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The Role of Antioxidants from Medicinal Plants in Malaria Therapy

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ABSTRACT

Malaria remains a critical global health concern, particularly in sub-Saharan Africa, where Plasmodium falciparum infection accounts for significant morbidity and mortality. The rise of drug-resistant malaria strains necessitates alternative therapeutic strategies. Antioxidants derived from medicinal plants have gained attention for their potential in malaria treatment due to their ability to counteract oxidative stress, which plays a role in disease progression. These natural compounds, including flavonoids, phenolics, and alkaloids from plants such as Neem, Turmeric, and Moringa, help restore redox balance, modulate immune responses, and reduce inflammation. While preliminary studies suggest that plant-based antioxidants may enhance host resilience and inhibit parasite survival, their precise mechanisms and clinical efficacy remain under investigation. This review explores the role of antioxidants from medicinal plants in malaria therapy, highlighting their potential benefits, challenges, and future research directions.

Keywords: Malaria, Plasmodium, oxidative stress, antioxidants, medicinal plants, drug resistance, redox balance.

INTRODUCTION

Malaria, caused by Plasmodium parasites transmitted by Anopheles mosquitoes, poses a significant global public health challenge, particularly in sub-Saharan Africa, where drug resistance and high transmission rates complicate prevention efforts. The disease not only impacts health but also socio-economic development in endemic regions. There is a pressing need to understand the relationship between Plasmodium and the host to identify new drug targets. Recent interest has emerged in plant extracts and natural products with antioxidant properties, which could modulate cellular signaling pathways and help restore the host's redox balance. Such modulation may offer a novel approach to malaria therapy. Various plants with demonstrated antioxidant properties have shown efficacy in cell-based assays, leading to potential drug repositioning strategies against malaria. The activities of these extracts, including schizonticide and antiparasitic effects, were evaluated alongside their influence on the host's redox balance [1, 2].

Epidemiology and Global Burden

Malaria is a life-threatening malady caused by a protozoan parasite in the genus of Plasmodium and transmitted via the Female Anopheles mosquito's bites. Presently, about 3.2 billion individuals across 97 countries are considered at high risk of contracting malaria. The malady is believed to affect over 219 million people annually in 87 countries, with a variety of close to half a million fatalities - many of which were African children aged under 5 years. The most vulnerable groups affected by malarial infections entail expectant mothers and children aged between 0 and 5 years. Infections from P. vivax and P. ovale are considered unfamiliar to a majority of individuals having no access to medication and, therefore, potentially dangerous. However, the majority of malarial infections are the result of while infected female Anopheles mosquito bites only having the potential to be life-threatening if not attended to promptly. In Kenya, 3,215,116 cases of Plasmodium falciparum were reported in 2017 alone. It is worth mentioning

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that Kenya is concluding the elimination phase, and the number of cases identified would increase in nations aiming for elimination. If the geographical scope is broadened to incorporate the entire continent, half of the world's population in Africa reside in malarial transmission areas, and this would result in a 216 million populace having the potential of contracting malaria. In countries with ongoing intensive control measures, the number of resultant cases has increased between 2014 and 2017. In 2017 alone, 219,900,000 cases of malarial infections were identified, particularly within the sub-Saharan African territories. At a most transmission potential, the P. falciparum charge exceeds 90 percent, although in nations presenting with P. vivax transmissions, relapses are daunting to thwart. Malarial transmission within the Anopheles mosquito is abruptly rooted on the prior meal having infected the blood, therefore advocating a correlation with the time limit between sickness manifestations [3, 4].

Antioxidants and Their Mechanisms of Action

Antioxidants protect cells from free radicals, which are produced during food breakdown and exposure to harmful environmental factors. They neutralize free radicals by donating electrons, with enzymatic antioxidants like superoxide dismutase and catalase targeting specific radicals. Non-enzymatic antioxidants, such as Vitamin C, Vitamin E, and glutathione, have detoxification abilities. Further clinical trials are needed to assess the benefits of antioxidant treatment for infectious disease patients. Antioxidants and their mechanisms of action. Oxidative damage typically leads to a cellular response and chronic inflammation. Understanding how reactive species are sensed during oxidative stress is essential for connecting antioxidant-based treatments with host inflammation. This review discusses (i) the sensing of reactive species and their signaling to gene expression, (ii) activation of cellular pathways under oxidative stress, including antioxidant defenses and pro-inflammatory responses, and (iii) potential therapeutic implications for developing effective antioxidant treatments. Malaria parasites alter the host's redox balance, generating reactive species that can cause significant pathologies and contribute to inflammatory responses in various diseases. The role of oxidative stress in health and disease is examined, particularly its impact on malaria and its broader implications for other infectious and chronic inflammatory diseases. Antioxidant-mediated therapies may enhance immune response or reduce damage from parasitized red blood cells. [5, 6].

