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Quinine: Past, Present, and Future Perspective in Malaria and Autoimmune Disorder

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Abstract

Quinine, a natural alkaloid extracted from the bark of the cinchona tree, has traditionally played a key role in treating malaria, a disease caused by parasites of the Plasmodium genus. Since its discovery in the 17th century, quinine has evolved from a rudimentary treatment to an essential component of modern antimalarial therapies. This article explores the historical use of quinine in the fight against malaria, its role in current treatment regimens, and its future applications. In addition, we review emerging evidence suggesting the utility of quinine in autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis, where its immunomodulatory effects may provide new avenues for treatment. Although the role of quinine in the treatment of malaria remains indispensable, resistance to its use is increasing, requiring a move towards alternative drugs and combined therapies. At the same time, the growing understanding of quinine's impact on immune regulation paves the way for its repurposing in the management of autoimmune diseases. This review provides an overview of quinine's historical importance, its current role in medicine, and its promising future in therapies for malaria and autoimmune diseases.

Keywords: Autoimmune disorders, cinchona officinalis, herbal medicine, malaria, quinine

INTRODUCTION

Quinine, extracted from the bark of the cinchona tree, has been a crucial treatment for malaria for centuries [1]. It was one of the first effective remedies for the disease, helping to save countless lives from this often-fatal illness. Malaria, caused by Plasmodium parasites transmitted through the bites of infected mosquitoes, remains a significant global health issue, especially in tropical and subtropical areas [2]. Before the discovery of quinine, malaria was treated with various means, many of which were ineffective. The introduction of quinine in the 17th century, followed by its widespread use in the 19th and 20th centuries, revolutionized the management of the disease [3]. Despite the advent of new antimalarial drugs and the development of artemisinin-based combination therapies (ACTs), quinine remains a crucial treatment in some clinical settings, particularly for severe cases of malaria [4, 5]. In recent years, quinine has also gained attention for its potential role in the treatment of autoimmune diseases, characterized by an abnormal immune response that prompts the body to attack its own tissues [6, 7]. Although the use of quinine for autoimmune diseases is less established than for the treatment of malaria, its immunomodulatory effects have led to exploration in disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis [8]. Quinine, obtained from the bark of the Cinchona tree, has been a vital treatment for malaria for centuries. This alkaloid, which has been a cornerstone in the fight against one of the deadliest infectious diseases, was first used by the indigenous populations of South America to treat

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fever long before its properties were recognized by the community European science. Since then, quinine has been one of the most powerful antimalarial drugs, although new treatments have emerged in the fight against Plasmodium parasites. In addition to its antimalarial properties, quinine has shown promise in the management of autoimmune diseases, although its role in this area is less established. This review explores the historical use of quinine in the treatment of malaria, its current applications, its emerging potential in autoimmune diseases and its prospects. Quinine, an alkaloid extracted from the bark of the cinchona tree, has a rich and lengthy history in the treatment of malaria. First used in the 17th century by the indigenous populations of South America, quinine has become a basis of the global fight against malaria, especially in tropical and subtropical regions where the disease is endemic. Despite the advent of synthetic antimalarial drugs, quinine has retained its importance, especially in cases of severe and drug-resistant malaria. In addition to its role in the treatment of malaria, quinine has been explored for its potential therapeutic effects in autoimmune disorders, although its use in this context remains less established. Quinine, a natural alkaloid, has a longstanding history in treating malaria. It is extracted from the bark of the cinchona tree, native to South America, and has been used for centuries as a remedy for the disease. This compound played a central role in the global fight against malaria before the advent of synthetic antimalarial drugs. Despite the emergence of new therapies, quinine remains an essential tool, especially in the treatment of severe cases of malaria. In addition, recent research has highlighted quinine's potential applications beyond malaria, including in autoimmune diseases, such as rheumatoid arthritis and lupus, where its immunomodulatory properties have been explored. Structure and quinine plants are shown in Figures 1 and 2.

