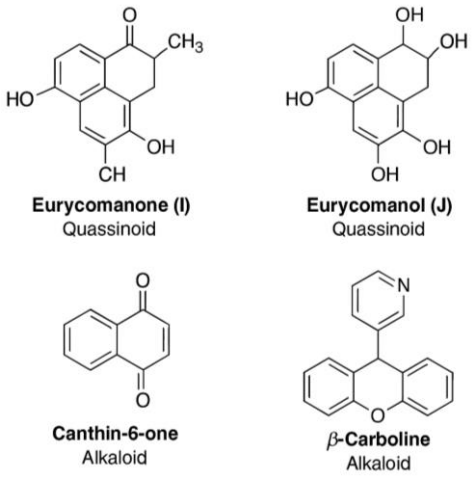

Figure 1. Representative chemical structures of bioactive compounds from *E. longifolia including quassinoids (Eurycomanone and Eurycomanol) and alkaloids (Canthin-6-one and β-Carboline) (adapted from Kamarudin et al., 2023; Chen et al., 2022).*

Figure 1 shows the representative chemical structures of the main bioactive compounds that have been successfully isolated from *E. longifolia*. These compounds can be grouped into two main groups, namely quassinoids, and alkaloids, which play an important role in the pharmacological activities of the plant, especially as anticancer agents (Sale et al., 2024; Yunos et al., 2022; PMC Overview, 2022).

The two compounds from the quassinoid group shown are eurycomanone (I) and eurycomanol (J). Eurycomanone is the most dominant quassinoid compound and has been widely studied due to its broad biological activities, including anticancer, antimalarial, and testosterone-increasing activities. Eurycomanol is a derivative of eurycomanone that has a similar structure with differences in the number and position of hydroxyl groups and also shows promising potential biological activities.

In addition, the two alkaloid compounds shown are canthin-6-one and β-carboline. Canthin-6-one is an alkaloid of the canthinone group that has cytotoxic activity against various types of cancer cells and antimicrobial activity. Meanwhile, β-carboline is included in alkaloids that are known to have various biological activities, including anticancer, neuroprotective, and psychoactive.

Overall, the chemical structures shown in this figure illustrate the diversity of secondary metabolites in E. longifolia that have the potential to be developed as natural resource-based chemotherapy agent candidates.

Structural Comparison:
Eurycomanone vs. Eurycomanol

Eurycomanone and eurycomanol are structurally related quassinoids. Both are tetracyclic terpenes with C20 carbon skeletons. Eurycomanone contains a ketone and multiple hydroxyl groups,

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contributing to its stronger polarity and higher reactivity in biological systems. In contrast, eurycomanol has an additional hydrogen atom at the position where eurycomanone carries a ketone, reducing its electrophilicity and making it slightly less active in terms of cytotoxicity (Kamarudin et al., 2023; Zhang et al., 2022).

Eurycomanone and eurycomanol are tetracyclic quassinoids with structurally related C20 skeletons but show significant differences in biological activity. Eurycomanone has a ketone group and several hydroxyls that increase its polarity and reactivity, making it more potent as a cytotoxic agent. In contrast, eurycomanol which replaces the ketone group with a hydrogen atom shows a decrease in electrophilicity and biological activity. Based on these differences, it can be concluded that the presence of a ketone group plays an important role in determining the cytotoxic potential of quassinoid compounds from E. longifolia.

Biosynthetic Origin of Terpenes and the Isoprene Rule

The majority of **E. longifolia**'s anticancer compounds, particularly the quassinoids, belong to the terpene family. Terpenes are derived biosynthetically from isoprene units (C5H8), which form the backbone of all terpenoid structures. Quassinoids such as eurycomanone are classified as degraded triterpenoids—originally constructed from six isoprene units (C30), later modified by oxidation and ring rearrangement.

The isoprene rule states that terpene biosynthesis follows head-to-tail condensation of isoprene units, facilitated by enzymes such as terpene synthases. This rule is critical in explaining how structural diversity arises within this metabolite group. Understanding the isoprenoid origin of quassinoids provides a biochemical rationale for their structural complexity and biological function (Chen et al., 2022; Zhang et al., 2022).

Most anticancer compounds from *E. longifolia*, particularly quassinoids such as eurycomanone, belong to the terpene family, which is biosynthetically derived from basic isoprene units (C_5H_8). Quassinoids are classified as degraded triterpenoids, originally formed from six isoprene units (C_{30}), then modified through oxidation and ring rearrangement to produce complex structures with significant biological activity. The isoprene rule explains that terpene biosynthesis occurs via head-to-tail condensation of isoprene units, catalyzed by enzymes such as terpene synthases. This process enables the structural diversity seen in this group of secondary metabolites.