Definition and Types of Antioxidants

Antioxidants protect biological systems from harmful reactive oxygen species (ROS) and reactive nitrogen species (RNS). The antioxidant system defends against imbalances caused by these species, acting as oxygen scavengers to limit macromolecule damage, including DNA, proteins, and lipids. Antioxidants can be enzymatic, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, or non-enzymatic, represented by natural (tinted) and synthetic molecules. Key water-soluble non-enzymatic antioxidants include ascorbate, proteins, and urates, contributing to the plasma antioxidant shield. Small molecules like N-acetylcysteine, vitamins C and E, ubiquinone, and glutathione interfere with free-radical reactions. Over one hundred dietary antioxidants are recognized, necessitating a network and balance for optimal oxidative stress protection, found in foods like carotenoids and α-tocopherol. Fat-soluble antioxidants reside in LDL compartments, while water-soluble ones exist in surface monolayers. Increased resistance to oxidative damage occurs with combined vitamin C and E supplementation, highlighting the synergistic effect and regenerative capabilities among antioxidants. An imbalance toward pro-oxidants can lead to disorders, such as neurotoxicity from amyloid-β in Alzheimer's and cancer linked to oxidative stress markers in various population studies. Inblook cells experience oxidative stress, where high hemin levels generate hydroxyl radicals via the Fenton reaction, impacting macrophage oxidative bursts and malaria spore clearance. The infectious disease is related to oxidative stress, with ROS released during infection cycles. Initially, parasitized red blood cells become protected from the spleen, allowing numerous parasites to circulate and impair endothelial blood vessel interaction. As the infection develops, ring-stadium parasites secrete basophilian components, leading to their release into the bloodstream, and free heme escapes digestion to promote Fe (II) availability, aiding parasite growth and producing Fe(III), a Fenton catalyst, which protects against chemical destruction. A recent study using flowerlike nano zeolitic imidazole frameworks@graphene oxide (FNA-MT) connected to FeO quantified mesoscopic stress in erythrocytes, inducing rupture and confirming this method to supply iron to malaria parasites [7, 8].

Medicinal Plants as a Source of Antioxidants

Antioxidants are a class of biologically active molecules that decrease the cell damage occurring due to reactive oxygen species. A wide variety of different natural compounds can act as antioxidants, and a

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large number of these are found in the plant kingdom. With increasing frequency, plants have found a place in modern standard therapeutic protocols. Significant parts of the world's human population are still dependent upon plants for treatment of various health problems. Although great progress has been made in allopathic medicine, the use of medicinal plants has increased in recent years. Several useful drugs have been introduced from these sources. It is now well understood that oxidative damages due to free radicals generated in the body are implicated in many pathological processes such as atherosclerosis, inflammatory disorders, ischemia-reperfusion injury, and cancer. Reactive oxygen species (ROS), free radicals, and other reactive chemicals are always formed in living systems. ROS and free radicals are reported to prevent oxidative damage caused by free radical chain reactions. ROS can damage lipids, proteins, and nucleic acids and can cause numerous diseases in humans. The medicinal plant material studied has high antioxidant activity and is often significantly more than three times as effective as the standard antioxidant. Medicinal plant screening is of interest as it can provide the plant kingdom as a possible source of naturally occurring antioxidants and also give rise to a perception as to which compounds might be of structural interest regarding the development of new antioxidants to be used in the prevention of various diseases. Phenolic compounds possess strong antioxidant activity. In vitro screening using lipid per oxidation inhibition as the antioxidant efficacy indicator has revealed that these phenolic compounds can assist in preventing oxidative damage. There are numerous ways in which such compounds may help protect animal cells against the oxidative damage caused by ROS by neutralization of ROS or by minimization of ROS formation or by a combination of both mechanisms. This research shows that a large number of different biologically active and potentially therapeutic constituents can be drawn from the plant kingdom [9, 10].

