



MOLECULAR MODIFICATION OF BIOACTIVE COMPOUNDS FROM MEDICINAL PLANTS IN THE DEVELOPMENT OF ANTIMALARIAL AGENTS: AN EFFORT TO ENHANCE KNOWLEDGE AND UTILIZATION OF MEDICINAL PLANTS WITHIN THE COMMUNITY

Nerdi 1, Salman2, Rahma Yulia3, Syaila Sadika4, Revalia Putri Nirwana 5, Fajar Nabila Jufira 6, Jovand Christian Sitorus7.

Universitas Tjut Nyak Dhien, Medan, Indonesia

nerdy190690@gmail.com , salman@utnd.ac.id , abelia@utnd.ac.id ,
syadilasadikaaa@gmail.com revaliaputri52@gmail.com fajarnabila654@gmail.com ,
sitorusjovand@gmail.com .

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Abstrak: Malaria caused by *Plasmodium falciparum* remains a health problem due to increasing resistance to antimalarial drugs, including artemisinin-based therapy. This study aims to examine the potential and strategies for molecular modification of bioactive compounds in medicinal plants as effective and safe new antimalarial candidates. The method used was a descriptive-qualitative literature review of 19 scientific articles published in 2011–2026 and obtained from Google Scholar, PubMed, and ScienceDirect. The results of the study indicate that plants such as *Momordica charantia*, *Fraxinus griffithii*, *Piper sulcatum*, and *Eucalyptus globulus* contain secondary metabolites in the form of alkaloids, flavonoids, and terpenoids that have potential as antiplasmodials. Chemical modifications, such as methylation, acetylation, and esterification, supported by in silico modeling and biological tests can improve the stability, affinity, bioavailability, and selectivity of compounds. Thus, molecular modification based on structure-activity relationship (SAR) has the potential to be a strategy for developing new antimalarial drug candidates to address drug resistance.

Introduction

Malaria is an infectious disease that remains a global public health problem, particularly in tropical and subtropical regions. It is caused by parasites of the genus *Plasmodium*, which are generally transmitted to humans through the bite of infected female

Anopheles mosquitoes. Five species of Plasmodium are known to cause malaria in humans: Plasmodium falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi. Among these species, P. falciparum is the most deadly malaria parasite and is found predominantly in Africa, while P. vivax is the dominant species in most areas outside Sub-Saharan Africa. Malaria infection, particularly that caused by P. falciparum, can progress to severe disease and cause life-threatening complications if not treated promptly and appropriately (WHO, 2025).

According to the World Malaria Report 2025, the WHO estimates that there will be approximately 282 million malaria cases and 610,000 deaths in 80 countries by 2024. These figures indicate that malaria continues to pose a significant global health burden. The WHO African Region is the region with the highest malaria burden, accounting for approximately 95% of cases (265 million) and 95% of deaths (approximately 579,000) in 2024. Children under five are particularly affected, accounting for approximately 75% of malaria deaths in the region (WHO, 2025).

Although various interventions have made progress in malaria control, the disease still faces a number of challenges. The WHO reports that various malaria prevention and control tools used by 2024 are estimated to have prevented approximately 170 million cases and one million deaths. However, the increasing number of cases globally indicates that malaria elimination efforts still require continued strengthening. In addition to biological factors, changing climate patterns, conflict and instability, limited access to health services, and funding gaps also impact the success of malaria control in various regions (WHO, 2025).

Malaria control is carried out through various approaches, including mosquito bite prevention using insecticide-treated bed nets, indoor residual insecticide spraying, early diagnosis, and appropriate antimalarial therapy. For malaria caused by P. falciparum, artemisinin-based combination therapy (ACT) remains one of the main therapies recommended by WHO. However, the effectiveness of this treatment faces challenges due to the emergence of parasite resistance to antimalarial drugs. The WHO, in its World Malaria Report 2025, highlighted the confirmed or suspected partial resistance to artemisinin derivatives in several African countries, in addition to the resistance that had previously been a concern in the Greater Mekong Subregion (WHO, 2025).

The issue of drug resistance is becoming increasingly important because it can reduce treatment success and hinder malaria control and elimination efforts. The WHO states that resistance to antimalarial drugs has been documented in three of the five Plasmodium species that infect humans: P. falciparum, P. vivax, and P. malariae. Therefore, regular monitoring of drug effectiveness is necessary to detect changes in parasite sensitivity and ensure that treatment policies remain appropriate to evolving epidemiological conditions (WHO, 2025).

