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An Overview of Interactions Between Antimalarial Herbal Remedies and Standard Antimalarial Medications

Timir Kanta Padhan[1] and Dr. Alok Upadhyay[2]
Research Scholar, Department of Pharmacy[1]
Professor, Department of Pharmacy[2]
Sunrise University, Alwar, Rajasthan, India

Abstract: *Malaria parasites' resistance to standard antimalarial treatments has revived herbal medicine research. Herbal antimalarial therapies are increasingly used alongside conventional medications, prompting researchers to study potential herb-drug interactions. Herbal and conventional antimalarial medication interactions were examined in this study. English peer-reviewed scientific journals from 2003 to 2020 were searched for relevant publications using Pubmed and Google scholar. Search phrases include "antimalarial-herbal drug interaction", "antimalarial medicinal plant interactions with conventional antimalarial drugs", "drug-herbal interactions", and "antimalarial drugs and medicinal plants". In 30 research, synergistic, antagonistic, and no effects were observed. 14 of 18 in vivo experiments on P. berghei and P. yoelii nigerense-infected mice showed synergism, 3 showed antagonism, and 1 demonstrated both effects with three plants. In 9 normal animal in-vivo trials, 2 exhibited antagonism, 2 synergism, and 5 showed no impact. Garcinia kola lowered plasma quinine and halofantrine in two human investigations and one in vitro quantitative research. Most herbal antimalarials synergized with CAMDs. The most-studied plant was Vernonia amygdalina. Thus, herbal medicines that synergized with conventional antimalarial pharmaceuticals may be candidates for standardisation and development of antimalarial-medicinal plant combination therapy to reduce malaria resistance.*

Keywords: Pharmacokinetics, Antimalarial-herb drug interaction, Medicinal plants.

I. INTRODUCTION

The malaria encumbrances

Malaria is caused by four Plasmodium species: falciparum, vivax, malariae, and ovale. P. falciparum is still the most dangerous. Malaria causes major death and morbidity in sub-Saharan Africa, Asia, and Latin America. About 3 billion individuals are exposed to malaria annually, and 1.2 billion are at high risk. Recent estimates show that malaria is the most common illness in tropical nations, with 219 million symptomatic cases and 435,000 predicted fatalities. Pregnant women and children under five are especially susceptible in Africa, which has the most cases and fatalities.

After female anopheles mosquito bites, Plasmodium parasites mature in the bloodstream and reproduce in the liver, causing malaria symptoms like headache, fever, weakness, pain, nausea, abdominal distress, and excessive perspiration. Malaria left untreated may cause severe anaemia, brain tissue damage, renal failure, lung edoema, and skin yellowing.

Despite tremendous malaria progress, the discovery of P. falciparum variants resistant to artemisinin combination therapy has raised concerns.

Conventional antimalarial drugs and their limitations

The major treatment for malaria is chemotherapy, which comes in single or combination forms. Quinine (Cinchona alkaloid), Amodia-quine, Piperaquine, Chloroquine, Primaquine Pyri-methamine, Sulfadoxine Artesunate and Artemeter Mefloquine Lumefantrine and Halofantrine Atorvaquone and Proguanil. Combination therapies

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include non-artemisinins like Sulfadoxine + Pyrimethamine, Sul-fadoxine + pyrimethamine + amodiaquine, and artemisinins like ART + amodiaquine, meflquine, lumefantrine, and sulfadoxine/pyrimethamine.

Non-artemisinin anti-malarial medications have limited effectiveness, high cost, and toxicity, which reduces patient compliance. However, resistance is the biggest challenge confronting antimalarial medications since many are chemically linked. The cross resistance between 4-aminoquinolines, CQ and AQ, is one example. CQ was an effective and economical antimalarial before resistance. However, artemisinin and its semi-synthetic derivatives were more effective than quinine, so artemisinin-based combination therapy was recommended as the first-line treatment for P. falciparum malaria. Despite the recommendation of ACTs as frontline antimalarial therapy in most tropical countries, artemisinin-resistant Plasmodium parasites still exist in some areas, requiring more research on safer and more effective alternatives.