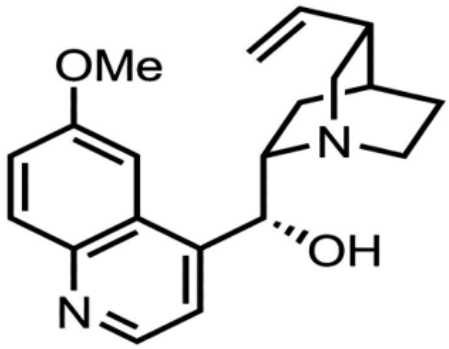

Figure 1. Structure of Quinine.

Figure 2. Quinine Plant.

HISTORICAL BACKGROUND OF QUININE

The discovery of quinine is regarded as one of the most fortunate medical breakthroughs of the 17th century, with its use in treating malaria marking the first successful application of a chemical compound to combat an infectious disease [9]. Quinine, derived from the bark of the cinchona tree (quina-quina),

has been used to treat malaria since the 1600s, when it was known as "Jesuit bark," "cardinal bark," or "holy bark" [10]. These names stem from its use in the 1630s by Jesuit missionaries in South America, although some legends suggest it was used even earlier by the indigenous people. One such tale recounts an Indian suffering from a high fever that became lost in the Andean jungle. Thirsty, he drank water from a stagnant pool and found it bitter. He realized that the water was contaminated by the cinchona trees that surrounded it, and he believed that it was poisoned.

Surprisingly, his fever quickly subsided, and he was accidentally discovered by other villagers, who later used the Chinese bark extracts to treat the fever. The European version of the quinine discovery legend differs and involves the Spanish Countess of Cinchona, who, while in Peru, had her fever cured by the bark of a tree. Upon returning to Spain with the bark, she introduced quinine to Europe in 1638 [11]. In 1742, the botanist Carl Linnaeus named the tree "Cinchona" in her honor. Prior to 1820, the bark was dried, ground into a fine powder, and mixed with a liquid (usually wine) before being consumed. In 1820, quinine was extracted and isolated from the bark by Pierre Joseph Pelletier and Joseph Caventou. Later, purified quinine became the standard treatment for malaria, replacing the bark [11]. During World War II, millions of soldiers received malaria prevention and malaria surveillance. Erythema and arthritis improved the inflammatory disease of the soldiers, leading to the first trial showing the effectiveness of an antimalarial drug in systemic lupus erythematosus. In addition to malaria, quinine has attracted attention for its potential role in the management of autoimmune diseases [12, 13].

PRE-COLONIAL USE

The indigenous peoples of the Andean region of South America were the first to discover the antimalarial properties of China, also known as "the fever tree". Long before European colonization, the Quechua knew that the bark of the China tree could treat "fever," a term used to describe the intermittent fever characteristic of malaria. The use of the bark of the tree for medicinal purposes was passed down from generation to generation, but this knowledge did not reach Europe until the 17th century.

INTRODUCTION TO EUROPE

The introduction of quinine in Europe can be attributed to the Spanish missionaries of the Jesuits. In the early 1600s, Jesuit priests began using Chinese bark as a remedy for the fevers that were plaguing the European colonies in America. By 1633, the medicinal properties of the bark had reached Europe, and it was known as "Jesuit powder" due to the involvement of missionaries in its distribution. Over time, quinine became an essential treatment for malaria, especially in areas where epidemics are common, such as parts of Africa, Asia, and the Mediterranean.

QUININE IN THE 19TH AND EARLY 20TH CENTURIES

During the 19th and early 20th centuries, quinine became the most widely used treatment for malaria, saving millions of lives. It was the standard treatment until the discovery of synthetic antimalarial drugs, such as chloroquine in the mid-20th century. However, the widespread use of quinine also led to the development of resistance, which is a recurring problem in the treatment of malaria.

MECHANISM OF ACTION OF QUININE

The mechanism of action of quinine in malaria is well known, although its exact biochemical pathway involves several steps. Quinine exerts its antimalarial effect by interfering with the parasite's ability to metabolize hemoglobin, an essential nutrient that must be broken down to survive and multiply in the host's red blood cells.