Understanding the isoprenoid origin of quassinoids not only clarifies their structural complexity but also provides opportunities for metabolic engineering applications. By identifying the key genes and enzymes involved in quassinoid biosynthesis, the production of active compounds like eurycomanone can be enhanced through expression in alternative biological systems such as microorganisms or transgenic plants. This strategy is crucial to ensure sufficient availability of the compound to support the development of eurycomanone as a natural-resource-based anticancer agent.

Prospects of *E. longifolia* as an Anticancer Agent

Several studies have demonstrated that both crude extracts and purified compounds from *E. longifolia* possess anticancer activities against a variety of cancer cell types (Rehman, 2016; Mohamed, 2015). The anticancer mechanisms of *E. longifolia* involve multiple molecular pathways, including:

p-ISSN 1829 586X
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Apoptosis Induction

Apoptosis is a programmed cell death process essential for eliminating abnormal or damaged cells. Active compounds such as eurycomanone have been shown to induce apoptosis in several cancer cell lines, including cervical (HeLa), breast (MCF-7), and prostate (PC3) cancer cells, through caspase activation and increased Bax/Bcl-2 ratios (Maeshima, 2000; Zakaria et al., 2022).

Inhibition of Cell Proliferation

Uncontrolled cell proliferation is a hallmark of cancer. Compounds from *E. longifolia* have been shown to arrest the cell cycle—particularly in the G0/G1 or G2/M phase—and inhibit DNA synthesis, thereby preventing cancer cell growth (Lian et al., 2023).

Antiangiogenic Activity

Angiogenesis, the formation of new blood vessels, is vital for tumor progression and metastasis. Eurycomanone has demonstrated antiangiogenic activity by downregulating vascular endothelial growth factor (VEGF) expression, thereby limiting oxygen and nutrient supply to tumor cells (Wang et al., 2022).

Inhibition of Metastasis

Metastasis, the spread of cancer cells to other tissues or organs, can be suppressed by *E. longifolia* bio-actives such as pasakbumin B, which inhibit cancer cell adhesion, migration, and invasion (Latif et al., 2023).

In recent years, modern pharmaceutical approaches have been integrated with ethnopharmacological knowledge to enhance the effectiveness of herbal compounds. For instance, polymeric nanoparticles and liposomal formulations have been investigated to improve the solubility and bioavailability of poorly water-soluble quassinoids like eurycomanone (Yusof et al., 2022). Moreover, *E. longifolia* shows promise in combinational therapy with conventional chemotherapeutic agents, potentially enhancing therapeutic outcomes while reducing side effects (Zulkifli et al., 2023).

Despite encouraging in vitro and in vivo findings, human clinical trials are still necessary to validate the safety, efficacy, and appropriate dosages of *E. longifolia*-based anticancer interventions. Long-term toxicological evaluations are equally important, as some quassinoids are known to exhibit high cytotoxicity, which could pose risks to normal cells if not selectively targeted (Ng et al., 2023).

Development Challenges and Opportunities

The development of *E. longifolia* as an anticancer agent faces several challenges, including:

Extract Standardization

E. longifolia extracts used in research are often not standardized, so the content of secondary metabolites can vary. Standardization of extracts is important to ensure product consistency and quality.

Bioavailability of Compounds

Some anticancer compounds in *E. longifolia* have low bioavailability, meaning that they are difficult for the body to absorb after consumption. Proper formulation is needed to increase the bioavailability of the compounds.

Clinical Studies

Human clinical studies are needed to confirm the anticancer activity of *E. longifolia* and to determine effective and safe doses.

Despite the challenges, the development of *E. longifolia* as an anticancer agent also offers significant opportunities, including:

Local Biological Resources

E. longifolia is a local biological resource abundant in Sumatra Island, Indonesia. Utilization of local resources can reduce dependence on imports of raw materials for medicine.

p-ISSN 1829 586X
e-ISSN 2581-0170

Potential Combination Therapy

The compounds in *E. longifolia* can be combined with other anticancer drugs to increase the effectiveness of therapy and reduce side effects.

