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Malaria Is Associated with Diminished Levels of Ascorbic Acid: A Systematic Review and Meta-Analysis

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Abstract

Background: It is still unclear how ascorbic acid levels relate to the pathogenesis of malaria. This systematic review synthesized different ascorbic acid levels in malaria patients with different severity levels of malaria and *Plasmodium* species.

Methods: The systematic review protocol was registered in the PROSPERO database (CRD42023394849). A systematic search of PubMed, Embase, MEDLINE, Ovid, Scopus, and Google Scholar was conducted to identify studies that reported ascorbic acid and malaria. The pooled standardized mean difference (Cohen's *d*) with 95% confidence intervals (CIs) was calculated using the random-effects model.

Results: A total of 1480 articles were obtained from the searches of the databases, and 30 studies were included for syntheses. The meta-analysis revealed that patients with malaria had lower levels of ascorbic acid than those without malaria or uninfected controls ($p < 0.01$, Cohen's $d = -3.71$, 95% CI = −4.44 to −2.98, $I^2 = 98.87\%$, 30 studies). Comparable levels of ascorbic acid were observed between patients with severe malaria and those with nonsevere malaria ($p = 0.06$, Cohen's $d = -1.39$, 95% CI = −2.85 to 0.07, $I^2 = 96.58\%$, 4 studies). Similarly, levels of ascorbic acid were comparable between patients with *Plasmodium falciparum* and *Plasmodium vivax* malaria ($p = 0.34$, Cohen's $d = -1.06$, 95% CI = −3.23 to 1.12, $I^2 = 97.30\%$, 3 studies).

Conclusions: The meta-analysis reveals diminished levels of ascorbic acid in malaria cases. Manipulating the host's nutritional status, such as by supplementing it with ascorbic acid to restore reactive oxygen species balance, may alter the progression of malarial infection and prevention of disease severity.

Keywords: ascorbic acid, vitamin C, malaria, *Plasmodium*, systematic review, meta-analysis

Introduction

Plasmodium parasites, which are spread by the *Anopheles* mosquito, are the source of the parasitic disease malaria (Buck and Finnigan, 2022). If therapy is put off, severe malaria complications may develop. The majority of the severe complications of malaria are caused by *Plasmodium falciparum* (Zekar and Sharman, 2022). However, other *Plasmodium* species, such as *Plasmodium vivax* (Naing et al., 2014) and *Plasmodium knowlesi* (Kotepui et al., 2020; Vasquez et al., 2021), have the potential to cause serious disease outcomes. To help host cells eliminate parasites, reactive

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oxygen species (ROS) may be produced in overabundance, and this could harm the host cells and lead to severe malaria (Vasquez et al., 2021).

Ascorbic acid, also known as vitamin C, is a water-soluble vitamin that can be found in fruits and plants. It is one of the nonenzymatic antioxidants (Abdullah et al., 2022). Ascorbic acid participates in collagen production as well as serves as an antioxidant by scavenging ROS (Abdullah et al., 2022). According to an *in vitro* experiment, ascorbic acid induces the production of ROS in parasite-infected erythrocytes before inhibiting the parasites' blood stage (Shi et al., 2021). Supplementation of ascorbic acid with antimalarial treatment, such as artesunate–amodiaquine, increases the antioxidant enzyme gene expression in bone marrow cells of *Plasmodium berghei*-infected mice (Ebohon et al., 2021).

In addition, coadministration of artemether and ascorbic acid can increase parasite clearance rates in *P. berghei*-infected mice (Ganiyu and Fola, 2012). However, contrary evidence in mice studies indicates that decreased levels of ascorbic acid might inhibit growth of *Plasmodium* parasites (Herbas and Suzuki, 2010) (Farombi et al., 2003; Hassan et al., 2004; Njoku et al., 1995). Other studies have documented elevated levels of ascorbic acid in malaria cases, indicating that ascorbic acid serves as a free radical scavenger (Asaolu, 2009; Narsaria et al., 2012). Other findings have also documented comparable levels of ascorbic acid in people with malaria and healthy controls (Nmorsi et al., 2007).

According to reports, the antioxidant impact of erythrocytes is influenced by glutathione levels. Ascorbic acid exhibits synergistic antioxidant effect against hemoglobin-mediated cell damage when glutathione is present (Li et al., 2006). Ascorbic acid can combine with iron or substances containing iron to produce hydrogen peroxide or hydroxyl radicals, which can enhance the hemolytic processes in malaria. This frequently occurs in parasitized erythrocytes due to oxidative stress as the parasitized erythrocytes become deficient in glutathione (Li et al., 2006; Mendiratta et al., 1998). Restoring antioxidant status and ascorbic acid levels could prevent *Plasmodium* infection or serious consequences by maintaining the equilibrium of ROS formation.

The primary goal of this study was to examine the levels of ascorbic acid in patients with malaria in comparison with those without malaria because the information about ascorbic acid levels and the pathogenesis of malaria is conflicting and requires further research. Synthesis of the differences in ascorbic acid levels across different *Plasmodium* species and across varying malaria severity was the secondary goal of this study.

Results

Search results

A total of 1480 articles were obtained from the searches of the following databases: Embase ($n=510$ articles), MEDLINE ($n=212$ articles), Ovid ($n=119$ articles), PubMed ($n=146$ articles), and Scopus ($n=493$ articles). Duplicate records were removed ($n=780$), and the remaining records ($n=700$) were screened. Two hundred (200) articles had their full texts reviewed, and those that did not fulfill the requirements were omitted from the study ($n=500$).

