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AI-Guided Design and Optimization of Curcumin Nanoemulsions Derived from *Curcuma longa* for the Prevention of *Plasmodium falciparum* Malaria in the Context of Emerging Partial Artemisinin Resistance

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ABSTRACT

Malaria remains a major public health challenge in tropical countries, particularly in Indonesia, where Plasmodium falciparum is the predominant causative agent and contributes significantly to morbidity and mortality. The emergence of partial resistance to artemisinin-based combination therapies (ACT), primarily associated with mutations in the Kelch 13 (K13) gene, poses a critical threat to current treatment efficacy and underscores the urgent need for alternative therapeutic strategies. Curcumin, a bioactive polyphenolic compound derived from Curcuma longa, has demonstrated promising antimalarial activity through multiple mechanisms, including inhibition of hemozoin formation, modulation of parasite-specific molecular targets, and regulation of host inflammatory responses via suppression of NF-κB signaling and oxidative stress. Despite its therapeutic potential, the clinical application of curcumin is limited by its poor bioavailability, rapid degradation, and low gastrointestinal absorption. Nanoemulsion-based drug delivery systems have emerged as a viable approach to overcome these limitations by enhancing solubility, stability, and systemic availability. Furthermore, the integration of artificial intelligence, particularly artificial neural networks (ANN), offers a powerful tool for optimizing nanoemulsion formulations by accurately modeling complex, non-linear relationships among formulation variables and predicting critical parameters such as particle size, stability, and drug release profiles. This study highlights the potential of AI-guided curcumin nanoemulsions as an innovative and sustainable strategy for malaria prevention and management in the context of emerging drug resistance. By combining Indonesia's rich natural resources with advanced computational approaches, this paradigm may contribute to the development of more effective, accessible, and personalized antimalarial therapies.

Keywords: Malaria; Artemisinin resistance; *Curcuma longa*; Drug delivery system; Bioavailability; Tropical diseases;

INTRODUCTION

Indonesia, known as the 'Emerald of the Equator', is located right on the equator so it holds millions of secrets as well as potential. However, on the other hand, this position

also makes Indonesia a tropical country with constant exposure to sunlight throughout the year. This causes many pathogens that can synthesize and multiply, especially pathogens that cause tropical diseases. To date, malaria is still a global threat because it is an often overlooked tropical disease (neglected tropical disease). Although often overlooked, the disease has a significant impact on mortality and quality of life. The risk of infection is always present in people living in endemic areas, and some untreated cases can develop into serious complications, such as cerebral malaria, one of the deadliest types of malaria. According to the World Malaria Report 2024: Addressing inequity in the global malaria response, the trend of malaria in Indonesia from 2000 to 2023 continues to fluctuate. In 2000, malaria cases were estimated to reach about 1.1 million cases and caused more than 1,500 deaths. This figure rose sharply in 2010 to nearly 2 million cases and caused more than 3,200 deaths. Then, there was a significant decrease, with cases dropping to around 700 thousand and deaths as many as 1,600 people in 2020. However, this decline has not continued consistently. In 2022–2023, the number of cases again increased to more than 1 million cases and caused around 2000 deaths.[1]

Indonesia's position in the Asian region provides evidence that Indonesia's condition is concerning. Indonesia accounted for 46% of the reported malaria cases in Southeast Asia in 2023, followed by India and Myanmar, at 25% each. In terms of mortality, the number of malaria deaths in these regions has dropped dramatically to 90% compared to 2010, but Indonesia still accounts for the largest with 52% of all deaths, followed by Indonesia's position in the Asian region provides evidence that Indonesia's condition is concerning. Indonesia accounted for 46% of the reported malaria cases in Southeast Asia in 2023, followed by India and Myanmar, at 25% each. In terms of mortality, the number of malaria deaths in these regions has dropped dramatically to 90% compared to 2010, but Indonesia still accounts for the largest with 52% of all deaths, followed by India (36%) and Myanmar (7%)India (36%) and Myanmar (7%). This places Indonesia as the epicenter of malaria burden in the region.[1] This is certainly very worrying because Indonesia, which is a tropical country, has a high tendency to be the location for the spread of various types of malaria parasites. Based on the type of parasite, P. falciparum is the most found, with a prevalence of 47.9%, followed by P. vivax with a prevalence of 38.3%.[2] These conditions indicate that P. falciparum is still the main parasite that causes malaria in the region so treatment strategies should focus on effective therapies against P. falciparum, including the selection of appropriate antimalarial regimens, monitoring of treatment responses, and prevention of the emergence of drug resistance.