This resistance issue is also relevant to Indonesia. A February 2026 WHO Indonesia report stated that the Greater Papua region remains a high malaria burden area, with six provinces in the region contributing more than 90% of malaria cases in Indonesia. Drug effectiveness monitoring conducted from August 2024 to October 2025 in Keerom Regency and the Yapen Islands showed that several tested therapies, namely dihydroartemisinin-

piperaquine (DHA-PPQ), artesunate-pyronaridine (ASPY), and artemether-lumefantrine (AL), remained highly effective at the study sites. Nevertheless, the WHO emphasizes the importance of continuous monitoring to detect changes in resistance patterns early (WHO Indonesia, 2026).

This situation indicates that the development of new antimalarial drug candidates remains necessary as part of a long-term strategy to address potential resistance. One approach that can be developed is the exploration of natural resources, particularly medicinal plants that contain diverse bioactive compounds. Medicinal plants have long been used empirically by communities to treat various diseases and have the potential to be sources of active compounds with pharmacological activity.

Research Methods

This study employed a literature review with a descriptive-qualitative approach. This approach was used to obtain a comprehensive overview of the utilization of natural compounds, the application of computational technology (in silico), and molecular modification strategies in modern drug development. Information obtained from various previous studies was then reviewed, compared, and synthesized to obtain a comprehensive understanding of the development of this field. The equipment used in this study was a laptop or computer supported by an internet connection. The software used included Microsoft Word for article preparation and reference management applications, such as Mendeley or Zotero, which were used to organize citations and compile a systematic bibliography. The research material consisted of secondary data obtained from scientific literature. The literature analyzed consisted of 19 scientific articles collected from various databases and academic publication sources relevant to the research topic. Data collection was carried out through a structured literature search in several scientific databases, namely Google Scholar, PubMed, and ScienceDirect. The search was conducted using keywords related to natural compounds, medicinal chemistry, molecular modification, in silico technology, and drug development. The obtained literature was then selected based on inclusion and exclusion criteria to ensure the relevance and quality of the sources used in the study.

Inclusion criteria included: (1) original scientific journal articles published between 2011 and 2026; (2) related to medicinal chemistry; (3) discussing natural compounds or bioactive compounds and their structural or molecular modifications; and (4) presenting clearly identifiable and explainable research methods. Exclusion criteria included non-scientific articles, such as blogs and popular articles; incomplete manuscripts or drafts; and literature not directly related to the research focus, particularly regarding the molecular modification of natural compounds in drug development. The obtained data were analyzed qualitatively using a descriptive-comparative and interpretive approach. The analysis process was carried out in stages to identify important information from each article that met the

research criteria. The analysis stages included: The initial stage was carried out by thoroughly reading and reviewing the 15 selected articles. The review focused on several key aspects, including the research objectives, methods used, types of compounds studied, molecular modification strategies or techniques, research results, and conclusions drawn from each study. Key information obtained from each article was then extracted and grouped according to specific themes. Categorization was carried out by considering the types of natural compounds used, the characteristics of the bioactive compounds, the types of molecular modifications applied, and the purpose of these modifications in drug candidate development. Results from various studies with similar themes were compared to identify similarities, differences, patterns, and developments in the approaches used. An analysis was also conducted of the effectiveness of synthesis or molecular engineering strategies, including the advantages and limitations of each approach in supporting drug discovery and development.

The final stage was carried out by integrating all analytical results from the reviewed literature into a narrative synthesis. This synthesis was used to describe research progress, the potential and effectiveness of molecular modification of natural compounds, and opportunities for developing these strategies in future drug candidate research and discovery.

Results and Discussion

The development of natural-based drugs begins with a systematic approach that integrates ethnopharmaceutical studies the exploration of traditional knowledge of local communities with a review of relevant scientific literature (Rahman et al., 2021). The ethnopharmaceutical approach has proven highly effective in identifying various local plant species that hold potential as sources of new therapeutic agents (Rahman et al., 2021). Field exploration and taxonomic identification have led researchers to the discovery of various bioactive plants that have significant abilities to inhibit pathogen development and modulate biological responses (Rahman et al., 2021).

The biological activity of plant extracts is measurably evaluated through in vitro testing on specific biological target models (Hidayat et al., 2024). The results of the biological tests indicate that potential plant extracts are capable of producing very low 50% Inhibitory Concentration values, indicating that only a very small concentration of the extract is required to inhibit 50% of the activity of the biological target or pathological cells (Hidayat et al., 2024). This very low value is a key indicator of the high level of biological activity and efficacy of a plant isolate (Hidayat et al., 2024).

Secondary metabolites from natural products, such as flavonoids, alkaloids, and terpenoids, offer enormous potential as modern drug candidates (Amin & Wulandari, 2025; Newman & Cragg, 2020). The primary advantage of this group of compounds lies in their extensive chemical architecture diversity and their specific ability to modulate various biological targets (Newman & Cragg, 2020). This fact reinforces the findings of Newman and Cragg (2020), who asserted that the majority of therapeutic agents currently used are direct

derivatives or molecules inspired by the architecture of natural products, either in pure isolate form or through structural modification.