Medicinal plants as alternatives to conventional

Antimalarial drugs

Medicinal herbs have been used to cure malaria and reduce Plasmodium parasite resistance to standard antimalarials. Herbal medicine has been used to cure malaria for millennia. The first antimalarial medication was obtained from Cinchona bark, a Rubiaceae shrub. In early 1632, Cinchona bark infusion treated malaria. Another oldest millennial medicinal herb unearthed in China was Artemisia annua, from which artemisinin was extracted. Herbal medicine has raised scientific concerns in the study of new antimalarial medications from natural ingredients, which are beneficial in malaria control. Herbal medicine is becoming more popular in developed and developing nations owing to its affordability, accessibility, acceptance, and availability. About 2000 plant-derived compounds shown antimalarial activity against P. falciparum in 2001–2017 studies.

Antimalarial drugs-antimalarial medicinal plant

Combination therapy

Due to resistance, strong patronage, and belief in herbal therapies, herbal antimalarials are used alongside conventional medications. Some patients use this method to improve effectiveness and compliance. Though herb-drug interactions may have adverse effects. Combination therapy is widespread in tropical malarial endemic nations when standard antimalarial medications are too costly for certain rural residents. Combination treatment is also recommended to boost effectiveness and reduce parasite strain resistance.

Some patients self-medicate by taking herbal medicines before taking conventional medicines without telling their doctors, increasing the risk of herbal-drug interactions. This approach includes herbal therapy before, during, and after conventional antimalarials.

The affluent and educated also use conventional and natural antimalarial medications together. These methods have therapeutic consequences since such medications may interact antagonistically, additively, or synergistically. However, the therapeutic influence of pharmacists via proper pharmaceutical treatment offers optimism for patient outcomes.

Researchers are investigating the consequences of herb-drug interactions as herbal therapies are combined with standard antimalarial medications at higher rates. It is also clear that most doctors seldom consider the interaction of conventional medications and botanicals. No one has specifically examined anti-malarial herbal medicines and standard antimalarial pharmaceuticals like this review.

Method

This study used PubMed and Google Scholar to find peer-reviewed English scientific journal publications from 2003 to 2020. Antimalarial-herbal drug interaction, medicinal plant interactions with conventional medications, drug-herbal interactions, and herbal and synthetic antimalarials were searched for. The review included articles that fit the subject. Selected papers' references were examined for study-context titles. In-vivo studies involving animals induced with malaria and treated with plant extracts and conventional antimalarial drugs, in-vivo studies involving animal or human volunteers without malaria but given plant extracts and conventional drugs, and in-vitro

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quantitative studies on conventional antimalarial drug concentrations after combination with In non-interaction investigations, plant extracts were not combined with standard antimalarial medicines.

This study will inform researchers about herbal antimalarial-conventional antimalarial interactions and their clinical consequences in malaria treatment as drug-herb interactions increase.

Interaction studies on herbal-conventional antimalarial drugs

Herbal medicines are becoming more popular worldwide, and when combined with prescription or over-the-counter treatments and certain diets, they may improve or worsen conventional medicinal effects.

Unlike conventional medications, medicinal plants contain numerous chemicals. Medicinal plant chemical composition also depends on plant part, environment, growth circumstances, harvesting, and storage. Several studies have demonstrated that various medicinal plants may change the pharmacokinetic properties of standard antimalarial medicines, enhancing or lowering their efficacy.

Results

In 30 trials, herbal and supplementary antimalarial medications showed 8 antagonism, 16 synergism, 5 non-effects, and 1 of both effects. The three main categories of such studies are P. berghei and P. yoelii nigerense model, normal animal model, and human volunteer and in-vitro model. The most researched herbal treatment was verno-nia amygdalina. CAMD frequencies include chloroquine artesunate amodiaquine quinine and halofan-trine.