Of the 200 articles with full text reviewed, 182 articles were excluded, while 18 studies met the inclusion criteria and were included for the synthesis (Abdullahi et al., 2021; Abubakar et al., 2016; Aghedo et al., 2013; Aqeel et al., 2019; Das and Nanda, 1999; Das et al., 1996; Egwunyenga et al., 2004; Farombi et al., 2003; Hassan et al., 2004; Johnkennedy and Uche, 2012; Narsaria et al., 2012; Njoku et al., 1995; Nnodim et al., 2012; Nsiah et al., 2019; Okon et al., 2022; Prasannachandra et al., 2006; Raza et al., 2010; Upadhyay et al., 2011).

The excluded studies included the following: *in vitro* studies ($n=48$), animal studies ($n=47$), reviews ($n=32$), clinical trials ($n=13$), no investigation of ascorbic in malaria ($n=13$), case studies ($n=7$), supplementation with vitamins and foods ($n=10$), no full-texts found ($n=4$), review of the literature ($n=2$), inability to extract data ($n=2$), nonblood sample ($n=1$), *in silico* study ($n=1$), conference abstracts ($n=1$), and a study that used similar group of participants ($n=1$).

Additional 12 studies were identified from Google Scholar, and matched the inclusion criteria and were included for the synthesis (Abduljalil et al., 2021; Asaolu, 2009; Ekeanyanwu et al., 2009; Erel et al., 1997; Ezzi et al., 2017; Nmorsi et al., 2007; Nwosu et al., 2016; Ogbodo et al., 2016; Ojongnkpot et al., 2023; Onyeneke et al., 2018; Erhabor et al., 2008; Udiong et al., 2014). In all, 30 studies were included for synthesis (Abduljalil et al., 2021; Abdullahi et al., 2021; Abubakar et al., 2016; Aghedo et al., 2013; Aqeel et al., 2019; Asaolu, 2009; Das and Nanda, 1999; Das et al., 1996; Egwunyenga et al., 2004; Ekeanyanwu et al., 2009; Erel et al., 1997; Ezzi et al., 2017; Farombi et al., 2003; Hassan et al., 2004; Johnkennedy and Uche, 2012; Narsaria et al., 2012; Njoku et al., 1995; Nmorsi et al., 2007; Nnodim et al., 2012; Nsiah et al., 2019; Nwosu et al., 2016; Ogbodo et al., 2016; Ojongnkpot et al., 2023; Okon et al., 2022; Onyeneke et al., 2018; Erhabor et al., 2008; Prasannachandra et al., 2006; Raza et al., 2010; Udiong et al., 2014; Upadhyay et al., 2011) (Fig. 1).

Summary of characteristics and quality of included studies

Majority of studies were published between 2011 and 2023 (60%). Most were cross-sectional (53.3%). The majority of studies were performed in Africa (70%) with Nigeria being the major study site in Africa (90.5%). More than half of the studies enrolled children as participants (56.7%). Most studies enrolled patients reported to be infected with *P. falciparum* alone (86.7%). Symptomatic malaria (66.7%) was the leading clinical status of participants in the included studies. Microscopy was the predominant method used in identifying *Plasmodium* parasites in the included studies (83.3%) (Table 1). The details and characteristics of the included studies are shown in Supplementary Table S2. The detailed quality of the included studies is shown in Supplementary Table S3.

Ascorbic acid in malaria and nonmalaria

The meta-analysis found that patients with malaria had lower ascorbic acid levels than those who did not have malaria ($p<0.01$, Cohen's $d=-3.71$, 95% confidence interval [CI] $=-4.44$ to -2.98, $I^2=98.87\%$, 30 studies; Fig. 2). The meta-regression analysis showed that publication period, study design, participants, and method for the identification