The malaria-causing parasite Plasmodium falciparum has a wide range of symptoms, ranging from asymptomatic infections to severe malaria, including potentially fatal cerebral malaria. The average incubation period of these parasites is twelve days, and the initial symptoms of the disease they cause are usually non-specific, such as fever, chills, headache, myalgia, anorexia, and sometimes also digestive or respiratory problems appear. Symptoms include prostration, impaired consciousness, respiratory distress, multiple seizures, pulmonary edema, abnormal bleeding, acute kidney injury, jaundice, shock, and coma. One of the most severe forms of cerebral malaria causes impaired consciousness, coma, and seizures, and is a major complication that can be life-threatening.[3,4]

The effectiveness of malaria falciparum treatment can be threatened by drug resistance, especially in P. falciparum as in ACT which is still the therapy of choice, but its effectiveness is increasingly threatened by drug resistance. Surveillance studies in Papua, Indonesia, show that, with considerable variation in malaria incidence

across the region, drug resistance is a major problem. This shows how important genetic parasite monitoring is to ensure treatment remains effective in various areas[5] Certain genetic mutations cause P. falciparum to be drug-resistant. Partial resistance to artemisinin, which is demonstrated by delayed parasite clearance (delayed parasite clearance), is associated with mutations in the Kelch 13 (K13) propeller domain. The delayed spread of these parasites has significant clinical consequences because parasites that last longer in the blood increase the risk of complications, including cerebral malaria, and can decrease the effectiveness of artesunate, which has been considered the gold standard for severe malaria. Other transporter proteins such as PfMDR1 also play a role in resistance by reducing drug accumulation on the parasite's intracellular target.[6,7]

The focus of research is now on the use of alternative sources of medicine from natural wealth as drug resistance to ACT emerges, such as delayed parasite clearance that occurs in P. falciparum. One promising candidate is curcumin, the active compound of turmeric (Curcuma longa) that has shown antimalarial activity in vitro.[8] Rhizoma in turmeric contains curcumin which has the potential as an antimalarial. Although curcumin can also be found in other plants, the fact that turmeric is an easily available plant in Indonesia is the background for this innovation in the selection of turmeric as a source of curcumin.

Based on in-vivo studies, curcumin was shown to directly inhibit host GSK3β, which leads to phosphorylation of NF-κB, thereby modulating the regulation of pro-inflammatory cytokines (TNF-α, IFN-γ, and IL-18) as well as anti-inflammatory cytokines (IL-4 and IL-10).[9] Inhibition of the NF-κB pathway by curcumin has also been shown to suppress the formation of reactive oxygen species (ROS) thereby weakening the excessive inflammatory response that plays a role in the pathogenesis of cerebral malaria.[10]

However, one of the main obstacles to the therapeutic use of curcumin is its low bioavailability because curcumin is easily degraded and its gastrointestinal absorption is limited.[11] Therefore, the nanoemulsion method can be used to make the nanoparticles that dissolve curcumin in a stable emulsion system. This improves the stability, cellular penetration, and biological availability of these molecules. In addition, AI-guided drug design can accelerate the modeling of curcumin interactions with parasite targets, optimize nanoemulsion formulations, and predict clinical efficacy. This approach not only offers a scientific solution to ACT resistance due to K13 mutations, but also leverages Indonesia's natural wealth with the support of renewable technology so that it has the potential to become a new paradigm in malaria therapy.

