Journal of Current Health Sciences. 2026, 6(1): 11-20
DOI:10.47679/jchs.2026145
ISSN 2809-3275 (print), ISSN 2809-2236 (online)

REVIEW ARTICLE

A Systematic Review of Regional Practices and Nutraceutical Management Strategies in the treatment of Dengue Fever

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Published online: 15 January

Abstract

Dengue fever (DF), one of the common mosquito-borne viral diseases in humans, is still a serious public health problem throughout the world with special emphasis on tropical and subtropical areas. Though there are significant morbidity and mortality, treatments are mainly supportive; thus, additional approaches that may decrease disease severity are warranted. There is accumulating evidence that micronutrient status may potentially affect immune responses and clinical outcome in DF, thus supporting more general observations of nutritional modulation of susceptibility to, disease progression or outcome from infectious diseases. To assess this possibility, we considered the literature on micronutrient supplementation for DF patients. Vitamin C, Vitamin D, vitamin E and zinc were reported in some studies to potentially reduce recovery time, improve platelet trends and decrease severity of illness. In contrast, folic acid did not have any significant effects on clinical end points. However, as the available literature is fraught with obvious weaknesses such as small sample size, differing results between studies and an inadequate assessment of patients' nutritional status at the outset, any clinical recommendations are weakened. Although vitamins D and E have shown promise in preliminary trials, the existing body of evidence is not clear and coherent. This review addresses the increasing attention on micronutrient interventions in DF as well as the necessity of good quality randomized controlled trials that provide better exposure to their therapeutic effects and evidence-based recommendations.

Keywords: Dengue fever (DF), Supplement, Vitamin, Zinc, Tropical Diseases.

INTRODUCTION

Dengue virus (DENV), an icosahedral positive sense single strand RNA enveloped virus of the Flaviviridae family, is now the most widespread arthropod-borne viral pathogen in humans. First disseminated by Aedes aegypti and Aedes albopictus flies, DENV is one of over 70 viruses that belong to this family (Surasombatpattana et al., 2011; BioLEAGUES, 2024). Four antigenically different serotypes [DENV-1, DENV-2, DENV-3 and DENV-4] are worldwide spread and have infection potential. The clinical spectrum of disease following infection is broad, from asymptomatic through to an unrecognized febrile illness and the classical continuum of DF, DHF and the most severe form DSS. Nearly 50 percent of the infections are asymptomatic; and, in DF, symptoms such as flu-like symptoms. Advancement to DHF or DSS correlates significantly with increased risk for complications and mortality, levels of viremia being 100–1,000 times higher in these severe forms than those detected in DF (Mahedi et al., 2025). Clinical presentations in children are usually relatively more severe when compared to adults (Bhatt et al., 2013).

The incidence of dengue has increased around 30-fold over the last 50 years. More than 100 countries now document endemic transmission, endangering an estimated two and a half billion people. Worldwide statistics indicate approximately 100 million cases of DF per year along with 250,000 cases of DHF and about 25,000 deaths. Nevertheless, recent modeling studies suggest that the true disease burden may be substantially underestimated, underscoring dengue as a persistent and expanding global public health challenge (Rothman 2012).

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Submitted: 21 October 2025 Revised: 28 December 2025 Accepted: 07 January 2026

The immunopathogenesis of DENV is only partially illuminated, but some mechanisms are recognized. The main pathologic findings include capillary leak due to endothelial damage, and severe thromboycytopenia, leukopenia, and hemorrhage (Afrin et al., 2024). Entry is mediated by the envelope (E) glycoprotein, and replication takes place primarily within monocytes. These infected cells induce the activation and secretion of interferon-α and interferon-β. Viral proteins, predominantly E, precursor membrane (pre-M), and nonstructural protein 1 (NS1) drive the production of antibodies in response to infection, whereas DENV-specific $CD4^+$ and $CD8^+$ T cells recognize infected cells and release interferon-γ plus tumor necrosis factor-α. The primary infection induces lifelong immunity to the infecting serotype, but not against other serotypes, which could explain an increased risk upon secondary infection (Ahmed et al., 2014).

Nutritional status is a critical determinant of immune competence, and micronutrient deficiencies remain a leading global cause of immune dysfunction, particularly among children in low- and middle-income countries. In this review, the term micronutrient supplementation is operationally defined as the therapeutic or adjunctive administration of essential vitamins and trace minerals (e.g., vitamin C, vitamin D, vitamin E, folic acid, and zinc), distinct from the broader concept of nutraceuticals, which may encompass functional foods, herbal products, or bioactive compounds beyond essential nutrients (Maron et al., 2010; Jamali et al., 2023). Given that micronutrients have an impact on immune regulation, oxidative equilibrium and tissue regeneration clinicians at various centers induct, micronutrient supplementation as a supplement to the standard dengue management. These supplements are inexpensive and biologically plausible adjuncts to therapy, with a myriad of proposed mechanisms summarized in Table 1 (including cytokine modulation, and oxidative stress reduction).