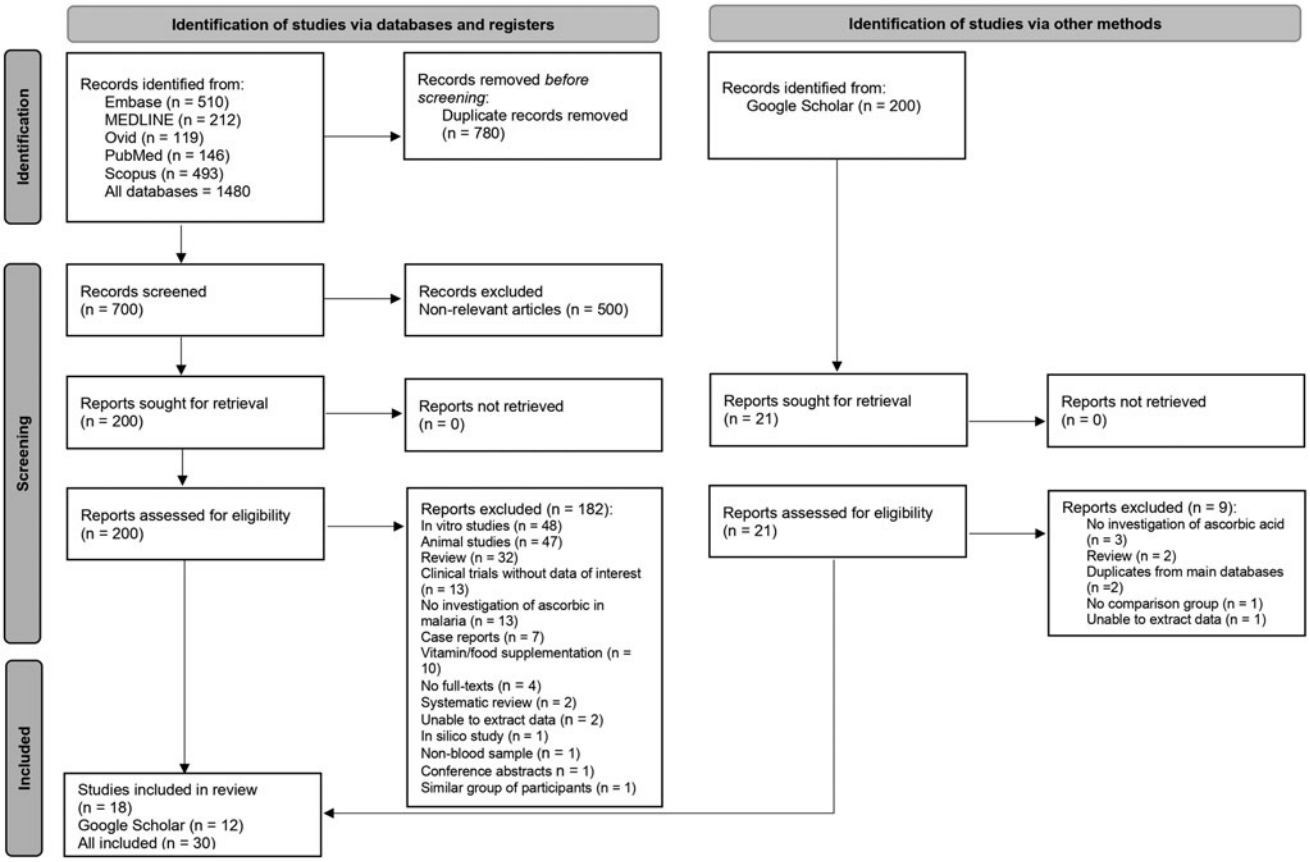

FIG. 1. Study flow diagram.

of *Plasmodium* parasites were the potential sources of heterogeneity in levels of ascorbic acid between the included studies ($p < 0.05$). Residual heterogeneities between the studies were not accounted for by the moderators (Supplementary Table S4).

Subgroup analysis of publication period revealed the lowest Cohen's d in studies that were conducted between 2000 and 2010 ($p < 0.01$, Cohen's $d = -5.91$, 95% CI = −7.84 to −3.98, $I^2 = 99.25\%$, 8 studies), followed by studies conducted between 2011 and 2023 ($p < 0.01$, Cohen's $d = -3.76$, 95% CI = −4.77 to −2.76, $I^2 = 98.92\%$, 18 studies) and studies conducted before the year 2000 ($p < 0.01$, Cohen's $d = -1.32$, 95% CI = −1.80 to −0.83, $I^2 = 85.64\%$, 4 studies; Supplementary Fig. S1), respectively.

Subgroup analysis of study design revealed lower levels of ascorbic acid in patients with malaria than those without malaria in cross-sectional studies ($p < 0.01$, Cohen's $d = -5.09$, 95% CI = −6.35 to −3.84, $I^2 = 98.96\%$, 16 studies) and in case–control studies ($p < 0.01$, Cohen's $d = -2.42$, 95% CI = −3.26 to −1.59, $I^2 = 98.46\%$, 12 studies). In prospective observational studies, no difference in levels of ascorbic acid was observed between the two groups ($p = 0.64$, Cohen's $d = -1.75$, 95% CI = −9.03 to 5.53, $I^2 = 99.69\%$, 2 studies; Supplementary Fig. S2).

In studies that enrolled children ($p < 0.01$, Cohen's $d = -4.71$, 95% CI = −5.82 to −3.60, $I^2 = 99.12\%$, 17 studies) and adults ($p < 0.01$, Cohen's $d = -4.05$, 95% CI = −5.33 to −2.77, $I^2 = 96.97\%$, 7 studies), patients with malaria had lower levels of ascorbic acid than those without malaria. However, the levels of ascorbic acid were similar between the two groups in studies that enrolled pregnant women ($p = 0.11$, Cohen's $d = -2.06$, 95% CI = −4.61 to 0.48, $I^2 = 98.96\%$, 3 studies; Supplementary Fig. S3).

In studies using microscopy alone ($p < 0.01$, Cohen's $d = -4.17$, 95% CI = −4.97 to −3.36, $I^2 = 98.86\%$, 25 studies) and rapid diagnostic test (RDT) alone ($p < 0.01$, Cohen's $d = -0.94$, 95% CI = −1.42 to −0.46, $I^2 = 99.14\%$, 2 studies), patients with malaria had lower levels of ascorbic acid than those without malaria. No difference in levels of ascorbic acid was found between the two groups in studies that used both microscopy and RDT for the identification of *Plasmodium* species ($p = 0.96$, Cohen's $d = 0.09$, 95% CI = −3.57 to 3.75, $I^2 = 99.14\%$, 2 studies; Supplementary Fig. S4).

