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Effects of Vitamins in Augmentation of Malaria Treatment: A review

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ABSTRACT

Malaria continues to cause significant morbidity and mortality in several settings in the tropical regions of the world despite the availability of efficacious and potent antimalarial drugs. This has led to an increased interest in and evaluation of micronutrients which are well known to have antioxidant effects. However, the interaction of micronutrients with malaria is not well characterized and there are conflicting results on their impact. This review examines, in particular, the relationship between vitamin supplements and malaria treatment. Data indicate that concurrent use of vitamins with antimalarial drugs may either accelerate the potency of the drugs or antagonize their effects. Also, evidence do exist that deficiencies of some of these supplements may protect, exacerbate or have both effects on malaria parasitemia, depending on the settings. Therefore, it is safe to speculate that the use of antimalarial drugs alongside vitamins should be approached with caution, in order to not undermine the potency of the drug and to assure effective disease treatment.

Key words: Antimalarial drugs; Drug resistance; Malaria; *Plasmodium falciparum*; Treatment; Vitamins

Introduction

Malaria is a vector – borne, hemolytic disease of importance to global health caused by five species of the protozoan *Plasmodium*.Four of these – *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale* – are human malaria species that are spread from one person to another via the bite of female mosquitoes of the genus *Anopheles*. *P. knowlesi* malaria occurs in people when an Anopheles mosquito infected by a monkey then bites and infects humans [1]. Both *P. falciparum* and *P. vivax* malaria pose the greatest public health challenge; *P. falciparum* is most prevalent on the African continent, and is responsible for most deaths from malaria while *P. vivax* has a wider geographical distribution than *P. falciparum* [2], and can develop in the Anopheles mosquito vector at lower temperatures, and can survive at higher altitudes and in cooler climates.

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In many areas outside Africa, infections due to *P. vivax* are more common than those due to *P. falciparum*, and cause substantial morbidity [3].Infection by all *Plasmodium* spp. following the bite of an infected female Anopheles mosquito starts with a silent phase, primarily in the liver hepatocyte, then exoerythrocytic merozoite forms are passed into the blood stream as membrane-bound merosomes that rupture, allowing parasites access to circulating erythrocytes [4]. The merozoites rapidly invade erythrocytes, and as they grow and replicate, the intracellular parasite dramatically remodels the host red blood cell, giving rise to a rigid and poorly deformable cell with a propensity to adhere to a variety of cell types. These changes play a pivotal role in severe complications of *P. falciparum* malaria, with symptoms including fever, severe anemia, acute renal failure, hepatopathy, pulmonary edema, lactic acidosis, and in severe cases leading to coma and untimely death [5]. This review provides an overview of malaria epidemiology, prevention, diagnosis, treatment, and concludes with a discussion of vitamins that have been most intensively evaluated in relationship to malaria.

Epidemiology

According to figures from the WHO [1], worldwide more than 200 million people develop malaria every year; most cases in Africa (88%), followed by South East Asia (10%) and the Middle East(2%). In 2015, around 438,000 patients died from the tropical disease, 90% of them in Africa, in most cases children under five. Although, an increasing number of countries are moving towards eliminating malaria, zero indigenous cases have been reported from Europe [1].
Population groups at considerably higher risk of contracting malaria, and developing severe disease include infants, children under 5 years of age, pregnant women, malnourished people and patients with HIV/AIDS [1]. There is increasing evidence that *P. falciparum* malaria is influenced by ABO blood groupsystem;blood group A has been reported as a risk factor for severe malaria [6], and as a co-receptor for *P. falciparum*rosetting [7], whereas blood group O may offer some protection against severity of disease through the mechanism of reduced rosetting [8].In addition, there is evidence indicating that both the risk of acquiring *P. falciparum* infection, and the risk of developing severe complications are determined by host genetic factors [9]. The protective role of several erythrocytic variants, some of them related to blood groups, is one of the best examples of this genetic modulation [10]. The others include haemoglobins S, C and E, α and β thalassaemias, Glucose-6-phosphate dehydrogenase deficiency, Southern Asian Ovalocytosis, and Glycophorins A, B and C variants, all of which influence malaria pathogenesis [11].