Table 1. Micronutrients and Their Suggested Biological Actions (Langerman & Ververs, 2021).

Micronutrients	Key Biological Actions Linked to Clinical Improvement
Vitamin A	Supports proliferation of B lymphocytes and activation of T lymphocytes; influences the functional activity of macrophages and natural killer cells.
Vitamin C	Neutralizes reactive oxygen species, enhances interferon synthesis, and strengthens leukocyte-mediated phagocytosis.
Vitamin D	Modulates toll-like receptor pathways (notably TLR3 and TLR9), limits excessive inflammatory responses, boosts Interleukin-10 production, and promotes suppressor of cytokine signaling pathways.
Vitamin E	Stabilizes cellular membranes against oxidative injury, removes peroxyl radicals, and augments immune responsiveness through enzyme regulation and gene expression changes.
Folic Acid	Contributes to hematopoiesis and supports recovery of blood cell parameters.
Zinc	Aids in the maturation of lymphocytes, enhances cytokine secretion, strengthens T-cell and neutrophil activity, and promotes timely cell apoptosis.

Nutritional adjuncts such as vitamin C, vitamin D, vitamin E, folic acid, and zinc have each been evaluated in clinical or quasi-clinical studies for their effects on hematological recovery, immune modulation, symptom duration, and disease progression in dengue fever. However, these studies remain fragmented, heterogeneous in design, and variable in quality. To date, no comprehensive synthesis has systematically evaluated and integrated clinical trial evidence within a clearly defined methodological framework.

Therefore, the objective of this review is to synthesize clinical trial findings published between 2010 and 2025 that examine the role of micronutrient supplementation as an adjunctive therapy in dengue fever, to identify mechanistic and clinical evidence gaps, and to propose a focused research agenda for future well-designed randomized controlled trials. While micronutrient supplementation is unlikely to replace vaccination as a primary preventive strategy, immunological and physiological evidence supports its potential role in optimizing host responses and attenuating disease severity when used alongside standard dengue care. The studies reviewed herein provide preliminary signals of benefit, warranting further rigorous investigation to establish clinical efficacy and translational relevance.

STATEMENT OF THE PROBLEM

Despite the growing clinical interest in micronutrient supplementation as an adjunct to standard dengue management, the existing evidence base remains diffuse, methodologically heterogeneous, and clinically inconclusive. Published trials and quasi-experimental studies have evaluated a wide range of micronutrients and outcomes, often without a clearly prioritized clinical endpoint. As a result, current syntheses risk being overly broad, limiting their ability to generate clinically actionable conclusions or to guide future trial design.

In particular, there is no focused synthesis that systematically examines whether micronutrient supplementation influences key patient-centered outcomes in dengue fever, such as length of hospital stay (LOS) or progression to severe dengue (DHF/DSS), which are critical indicators of disease burden, healthcare utilization, and prognosis. Secondary but clinically relevant outcomes that includes platelet count recovery, changes in hepatic transaminases (AST/ALT), and markers of plasma leakage that have been inconsistently reported and have not been evaluated within a coherent outcome hierarchy. This lack of outcome prioritization obscures interpretation of therapeutic benefit and hampers comparison across studies. Accordingly, the core problem addressed in this review is the absence of a focused, outcome-driven synthesis that integrates clinical trial evidence on micronutrient supplementation in dengue fever. By prioritizing primary outcomes (LOS and progression to severe dengue) and systematically evaluating secondary laboratory and clinical markers, this review aims to clarify the current state of evidence, identify mechanistic and clinical gaps, and provide a structured framework to inform future randomized controlled trials and translational research in dengue therapeutics.

METHODS

This review was conducted in accordance with PRISMA guidelines to identify and synthesize evidence on the role

of micronutrients in dengue infection. A comprehensive literature search covering the period from 2015 to 2025 was performed using PubMed and ProQuest databases. Eligibility criteria were predefined. Studies were included if they: (i) evaluated micronutrient status, supplementation, or nutritional biomarkers as primary or secondary outcomes; (ii) used observational or interventional study designs; and (iii) were published within the specified time frame. Exclusion criteria comprised: non-dengue-focused studies, animal or in vitro studies, narrative reviews, editorials, conference abstracts without full text, and studies lacking extractable micronutrient-related outcomes. PubMed searches employed combinations of the keywords micronutrients AND dengue, with specific terms including vitamin, retinol, folic acid, zinc, and antioxidants, yielding 115 records. A broader ProQuest search strategy incorporating terms related to nutrition, dietary supplements, metabolism, public health, vitamin and nutrient deficiencies, antioxidants, and evidence-based healthcare generated 3,382 records. In total, 3,497 records were identified. Prior to screening, 512 duplicate records and 120 records flagged as ineligible by automation tools were removed. The remaining 2,865 records underwent title and abstract screening, resulting in the exclusion of 2,650 records. Full texts were sought for 215 reports, of which 25 could not be retrieved. A total of 190 full-text articles were assessed for eligibility, and 150 were excluded due to lack of relevant micronutrient outcomes (n = 65), non-dengue focus (n = 60), or non-original study design such as reviews or commentaries (n = 35). Ultimately, 30 studies met the predefined inclusion criteria and were included in the final qualitative synthesis.