Ascorbic acid and malaria disease severity

The meta-analysis revealed no difference in levels of ascorbic acid between patients with severe malaria and those with nonsevere malaria ($p = 0.06$, Cohen's $d = -1.39$, 95% CI = −2.85 to 0.07, $I^2 = 96.58\%$, 4 studies; Fig. 3). According to two investigations, patients with severe malaria had lower ascorbic acid levels than those with nonsevere malaria (Abdullahi et al., 2021; Okon et al., 2022). Two other investigations, however, revealed no distinction in ascorbic acid levels between patients with severe malaria and those with nonsevere malaria (Das et al., 1996; Nsiah et al., 2019). Meta-regression

Table 1. Summary Characteristics of the Included Studies

Characteristics	N *(30 studies)*	%
Publication year		
2011–2023	18	60.0
2000–2010	8	26.7
Before 2000	4	13.3
Study designs		
Cross-sectional studies	16	53.3
Case–control studies	12	40.0
Prospective observational study	2	6.67
Study areas		
Africa	**21**	**70.0**
Nigeria	19	90.5
Cameroon	1	4.76
Ghana	1	4.76
Asia	**9**	**30.0**
India	7	77.8
Turkey	1	11.1
Turkey	1	11.1
***Plasmodium* spp.**		
P. falciparum	26	86.7
P. falciparum, *P. vivax*	3	10.0
P. vivax	1	3.30
Participants		
Children	17	56.7
Adults	7	23.3
Pregnant women	3	10.0
All age groups	1	3.33
Not specified	2	6.67
Clinical status		
Symptomatic malaria	20	66.7
Symptomatic, asymptomatic malaria	2	6.67
Not defined status	8	26.7
Methods for malaria detection		
Microscopy	25	83.3
RDT	2	6.67
Microscopy, RDT	2	6.67
Not specified	1	3.33

RDT, rapid diagnostic test.

and subgroup analyses of levels of ascorbic acid between severe and nonsevere malaria were not conducted due to the small number of studies included in the meta-analysis.

Ascorbic acid in P. falciparum *and* P. vivax *malaria*

Overall, levels of ascorbic acid were similar between patients with *P. falciparum* and *P. vivax* malaria ($p = 0.34$, Cohen's $d = -1.06$, 95% CI = −3.23 to 1.12, $I^2 = 97.30\%$, 3 studies; Fig. 4). Two studies demonstrated lower levels of ascorbic acid in patients with *P. falciparum* malaria than those with *P. vivax* malaria (Aqeel et al., 2019; Upadhyay et al., 2011), while one study showed similar levels of ascorbic acid between patients with *P. falciparum* and *P. vivax* malaria (Prasannachandra et al., 2006). Due to the small number of studies included in the meta-analysis, ascorbic acid levels between *P. falciparum* and *P. vivax* malaria cases were not subjected to meta-regression or subgroup analyses.

Association between ascorbic acid and parasitemia levels

Five investigations examined the relationship between ascorbic acid and levels of parasitemia (Egwunyenga et al., 2004; Nmorsi et al., 2007; Ogbodo et al., 2016; Raza et al., 2010; Onyeneke et al., 2018). Ascorbic acid levels were significantly lower in high parasite densities compared with low parasite densities, according to three investigations (Egwunyenga et al., 2004; Nmorsi et al., 2007; Ogbodo et al., 2016). According to one study, persons with higher parasitemia had considerably higher amounts of ascorbic acid than those with lower parasitemia (Raza et al., 2010). Similar levels of ascorbic acid were identified in participants with higher and lower parasitemia in a study that included pregnant women (Onyeneke et al., 2018).

Sensitivity analysis

The leave-one-out method demonstrated lower levels of ascorbic acid in patients with malaria than in those without malaria in all rerun analyses ($p < 0.05$; Fig. 5), indicating that there is no impact of an individual study on the statistical significance of the overall results. Due to the few studies included in the meta-analysis, a leave-one-out method of detecting ascorbic acid levels between severe and nonsevere malaria and between *P. falciparum* and *P. vivax* malaria patients could not be performed.

Publication bias

The funnel plot was asymmetric (Fig. 6), indicating publication bias in the analysis. Egger's test showed a small-study effect ($p < 0.05$), confirming the asymmetry of the funnel plot. The publication bias for the ascorbic acid meta-analysis between severe and nonsevere malaria and between *P. falciparum* and *P. vivax* malaria could not be investigated because only a few studies were included in the meta-analysis.

Discussion

This study found that patients with malaria had significantly lower levels of ascorbic acid than those without malaria. These results confirmed that infection with *Plasmodium* species led to decreased amounts of ascorbic acid. The mechanism of decreased ascorbic acid in malaria could be explained by the fact that ascorbic acid can reduce the oxidative stress brought on by the ROS produced during infection.

During a malaria infection, it has been reported that ROS such as superoxide anion, hydroxyl radical, malondialdehyde, and nitric oxide are increased (Ojongnkpot et al., 2023; Postma et al., 1996). These ROS are most likely produced by the activation of immune cells such as macrophages and dendritic cells, as well as by processes such as lipid peroxidation and hemoglobin oxidation (Alayash, 2022; Gotz et al., 2019; Kennel and Greten, 2021; Postma et al., 1996; Ty et al., 2019). Ascorbic acid can turn ROS into inactive by-products, and prevent them from interacting with DNA, RNA, and proteins (Pehlivan, 2017).