Inhibition of Hemozoin Formation

During the life cycle of the Plasmodium parasite, it infects red blood cells and consumes the host cell's hemoglobin to support its rapid growth. During this process, the parasite produces a toxic byproduct called heme, which, if left unchecked, damages the parasite's cellular structures. To

neutralize this toxic heme, the parasite converts it into an inert substance called hemozoin. Quinine interrupts this process by binding to free heme molecules in the parasite's digestive vacuole, preventing the formation of hemozoin and thus increasing heme toxicity. This leads to oxidative damage in the parasite, causing its death [4, 9].

Interruption of Parasite Protein Synthesis

Quinine also inhibits the synthesis of proteins essential for the parasite's survival. By interacting with the parasite's ribosomes, quinine reduces protein translation, inhibiting the parasite's ability to reproduce and repair itself [14].

Alteration of Intracellular Calcium Levels

Quinine can alter the flow of calcium into the parasite. Calcium ions are crucial in regulating several cellular processes, including the parasite's ability to maintain its shape and function. By disrupting calcium homeostasis, quinine alters parasite mobility, digestion, and cell division [15].

Inhibition of Parasite Metabolism

Quinine has also been suggested to affect parasitic mitochondrial function, although this mechanism is less well characterized. By disrupting mitochondrial function, quinine interferes with the production of energy needed for parasite replication.

Modulation of the Host's Immune Response

Quinine has been found to have immunomodulatory effects on the host. Some studies suggest that quinine may influence the host's immune response to malaria, possibly by increasing the activity of phagocytic cells and altering the balance of cytokines involved in the immune response [6, 16].

Steps Involved in Quinine Autoimmune Disorders

a. Quinine enters the body (quinine is absorbed into the blood and reaches the tissues).
b. Binding to DNA/RNA (kinin has an affinity to bind to nucleic acid, which prevents their replication and transcription).
c. Inhibition of RNA/DNA synthesis (This disruption prevents the synthesis of RNA and DNA in growing cells, including immune cells).
d. Kinin can help reduce inflammation by directly inflammatory pathways and inhibiting the production of pro-inflammatory cytokines.
e. Modulation of the immune system (The drug reduces the immune responses that lead to autoimmunity, such as: TT the decrease in the production of autoantibodies and the activation of T cells).
f. Suppression of autoimmunity (By modifying the behavior of the immune system, quinine helps to control autoimmune diseases, reducing symptoms, such as inflammation and tissue damage).

CURRENT APPLICATION IN THE TREATMENT OF MALARIA

Treatment of Uncomplicated Malaria

Quinine is still used as a first-line treatment for Plasmodium falciparum malaria in some areas, especially when artemisinin combination therapies (ACTs) are not available or when ACTs fail due to "resistance".

Alternative to Drug Resistance

In cases of resistance to artemisinin-based treatments, quinine is sometimes used as part of a combination therapy, although this is less common due to side effects and the development of resistance to quinine itself [2, 3].

Severe Malaria

Quinine remains an essential part of the treatment of severe *Plasmodium falciparum* malaria, where intravenous administration is required for rapid action. It remains one of the drugs of choice in cases of

severe malaria where other options may not be available or effective [1, 5].

Second-Line Treatment

In cases of resistance to more commonly used drugs, such as artemisinin combination therapies (ACT), or when patients do not tolerate other treatments, quinine can be used as an additional treatment. Its use is limited to more serious or complicated cases due to its potential toxicity.

Pregnancy

Quinine is considered relatively safe during pregnancy, especially during the second and third trimesters, and is often used when artemisinin medications are contraindicated in pregnant women, especially during the first trimester [17].

Chloroquine Resistance

In some areas where *Plasmodium falciparum* or *Plasmodium vivax* have developed resistance to chloroquine, quinine can be used as an alternative to combination therapies.

Application of Quinine in Autoimmune Diseases

Autoimmunity is characterized by an overactive immune system, involving both innate and adaptive immunity. The innate immune system is responsible for the initial detection of pathogens, primarily through antigen-presenting cells (APCs), such as dendritic cells, which then activate the adaptive immune system. Hydroxychloroquine and chloroquine influence various aspects of both innate and adaptive immune responses, helping to reduce inflammation and lessen the severity of autoimmune diseases.