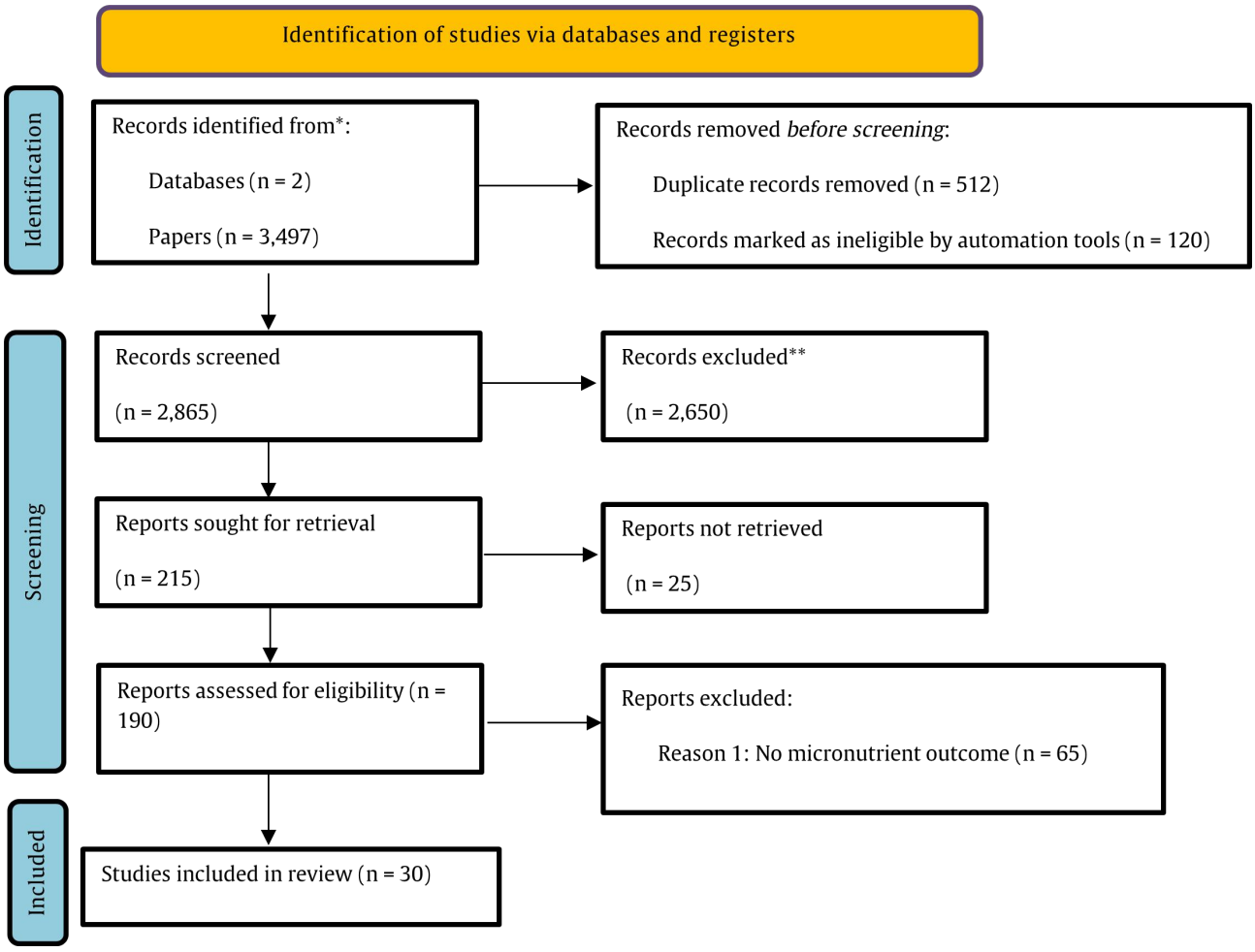

Figure 1. Prisma flow diagram

RESULTS OF STUDY

Vitamin A

Vitamin A is critical for preserving host immune competence, and deficiency causes loss of humoral & cell-mediated immunity with impairment of, epithelial barriers in the eye and respiratory/lower GI tracts. This damage makes individuals susceptible to infection. Vitamin A has functional effects on macrophages, natural killer (NK) cells and lymphocytes where by B-cells and T-cell activation are involved in the sustained process of vitamin A. Low-dose vitamin A supplementation may substantially lower the rates of illness and death due to a number of infections, as demonstrated in low-resource settings. Its use has been associated with decreased severity of illness and lower mortality in malaria, as well as with higher survival rates in measles (Ahmed et al., 2014).