Examples of Antioxidant-Rich Medicinal Plants

Medicinal plants are frequently used in malaria treatment due to their antioxidative properties, immune system support, and ability to alleviate health issues linked to malaria. Their natural origin poses fewer risks compared to synthetic alternatives. These plants provide reliable antioxidants that combat oxidative stress-related diseases like heart disease, cancer, and diabetes. This basis encourages the use of plants in treating conditions stemming from oxidative stress. Interest in searching for novel natural antioxidants has grown, leading to significant research into medicinal plants as sources of these compounds. A literature review on the antioxidant role of medicinal plants in malaria therapy showcases their benefits. Notable examples of antioxidant-rich plants include Neem, known for its alkaloids, flavonoids, and saponins, and Turmeric, containing Curcumin, which may slow cancer progression. Moringa, or the Drumstick tree, is also identified as a natural antioxidant source. Incorporating these plants in malaria treatments enhances the immune system and mitigates the toxic effects of conventional therapies. The pharmaceutical and scientific communities increasingly focus on traditional medicinal plants, exploring bioactive compounds for potential Western drug formulations. Studies support the review of antioxidants from these plants in malaria therapy, addressing knowledge gaps and setting the stage for future clinical research [11, 12].

Malaria Pathophysiology

Malaria is an infectious disease caused by the Plasmodium protozoan parasite, primarily transmitted by Anopheles mosquitoes. The disease's physiopathology involves complex interactions between the parasite, host, and vector, disrupting normal biological functions. Immune mediators like cytokines and chemokines play a crucial role in both host defense and detrimental effects. They enhance the phagocytic activity of macrophages and neutrophils when Plasmodium enters the bloodstream and interacts with endothelial cells and leukocyte adhesion molecules, contributing to disease symptoms. Inflammation leads to oxidative stress, disrupting homeostasis of reactive species and increasing toxic free radicals, which may damage host cell DNA and tissues. The malaria parasite undergoes multiple life stages in vertebrate hosts and vectors, interacting with various host molecules to establish infection. The development of effective vaccines, drug therapies, and vector controls is challenged by the parasite's complex life cycle and immune evasion strategies. Understanding these mechanisms can help develop new drug combinations and immunological treatments to control malaria effectively [13, 14].

Life Cycle of the Malaria Parasite

Malaria is a common parasitic disease spread by Anopheles mosquitoes and caused by Plasmodium protozoan parasites. Transmission occurs when a mosquito bites, injecting sporozoites into the skin [15, 16, 17]. These sporozoites enter the bloodstream and target the liver, invading hepatocytes and beginning the liver stage of infection. Here, the parasites transform into merozoite-like forms, released

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into the bloodstream to enter red blood cells (RBCs) and multiply asexually, causing damage to the hosts. As the disease progresses, blood becomes co-infected with gametocytes, which develop into male and female forms capable of producing infective gametes when a mosquito feeds. Merozoites infect new RBCs, leading to cell lysis and impaired functions, contributing to anemia, splenomegaly, fever, and liver enlargement [18, 19, 20]. New parasites enter the bloodstream every 24 to 48 hours, causing chills and fever. After multiple asexual divisions, some parasites transition to a sexual stage, losing PfEMP surface proteins and sequestering in deep tissues [21, 22, 23, 24]. Male gametocytes are distinguishable as 8-shaped cells, while female gametocytes resemble asexual forms. The process of gametocytemia is key for parasite dissemination and further infection, as infected RBCs can only support two generations of parasites during their lifecycle. Only five Plasmodium species can form transmissible gametocytes [15, 16].

Current Antimalarial Therapies

There have been attempts to utilize medicinal plants that have shown promise in the holistic approach to malaria therapy. A known alternative therapy has been through the use of antioxidants from medicinal plants. The use of antioxidants obtained from medicinal plants has generated interest in the fight against malaria due to their immunostimulatory and immune-protective properties [17, 18, 19, 20, 21]. An important discussion is the evaluation of conventional drug treatments alongside current preventative measures to provide an insight into the effectiveness of existing strategies, then offer discussion on notable limitations that necessitate more research and development in the area of antioxidants. Malaria is an infectious vector-borne disease and remains a global public health threat [22, 23, 24, 25]. Malaria strategies have been employed, combining preventative measures with chemotherapeutic approaches using antimalarial drugs. There has been a significant reduction in morbidity and mortality from 2000 to 2017 as a result of the roll-out of these strategies. However, the success is tenuous as the continued emergence and spread of drug-resistant parasites require innovation for the development of new and effective antimalarial drugs [26, 27, 28, 29, 30]. Furthermore, current drug treatments show marked variations in effectiveness in global comparison, highlighting gaps in control and a need to bolster treatment and preventative strategies. In 2016, there was a total of 216 million cases of malaria, with 445,000 deaths [31, 32, 33, 34]. The Democratic Republic of the Congo and Nigeria accounted for almost 40% of the global malaria burden. The highest rates of malaria are reported in the African region, with children under 5 years being most at risk. An overall 3.2% decrease in mortality has been reported. However, a substantial increase in cases in malaria-endemic countries without improvements has raised concerns about the ability to eliminate malaria. In this respect, important challenges remain in the context of drug resistance, with the emergence of the first P. falciparum parasite strain to be resistant to both artemisinin and its partner drug, piperaquine, detected in Cambodia [35, 36, 37].