LITERATURE REVIEW

The Potential of Curcumin as an Antimalarial Agent

Curcumin is a major polyphenol compound that can be found in *Curcuma longa* (turmeric).[8] This compound has extensive biological activity, including as an antimalarial. Curcumin's antimalarial activity works through two main pathways, namely direct effects on parasites and modulation of the host's immune response. Curcumin as an antimalarial can work by 3 mechanisms, namely having a direct effect on Plasmodium, having an effect on the host's immune response, and producing synergistic effects when combined with other ingredients such as dihydroartemisinin and piperine.[12]

The first mechanism is to have a direct effect on Plasmodium by inhibiting the formation of hemozoin and targeting enzymes that are important for Plasmodium metabolism. When sucking blood, Plasmodium digests hemoglobin and produces large amounts of free heme. Because free heme is toxic to cells, Plasmodium converts it into an insoluble form of hemozoin crystals to prevent

damage. 101 In addition to inhibiting the formation of hemozoins, curcumin also targets parasitic enzymes. Several in silico and in vitro studies have shown that curcumin and its derivatives are able to interact with the important protein of Plasmodium falciparum, namely PfATP6 (a target also targeted by artemisinin), PfGCN5 histone acetyltransferase (HAT) which affects the regulation of parasite genes, PfRIO2 kinase which is associated with parasite development within host cells, as well as PfDXR which is part of the MEP/isoprenoid pathway which is important for the synthesis of Plasmodium metabolites.[12]

The mechanism of curcumin as a second antimalarial agent is by having a direct effect on the host's immune response. Curcumin suppresses NF-κB activation thereby lowering the production of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and COX-2 which causes curcumin to not only limit systemic inflammation but also reduce the risk of severe complications such as cerebral malaria. Curcumin also neutralizes excess ROS (Reactive Oxygen Species) in host cells which can trigger malaria infection.[12]

The third mechanism is to work synergistically with other drugs. When combined with dihydroartemisinin, curcumin produces synergistic effects thereby increasing its antimalarial potential. Based on the results of in silico studies, curcumin and artemisinin have a similar inhibition mechanism to the topoisomerase VI enzyme belonging to Plasmodium falciparum. Both can bind to the active sites of the enzyme, thereby inhibiting the process of parasite DNA replication. Interestingly, the docking results showed that curcumin has a stronger bond affinity (-363.6 kJ/mol) than artemisinin (-185 kJ/mol) so that it is theoretically able to provide a more significant inhibitory effect.[13]

However, based on the results of the ProTox-3.0 prediction, curcumin has the potential for toxicity to several organs. This substance is estimated to be hepatotoxic with a probability of 69%, neurotoxic with a probability of 87%, and very likely to cause toxicity to the immune system (96%) and respiratory system (98%). In contrast, these compounds are predicted to be non-toxic to the kidneys (90%), heart (77%), and not directly toxic (93%). Predictions show that this compound is not carcinogenic (62%), mutagenic (97%), or penetrates the cerebral blood barrier (97%), or penetrates the cerebral blood barrier (100%), so it is relatively safe in terms of cancer risk, genetic changes, and penetration into the central nervous system. These findings suggest that, while the compound demonstrates a relatively favorable safety profile with respect to carcinogenicity, mutagenicity, and general cytotoxic effects, there remains a significant concern regarding its potential toxicity to the hepatic, neurological, pulmonary, and immune systems. Therefore, the development of nanoemulsion-based delivery systems is warranted to mitigate these limitations by enhancing stability, controlling bioavailability, and potentially reducing systemic toxicity.