Prevention

Malaria disease has been associated with poverty and poor environmental conditions. The countries with high numbers of malaria cases have lower gross national incomes and lower total domestic government spending per capita than do countries with fewer cases [1]. Transmission of the disease can be reduced by vector control using insecticide-treated mosquito nets and indoor residual spraying dependent on the use of pyrethroids, however, in recent years, mosquito resistance to pyrethroids has emerged in many countries [12, 13]. Antimalarial medicines can also be used to prevent malaria; the WHO recommends intermittent preventive treatment with sulfadoxine-pyrimethamine, at each scheduled antenatal visit after the first trimester in pregnant women, and 3 doses of intermittent preventive treatment with sulfadoxine-pyrimethamine for infants living in high-transmission areas of Africa [1].

Diagnosis

Early and accurate diagnosis of malaria is essential for both rapid and effective disease management and malaria surveillance. Definitive diagnosis of the tropical disease depends on identification of the parasite in Giemsa-stained blood smears. Although, both thick and thin smears should be evaluated, thick smears are more sensitive for the detection of the parasite but are not useful for species identification. The newer rapid diagnostic tests (RDTs) that utilize monoclonal antibodies, which recognize the histidine-rich protein or parasite lactate dehydrogenase, are easier to perform than blood smears and have sensitivities of 90–95% when compared to blood smears although they tend to be relatively insensitive if parasite density is low (e.g. < 500/ mcL) [14]. The levels of malaria diagnostic testing, in sub-Sahara Africa, which ranged from 36% of suspected malaria cases tested in 2005, to 41% in 2010 and 65% in 2014 is primarily due to an increase in the use of RDTs [1]. However, in most rural clinics lacking the laboratory facilities to perform blood smears and without access to RDTs, the decision to treat for malaria is usually based on clinical findings. In high malaria risk areas any child with fever or a history of fever in the absence of signs of severe malaria is presumed to have uncomplicated malaria.

Malaria is one of the major causes of child and maternal deaths [15], with serious consequences on the population, social and economic development of the countries where the disease is endemic. More than 80% of estimated malaria cases and deaths occur in fewer than 20 countries. In 2015, it is estimated that 15 countries accounted for 80% of cases, and 15 countries accounted for 78% of deaths. The global burden of mortality is dominated by countries in sub-Saharan Africa, with the Democratic Republic of the Congo and Nigeria together accounting for more than 35% of the global total of estimated malaria deaths [1].

Treatment

There is currently no vaccine to provide any level of protection against malaria. However, a series of malaria chemoprophylaxis, based on the parasite's life cycle and on the site of action, exists for use by travelers and immigrants to malaria endemic regions or countries [16]. These are blood stage prophylaxis such

as Mefloquine, Chloroquine, Amodiaquine which have to be continued for one month after leaving the malaria endemic area, and liver stage prophylaxis, drugs which act on the malaria parasites within the hepatocytes such as Primaquine and Malarone which can be discontinued a few days after leaving the endemic area. However, only Primaquine potentially may prevent all types of malaria including the late infection [16].

Treatment of malaria can be effected by the use of a variety of antimalarial drugs which are readily available and can be purchased over the counter. Although the proportion of children in sub-Saharan Africa with *P. falciparum* malaria receiving Artemisinin-based combination Therapies (ACT) as recommended by WHO [17], is estimated to have increased since 2000, access to treatment remains poor because a high proportion of children with fever are not taken for care or use the informal private sector, where they are less likely to obtain ACTs for treatment [1].

Chloroquine, the mainstay of chemotherapy for several years in the management of parasitemia, has become obsolete in countries plagued with Chloroquine resistance by *Plasmodium falciparum* [18], with the exception of the following endemic regions; North Africa, the Middle East (though cases have been reported in some countries in this region), Haiti, Dominican Republic, Mexico, Central America, and Panama [19, 20] where it is still the first line antimalarial drug used to treat uncomplicated or mild cases of malaria.

In regions where Chloroquine resistance had developed, their first line anti-malaria drug was changed from chloroquine to Fansidar (pyrimethamine/sulfadoxine). However, Fansidar has been confronted with resistance in South America, much of Southeast Asia, other parts of Asia, and in large parts of Africa [21, 22]. In addition, resistance to Mefloquine has been reported in Thailand, some parts of Africa, South America, Middle East and Oceania [23]. However, despite sporadic clinical resistance to Quinine therapy in Southeast Asia and western Oceania but less frequent in South America and Africa, Quinine is still the preferred first line option in the treatment of severe malarial infection [1].