Challenges and Limitations

Understanding the severe manifestations of malaria and developing strategies to combat the parasite are priorities for research groups. Challenges in achieving these objectives persist. Antimalarial drugs like chloroquine and quinine have been used historically, yet Plasmodium falciparum malaria causes nearly one million deaths annually, primarily among young children in sub-Saharan Africa [38, 39, 40, 41]. The limited development of new drugs has resulted in widespread drug resistance, including multi-drug resistance. Urgent action is needed for effective malaria management. Various factors worsen the malaria crisis, such as poverty, lack of education, inadequate governance, and poor economic policies, which together promote parasite proliferation. Traditional treatments are often the only available options [42, 43, 44, 45, 46]. Key challenges in combating malaria include: (a) reliance on a limited number of chemically similar drugs, leading to increased resistance, making artemisinin-based therapies ineffective in some regions; (b) widespread resistance of Anopheles gambiae to DDT and pyrethroids, coupled with constrained government budgets, compromising vector control effectiveness; (c) neglect of the Millennium Development Goals aimed at improving health in developing countries by post-colonial leaders, who favor cheap and authoritarian policies over democratic governance. However, successful anti-malaria interventions led by NGOs highlight that progress is achievable, especially with a proposed reversible transition of P. falciparum 19 kDa protein during the emergence of artemisinin-resistant strains [19, 20].

Evidence of Antioxidant Efficacy in Malaria

Malaria remains a significant global health issue, particularly as resistance to current antimalarial drugs rises. The demand for efficient and tolerable compounds is urgent, leading to interest in the antimalarial

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properties of plant materials [47, 48, 49, 50]. While many studies highlight the efficacy of various medicinal plants against malaria, most are based on in vitro results, prompting calls for more in vivo research. A systematic review noted the complex biology of malaria parasites, which can complicate the detection of antimalarial effects in clinical studies. Despite these challenges, sufficient data suggests that plant antioxidants could be effective adjuncts in malaria treatment, though concrete proof of clinical efficacy is limited, with no papers found on the subject. Thus, the upcoming discussion will evaluate available experimental data on antioxidants in malaria treatment and acknowledge clinical studies focused on antioxidant prevention. Additionally, it will explore oxidative stress linked to malaria and examine research on the ability of antioxidant-rich substances to impact parasite growth, ultimately considering future research directions [51,52].

In Vitro Studies

Research indicates that antioxidants can effectively combat malaria. Initial assessments often involve in vitro studies to evaluate the antioxidant potential of compounds, plant extracts, or herbal remedies through free radical scavenging assays, antioxidant enzyme measurements, and oxidative stress induction. Many plants with high bioactive compounds like terpenoids, phenolics, flavonoids, and steroids exhibit antimalarial properties. Certain antioxidants have been shown to inhibit P. falciparum growth, although most studies concentrate on a limited range of high-purity synthetic compounds. 6.1.2. In Vitro Findings Suggest Antioxidants as Effective Malaria Treatments This paper highlights the inhibitory effects of antioxidants categorized into classes: flavonoids, phenolic acids, terpenes, alkaloids, Momordica charantia L. bioactive compounds, non-plant cellulose, antioxidant mixtures, and Australian honeys. The distinct physicochemical characteristics of these antioxidants—such as varying molecular weights, HOMO and LUMO energies, and polarities—suggest that the antioxidative efficacy against the P. falciparum parasite is not dependent on a single chemical group. Additionally, antioxidants may function as redox cyclers or shuttles and may bind to specific proteins tied to redox processes. Some studies revealed that the parasite couldn't escape host cells, indicating endocytosis. Antioxidants likely inhibit the P. falciparum protein GPI-PLC, which is vital for releasing infected RBCs. The specific mechanisms by which antioxidants hinder parasite development remain largely unexplored. Their action may involve disrupting pathways crucial for hemozoin formation or affecting mitochondrial respiration and redox balance. Quercetin, for instance, can inhibit enzymes involved in hemozoin synthesis, while compounds like para-cymene and menthol significantly downregulate glycolysis-related proteins throughout P. falciparum's asexual development [23, 24].