It is reasonable to hypothesize that ascorbic acid functions as a buffer for malaria and may aid in preventing severe cases of the disease based on the results of the meta-analysis. Stimulation of mononuclear phagocytes, which can destroy

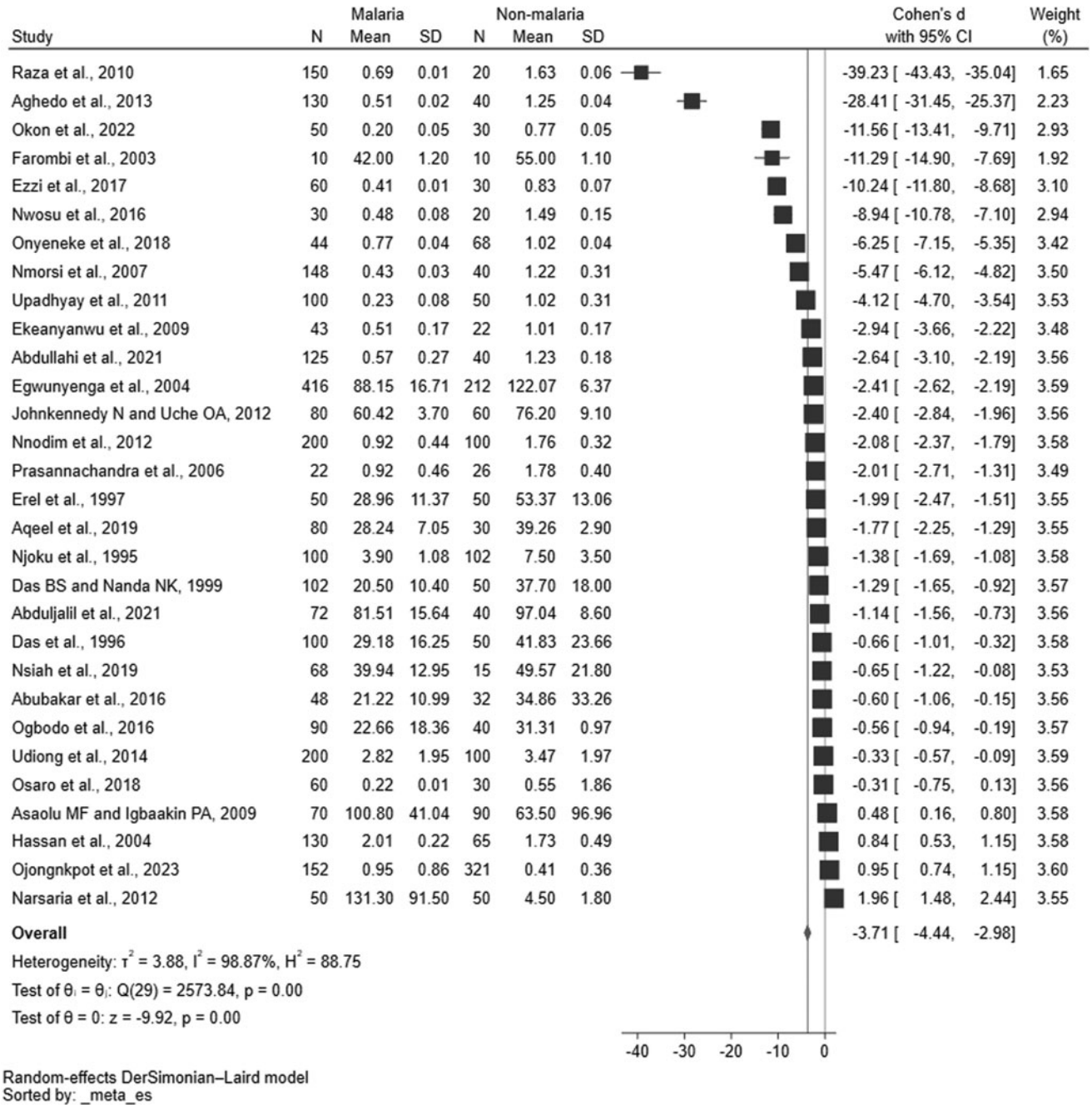

FIG. 2. The forest plot shows the difference in the SMD of ascorbic acid levels between patients with malaria and uninfected controls. CI, confidence interval; mean, mean difference; *N*, number of participants; SD, standard deviation; SMD, standardized mean difference.

ascorbic acid molecules, may be the cause of low levels of ascorbic acid in malaria (Aqeel et al., 2019). Reduced levels of other antioxidants, such as retinoic acid and tocopherol (Abduljalil et al., 2021), have been observed in malaria patients in addition to reduced ascorbic acid, suggesting a role of these antioxidants in the pathophysiology of the disease.

This study found lower levels of ascorbic acid in patients with malaria than those without malaria in studies that enrolled children and adults, but similar levels of ascorbic acid between patients with malaria and those without malaria in studies that enrolled pregnant women. Pregnancy raises levels of oxidative stress as a result of an increase in ROS production brought on by an increased metabolism and tissue expansion (Pereira and Martel, 2014).