Nanoemulsions to Improve Bioavailability

Curcumin has a very low solubility in gastrointestinal fluids, making it difficult to pass through the mucous layer and be absorbed by intestinal epithelial cells. In fact, more than 90% of curcumin consumed is excreted through feces within 72 hours, with very low bioavailability. This is also exacerbated by the fact that its stability is also low because the neutral or alkaline pH in the intestine makes curcumin degrade quickly. After admission, plasma levels remained very low even though *the intake* was in high doses because most of it was confined to the small intestine. In the intestines and liver, curcumin is glucocorinated and sulfated by the enzymes

UGT and SULT producing polar metabolites that are easily eliminated because they are easily soluble in water so they are quickly excreted by urine.[14]

These curcumin deficiencies are the reason why curcumin needs to be nanoemulsified. The nanoemulsion envelops curcumin in nano-sized oil droplets, protecting curcumin from chemical degradation. Its small size also makes it easier for curcumin to pass through the intestinal mucus and enter enterocytes, making it easier to absorb it in the small intestine. In addition, encapsulation can slow down metabolism in the intestines and liver so that more curcumin will actively enter the circulation, reducing the first-pass metabolism. Plus, with more efficient protection and transport, nanoemulsions can increase plasma curcumin levels compared to free form, reduce conjugated curcumin levels, thereby increasing systemic bioavailability.[14]

The Role of Artificial Intelligence in Formulation Optimization

The development of contemporary drug delivery systems, such as nanoemulsions, requires precise control of formulation and process parameters. Final characteristics such as long-term stability, release profile, and particle size are strongly influenced by a complex and non-linear combination of factors, making their prediction difficult with conventional statistical methods.[15] Artificial Neural Networks (ANNs) are excellent computational methods because they can recognize non-linear patterns and model the complex relationships between the final properties of the drug delivery system and the formulation.[16]

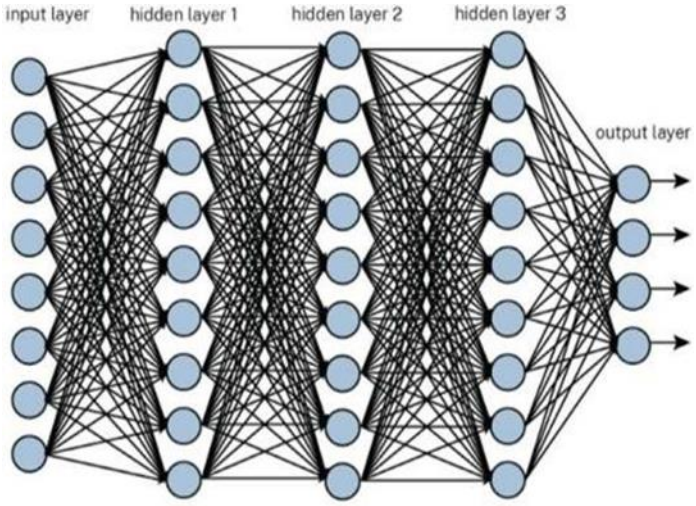

Figure 1. Modeling of artificial neural network work steps.[18]

The propagation of data from the input layer to the output layer through various hidden layers ensures the performance of ANN. Each neuron receives a weighted input, sums it up, and then performs an activation function to generate a signal. Using learning algorithms such as backpropagation, the weight of the connection is adjusted during the training process to reduce errors between the prediction output and the actual target. With this mechanism, ANN can easily predict, classify, and model non-linear data.[17]

ANN has been widely reported to be used in the pharmaceutical field. For example, ANN is used to simulate drug solution profiles with input variables such as excipient composition, pH, active substance content, and release curve as outputs. The similarity of the prediction profile with the results of the experiment was assessed with a value of f2. The study showed that ANN is more accurate than conventional statistical methods. In addition, ANN has been shown to be able to predict nanoparticle size, model-controlled release in matrices and

liposomes, and evaluate the physical stability of formulations using polydispersity, viscosity, and zeta potential.[18]