Synopsis of studies on herbal-antimalarial drugs
interactions in P. berghei model

This category used Plasmodium berghei-infected mice, a reliable model for evaluating potential antimalarials. These studies' results are in Tables 1 and 2.

Ihekwereme et al. studied the interaction between artemisinin combination therapies and Vernonia amygdalina methanol leaf extract. Rane's curative test in P. berghei showed dose-dependent antagonism of ART on VA's antimalarial activity. Parasite clearance was 80.49% and 97.05% with 125 mg/kg VA and 35.14 and 2.86 mg/kg ART. The authors advised against combining greater doses of ART and VA and recommended 125 mg/kg of VA in malaria patients.

VA and Amodiaquine, AQ, and ART were examined in P. ber-ghei-infected swiss albino mice in a separate investigation. VA, AQ, and AR received subtherapeutic dosages of 100, 2, and 2.4 mg/kg. When combined with VA extract, AQ and ART increased parasite clearance and chemo-suppression. Animals given VA, AQ, and AR had a longer mean survival duration than placebo.

Combining kaempferol and CQ was tested for antimalarial action. Kaempferol alone and in combination with CQ showed moderate antimalarial efficacy and extended life of P. berghei strain-infected mice. Kaempferol had no significant impact compared to CQ. Surpressive, prophylactic, and curative tests showed 70–95.98% suppression at the combined dosages.

P. berghei at 500, 1000, and 2000 mg/kg suppressed Gynostemma pentaphyllum and Moringa oleifera ex- tracts by 45, 50, and 55% and 35, 40, and 50%, respectively, in a 4-day test. When taken with ART, G. pentaphyllum leaf extract suppressed malaria by 78, 91, and 96% and Moringa oleifera by 73, 82, and 91%. Their combination with ART indicated promising antimalarial combination treatment potential, the scientists said.

Sibhat and Hiben used a four-day suppressive approach in P. berghie-infected mice to test the antimalarial impact of co-administration of Balanites aegyptiaca fruit extract and Aloe camperi leaf latex. Study found that Balanites aegyptiaca and Aloe camperi leaf latex boosted CQ parasitemia suppression.

Adepiti et al. tested AQ and MAMA herbal antimalarial decoction, made from Mangifera indica, Alstonia boonei, Morinda lucida, and Azadirachta indica leaves, in CQ-sensitive P. berghei. Therapeutic combo dosage against CQ-sensitive P. berghei cleared para-sites completely. None of these dosages showed significant effect against CQ-resistant P. berghei. Uvaria chamae methanol leaf extract may interact with AQ in mice infected with CQ-sensitive P. berghei in four-day, curative and prophylactic antimalarial test models, according to Adepiti and Iwalewa. AQ and 400 mg/kg extract were also given to CQ-resistant P. berghei mice in four-day prophylactic and curative test scenarios. The interaction investigation found that low-dose leaf extract and AQ had improved antimalarial activity

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in CQ-sensitive murine malaria but not CQ-resistant malaria. Ocloo and colleagues gave aqueous root extract of Cryptolepis sanguinolenta and ART to P. berghei-infected male Sprague-Dawley rats to assess the interaction effect. ART was less effective after concurrent treatment of the extract, according to the research. This combination may inhibit malaria ART. Thus, patients using the combo should be cautious.

The aqueous fresh leaf extract of Azadirachta indica at 100, 500, and 1000 mg/kg and 6, 15, and 20 mg/kg artesunic acid alone and in combination were tested for schizontocidal activity in malaria-infected swiss albino mice. At 1000 mg/kg of the extract and 15 mg/kg of artesunic acid, parasitemia decreased by 96.87%, compared to 68.14% at 20 mg/kg. Artesunic acid alone did not cure on day 30, but the extract and acid did.

Adegbolagun et al. used a curative model in P. berghei-infected mice to examine how Telfaria occidentalis aqueous leaf extract affected ART biological activities. The study found that the extract, ART, and combination of both reduced parasite aemia by 72.17±4.07%, 70.43±4.27%, and 85.43±3.65% after 48 hours, indicating a synergistic effect on P. berghei infection clearance.