Despite this, antioxidant levels rise throughout a healthy pregnancy, particularly in the second and third trimesters (Hussain et al., 2021), and could counteract the elevated ROS levels. Therefore, there may not be a difference in ascorbic acid levels between pregnant women with and without malaria due to higher-than-normal antioxidant levels during pregnancy. In addition, the results seen here may possibly be explained by vitamin C (ascorbic acid) supplementation,

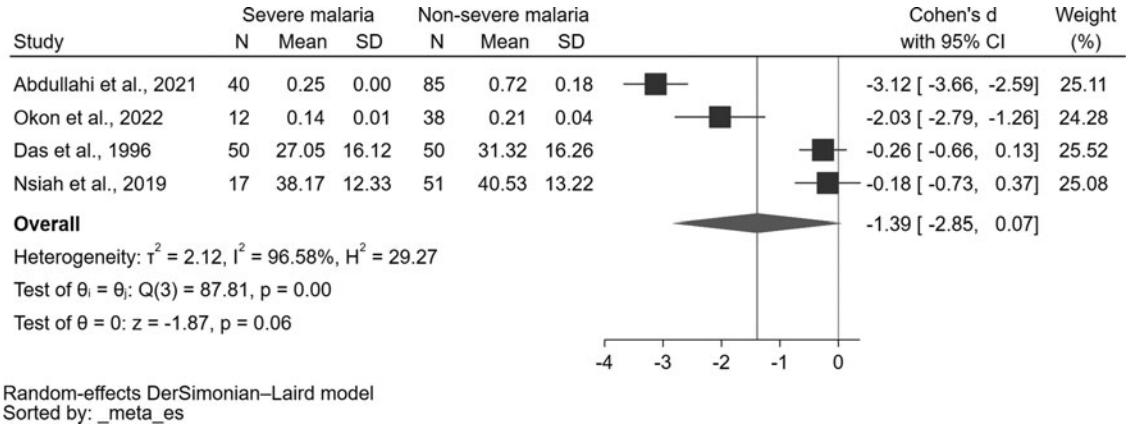

FIG. 3. The forest plot shows the difference in the SMD of ascorbic acid levels between patients with severe malaria and those with nonsevere malaria.

which is provided to pregnant mothers in malaria-endemic areas as part of normal prenatal clinics due to its potential role in preventing placental abruption and prelabor membrane rupture (Rumbold et al., 2015).

Because ascorbic acid may potentially act as a buffer to reduce malaria disease severity, its levels may be low at the early stages of disease. Some studies reported a negative correlation between ascorbic acid and parasite density (Nmorsi et al., 2007; Ogbodo et al., 2016; Raza et al., 2010), suggesting the mobilization of the ascorbic acid in response to reducing oxidative stress and the adverse effects of high parasitemia (Ogbodo et al., 2016). In cerebral malaria, oxidative stress may be associated with the sequestration of infected erythrocytes to the vascular endothelial cells *via* increased expression of adhesion molecules such as ICAM-1 and CD36 (Becker et al., 2004).

In addition to inducing oxidative stress, *Plasmodium* parasites can activate cytokine storms in malaria patients, and both cytokine levels and oxidative stress are positively associated with increased malaria severity, indicating a link between inflammatory cytokines and oxidative stress in malaria pathogenesis (Abdullahi et al., 2021; Clark et al., 2008; Clark et al., 2006). The results of this study show no distinction in levels of ascorbic acid between patients with severe and nonsevere malaria. Based on the limited number of studies included in this meta-analysis, the role of ascorbic acid in the pathogenesis of severe malaria remains unclear. Considering that malaria disease progression depends on other characteristics of an individual patient that could vary between studies, more population-based studies are needed to confirm the link between ascorbic acid and malaria severity.

The meta-analysis found no distinction in ascorbic acid levels between *P. vivax* and *P. falciparum* malaria patients. This finding is inconclusive since the meta-analysis only included a small number of studies that examined ascorbic acid levels in both *Plasmodium* species. Due to antioxidant depletion at the early stages of the disease, ascorbic acid levels in *P. falciparum* malaria have been reported to be considerably lower than those in *P. vivax* malaria (Aqeel et al., 2019).

Such a report has led to the hypothesis that *P. falciparum* malaria generates more ROS than *P. vivax* malaria. As a result, patients with *P. falciparum* malaria should have reduced ascorbic acid concentrations in comparison with patients with *P. vivax* malaria. Given the small number of studies included in the meta-analysis, more research is required to understand the relationship between different *Plasmodium* species and ascorbic acid levels in participants exposed to natural infections.

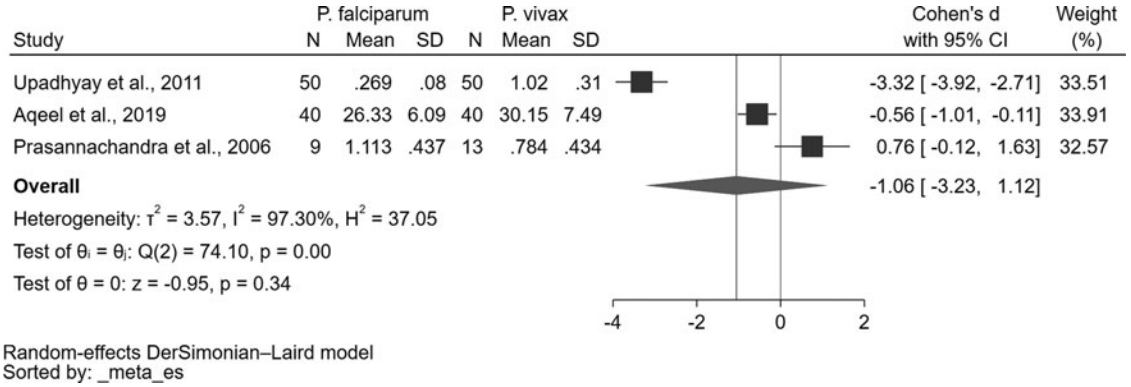

FIG. 4. The forest plot shows the difference in the SMD of ascorbic acid levels between patients with *Plasmodium falciparum* and those with *Plasmodium vivax* malaria.