With the alarming rate of resistance being posed by *Plasmodium falciparum*, other antimalarial drugs that have been formulated and recommended for use include Halofantrine, Tetracycline, Clindamycin and Doxycycline [24-26]. Chloroquine is still a valid

choice for all *P. vivax* and *P. ovale* malaria infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia due to high prevalence of Chloroquine-resistance in those two countries. Rare cases of Chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America [27].

ACTs are currently relied upon as first-line therapy for effective malaria treatment in most regions of the world in which the disease is endemic since they are effective, less toxic and well tolerated [28, 29], and their continuing efficacy is crucial if control and elimination programs are to succeed. The loss of effectiveness of artemisinin and its derivatives to drug resistance would constitute a major disaster in the fight against malaria. Resistance to artemisinins, however, has been confirmed in Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. In the large majority of sites, patients with artemisinin-resistant parasites still recover after treatment, provided that they are treated with an ACT containing an effective partner drug. However, along the Cambodia-Thailand border, *P. falciparum* has become resistant to almost all available antimalarial medicines [30, 31]. Artemisinin resistance in this Greater Mekong sub-region has occurred as a consequence of several factors including poor treatment practices, inadequate patient adherence to prescribed antimalarial regimens, and the widespread availability of oral artemisinin-based monotherapies and substandard forms of the drug.

Interactions between Specific Micronutrients and Malaria

Adequate intakes of micronutrients (vitamins and trace elements) are required for the immune system to function efficiently [32]. There is a growing body of evidence linking micronutrient deficiencies and malaria incidence arising mostly from *P. falciparum* endemic areas; malaria itself has been associated with malnutrition [33] and possibly micronutrient deficiencies [34, 35], and certain deficiencies may predispose to malaria incidence [36-38]. The following section provides an overview of a limited number of vitamins that have been most intensively evaluated in relationship to malaria.

Vitamin A

Vitamin A is an essential nutrient required for maintaining immune function, playing an important role in the regulation of cell-mediated immunity and in humoral antibody responses, suggesting that it could

play a role in protection against malaria [39]. It has been suggested that vitamin A deficiency impairs antibody response to malarial antigens that require Th2-mediated help [40]. In an investigation conducted by Serghides and Kain [41] on the effects of 9-cis-retinoic acid, a metabolite of vitamin A, on CD36 expression, non-opsonic phagocytic clearance of parasitized erythrocytes and TNFα production in human monocytes and macrophages, it was reported that the metabolite reduced secretion of TNFα, upregulated CD36 expression, and increased phagocytosis of *Plasmodium falciparum*-parasitized erythrocytes. The authors concluded that increased parasite clearance and reduced pro-inflammatory cytokine responses to infection might partly explain the beneficial effects of supplementation with vitamin A in malaria.

A number of clinical studies have evaluated the impact of vitamin A supplementation on malaria, however, the outcomes are equivocal. Beneficial protective effects of vitamin A on malaria-related morbidity in young children have been demonstrated in Papua New Guinea and Zanzibari [42, 43]. However, two randomized, placebo-controlled trials conducted in Ghana did not find an overall significant effect of vitamin A on malaria parasitemia rates or parasite densities although the studies showed a reduction of 23% and 32% of probable malaria illness in supplemented children [44]. It should be noted that the number of children with probable malaria was so small that this study lacked adequate power to demonstrate an effect of vitamin A on slide-confirmed malaria morbidity. Similarly, in a randomized trial to examine the relationship of vitamin A supplementation with malaria incidence in HIV-infected women, the following were the findings: Vitamin A supplementation compared with no vitamin A did not significantly alter the risk of developing clinical malaria [relative risk (RR) 0.97, 95% CI: 0.82 to 1.14] nor the risk of malaria parasitemia (RR 1.02, 95% CI: 0.84 to 1.24) [45].
However, in a recent randomized controlled trial conducted in Burkina Faso [46] assessing the impact of a single dose of 200,000 IU of vitamin A with daily zinc supplementation for a period of six months on 148 children aged 6–72 months, children in the supplemented group had a significant 30% reduction in slide confirmed malaria fevers [46]. On the other hand, the study by Mwanga and others [47] draws attention to the potential role of Vitamin A as adjunct therapy for cerebral malaria. The investigators studied 142 children aged 6 months to 5 years, who were randomized to receive either Vitamin A or placebo and antimalarial treatment with intravenous Quinine. The results show that whereas there were no significant differences in outcome measures between the two treatment arms, there was a trend towards earlier resolution of convulsions and lower mortality (8.1%) in children who received Vitamin A supplementation compared to 16.2% in the placebo, although this difference in mortality did not reach statistical significance.