Vitamin C.

Ramalingam et al. (2019) and Rammohan et al. (2018) examined the therapeutic role of vitamin C in dengue fever (DF), focusing on hematological outcomes and recovery

patterns. Ramalingam et al. conducted a retrospective evaluation of 200 confirmed dengue cases treated across multiple hospitals in India. Half of the patients received vitamin C, although the study did not specify the dosage. The distribution of administration routes varied: 67% received vitamin C orally, 28% intravenously, and 5% received a combination, classified by the authors as more severe presentations. Despite limited demographic details apart from noting that 35.5% were children aged 0–15 years where the study reported substantial improvements in platelet recovery among those given vitamin C. The mean platelet rise was markedly higher in the supplemented group (363%) compared with controls (105%), with a statistically significant difference (P = 0.00). Hospital stay length also differed considerably; 39% of supplemented patients were discharged in under five days, contrasted with only 3% in the nonsupplemented group. However, the study did not stratify outcomes by route of vitamin C administration and lacked baseline nutritional assessments or dietary information, leaving uncertainty regarding preexisting micronutrient deficiencies that may have influenced clinical responses.

In contrast, Rammohan et al. (2018) performed a prospective observational study involving 123 thrombocytopenic dengue patients in Bangalore, India. Details were limited to a conference abstract, with no demographic data or full numerical effect sizes reported. Participants were assigned either standard therapy alone (n = 60) or standard therapy plus high-dose oral vitamin C (500 mg four times daily; n = 63). Hemoglobin and white blood cell (WBC) counts were measured on day seven. Hemoglobin remained unchanged in both groups, whereas WBC levels increased across the cohort. Notably, the rise in WBC count was significantly greater in the vitamin C group (P = 0.00), suggesting a potential immunomodulatory effect. Although promising, the lack of detailed methodological reporting and absence of platelet data limit interpretation and hinder comparison with Ramalingam et al.'s findings. Overall, both studies suggest possible hematologic benefits of vitamin C in DF, but methodological gaps underscore the need for more rigorous controlled trials.

Vitamin D.

An important function of vitamin D is to maintain immune homeostasis and deficiency in vitamin D has been implicated in susceptibility to autoimmune and viral diseases. As an immunoregulatory hormone, vitamin D impacts on both innate and adaptive immune pathways by promoting T-cell activation, monocyte differentiation as well as modulating the functions of B cells, dendritic cells (DCs) and other immune subsets through its binding to the VDR (Grant et al., 2010). Activation of the VDR induces expression of numerous vitamin D–responsive genes that contribute to antimicrobial defense and facilitate increased pathogen clearance. Clinical observational studies and RCTs have also suggested that Vitamin D supplementation may be associated with favorable outcomes in other viral infections such as influenza (Aranow, 2011), suggesting a more general (antiviral) effect of this vitamin.

Recent experimental studies also suggest potential mechanisms by which vitamin D may affect DENV infection (Urashima et al., 2010). An in vitro study from Mexico investigated the impact of 1,25-dihydroxyvitamin D_3 on human hepatic (Huh-7) and monocytic (U937) cells infected with DENV-4. Inhibition of infected cells by the active vitamin D metabolite was given, with the strongest suppression in monocytic cells that are known to be DENV target cells. The intervention also reduced the secretion of important proinflammatory cytokines, such as TNF-α IL 6, IL-12p70 and IL-1β. Furthermore, the inhibitory effect on virus infection was dose dependent; the most powerful inhibition occurred at a maximal dose (10 μM) of the compounds (Puerta-Guardo et al., 2012).

These observations are consistent with our knowledge of DENV biology. Viral Life Cycle Successful replication of the virus depends on the activation of host signaling pathways that include among others, Toll-like receptors (TLRs), NF-κB/RelA and mitogen-activated protein kinases (MAPKs) including p38, p42/44 and JNK. These routes are exploited for macrophage infection as well as enhanced proinflammatory cytokine production, leading to clinical phenotypes such as capillary leakage and hemorrhagic symptoms. By TLR inhibition (with a resulting reduction in the expression of TLR) followed by MAPK phosphorylation blockade, VD_3 interferes with pivotal intracellular cascades necessary for virus survival. Thus, the observed decreases in infected cells and cytokine levels likely reflect the specific disruption of DENV-mediated inflammatory cascades by the compound, raising the question as to whether such a mechanism could be involved in vitamin D-mediated reduction of disease severity observed in humans (Ceballos-Olvera et al., 2010).

Vitamin E.