Systemic Lupus Erythematosus (SLE)

Quinine has been utilized in managing SLE, a chronic autoimmune condition where the immune system mistakenly attacks the body's own tissues. It is believed that quinine's immunomodulatory effects may help reduce autoimmune activity in SLE, including modulating T cell function and decreasing inflammation. However, quinine's role in SLE is typically complementary, with other standard treatments, such as corticosteroids and immunosuppressive drugs, being more central to management [7, 8].

Rheumatoid Arthritis (RA)

RA is another autoimmune disorder marked by joint inflammation and destruction. Several studies have explored quinine's potential to modulate inflammation in RA by affecting immune cell function, although this has not yet become a primary treatment.

Quinine's effect on cytokine levels can help reduce joint inflammation, but it is generally used as an adjunctive therapy rather than a first-line treatment [18].

Multiple Sclerosis (MS)

MS involves the immune system attacking the protective layer of nerve fibers, resulting in neurological symptoms. Quinine's potential to modulate immune responses and reduce inflammation may be beneficial in MS, although clinical evidence supporting its use in MS remains limited. Most MS treatments focus on more specific immunotherapy [14].

OTHER AUTOIMMUNE DISEASES

In diseases, such as psoriasis, scleroderma, or inflammatory bowel disease (IBD), the potential effects of quinine on inflammation and immune regulation may provide some benefit, although its application clinical in these conditions is still under investigation.

Inflammatory Myopathies

Diseases, such as polymyositis and dermatomyositis involve inflammation of muscle tissue. The anti-

inflammatory effects of quinine can help reduce muscle inflammation and improve muscle strength in these conditions.

THE CHALLENGES OF QUININE

In Treatment of Malaria

Quinine has been utilized for centuries in the treatment of malaria, and although it continues to be effective, its use presents several challenges. These challenges may affect their efficacy, safety and practicability as a therapeutic option. Here are some of the main challenges.

TOXICITY AND SIDE EFFECTS

Quinine is Linked to Several Potential Side Effects, some of Which can be Severe

- *Cinchonism:* This is a group of symptoms that include tinnitus, hearing loss, headache, nausea, dizziness and visual disturbances. It is dose dependent and can occur even at therapeutic doses. Cardiotoxicity: Quinine can affect the heart, especially in patients with underlying heart problems, causing arrhythmias (irregular heartbeats) and even fatal cardiac arrest.
- *Hypoglycemia:* Quinine can stimulate the release of insulin, causing blood sugar levels to drop, which is dangerous, especially in children or people who are malnourished. Allergic reactions: In some individuals, quinine can trigger allergic responses, such as rashes, fever, and, in rare instances, severe anaphylaxis.

Development of Resistance

Although quinine has historically been the mainstay of malaria treatment, resistance to it is developing, although less rapidly than to other antimalarials, such as chloroquine. Resistance mechanisms can be linked to genetic mutations in the Plasmodium parasite, which can reduce the effectiveness of quinine over time. However, resistance to quinine remains less common than to other treatments, particularly in the case of *Plasmodium falciparum*, the deadliest parasite of malaria.

Challenges Related to Dosage and Administration

Quinine needs to be dozed carefully because of its narrow therapeutic index, meaning the gap between a therapeutic dose and a toxic dose is small. This makes its administration more complex and increases the risk of side effects. Additionally, quinine must be administered orally or intravenously, and the latter may require close monitoring, especially in severe cases of malaria, to avoid complications, such as hypoglycemia or cardiovascular effects.

Limited Availability and Cost

In some areas, quinine is less available than other antimalarial drugs, such as artemisinin combination therapies (ACT). In addition, quinine can be more expensive to produce and distribute than newer therapies, which may limit its use in low-income settings where malaria is most prevalent.

First-Line Alternative Treatments

Due to the development of more effective artemisinin combination therapies (ACTs) with fewer side effects, quinine is no longer considered a first-line treatment for uncomplicated malaria. ACTs are currently the standard treatment for Plasmodium falciparum malaria, especially in regions where resistance to artemisinin has not yet become widespread.

Therefore, quinine is increasingly reserved for more serious or complicated cases, for example when patients cannot tolerate other treatments.