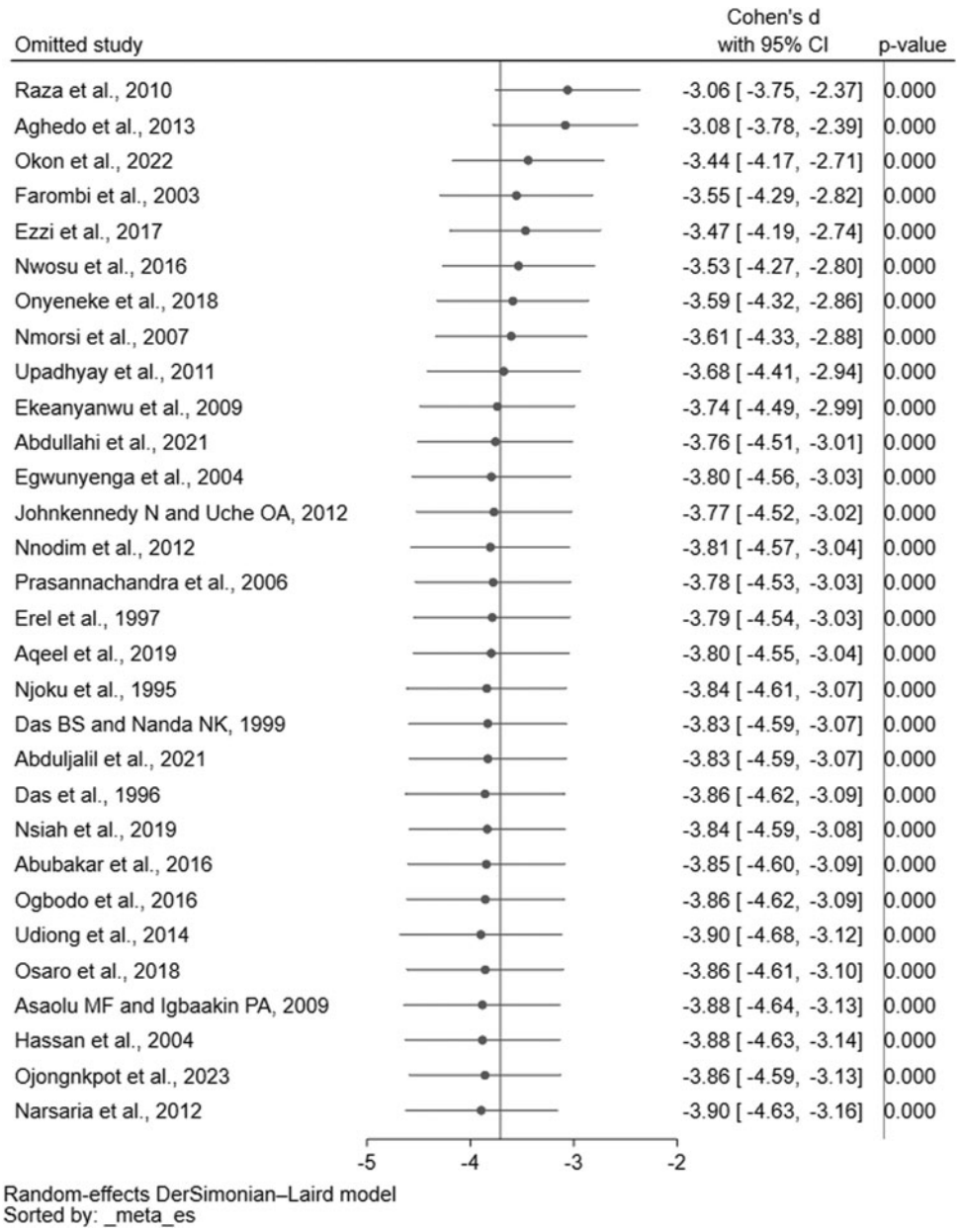

FIG. 5. The leave-one-out method showing an outlier in the meta-analysis of the difference in the SMD of ascorbic acid levels between patients with malaria and uninfected controls.

This study had certain limitations. First, there was significant heterogeneity in the results across the included studies despite meta-regression and subgroup analysis of numerous parameters, and the study moderators could not account for the residual heterogeneities between the studies. Second, the results of the meta-analysis may be constrained by the fact that few research studies in the literature have examined ascorbic acid levels during various phases of malaria. Third, publication bias might have impacted the meta-analysis's conclusion, indicating that additional investigation into the relationship between ascorbic acid and malaria severity is necessary.

Conclusion

The meta-analysis reveals diminished levels of ascorbic acid in malaria cases. Manipulating the nutritional status of the host, such as by supplementing with ascorbic acid to restore ROS balance, may alter the progression of malarial infection and may prevent the disease's severity. To ascertain whether ascorbic acid supplements might lessen oxidative stress and enhance the prognosis of malaria patients, future clinical trials should study the role of ascorbic acid supplementation as a management strategy for individuals with malaria.