A total of 216 extracts from 50 Western Ghats traditionally used to treat malaria were evaluated for in vivo antiplasmodial efficacy alone and with CQ against CQ-tolerant P. berghei strain. The research found that over 70% of plant extracts had moderate to high in-vivo antimalarial activity alone and with CQ.

Fresh Carica papaya leaf alone and in combination with artesunic acid were tested for antimalarial activities in P. berghei-infected mice using Peter's 4-day suppression test. According to the research, Carica papaya and artesunic acid were antagonistic. The authors found limited potential in artemisinin-Carica papaya combo therapies.

Aqueous Ageratum conyzoides leaf extract, CQ, and ART were tested in mice with P. ber-ghei infection for four days. Both extract-drug combinations suppressed more than individual medications, with extract-CQ acting most strongly. Two extract-drug combinations had higher absolute survival than individual medicines. The scientists found that Ageratum conyzoides aqueous extract enhances CQ and ART antimalarial activity.

Ethanol stem bark extract of Khaya grandifolia was tested with two antimalarial medicines in Plasmodium yoelii nigerense-infected mice. When coupled with CQ or halofantrine, the extract had higher antiplasmodial action and mean survival time. When combined with Khaya grandifolia, reduced therapeutic dosages of halofantrine may improve parasite elimination, a major benefit over cardiotoxic halofantrine.

Aqueous VA leaf extract enhanced CQ's antimalarial activities in CQ-sensitive and resistant P. berghe. CQ at 5 mg/kg was given with 31.25, 62.5, and 125 mg/kg extract. CQ-VA 62.5/125 combination at 30 mg/kg for 3 days decreased parasite clearance times from 4.8 to 2.6–4.4 days, prolonged recrudescent times, and improved cure rate in P. berghei-infected mice on day 14 compared to CQ monotherapy.

Methanol extracts of 15 medicinal plants from 11 Kenyan families used to treat malaria were tested for in vivo antimalarial efficacy against CQ-tolerant P. berghei. Albizia gummifera, Ficus sur, Rhamnus pri- noides and staddo, Caesalpinia volkensii, Maytenus senegalensis, Withania somnifera, Ekebergia capensis, Toddalia asiatica, and Vernonia lasiopus suppressed parasitemia by 45.5 to 85.1% compared to when they were combined with CQ. Parasitemia reduction by extracts and CQ increased mouse survival compared to the control.

In a follow-up investigation, hot water extracts of 18 medicinal plants from five Kenyan families used to treat malaria were tested against CQ-resistant P. berghei alone or in combination with CQ. When combined with CQ, extracts suppressed parasitemia and increased mouse survival compared to controls.

Idowu and colleagues examined the effects of Morindamorindiodes root, Morindalucida leaf, and Vernonia amygdalina leaf on artemisinin derivative effectiveness in 2020. Artesunate eliminated parasites in the research. Mm and ML extracts alone had significant antiplasmodial actions, however artesunate did not completely eliminate parasites. VA provided greater chemosupression with artesunate than alone. The authors stressed the need of public education on the potential risks of using antimalarial botanicals with conventional medications.

Synopsis of studies on herbal-antimalarial drugs interactions with normal animals

This section contains pharmacokinetic research on healthy animals without P. berghei or other malaria infections. After co-administration with herbal treatments, standard antimalarial medication concentrations were determined. Table 3 summarises these investigations' findings.

Adepiti and colleagues examined how MAMA antimalarial decoction affected mouse AQ pharmacokinetics. Blood samples were taken between 0 and 96 h for AQ and major metab-olite measurement using validated high-

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performance liquid chromatography. The decoction increased AQ maximum concentrations by 12%, whereas mice pretreated for 3 days showed an 85% increase. Increased active metabolites were also observed. The authors concluded that the decoction affected AQ and desethylamodiaquine pharmacokinetics.