Access Patients

Because of the frequency of dosing and the risk of side effects, patient adherence to quinine-based regimens can be difficult. If the doses are missing or the treatment is not complete, there is a risk of a relapse or treatment failure. On the other hand, some new therapies, such as ACT, require fewer doses and are better tolerated.

Pregnancy and Children

Pregnancy

Quinine is regarded as one of the safest options for treating malaria during pregnancy, particularly in the second and third trimesters. However, there are concerns about the risk of side effects, such as fetal hypoglycemia and premature birth. During the first trimester, quinine should only be used when there is no other option.

Children

Although quinine is used to treat malaria in children, especially in severe cases, it can be more difficult to dose the drug correctly in children, and side effects, such as hypoglycemia, are more common in this group. Furthermore, the bitter taste of quinine may be an obstacle to its oral administration, especially in children.

Drug Interactions

Quinine is metabolized by the liver enzyme, cytochrome P450, which means that it can interact with other medications that affect this pathway. This may increase the risk of toxicity, especially when quinine is taken concurrently with drugs that inhibit the enzyme, or conversely, reduce the effectiveness of quinine when combined with drugs that induce the enzyme.

In the Treatment of Autoimmune Diseases

Immunomodulatory Effects

Potential for interference with the immune system: Quinine can have immunomodulatory effects, potentially worsening some autoimmune diseases. It has been suggested that quinine can influence the immune response by affecting the function of T cells or the production of cytokines, which can aggravate autoimmune diseases, such as lupus, rheumatoid arthritis or multiple sclerosis.

Induction of Autoimmunity

Some reports indicate that quinine can cause or aggravate autoimmune phenomena. In rare cases, quinine can cause a condition known as drug-induced lupus erythematosus (DILE) or cause other autoimmune syndromes, such as hemolytic anemia or thrombocytopenia.

Adverse Effects and Toxicity

Cinchonism

Quinine can cause several side effects, collectively known as cinchonism, including tinnitus, dizziness, nausea, and visual disturbances. These side effects can complicate treatment in patients with autoimmune diseases that may already be treated with a variety of symptoms and medications.

Hematologic Toxicity

Quinine can lead to hemolysis, particularly in individuals with G6PD deficiency, a genetic condition that impacts red blood cells. This can exacerbate hematologic problems in autoimmune diseases, such as systemic lupus erythematosus (SLE), where anemia and thrombocytopenia are common.

Cardiovascular Toxicity

Quinine can cause QT prolongation and arrhythmias, which pose a risk to autoimmune patients who may already be taking medications that affect heart rhythm or who have pre- existing cardiovascular problems as part of their disease (e.g., lupus).

DRUG INTERACTIONS

Polypharmacy

Patients with autoimmune diseases often take multiple medications, such as corticosteroids, immunosuppressants (e.g., methotrexate, azathioprine), or biologic agents (e.g., TNF inhibitors). Quinine may interact with these drugs, either by altering their metabolism or increasing their toxic effects. For instance, quinine may interact with blood thinners like warfarin, raising the risk of bleeding.

Corticosteroids

The combination of quinine and corticosteroids may elevate the risk of gastrointestinal side effects, such as ulcers or bleeding, particularly in patients with autoimmune diseases who are already vulnerable to these complications.

EFFECT ON INFLAMMATION

Modulation of the Inflammatory Response

In autoimmune diseases, inflammation plays a key role in the progression of the disease. Although quinine has anti-inflammatory properties, its overall impact on autoimmune inflammation is not entirely clear and may be variable. For example, while quinine can reduce inflammation in diseases, such as malaria, it can exacerbate inflammatory responses in autoimmune diseases, especially if it alters immune cell function in unpredictable ways.

Limited Evidence of Efficacy in Autoimmune Diseases-Lack of Strong Clinical Data

Despite the established role of quinine in the treatment of malaria, there is little clinical evidence to support its use in autoimmune diseases. Therefore, their potential efficacy in the treatment of specific autoimmune diseases is unclear, and further research is needed to determine their safety and efficacy in these settings.

Prospects of Quinine

Advances in phytomedicine have contributed significantly to the support of traditional ethnopharmacological knowledge and ancient medical literature. India and China have rich systems of traditional medicine, based mainly on plants. Since malaria parasites also affect the immune system, effective immunomodulatory drugs can be developed and used in combination with antimalarials to boost immunity and reduce drug side effects.