Methods

Data sources and searches

This systematic review was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021). The systematic review was registered in the PROSPERO database

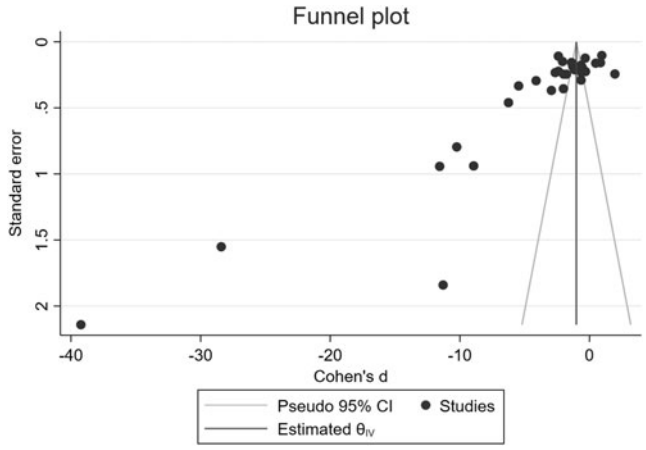

FIG. 6. The funnel plot showing an asymmetrical distribution of the SMD (X-axis) and standard error (Y-axis) of ascorbic acid levels between patients with malaria and uninfected controls.

(CRD42023394849). The medical subject heading terms were identified from the National Center for Biotechnology Information and used in the search strategy (Supplementary Table S1). Embase, MEDLINE, Scopus, PubMed, Ovid, and Google Scholar were searched for studies reporting levels of ascorbic acid in patients with and without malaria from January 20 to January 26, 2023. All references from the selected studies and review articles were screened to ensure that relevant studies were not missed. There was no limitation in the language or publication date of the articles.

Eligibility criteria

The inclusion criteria were studies that reported the levels of ascorbic acid in malaria patients. Observational studies (prospective and retrospective), randomized controlled trials (ascorbic acid at baseline before treatment), and case series were all considered. Exclusion criteria were *in vitro* studies, animal studies, reviews, clinical trials without data of interest, studies that did not evaluate ascorbic acid levels in malaria cases, case reports, studies in which participants were taking vitamin or food supplementation, studies without full-texts, systematic reviews, studies from which data of interest could not be extracted, and studies that used a nonblood sample for measurement of ascorbic acid.

Study selection

Two authors (M.K. and K.U.K.) independently screened and examined the articles. After removing duplicates, the titles and abstracts of the articles were assessed. Related abstracts relating to the outcomes were examined for full articles by following the eligibility criteria. The studies that fulfilled the inclusion criteria were then included in the review, while studies beyond the scope of the criteria were excluded with documented reasons. Google Scholar searches were also conducted to identify gray literature that may not be indexed in the main databases. The study selection disagreements were resolved by consensus with a third author (A.M.).

Data extraction and methodological quality assessment

The data from all studies were extracted by two authors independently into predefined forms. The following data were extracted from the studies: first author, study design, year of publication, study site, gender, age range, types of participants, ascorbic acid levels, clinical status, *Plasmodium* species, assays for *Plasmodium* identification, and assays for ascorbic acid determination. The methodological quality assessment of studies was performed by two authors independently using Joanna Briggs Institute critical appraisal tools for assessing the published articles (Moola et al., 2020).

Statistical analysis

The standardized mean difference (Cohen's *d*) with 95% CIs was used as the effect estimate. Differences in levels of ascorbic acid were synthesized between the disease groups as follows: (i) Malaria and nonmalaria; (ii) Severe and non-severe Malaria (Mild, Moderate, Uncomplicated, or Asymptomatic Malaria); and (iii) *P. falciparum* and *P. vivax* Malaria. The pooled standardized mean difference (Cohen's *d*) was computed using the random-effects model, assuming a heterogeneity of outcomes between studies (DerSimonian and Laird, 2015). The meta-analysis results were visualized by constructing the forest plots for all outcomes.

The inconsistency index (I^2 statistic) was used to assess study heterogeneity, with values >50% indicating significant heterogeneity (Higgins and Green, 2011). The meta-regression analyses were carried out to determine probable heterogeneity sources between included studies. The subgroup analysis was carried out to describe each subgroup's pooled effect estimate. The publication bias was considered by illustrating the symmetry of the funnel plot and Egger's test. The sensitivity analysis was conducted to determine whether outcome estimates were unaffected by the different decisions, indicating a higher degree of certainty (robustness). All analyses were performed using the statistical software STATA version 17.0 (StataCorp, USA). A p value <0.05 was considered statistically significant.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All authors consented to the publication of the study.

Availability of Data and Materials

All data relating to this study are available in this article and supplementary files.

Authors' Contributions

M.K., K.U.K., and A.M. carried out the study design, study selection, data extraction, and statistical analysis, and drafted the article. N.G.A. critically restructured the article content. F.R.M. and N.G.A. participated in editing of the article. All authors read and approved the final article.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

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Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Figure S4
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4

References

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Abbreviations Used

CIs = confidence intervals
RDT = rapid diagnostic test
ROS = reactive oxygen species
SMD = standardized mean difference