Chathurangana et al. (2017) carried out a randomized controlled trial involving 127 children aged 5–12 years who had been diagnosed with dengue fever and hospitalized at a tertiary care facility in Colombo, Sri Lanka. Participants were allocated to one of two study arms. The intervention arm received age-adjusted vitamin E supplementation that 200 mg daily for children aged 5–9 years and 400 mg daily for those aged 10–12 years that is administered for seven days alongside routine supportive management. The control arm received only standard supportive care. An extensive panel of clinical, biochemical, and hematological indices was monitored, including capillary leakage duration, liver enzyme levels (AST and ALT), albumin, serum cholesterol, serum calcium, white blood cell counts, platelet counts, and packed cell volume. Measurements were taken twice daily from the second through the seventh day of admission to capture dynamic changes during the critical phase of illness.

The trial demonstrated several statistically significant differences favoring the vitamin E group. Children receiving supplementation experienced a shorter duration of capillary leakage and showed higher mean WBC counts by day 6. Serum albumin levels were consistently higher in the intervention arm, while PCV values were slightly but significantly lower during early measurements, suggesting reduced hemoconcentration. Liver enzyme levels, particularly AST and ALT, were markedly lower in the vitamin E group during the mid-course of hospitalization, indicating potential hepatoprotective effects. Despite these favorable biochemical and hematologic trends, the intervention did not shorten overall hospitalization time nor alter the overall incidence of capillary leakage. Additionally, the study did not assess baseline micronutrient status or determine whether participants exhibited pre-existing vitamin E deficiency, limiting interpretation of the observed benefits.

A second study, conducted by Vaish et al. (2012), used a prospective randomized open-blinded design to evaluate vitamin E in adult dengue patients at a tertiary teaching hospital in Lucknow, India. The investigation enrolled 59

participants, with 31 assigned to the vitamin E group and 28 to the control group. The intervention consisted of administering 400 mg of vitamin E daily in addition to standard care. Baseline demographic features were comparable between groups, including mean patient age. Platelet counts were measured at four time points: days 0, 1, 4, and 7. Patients who received vitamin E demonstrated significantly higher platelet counts on days 4 and 7, indicating a more rapid hematologic recovery. The study, however, did not include assessments of vitamin E levels at enrollment, nor did it describe participants' baseline nutritional status or monitor adverse effects associated with supplementation. Together, these two studies provide preliminary evidence suggesting a possible role for vitamin E in improving selected hematologic and biochemical markers in dengue infection. However, limitations that particularly small sample sizes, incomplete nutritional profiling, and unclear baseline deficiency status which underscore the need for more rigorous, well-controlled trials to determine the clinical relevance and safety of vitamin E supplementation in dengue management.

Folic acid.

Syed et al. (2019) conducted a retrospective observational study with 1,464 dengue fever cases who were admitted to an urban tertiary hospital (in Karachi, Pakistan). The mean age of patients was 36.5 years. The main aim of this phase-I study was to assess an effect of FA on time needed for platelet recovery. Secondary end results were the incidence of death, ICU admission, and hospitalization as well as creatinine level. In the cohort, 1,322 individuals (90.3%) took folic acid and 142 (9.7%) did not. No differences between supplemented and non-supplemented groups were seen on any clinical outcomes, and no effect sizes were provided. The limitations of the study included no baseline nutritional assessments, lack of investigation for zinc deficiency and failure to monitor for potential adverse events related to the supplementation.

Zinc (Zn)

Rerksuppaphol and Rerksuppaphol (2018) conducted a randomized controlled trial among 50 pediatric dengue fever patients from an academic center in Bangkok, Thailand. Children (6.3 years old on average) were assigned to receive bis-glycinate zinc orally At enrollment, nearly half in each group were zinc-deficient with no difference at baseline. The intervention had no significant effect upon time to fever clearance: i.e., defervescence occurred at similar times in both zinc and placebo groups (29.2 vs 38.1 hours; P = 0.27). Zinc supplementation, in contrast, was significantly linked to shorter hospital stay. Zinc-treated children were discharged earlier than controls (62.5 h vs 84.7 h; P = 0.01), raising a possibility of zinc-mediated shortening of duration of hospital stay, even though it demonstrated less effect in resolving fever impact as compared to the control group.

Evidence from observational studies.

Iron (Fe)

The need for iron for proper immune function stems from its role in promoting the growth and differentiation of various immune cells; specifically, iron deficiency has been found to decrease mitogen responsiveness, NK cell activity, lymphocyte bactericidal activity, and neutrophil phagocytic activity while influencing cytokine activity in every stage of the immune response to infection (Ahmed et al., 2014).

Chromium (Cr)

Chromium, an essential trace element, is traditionally recognized for its role in regulating blood glucose by enhancing insulin activity. More recently, research has highlighted its influence on the immune system, including modulation of T and B lymphocytes, antigen-presenting cells such as macrophages, and cytokine production. In animal studies, chromium supplementation has been associated with enhanced immune function, potentially through reduction of serum cortisol levels. However, chromium exhibits complex biological effects: high doses or prolonged exposure to hexavalent chromium (Cr VI) can be cytotoxic, disrupting cellular processes, inducing gene mutations critical to immune responses, and generating oxidative stress. Environmental exposure to chromium has also been linked to adverse health outcomes, emphasizing that any therapeutic use of chromium must involve carefully controlled dosing.