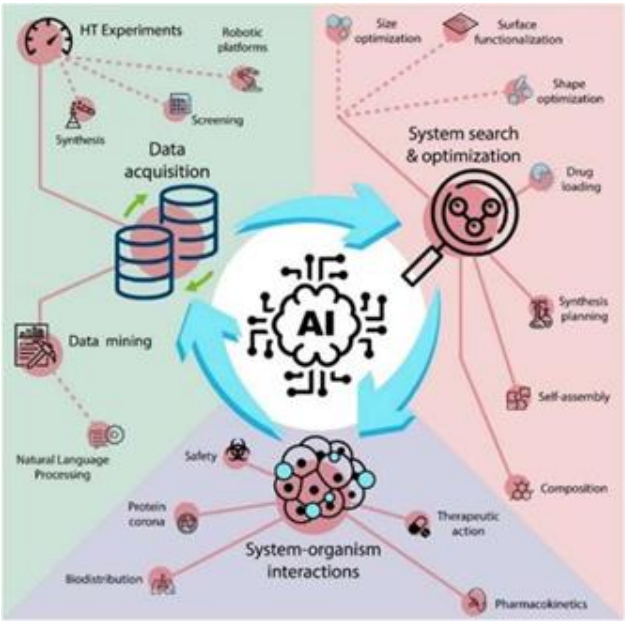

Figure 2. The Role of AI in *Nanomedicine Optimization and Evaluation*[18]

ANN is increasingly important for its application in curcumin nanoemulsions. Due to the solubility and poor stability of curcumin, small droplet size and system stability are essential to improve bioavailability. ANN can be used to predict the composition of surfactants, co-surfactants, and oils in droplets less than 200 nm in size, model ideal conditions for sonication and homogenization, and estimate curcumin release in gastrointestinal simulation media.[19]

In previous studies, ANN predicted microemulsion systems with an accuracy of more than 85% and produced a more accurate drug release profile than the Layer Response Method (RSM). These tissues are also used in QSAR/QSPR to predict the biological activity, solubility, and absorption of new compounds in the gut. Curcumin nanoemulsions, which require high stability, small droplet size, and optimal bioavailability, can be used easily with ANN, which is an important tool in the development of drug distribution systems. The ANN method for the formation of curcumin nanoemulsions accelerates the achievement of the best formulation without conducting repeated trials, while providing a prediction of the long-term stability of the nanoemulsion.[20] Therefore, incorporating ANN into the manufacture of curcumin nanoemulsions saves research time and costs. It also enhances the clinical potential of curcumin as a therapeutic candidate with high bioavailability.

CONCLUSION

As a tropical country, Indonesia faces a substantial burden of infectious diseases, particularly malaria caused by Plasmodium falciparum. The emergence of partial resistance to artemisinin-based therapies presents a significant challenge to current treatment strategies, thereby necessitating the exploration of alternative therapeutic approaches. In this context, curcumin, a bioactive compound derived from Curcuma longa (turmeric), represents a promising candidate due to its demonstrated antimalarial properties and widespread availability in Indonesia.

However, the clinical application of curcumin is hindered by its poor bioavailability. Nanoemulsion-based delivery systems offer a viable strategy to

overcome these limitations by enhancing solubility, stability, and systemic absorption, thereby improving its therapeutic efficacy. Furthermore, the optimization of curcumin nanoemulsion formulations is inherently complex and difficult to achieve using conventional statistical approaches due to non-linear interactions among formulation variables.

To address this challenge, artificial neural networks (ANN) have been increasingly utilized in pharmaceutical research as a robust computational tool capable of modeling, classifying, and predicting complex non-linear systems. The application of ANN enables efficient optimization of formulation parameters, reducing experimental workload, time, and cost. Moreover, this approach facilitates the development of more precise and potentially personalized therapeutic strategies, allowing curcumin-based interventions to be tailored to diverse patient conditions.

Declaration by Authors

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