Gnetum afri-cana was tested on CQ phosphate pharmacokinetics in overnight fasting albino rats by Eseyin et al. The extract significantly reduced Cmax Ka Ke Cl and CQ AUC (0–8). The extract raised CQ phosphate t1/2 and tmax. Since the ex- tract altered the phar-macokinetic parameters of CQ, malaria patients on CQ treatment should avoid consuming Gnetum africana with CQ, which could decrease the drug's therapeutic effect and lead to resistance.

Another research by Eseyin et al. examined the effects of VA leaf extract on dihydroartemisinin pharmacokinetics in rats. A UV spectrophotometer measured blood dihydroartemisinin levels at 0, 0.25, 0.5, 0.75, 1.0, 2.0, and 5 h on the final day of concurrent dihydroartemisinin and extract administration. Bioavailability absorption constant peak concentration decreased and apparent volume of distribution increased. A single dosage of the ex- tract reduced AUC and increased elimination constant. Patients using VA and dihydroartemisinin should be cautious, according to the authors.

The impact of Cryptolepis sanguinolenta aqueous root extract on ART pharmacokinetics in male Sprague-Dawley rats was examined. After two weeks of 36 g/kg extract exposure, mice received one oral dosage of ART. When ART was given with Cryptolepis, dihydroartemisinin clearance and elimination rate constant increased by 233 and 62.1%, respectively.

Compare sanguinolenta to ART alone. Cryptole-pis sanguinolenta may impair effectiveness owing to herb-drug interactions since dihydroartemesinin bioavailability volume of distribution and half-life decreased significantly. They recommended informing patients of the risks of taking Cryptolepis sanguinolenta and ART together.

Ethanol leaf extract of Lasianthera africana was tested for CQ pharmacokinetics. The first group got simply CQ, whereas the second received the extract and CQ. Serum CQ and protein were measured using UV-Vis spectrophotometer. The extract had a substantial impact on CQ pharmacokinetics, resulting in increased t½ tmax Vd and AUC and decreased Ka Kel Cmax and CL.

Eseyin and colleagues examined the effects of Heinsia crinata leaves on CQ pharmacokinetics in rats in 2010. Group 1 received CQ and the extract (200 mg/kg), whereas group 2 received just CQ (15 mg/kg). Blood serum taken by cardiac puncture under chloroform anaesthesia at 0.25, 0.50, 1.00, 2.00, 4.00, and 8.00 h was spectrophotometrically analysed at 344 and 260/280 nm. Concomitant oral dosing of CQ and Heinsia crinata ex-troit reduced most CQ pharmacokinetic parameters and increased a few. The authors imply that a greater CQ dosage may be needed when eating a vegetable meal with CQ due to the vegetable extract's lower bioavailability.

Etha-nolic leaf extract of VA and CQ were examined in rats for pharmacokinetics interaction. The extract was given before and with CQ. The research found AUC values of 297.52 ± 8.45 and 333.22 ± 24.99, with Cmax values of 74.60 ± 1.02 and 76.60 ± 3.07 for test and control groups. Test group elimination rate was greater than control. To minimise resistance, the authors advised against administering VA and CQ together.

Grapefruit juice was tested on mouse plasma CQ kinetics by Ali et al. Oral grapefruit juice was given to mice before CQ. CQ plasma concentration was fluorometrically measured 0, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 18, and 24 h after injection. Control and test had mean AUC, Cmax, and Tmax of 5.34 ± 0.38, 7.01 ± 0.66 mg•h/L, 763.4 ± 39.1 and 859.2 ± 45.2 mg/L, and 2.65 and 2.95 h, respectively. The authors found that GFJ treatment with CQ increases plasma CQ concentration.

Synopsis of studies on herbal-antimalarial drugs interactions in-vitro and in human volunteers

This section includes in-vitro and human volunteer research, whose results are in Table 4. Igbinoba et al. examined the interaction between quinine and Garcinia kola in an in vitro adsorption experiment at 37 ± 0.1 °C. HPLC quantified quinine absorbed and desorbed. In the research, quinine was adsorbed on G. kola, indicating that quinine and G. kola should not be used together. This might help prevent.