Table 2. Comparative Evaluation of Lipid profile, Hematological and Ancillary Biochemical parameters in patients of Dengue.

Hematological profile			
Parameter (Biomarker)	Dengue Fever Mean	Dengue Hemorrhagic Fever Mean	P-value
Hematocrit (%)	45.8673	52.32	< 0.001
Total leucocyte count /cumm	3.0551	3.0870	0.824
Platelet count/cumm	73.37	47.510	< 0.001
Lipid profile parameters			
Serum HDL (mg/dl)	17.68	56.115	< 0.001
Serum Cholesterol (mg/dl)	70.39	189.51	< 0.001
Serum LDL (mg/dl)	50.53	103.28	< 0.001
Ancillary Biochemical Parameter			
CRP	11.45	9.45	< 0.001
Serum Vitamin D (ng/ml)	20.46	7.92± 2.50	< 0.001
Serum Ferritin (ng/ml)	160.10	1128.80	< 0.001

Table 3. Overview of Evidence Quality and Study Characteristics for Micronutrient Interventions in Dengue (Amir et al., 2023).

Observed Micronutrient	Study Quality	Study Type	Daily Dose	Location	Target	Reference
Vit C	Weak	Retrospective, observational	-	India	Effect of vitamin C in the management of DF in the tertiary care hospitals	Ramalingam et al., 2019
Vit C	N/A	Prospective, observational	2000 mg	India	Effects of vitamin C on hemoglobin percentage and WBC count in patients with DF	Ramalingam et al., 2019
Vit D	Weak	RCT	200,000 IU	Pakistan	Risk and severity of development of DHF and dengue shock syndrome in patients receiving vitamin D supplement compared with those not receiving it	Zaman et al., 2017
Vit E	Moderate	RCT	200 mg	Sri Lanka	Effects of vitamin E supplementation on the clinical course of DF and DHF in 5- to 12-year-old Sri Lankan children	Chathurangana et al., 2017
Vit E	Moderate	Prospective randomized open-blinded evaluation	400 mg	India	Effect of vitamin E on thrombocytopenia in DF	Vaish et al., 2012
Folic acid	Weak	Retrospective, observational	5 mg	Pakistan	Compare the duration of recovery of thrombocytopenia in patients with dengue infection who received folic acid and those who did not	Syed et al., 2019
Zinc	Strong	RCT	45 mg	Thailand	Effects of zinc supplementation on dengue virus infection outcomes	Rerksuppaphol & Rerksuppaphol, 2018

Experimental studies in mice have explored the potential relationship between chromium and dengue virus (DENV) infection. In one study conducted in India, Shrivastava et al. exposed mice to hexavalent chromium prior to DENV infection. Mice pre-exposed to Cr (VI) displayed significantly less reduction in platelet counts compared with control mice, indicating a potential protective effect of chromium against thrombocytopenia caused by DENV. In a subsequent investigation by the same group, the impact of Cr (VI) on splenic morphology and immune function was examined. Spleen weights, which typically decrease during DENV infection, were further reduced in chromium-exposed mice, with the most pronounced effect observed after longer exposure periods. The chromium-treated group also exhibited heightened cytotoxic activity in spleen homogenates and reduced phagocytic function of splenic macrophages, suggesting altered immune responsiveness.

The mechanistic basis of these effects remains incompletely understood. It is known that immune cells convert Cr (VI) to the less toxic trivalent form (Cr III) upon entry into the body. During this conversion, Cr (VI) induces activation of the tumor suppressor gene p53 and promotes reactive oxygen species generation as including superoxide ions, hydroxyl radicals, and hydrogen peroxide that resulting in oxidative stress and potential damage to DNA and other macromolecules. Chromium has also demonstrated dose-dependent effects on alveolar macrophages, with low doses stimulating activity and high doses causing inhibition. Further investigations by Shrivastava and colleagues examined chromium picolinate (CrP), another chromium compound, in DENV-infected mice. Treatment with CrP similarly resulted in significant increases in platelet counts, reinforcing the possibility that chromium supplementation may modulate host responses to DENV infection. Nonetheless, these findings remain preliminary, as all studies have been conducted in murine models, and precise dosing and safety considerations must be rigorously addressed before any translational application in humans can be considered.

DISCUSSION

The lack of sufficient literature on the subject of micronutrients and DENV infection provides us with very few studies to make many specific recommendations. Most studies are observational with small sample sizes, and they include a limited assessment of potential confounding variables, such as inflammation, when assessing iron, vitamin A, or zinc status. Furthermore, the results are often inconsistent across different studies. Only vitamins D and E have been examined in the context of supplementation trials, with no control group and only five patients in the vitamin D trial, although the results are encouraging (Mahmud et al., 2022). Additionally, there is limited information on the optimal time during the course of the illness that nutritional supplementation may be most beneficial.