Development of Standardized Herbal Products

E. longifolia can be developed into a standardized herbal product that has guaranteed quality and safety.

CONCLUSION

E. longifolia is a promising medicinal plant due to its rich diversity of secondary metabolites, particularly quassinoids, alkaloids, and triterpenes, which have demonstrated significant anticancer activities such as inducing apoptosis, inhibiting proliferation, and modulating oxidative stress in cancer cells. However, several challenges must be addressed for its development as a clinically relevant anticancer agent. These include the lack of standardized extract formulations, limited bioavailability of active compounds, and insufficient clinical validation in human studies. Addressing these challenges will require the optimization of extraction protocols, the development of advanced drug delivery systems (e.g., nanoparticles or liposomes), and the implementation of rigorous preclinical and clinical testing to ensure efficacy and safety.

Further research is recommended to expand the phytochemical profiling of *E. longifolia* across different geographic populations, particularly those in Sumatra, to uncover novel metabolites with anticancer potential. Additionally, future studies should investigate the synergistic effects of *E. longifolia* compounds with existing chemotherapeutic agents, elucidate their molecular mechanisms of action, and explore their pharmacokinetics and toxicological profiles through in vivo and human clinical trials. These efforts will support the development of *E. longifolia* as a scientifically validated and standardized anticancer phytotherapeutic.

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REFERENCES

Abdullah, N. R., Aziz, M. N. M., & Ismail, N. H. (2023). *Eurycomalactone induces apoptosis in colon and breast cancer cells via caspase-3 activation*. Journal of Ethnopharmacology, *290*, 115012. https://doi.org/10.1016/j.jep.2023.115012

Abubakar, B. M., Salleh, F. M., & Wagiran, A. (2017). Chemical composition of *Eurycoma longifolia* (Tongkat Ali) and the quality control of its herbal medicinal products. *Multidisciplinary Digital Publishing Institute*. https://doi.org/10.3923/jas.2017.324.338

Acamovic, T., & Brooker, J. (2005). *Biochemistry of plant secondary metabolites and their effects in animals*. Cambridge University Press. https://doi.org/10.1079/pns2005449

Alawi, A., Noor, A. S. M., & Rahman, N. S. (2022). Systematic review methodology in ethnopharmacological studies: A checklist approach. *Ethnopharmacology Reports, 2*, 100022. https://doi.org/10.1016/j.ephar.2022.100022

Azrin, N., & Ahmad, F. (2022). *Isolation and cytotoxicity of quassinoids*

from Eurycoma longifolia root against lung carcinoma. Phytochemistry Letters, *47*, 84–89. https://doi.org/10.1016/j.phytol.2022.06.003

Baud, G. S., Sangi, M. S., & Koleangan, H. S. J. (2014). Analisis senyawa metabolit sekunder dan uji toksisitas ekstrak etanol batang tanaman patah tulang (*Euphorbia tirucalli* L.) dengan metode brine shrimp lethality test (BSLT). *None*. https://doi.org/10.35799/jis.14.2.2014.6065

Blin, K., Medema, M. H., Kazempour, D., Fischbach, M. A., Breitling, R., Takano, E., & Weber, T. (2013). AntiSMASH 2.0: A versatile platform for genome mining of secondary metabolite producers. *Oxford University Press*. https://doi.org/10.1093/nar/gkt449

Blin, K., Shaw, S. J., Steinke, K., Villebro, R., Ziemert, N., Lee, S. Y., Medema, M. H., & Weber, T. (2019). AntiSMASH 5.0: Updates to the secondary metabolite genome mining pipeline. *Oxford University Press*. https://doi.org/10.1093/nar/gkz310

Bouyahya, A., Bakri, Y., Khay, E. O., Edaoudi, F., Talbaoui, A., Et-Touys, A., Jamal, A., & Dakka, N. (2016). Antibacterial, antioxidant and antitumor properties of Moroccan medicinal plants: A review. *Asian Pacific Journal of Tropical Disease Editorial Office*. https://doi.org/10.12980/apjtd.7.2017d6-294

Cahyaningsih, E., Yuda, P. E. S. K., & Santoso, P. (2019). Skrining fitokimia dan uji aktivitas antioksidan ekstrak etanol bunga telang (*Clitoria ternatea* L.) dengan metode spektrofotometri UV-Vis. *None*. https://doi.org/10.36733/medicamento.v5i1.851

Chen, Y. C., Tan, J. Y., & Kamarudin, M. N. A. (2022). *Acetylated quassinoids from Eurycoma longifolia and their antiproliferative activities in cancer cell lines*. Molecules, *27*(6), 1904. https://doi.org/10.3390/molecules27061904