IN THE TREATMENT OF AUTOIMMUNE DISEASES

Exploring the Role of Quinine in Autoimmune Diseases

Given the immunomodulatory potential of quinine, future research should focus on exploring its therapeutic role in a broader range of autoimmune diseases. Targeted clinical trials examining quinine in diseases, such as RA, lupus, multiple sclerosis, and other inflammatory diseases may provide valuable information about its potential as an adjunctive treatment. The discovery of new molecular targets for quinine may also open additional avenues for its use in immunotherapy.

Nanomedicine and Drug Delivery Innovations

The application of nanotechnology in drug delivery can significantly improve the pharmacokinetics and therapeutic potential of quinine. Nanoparticles designed to encapsulate quinine may enable targeted delivery of the drug to infect red blood cells, thereby reducing off-target effects and improving drug concentration at sites of infection. In addition, nanomedicines can improve the penetration of quinine in difficult areas, such as the brain, which is particularly important in the treatment of cerebral malaria [19, 20].

Improve the Effectiveness of Quinine and Reduce Side Effects

Since quinine is an essential drug in the treatment of severe malaria, future research will focus on improving its effectiveness while minimizing side effects. The pharmacokinetics of quinine can be improved through advanced drug delivery systems, such as liposomes, nanoparticles or microneedles, which can improve drug targeting to the liver or red blood cells. Such systems can reduce systemic side effects and improve the accuracy of drug delivery, especially in the treatment of severe malaria or autoimmune diseases.

Combined Therapies

Future therapeutic strategies may include combining quinine with novel biologics or monoclonal antibodies that specifically target immune pathways involved in autoimmune diseases. Such

combination therapies can optimize the antimalarial and immunosuppressive effects of quinine, providing a multifaceted therapeutic approach [15, 19].

Long Term Outlook

As we move towards more personalized medicine, the future of quinine may involve tailoring its use based on genetic factors, such as plasmodium resistance profiles or host genetic factors that affect drug metabolism. Pharmacogenomics and advanced diagnostic techniques can provide more precise treatment regimens, ensuring that quinine is optimally used to combat malaria in each individual case [2].

IN THE TREATMENT OF MALARIA

The Role of Quinine in Severe Malaria

Severe malaria continues to be a significant global health issue, and quinine remains the preferred treatment for these cases. Despite the rise in ACT, the role of quinine in severe malaria is not expected to diminish soon, especially in settings where ACT fails due to resistance [1, 3].

Refine the Use of Quinine in Severe Malaria

The role of quinine in the treatment of severe malaria may evolve with more refined protocols, perhaps including more targeted administration, improved dosing regimens, and integration with supportive care measures (e.g., fluid management, intensive care). Research into the optimal use of quinine in intensive care units may help improve outcomes for patients with severe malaria.

Cerebral Malaria

Cerebral malaria, one of the most dangerous forms of malaria, requires rapid and aggressive treatment. The proven efficacy of quinine in these cases may support its continued role in the management of this critical illness, even as new antimalarial drugs are developed. Future research may focus on how quinine can be better distributed in the brain and how it can work synergistically with other therapies for optimal results.

Quinine in Malaria Vaccination Campaigns

While the development of malaria vaccines, such as RTS, S/AS01, is an exciting advance, quinine can be used alongside vaccination efforts to reduce parasite burden and prevent transmission of infection. Quinine may have a role as an adjunct to vaccines, particularly in high-risk populations or in malaria elimination strategies.

CONCLUSIONS

Quinine, a natural alkaloid extracted from the bark of the cinchona tree, has a long history and continues to be a vital medication in the treatment of malaria. Its discovery and use as a treatment for malaria dates back centuries, and despite the development of new antimalarial drugs, quinine remains important in modern medicine. Beyond its role in the treatment of malaria, potential therapeutic applications of quinine have emerged in the field of autoimmune diseases, highlighting its versatility and enduring importance. This review aims to explore the historical development, current use, and prospects of quinine in malaria and autoimmune diseases.

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