Biologically, nutritional status and supplementation are known to modulate immune function and likely to affect both the risk of DENV infection and the course of the illness. The biological plausibility for each of the

micronutrients is discussed above in Results. However, more research studies with sufficient sample size and comprehensive assessment of risk factors and confounders for DENV infection are urgently needed to shed more light on the exact mechanisms involved. For example, on one hand, vitamin D may contribute to dengue pathogenesis by altering the response of particular ILs and enhancing the expression of DENV entry receptors that promote viral entry into cells, which may explain why the observational studies reviewed above found elevated levels of vitamin D and vitamin D-binding protein in patients with dengue. On the other hand, vitamin D status is known to be associated with a lower risk of several other infections in many larger studies. High-dose vitamin D supplementation and hydroxychloroquine have also been shown to successfully treat immune thrombocytopenia in two cases (believed to be by the down-regulation of CD4+ T cells and up-regulation of T-regulatory cells by vitamin D3, leading to restored platelet levels). (Bockow & Kaplan, T2013) Similarly, leukopenia has long been associated with vitamin D deficiency (believed to be because of the requirement of white blood cell activation by vitamin D binding to vitamin D receptors on their surface), which suggests another possible mechanism by which vitamin D supplementation can reduce clinical severity of DENV infection.

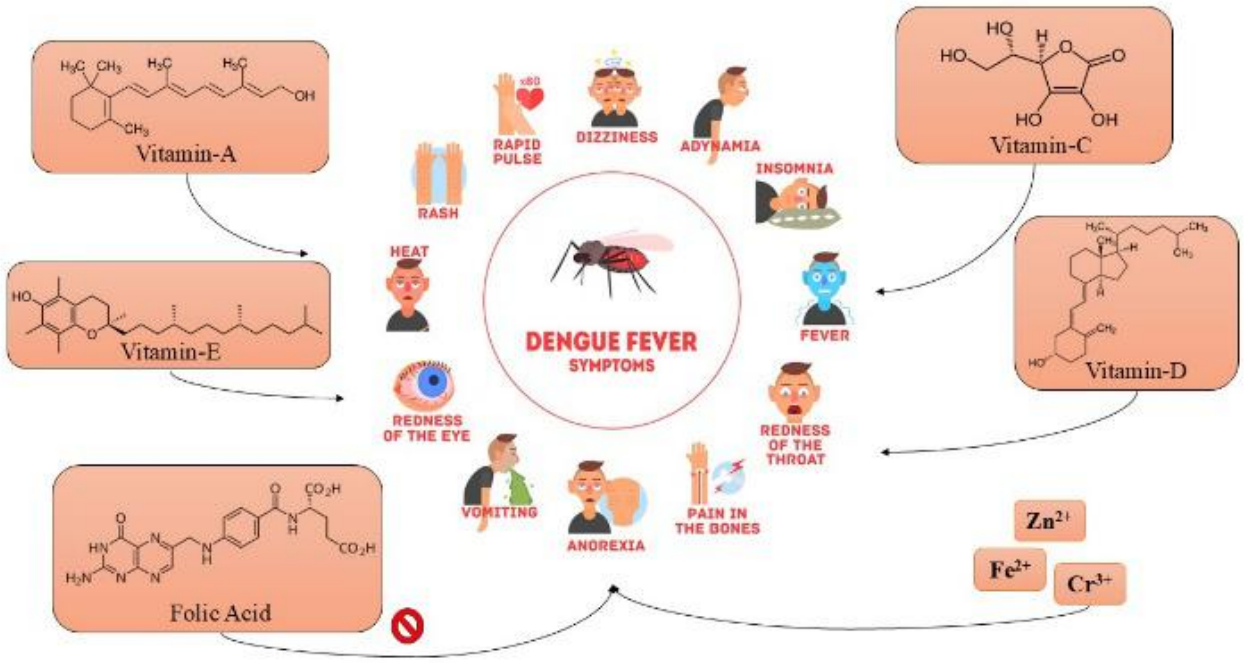

Figure 2. Micronutrients that affecting dengue symptoms (Bashetti, 2023; Finkelstein et al., 2020).

Smaller studies have found associations between vitamin D receptor polymorphisms and DENV infection. It is possible that defective vitamin D-receptor signaling (caused by certain polymorphisms) and thus, ineffective vitamin D response might result in increased TNF-α levels and decreased IL-10 levels, leading to DHF. However, a large genome-wide association study (GWAS) in Vietnam did not identify vitamin D receptor genes as being associated with DENV infection. (Khor et al., 2011) It is worth noting that this study only focused on DSS among children.