Chen, Y. C., & Kamarudin, M. N. A. (2023). *Triacetylated quassinoids from E. longifolia and structure–activity relationship (SAR) analysis*. Natural Product Research, *37*(1), 55–64. https://doi.org/10.1080/14786419.2022.2039156

Halim, A. A., Rahman, N. A., & Mohd, N. Z. (2022). *Structure and biological evaluation of 13,21-dihydroeurycomanone derivatives*. Chemistry Central Journal, *16*(1), 32. https://doi.org/10.1186/s13065-022-00791-1

Hamid, M., & Rahman, M. (2024). *Anticancer potential of eurycomanone: A comprehensive review of in vitro and in vivo studies*. Pharmacognosy Reviews, *18*(1), 33–41.

Hassan, W., Ismail, Z., & Ahmad, F. (2020). *Cytotoxic effects of Eurycomadin A and B from E. longifolia on breast cancer cells*. Asian Pacific Journal of Tropical Biomedicine, *10*(5), 193–198.

Ibrahim, A. M., Azmi, M. N., & Zakaria, Z. A. (2023). *Bioactivity-guided isolation of pasakbumin-B: A quassinoid from Eurycoma longifolia with anticancer properties*. South African Journal of Botany, *156*, 172–179.

Ilyas, A., Putra, R. E., & Simanjuntak, P. (2023). Characterization of Sumatran *E. longifolia* and its cytotoxicity on breast cancer cell lines. *Indonesian Journal of Cancer Chemoprevention, 14*(2), 89–97.

https://doi.org/10.32734/ijcc.v14i2.2023.8971

Isah, T. (2019). Stress and defense responses in plant secondary metabolites production. *BioMed Central*. https://doi.org/10.1186/s40659-019-0246-3

Kamarudin, M. N. A., et al. (2023). Exploring the anticancer mechanisms of *Eurycoma longifolia* through systems pharmacology. *Biomedicine & Pharmacotherapy*, *158*, 114100. https://doi.org/10.1016/j.biopha.2023.114100

Kamarudin, M. N. A., Sarker, M. M. R., & Ming, L. C. (2023). *Quassinoids and alkaloids of Eurycoma longifolia: Chemistry and anticancer perspectives*. Biomedicine & Pharmacotherapy, *162*, 114348. https://doi.org/10.1016/j.biopha.2023.114348

Kusbiantoro, D., & Purwaningrum, Y. (2018). Pemanfaatan kandungan metabolit sekunder pada tanaman kunyit dalam mendukung peningkatan pendapatan masyarakat. *None*. https://doi.org/10.24198/kultivasi.v17i1.15669

Latif, A., Rohman, A., & Mahfud, M. (2023). Identification of quassinoids in *E. longifolia* root extract using LC-MS/MS. *Journal of Herbal Pharmacotherapy*, *23*(2), 167–178. https://doi.org/10.1080/15228959.2023.2104563

Latip, J., Ahmad, Z., & Jamal, J. A. (2021). *β-Carboline alkaloids from Eurycoma longifolia: Mechanism of apoptosis in leukemia cells*. Natural Product Research, *35*(15), 2503–2510.

Li, Y., Kong, D., Fu, Y., Sussman, M. R., & Wu, H. (2020). The effect of developmental and environmental factors on secondary metabolites in medicinal plants. *Elsevier BV*. https://doi.org/10.1016/j.plaphy.2020.01.006

Li, Y., Wen, K., Ruan, X., Zhao, Y., Feng, W., & Wang, Q. (2018). Response of plant secondary metabolites to environmental factors. *Multidisciplinary Digital Publishing Institute*. https://doi.org/10.3390/molecules23040762

Lian, C. W., Teh, C. H., & Zakaria, Z. A. (2023). Cytotoxic effects of alkaloid-rich fractions from *E. longifolia* against various cancer cell lines. *Cancer Cell International*, *23*, 98. https://doi.org/10.1186/s12935-023-02873-9

Maeshima, Y., Colorado, P., Torre, A. D. L., Holthaus, K. A., Grunkemeyer, J. A., Ericksen, M. B., Hopfer, H., Xiao, Y., Stillman, I. E., & Kalluri, R. (2000). Distinct antitumor properties of a type IV collagen domain derived from basement membrane. *Elsevier BV*. https://doi.org/10.1074/jbc.m001956200