A follow-up randomised crossover trial in 24 healthy Nigerian volunteers examined the impact of concurrent G. kola seed administration on quinine pharmacokinetics. One group got 600 mg quinine sulphate per subject before and after G. kola dosage for seven days, while another received 12.5 g twice daily for six days and once on day seven. Quinine and its metabolites decreased in peak plasma levels after oral quinine and G. kola seed co-administration. The authors advised care while giving oral quinine with G. kola.

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In a study by Kolade et al., 15 healthy male volunteers got 12.5 g of kola nut and 500 mg of halofantrine. We analysed blood samples using HPLC. The research showed halofantrine and active metabolite plasma concentrations decreased significantly. Authors advised care while using halofantrine with caffeine-containing nutrients.

Rabbits were tested for CQ-Azadirachta indica aqueous leaf extract interactions. The simultaneous administration of both medicines significantly reduced CQ serum levels. Longer half-life and slower absorption and elimination of CQ. Significant decrease in maximum serum concentration absorption rate constant elimination rate area under the curve steady clearance rate, volume of distribution, and drug half-life increase.

Postulated interaction mechanism(s) between medicinal plants and conventional antimalarial drugs

A medicine combination may have little impact, particularly if the drugs do not interact. Such combination may reduce impact (antagonism), generally when one medicine reduces or eliminates the other's effect. Synergism accelerates or enhances one drug's action, creating an additive or potentiation effect.

It's remarkable that the aforementioned research discovered the three interaction effects. What mechanism or method underpinned such interactions?

Tannins, terpenoids, saponins, alkaloids, couma-rins, kaempferol, quinines, flavonoids, chalcones, sesqui-terpene lactones, quercetin, sesquiterpenes, polyphenols, and others in medicinal plants have anti-malarial properties and interact with conventional antimalarial drugs. Plant secondary metabolites may modify combination pharmacokinetics. Plant compounds may potentially reduce pharmacological action by interacting with drug transporters. Zinc may activate intestinal proteins that bind medicines and prevent their absorption into the bloodstream. Furthermore, flavonoids inhibiting Cytochrome P450 enzymes prolonged CQ half-life. Alkalinizing urine promotes tubular reabsorption, lowering CQ Ke. Green leafy greens are one example. Iwalokun suggested that VA's ability to extend CQ's elimination half-life explains its synergistic effect. Sibhat and Hiben claimed that certain herbal preparations might inhibit CQ absorption, distribution, and elimination, altering its pharmacokinetic characteristics.

In their in vitro study, Igbinoba and colleagues suggested that capacity-limited adsorption of quinine onto G. kola, which contains flavonoids with functional groups that promote complex formation, may have caused the interaction. Trace elements in G. kola may chelate drugs.

Medicinal herbs high in fat and fibre may impede oral medication absorption. Thus, combining plant-based meals with traditional antimalarial medications might increase or decrease their therapeutic or harmful effects.

The analysis found that chloroquine was combined with medicinal plants the most, confirming its affordability and residents' predilection for natural medications.

Food and phytoconstituents can affect pharmacokinetic parameters like elimination rate, constant absorption rate, peak serum concentration, elimination half-life, area under the curve, volume of distribution, maximum whole blood concentration, and drug clearance. For instance, simultaneous administration of C. sanguinolenta and ART increased cytochrome P4501A isozyme activity, decreasing bioavailability, half-life, clearance, volume of distribution, and elimination rate constant of dihyhroartemisinin, the active metabolite of ART.

II. CONCLUSION AND SUGGESTIONS FOR FURTHER STUDIES

The reviewed research found that certain conventional antimalarial medications lowered the efficacy of some extracts and some extracts decreased the efficacy of some conventional treatments. Studies on extracts that have additive effects with standard antimalarial medications recommend supplementing or replacing physicians' guidelines. They teach pharmacists, doctors, and researchers. Pre-application talks with knowledgeable doctors and researchers are recommended.

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