The trial with vitamin E supplementation provides exciting evidence that suggests its therapeutic potential for dengue patients with biological plausibility. The administration of vitamin E is safe and simple; nonetheless, additional investigation with larger trials is necessary to confirm this result. Because this study is limited to only DF patients, future studies should include DHF patients as well. Vitamin E has also been shown to mitigate oxidative stress and leukopenia in previous laboratory studies, which suggests possible mechanisms by which vitamin E supplementation can reduce clinical severity of DENV infection.

The evidence reviewed on chromium suggests a potential benefit of chromium supplementation for dengue patients and an overview of its mechanism of action. Limitations of the studies on chromium, however, include that they were all tested in mice and thus, cannot be directly applied to humans and that all evidence came from the same research team. Additional studies on CrP, such as laboratory studies on human cell lines and observational studies investigating a possible chromium deficiency in dengue patients, should be conducted.

Future research should investigate possible associations of DENV infection with other vitamins and micronutrients in addition to the ones reviewed here, because they have proven to be beneficial in other infections. Multivitamin supplementation (including vitamins B, C, and E) has been shown to be beneficial for patients with human immunodeficiency virus (HIV) and tuberculosis. (Mehta et al., 2011) Vitamin B12 has been shown to decrease viral replication and increase sustained viral response rates in patients of hepatitis C. Similarly, vitamin C supplementation has been shown to be beneficial against respiratory tract infections and pneumonia, whereas selenium supplementation has been shown to reduce parasitemia and the induced organ damage in parasitic infections, such as Trypanosoma (Rocco et al., 2013).

More trials need to be conducted with each of the specific micronutrients discussed in this review; vitamin D and vitamin E, in particular, both require larger observational studies followed by randomized trials to confirm the positive results shown in past studies, because

they propose the strongest cases for a possible benefit for dengue patients among all of the micronutrients reviewed here. Future studies should ideally include subjects of all ages instead of being restricted to only a particular age group (such as children) and investigate all severities of DENV infection (DF, DHF, and DSS) instead of being limited to just one to be applicable to a greater number of people and disease cases. The timing of supplementation needs to be evaluated, and because many biomarkers of micronutrient status are affected by the inflammatory response, measurements should be accompanied by assessing levels of either C-reactive protein or α-1 acid glycoprotein to facilitate accurate interpretation.

Considering the potential of micronutrient supplements to represent low-cost and simple adjuncts to improve treatment success in patients with dengue, it is surprising that the scope of research in this area has been rather limited. Researchers should also evaluate the possibility of nutritional status being a predictor of acquisition of DENV infection in endemic areas (da Silva et al., 2014).

CONCLUSION

Available evidence suggests that micronutrient status has a significant but poorly understood influence on host responses to dengue virus infection. Although the pathogenesis of dengue is multifactorial and influenced by multiple stages of the interaction between viral replication, immune activation and inflammatory dysregulation, few micronutrients such as vitamin D and E have plausible biological mechanisms that may modulate the progression of disease. Experimental and early clinical experience indicate that vitamin D may modulate proinflammatory cytokine generation and viral entry pathways while vitamin E might limit oxidative stress, protect endothelial integrity, and enhance hematological reconstitution. Vitamins C and folic acid, and zinc are questionable or marginally effective, while those of chromium are limited to animal studies that must be carefully interpreted because of toxicity. Despite positive signals, the existing literature is limited by small sample size, heterogeneity of study design, poor measurement of preexisting nutritional status, and inadequate control for confounding factors. Inadequate numbers of randomized controlled trials and focus on individual micronutrients limit the interpretation of clear clinical recommendations. Of note, the optimal timing of supplementation during natural infection is not known and rarely are patients recruiting throughout the range of dengue severity. With the high dengue disease burden worldwide and availability of low-cost micronutrient interventions, studies are urgently required to conduct well-designed large clinical studies and establish mechanisms. It is suggested that future studies should investigate different population groups and several micronutrients, include inflammatory and nutritional biomarkers, and encompass all clinical presentations of dengue. By building on this evidence base, micronutrient supplementation could be used safely and effectively as an adjunct to supportive care in treating dengue.

Acknowledgments

The authors would like to express their deepest gratitude to "QUEST Bangladesh Biomedical Research Center, Bangladesh, Bangladesh University of Professionals (BUP), Aristotle University of Thessaloniki, Dunstable University Hospital and State University of Bangladesh".

DECRALATION

Ethical Considerations

Note Applicable.

Consent for publication

The authors declare no conflict of interest

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Availability of data and materials

Note Applicable.

Competing interests

The authors declare no conflict of interest

Authors' Contributions

MD. Hassan Sazu, Atikah Islam Chowdhury, Hrishik Iqbal: Web-Survey Design, Supervised the Data Collection Process, And Checked Writing, Approved Methodology, Manuscript Editing and Supervised All Steps;

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