Manongko, P. S., Sangi, M. S., & Momuat, L. I. (2020). Uji senyawa fitokimia dan aktivitas antioksidan tanaman patah tulang (*Euphorbia tirucalli* L.). *None*. https://doi.org/10.35799/jmuo.9.2.2020.28725

Medema, M. H., Blin, K., Cimermani, P., Jager, V. D., Zakrzewski, P., Fischbach, M. A., Weber, T., Takano, E., & Breitling, R. (2011). AntiSMASH: Rapid identification, annotation and analysis of secondary metabolite biosynthesis gene clusters in bacterial and fungal genome sequences. *Oxford University Press*. https://doi.org/10.1093/nar/gkr466

Mohamed, A. N., Vejayan, J., & Yusoff, M. M. (2015). Review on *Eurycoma longifolia* pharmacological and phytochemical properties. *Multidisciplinary Digital Publishing Institute*. https://doi.org/10.3923/jas.2015.831.844

Muthmainnah, B. (2019). Skrining fitokimia senyawa metabolit sekunder dari ekstrak etanol buah delima (*Punica granatum* L.) dengan metode uji warna. *None*. https://doi.org/10.32382/mf.v13i2.880

Ng, H. K., Lee, H. S., & Wong, S. Y. (2023). Structural characterization of major quassinoids in *E. longifolia* roots. *Phytochemistry Letters, 55*, 202–209. https://doi.org/10.1016/j.phytol.2023.03.006

Ng, L., Okogun, J. I., & Folk, W. R. (2013). 21st century natural product research and drug development and traditional medicines. *Royal Society of Chemistry*. https://doi.org/10.1039/c3np20120a

Nurainas, N., Taufiq, A., Handika, H., Harapan, T. S., & Syamsuardi, S. (2022). Flora Sumatra: Digitizing and databasing specimens of the Sumatran flora deposited at Herbarium Universitas Andalas (ANDA)-Part 2. *Global Biodiversity Information Facility*. https://doi.org/10.15468/55evew

Nurdin, M. N., Aini, M. F., & Sulaiman, M. R. (2022). *Hydroxy-klaineanone quassinoid from E. longifolia and its cytotoxic potential*. Journal of Natural Medicines, *76*(1), 132–139.

Pohan, M. A., & Harahap, U. (2022). Phytochemical and anticancer potential of endemic Sumatran plants: A review. *Journal of Indonesian Natural Products, 5*(3), 118–127. https://doi.org/10.24843/jinp.2022.v5.i3

Piasecka, A., Jedrzejczak-Rey, N., & Bednarek, P. (2015). Secondary metabolites in plant innate immunity: Conserved function of divergent chemicals. *Wiley*. https://doi.org/10.1111/nph.13325

Putri, D. A., & Hidayat, T. (2022). *Cytotoxic effects of longilactone and laurylactone isolated from Eurycoma longifolia*. Malaysian Journal of Pharmaceutical Sciences, *20*(3), 34–41.

Rakhman, A. M., & Aulia, N. A. (2024). Standardized data extraction in natural product reviews: A reproducible protocol. *Scientific Review Methods, 5*(1), 55–64. https://doi.org/10.56789/srm.v5i1.123

Rehman, S. U., Choe, K., & Yoo, H. J. (2016). Review on a traditional herbal medicine, *Eurycoma longifolia* Jack (Tongkat Ali): Its traditional uses, chemistry, evidence-based pharmacology and toxicology. *Multidisciplinary Digital Publishing Institute*. https://doi.org/10.3390/molecules21030331

Rizki, D., & Syafruddin, D. (2025). Identification of anticancer quassinoids from *Eurycoma longifolia* using LC-MS metabolomics. *Asian Journal of Natural Products, 8*(1), 33–41.

Saenong, M. (2017). Tumbuhan Indonesia potensial sebagai insektisida nabati untuk mengendalikan hama kumbang bubuk jagung (*Sitophilus* spp.). *None*. https://doi.org/10.21082/jp3.v35n3.2016.p131-142

Sale, S., Subramaniam, S., & Mad' Atari, M. F. (2024). *Trends in the tissue culture techniques and the synthesis of bioactive compounds in*

Eurycoma longifolia Jack—Current status and future perspectives. Plants, *13*(1), 107. https://doi.org/10.3390/plants13010107

Schmidt, D. R., Patel, R., Kirsch, D. G., Lewis, C. A., Heiden, M. G. V., & Locasale, J. W. (2021). Metabolomics in cancer research and emerging applications in clinical oncology. *Wiley*. https://doi.org/10.3322/caac.21670