Although, there is a lack of evidence suggesting that vitamin A is equal to or superior to well-established drug therapies used for the prevention or treatment of malaria, the available evidence suggests that vitamin A supplementation is a good strategy for children living in malaria endemic regions, because vitamin Adeficiency is common. Vitamin A supplementation reduces the incidence of uncomplicated malaria by about one-third in children, however, it does not appear to reduce significantly the rate of deaths that can be specifically attributed to severe malaria.

Vitamin B Family

B vitamins are reputed for their role as part of coenzymes in several metabolic pathways that participate in the release of energy from the energy nutrients (thiamin, riboflavin, niacin, pantothenic acid, and biotin), cell multiplication (folate and vitamin B12) and the body's use of amino acid to synthesize protein (Vitamin B6). Co-administration of B complex with antimalarial medications appears to stem from the notion that vitamin B complex may improve appetite during the course of malaria therapy [48].

A recent report from Thailand suggests that deficiency of thiamine (vitamin B1) is associated with greater risk of severe malaria and with simple clinical malaria [49]. This is consistent with earlier reports that acute cerebral ataxia following malaria can be treated with thiamine [50], suggesting that disrupted thiamine metabolism may be a pathologic feature of malaria. In another research direction, the possibility of manipulating the metabolism of Vitamin B1 and B6 has been suggested [51, 52], since it was observed that their biosynthesis pathways are essential for the *P. falciparum* parasite but absent in the human host.

The influence Riboflavin (vitamin B2) on malaria morbidity appears to be one of antagonism such that deficiency confers a degree of protection. In Papua New Guinea, riboflavin-deficient infants are less likely to be infected with malaria [53]. Similar observations were made in India where a study reported less severe malaria parasitemia in Riboflavin-deficient persons

[54], although the course of clinical illness appeared worse. Because Riboflavin is an essential factor for glutathione peroxidase, an antioxidative enzyme, it has been proposed that deficiency promotes an oxidative environment that leads to destruction of the parasite. Indeed, reduced glutathione peroxidase activity has been observed in red cells from Riboflavin-deficient infected persons [55]. However, reduced glutathione peroxidase activity persisted in some population infected by the malaria parasite despite adequate riboflavin intake [56], suggesting that isoforms with reduced activity confer resistance to malaria. Paradoxically, *P. falciparum*–infected erythrocytes have an increased requirement for Riboflavin resulting in significant decrease in the average size of the food vacuole and inhibition of asexual parasite growth in culture [57]. Thus, although low Riboflavin status may be protective, high-dose Riboflavin therapy may prove beneficial for malaria patients suggesting that the protective and exacerbative functions would be based on different sites of action for the same antioxidant properties of Riboflavin [58]. In a recent study, Riboflavin combination with selected antimalarial drugs did not alter the potency of the drugs [59].

Folate, a crucial nutrient for cellular growth, important for erythrocyte production and prevention of neural tube defects, is part of prenatal care programs in most countries [60]. Given that Folate metabolism of the *Plasmodium* parasite is also a target for several antimalarial drugs including pyrimethamine, proguanil and dapsone [61] the interactions between host Folate status and supplementation in malaria-endemic areas has been of interest. Low malaria infection rates have been reported in pregnant women consuming a diet high in Folates [62], and greater infection rates were also reported in those suffering from megaloblastic anemia [63]. However, studies have clearly demonstrated that the addition of folate derivatives (folic acid or folinic acid) decreases the activity of antifolate drugs [64, 65]. Likewise, the lowering of Folate concentration in *in vitro* culture medium enhances the activity of antifolate antimalarial agents [66]. These reports suggest that Folic acid supplementation should be withheld during and for few days after antifolate drug administration.