Clinical Trials and Antioxidant Supplementation

The outcomes of clinical trials on antioxidant supplementation in malaria patients are examined based on six selected studies with varied results, demographics, and methodologies. These trials involved 99 patients with both complicated and uncomplicated malaria, mainly falciparum, across India, Thailand, and Kenya, testing various micronutrients and antioxidants. Two studies adhered to WHO guidelines for quality. Four trials were double-blind placebo-controlled and included children and adults, some nested within antimalarial drug trials. Friterazine was evaluated against antioxidants. Five of the six trials showed no significant effects of antioxidant supplementation on various clinical outcomes, leading to inconsistent findings where certain treatments appeared beneficial. A larger study in India with 2392 patients noted a decrease in early parasitological failure with Vitamin A. However, potential type I error and bias in reporting positive results cannot be overlooked. Clinical trials are discussed concerning their implications, addressing data limitations and methodological challenges related to recruitment, adherence, and power. Collecting complex data in low-income regions also complicates randomized trials. The exploration of antioxidants in malaria therapy suggests that inconsistencies in findings remain vital for scientific understanding. Further research is necessary to optimize antioxidant use for malaria treatment, and key points for future research questions are outlined [25].

Results and Implications

In numerous studies, antioxidant supplementation in malaria therapy has been examined with relevant clinical parameters. Observations indicate decreased oxidative stress levels in malaria patients receiving antioxidants compared to the placebo group, suggesting a positive outcome. The diverse sources of antioxidants explored in these trials demonstrate a significant reduction in oxidative stress, which could enhance treatment. Incorporating additional antioxidants in the malaria treatment protocol is beneficial as it may improve parasite elimination. Studies highlight the importance of considering a broader age range for antioxidant treatment and tailoring the antioxidant types used for malaria patients. There are

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many challenges regarding antioxidant supplementation in malaria patients, as variations in antioxidant intake trials exist across different communities. Critical analysis of clinical trials shows that a standard antioxidant protocol may not be suitable for every therapy, calling for precise design. Future work indicates a need for larger-scale trials, especially in combining antioxidants with vector eradication efforts. There is also a recommendation for health care workers in malaria-prone regions to use antioxidants prophylactically. Despite some criticisms, findings suggest that plant-derived antioxidants and low doses of vitamin C can potentially improve the clinical condition in certain cases [25].

Future Directions and Research Opportunities

The main challenge in malaria research is finding drug candidates with multiple roles, especially through medicinal plants. Despite understanding oxidative stress's role in malaria, the potential antioxidant mediators from these plants are not well-defined. It's crucial to identify antioxidative compounds and their protective roles alongside conventional antimalarial agents. Safety concerns about these mediators in malaria exist, and any pharmacological benefits must be weighed against potential toxicity. Investigating the antimalarial effects of cytotoxic compounds may uncover novel chemotherapeutic candidates. Although numerous antioxidant mediators are available from botanical sources, some exhibit limited biological activity. These compounds can serve as lead structures for developing new antimalarials. A synthetic approach can enhance these structures and their bioactivity from natural resources. Additionally, the availability and affordability of medicinal plants have heightened interest in natural malaria remedies. However, drug discovery may face challenges due to financial constraints. Exploring various disease models and commercially relevant medicinal plants is key to advancing malaria drug discovery [26,30].

CONCLUSION

The growing interest in antioxidant-rich medicinal plants presents an opportunity to complement conventional malaria treatment. These natural compounds have demonstrated the potential to mitigate oxidative stress-related damage, modulate immune responses, and improve therapeutic outcomes. However, despite promising in vitro and preliminary clinical studies, further large-scale research is needed to validate their efficacy, safety, and integration with existing antimalarial drugs. Addressing challenges such as bioavailability, standardization, and regulatory approval will be essential in harnessing the full potential of medicinal plant antioxidants in malaria therapy. Future studies should focus on identifying potent plant-derived antioxidants, optimizing their formulations, and conducting rigorous clinical trials to establish their role in mainstream malaria treatment strategies.

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