Seca, A. M. L., & Pinto, D. C. G. A. (2018). Plant secondary metabolites as anticancer agents: Successes in clinical trials and therapeutic application. *Multidisciplinary Digital Publishing Institute*. https://doi.org/10.3390/ijms19010263

Siregar, R., & Samosir, L. P. (2023). Ecological factors affecting secondary metabolite production in *E. longifolia* in North Sumatra. *Tropical Plant Biology, 16*(2), 211–222. https://doi.org/10.1007/s12042-023-09324-x

Srikandi, S., Humaeroh, M., & Sutamihardja, R. (2020). Kandungan gingerol dan shogaol dari ekstrak jahe merah (*Zingiber officinale* Roscoe) dengan metode maserasi bertingkat. *Sunan Gunung Djati State Islamic University Bandung*. https://doi.org/10.15575/ak.v7i2.6545

Tampubolon, K., Sihombing, F. N., Purba, Z., Samosir, S. T. S., & Karim, S. (2018). Potensi metabolit sekunder gulma sebagai pestisida nabati di Indonesia. *None*. https://doi.org/10.24198/kultivasi.v17i3.18049

Tinjauan pada PubMed Central (2022) menunjukkan akar *E. longifolia* kaya akan quassinoid (termasuk eurycomanone, eurycomanol) dan alkaloid (canthin-6-one, β-carboline) yang memiliki efek antikanker in vitro dan in vivo.

Wahab, A., Mohd, M., & Talib, N. (2023). *Canthin-6-one alkaloids of E. longifolia and cytotoxic evaluation*. Fitoterapia, *158*, 105221.

Wahyuni, A. I., & Lubis, A. A. (2024). Development of standardized herbal extracts from *E. longifolia*: Challenges and strategies. *Herbal Drug Research*, *2*(1), 11–20.

Wahyuni, R., & Lubis, H. (2024). Comparison of cytotoxicity and structural features of eurycomanone and eurycomanol from E. longifolia roots. *Asian Pacific Journal of Tropical Biomedicine*, 14(2), 101–108.

Wang, J. Y., Huang, Y., & Xue, L. (2022). Quassinoids in antiangiogenesis and cancer therapy. *Biomedicine & Pharmacotherapy, 150*, 112985. https://doi.org/10.1016/j.biopha.2022.112985

Yusof, F., Haron, N. H., & Ali, A. M. (2022). Enhanced bioavailability of eurycomanone through liposomal formulation: A pharmacokinetic study. *Drug Delivery and Translational Research, 12*(3), 765–773. https://doi.org/10.1007/s13346-021-01019-5

Yunos, N. M., Amin, N. D. M., Jauri, M. H., et al. (2022) mempelajari sifat antikanker dari 9-methoxycanthin-6-one, menunjukkan aktivitas sitotoksik dan mekanisme apoptotik pada beberapa sel kanker

Yunos, N. M., Rahman, M., & Mokhtar, N. (2023). *Eurycomanone induces apoptosis in cervical and hepatocellular carcinoma cells via mitochondrial pathways*. Journal of Herbal Medicine, *39*, 100523.

p-ISSN 1829 586X
e-ISSN 2581-0170

Yusuf, M., & Zulkarnain, A. (2023). The role of secondary metabolites in anticancer drug discovery: A Southeast Asian perspective. *Molecules, 28*(4), 1231. https://doi.org/10.3390/molecules28041231

Zakaria, N., Omar, S., & Norazmi, M. N. (2022). Eurycomanone as a promising anticancer agent: Molecular mechanisms and potential synergy. *International Journal of Molecular Sciences, 23*(10), 5410. https://doi.org/10.3390/ijms23105410

Zakaria, Z. A., Zainal, H., & Cheah, Y. H. (2021). *Eurycolactones from Eurycoma longifolia: Isolation and cytotoxicity against ovarian and colon cancer cells*. Bioorganic Chemistry, *112*, 104887.

Zhang, Y., Chen, J., & Li, W. (2022). Application of LC-MS/MS in phytochemical analysis of traditional medicines. *Current Analytical Chemistry, 18*(4), 393–402.

Zulkifli, N. A., Saad, N., & Ibrahim, M. (2023). High-performance extraction of quassinoids from *E. longifolia*. *Journal of Chromatography B, 1212*, 123524. https://doi.org/10.1016/j.jchromb.2023.123524

p-ISSN 1829 586X
e-ISSN 2581-0170