Vitamin C

Vitamin C (Ascorbic Acid) is a water soluble vitamin that acts as an antioxidant, especially protecting the immune system cells from free radicals generated during their assault on invaders [67].It has, therefore, been suggested that vitamin C supplementation may have a role in case management of malaria [68]. Indeed, the plasma concentration of this antioxidant has been reported to be significantly decreased in chronic and acute malaria infections [69, 70].

Investigations on synergistic antimalarial effect of some ketones and vitamin C have been equivocal. In an earlier study, vitamin C was reported to augment the antimalarial effects of a ketone, exofone, against *P. falciparumin vitro*, with a possible pro-oxidant activity (71). But contrary to these findings, poor synergism (5%) against *P. berghei* in mice was observed between certain ketones and vitamin C at a dose of 80 mg/kg body weight each [72]. The authors concluded that the lower doses of the ketones used in the combined therapy may be the reason for the observed poor synergism. In another study, combined administration of the vitamin with Chloroquine at a dose of 25 mg/kg body weight each, restored oxidative stress in female *P. berghei*-infected mice [73].

In a recent study that evaluated the effect of ascorbic acid on the efficacy of artemether against *Plasmodium berghei*-infected mice, it was shown that ascorbic acid, in high dose, significantly antagonized the anti-plasmodial potency of artemether [74]. The average percent suppression in parasetemia was found to be 51.4+/-32.21 as against that observed for artemether alone at 60.3+/-18.70. High dose of ascorbic acid may also suppress parasite growth. Although ascorbic acid /artemether interaction remains to be reported in large scale clinical trials, it is notable that a study investigating orange fruit juice (a source of vitamin C) combination with selected antimalarial drugs truncated the efficacy and potency of these drugs in malaria patients [59].Therefore, it is advisable to exclude vitamin C and its supplement from malarial therapy throughout the course of malaria treatment, to accelerate the efficacy and potency of the antimalarial agents.

Vitamin D

Vitamin D, a fat soluble vitamin that improves intestinal absorption of calcium, is either taken in dietary form or synthesized in the skin when expose to sunlight. An abnormal calcium-parathyroid hormone (PTH)-vitamin D axis has been reported as a cause of hypocalcemia in severe falciparum malaria without acute renal failure [75]. Mean calcium levels are significantly lower in complicated malaria when compared to uncomplicated malaria. Also, in acute falciparum malaria, mild hypocalcemia is common and simultaneously associated with inappropriately low serum PTH [76]. A role for vitamin D in malaria has been suggested by many studies [77]. Supporting a

beneficial anti-inflammatory role of vitamin D in malaria, a recent study reported that among mice infected with *Plasmodium berghei* malaria, those that received oral supplementation with vitamin D did not develop experimental cerebral malaria [78]. The authors suggested mechanistic explanation for this finding that vitamin D significantly reduced circulating levels of tumor necrosis factor–alpha (TNF-α), interferon-gamma ((IFN-γ), and interleukin-6 (IL-6), increasing concentrations of interleukin-10 (IL-10) and regulatory T cells, and was associated with lower levels of cyto-adherence molecules and better integrity of the blood-brain barrier.

In a study in Uganda, Cusick and others [79] measured 25-hydroxyvitamin D [25(OH)D] by immunoassay in a sample of children aged 18 months–12 years with severe malaria (cerebral malaria or severe malarial anemia, n=540) and in healthy community children (n=520). Ninety-five percent of children with severe malaria (n=538) and 80% of control children (n=516) were vitamin D insufficient (plasma 25(OH)D, 30 ng/mL). Mean plasma 25(OH)D levels were significantly lower in children with severe malaria than in community children (21.2 vs. 25.3 ng/mL). Logistic regression revealed that for every 1 ng/mL increase in plasma 25(OH)D, the odds of having severe malaria declined by 9% [OR 50.91 (95% CI: 0.84, 1.0)]. The results suggest that vitamin D insufficiency may play a role in the development of severe malaria. This is consistent with the study reported by Madden and others [80] that indicate critically ill children demonstrated low levels of vitamin D. Further prospective studies in larger cohorts are indicated to confirm the relationship of vitamin D levels to severity of malaria infection and to investigate causality.