Specifically, flavonoids, as a group of phenolic metabolites, have been shown to possess a broad pharmacological spectrum, encompassing antioxidant, anti-inflammatory, and even anticancer activities (Amin & Wulandari, 2025). Flavonoid interactions with biological receptors are maintained by non-covalent forces—such as hydrogen bonds and hydrophobic interactions that allow them to bind selectively to various sites of action (Amin & Wulandari, 2025). In addition to flavonoids, alkaloids are widely known for their potential as analgesics and antimicrobial agents, while terpenoids are widely developed as anti-inflammatory and antiviral agents (Amin et al., 2026). This diversity of molecular frameworks opens up vast opportunities for exploration, particularly in designing multi-target therapeutic strategies to treat complex diseases (Amin et al., 2026).

Studies on the use of medicinal plants as candidate antimalarial agents can be conducted through a systematic approach that combines ethnopharmaceutical studies with scientific literature searches. Ethnopharmacological studies include exploring and documenting local community knowledge regarding the use of plants as traditional medicines, which is then combined with relevant scientific research findings. This approach can help identify various plant species with the potential to be developed as sources of antimalarial compounds, particularly in areas with high malaria endemicity, such as North Sumatra and East Nusa Tenggara (Rahman et al., 2021).

The results of exploration and identification of various medicinal plants indicate that several species have the potential to inhibit the development of malaria parasites. Some plants reported to have antimalarial activity include *Momordica charantia* (bitter melon), *Fraxinus griffithii*, *Piper sulcatum*, and *Eucalyptus globulus*. The antimalarial potential of these plants can be evaluated through in vitro testing using *Plasmodium falciparum*, a *Plasmodium* species that plays a key role in causing malaria in humans. Parameters used in testing include the IC₅₀ (half maximal inhibitory concentration) value, which is the concentration of an extract or compound required to inhibit 50% of parasite growth or activity. The lower the IC₅₀ value, the higher the inhibitory potential demonstrated by the sample under certain test conditions. For example, bitter melon leaf extract reportedly has an IC₅₀ value of 0.17 µg/mL, while *Piper sulcatum* showed an IC₅₀ value of 0.20 µg/mL. These values indicate strong inhibitory activity against *P. falciparum* based on the test system used (Hidayat et al., 2024).

The next step in obtaining bioactive compounds is through the extraction process of plant material. Polar solvents, such as ethanol and methanol, can be used to extract various chemical components found in plant tissue. The extraction technique

Conclusion and Suggestions

Conclusion

Based on the analysis and discussion of various literature studies, the following conclusions can be drawn:

1. **Main Modification Strategies:** The process of transforming natural compounds into antimalarial drug candidates is carried out through three main strategies: functional group derivatization (such as methylation, acetylation, or ester formation at the hydroxyl, carboxyl, or amine groups), structural simplification (simplifying the chiral center or cleavage of secondary rings without damaging the core pharmacophore), and the application of isosterism and bioisosterism.
2. **Improvement of Physicochemical and Pharmacological Characteristics:** Chemical modification has proven highly effective in overcoming the intrinsic weaknesses often found in natural secondary metabolites, such as low aqueous solubility, poor bioavailability, and susceptibility to metabolic degradation. Through this engineering, analog compounds are obtained with improved stability, optimal pharmacokinetic (ADME) profiles, and increased ligand-receptor binding affinity and biological target selectivity to minimize side effects or off-target toxicity.
3. **The Importance of Structure-Activity Relationship (SAR) Studies:** A thorough understanding of SAR allows mapping of the specific regions of a molecule (pharmacophores) responsible for antimalarial biological activity. Thus, the geometric, spatial, and electron distribution configurations can be rationally engineered (rational drug design) to trigger the most optimal therapeutic response against Plasmodium parasites..

Recommendations

To follow up and develop the results achieved in this study, the following are recommended:

1. **Integration of Computational Screening (In Silico):** Future research is expected to more intensively integrate computational screening (such as more specific molecular docking and in-depth ADME-Tox prediction) before entering the laboratory synthesis stage. This is crucial for increasing efficiency in time, effort, and saving research costs.
2. **Application of Green Chemistry Principles:** The development of chemical modification techniques and the synthesis of new derivatives should adopt the principles of green chemistry to minimize the use of toxic organic solvents and reduce the production of hazardous waste during the derivatization process of natural product compounds.
3. **Further Exploration (In Vivo and Clinical Trials):** Given the limited data available, studies on potential modified derivatives should proceed to comprehensive in vivo testing in animal models, followed by long-term toxicity testing and clinical trials. This is necessary to ensure that the drug candidate is not only active at the laboratory level but also safe and effective when working in the more complex human biological system.

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