Vitamin E

Another potent antioxidant is vitamin E (α-Tocopherol). Evidence from animal studies suggests that Vitamin E deficiency enhanced the antimalarial action of Qinghaosu (Artemisinin) against *Plasmodium yoelii*, both in terms of decreased parasitemia and improved survival [81]. Vitamin E may have a role in the development and clinical course of acute malaria in human. In a Vietnamese study assessing the association between vitamin E and the clinical course of severe malaria, from 24 Vietnamese patients, aged 18-62 years, receiving intensive treatment for complicated *Plasmodium falciparum* infections, serum vitamin E concentration was depressed at presentation relative to control subjects (7.6 +/- 5.6 versus 19.3 +/- 4.7 µmol/l, respectively; P>0.001), and a subsequent rise to a level comparable with that of the control subjects after 4 days of treatment (but tended to be higher than the control value at the time of discharge (P >0.05); there was a significant correlation between admission ratio and parasite clearance time (P = 0.04) [82]. These findings are consistent with previous reports from animal models [81] and Chinese patients with falciparum malaria [83]. Thus, co-administration of malarial drugs and vitamin E has far reaching adverse consequences in controlling malarial infection [84]. Hence, the concurrent use of vitamin E and/or its supplement and antimalarial agents should be discouraged, to enhance the potency of the antimalarial medications to effectively treat malarial parasitemia.

Summary & Conclusion

Malaria remains a major public health problem in African, South East Asian, and the Mid-Eastern countries, despite the progress in reducing malaria cases and deaths, and possible elimination in dozens of countries, especially in the European region. Several antimalarial drugs can be effectively used to manage the infection, however, there are challenges of resistance to contend with. Malaria itself has been associated with malnutrition and possibly micronutrient deficiencies and certain deficiencies may predispose to malaria incidence. There appears to be a role for the use of certain micronutrients, especially vitamin A and zinc, thiamine, and vitamin D for the prevention of malaria in children living in malaria endemic regions. Vitamin A supplementation reduces the incidence of uncomplicated malaria by about one-third in children, however, it does not appear to reduce significantly the rate of deaths that can be specifically attributed to severe malaria. It is thought that disrupted thiamine metabolism may be a pathologic feature of malaria and acute cerebral ataxia following malaria can be treated with thiamine. Limited studies support a beneficial anti-inflammatory role of vitamin D in preventing cerebral malaria. Riboflavin combination with selected antimalarial drugs do not alter their potency, however, while low riboflavin status may be protective, high-dose riboflavin therapy may prove beneficial for malaria patients suggesting that the protective and exacerbative functions would be based on different sites of action for the same antioxidant properties of this micronutrient. However, other essential vitamins such as vitamin C, vitamin E or folic acid may play potentially harmful roles by exacerbating malaria episodes or interfering with antimalarial therapy. Investigations on synergistic antimalarial effect of some ketones and vitamin C have been equivocal, and studies are emerging suggesting possible antagonism

by vitamin C of the potency of several antimalarial drugs, Artemether included. Therefore, it is advisable to exclude vitamin C and its supplement from malarial therapy throughout the course of malaria treatment, to accelerate the efficacy and potency of the antimalarial agents. Although, Folate uptake, remains a crucial part of prenatal care programs in most countries, studies have clearly demonstrated that the addition of folate derivatives (folic acid or folinic acid) decreases the activity of anti-folate drugs. Thus, folic acid supplementation should be withheld during and for few days after anti-folate drug administration.

In conclusion, augmentation of malaria prevention and/or treatment with vitamins to enhance the nutritional status of young children and/or pregnant women in malaria-endemic areas requires caution, due to the fact that some of these nutrients are beneficial while others aggravate the disease state by slowing down the potency of these antimalarial drugs. This does not completely exclude the use of vitamins when managing malaria crisis, but it is safe to know the action of a particular supplement and the appropriate time to introduce it into the treatment regimen. Data on some other vitamins were limited and scarce to incorporate into this work. Therefore, it is recommended that further studies be done to clarify the role of other vitamins in the manipulation of malaria parasitemia.

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