JOURNAL OF ORTHOMOLECULAR MEDICINE

OPEN ACCESS

VOLUME 39, NUMBER 3
PUBLISHED: 1 DECEMBER 2024

EDUCATIONAL ARTICLE

A Review of Orthomolecular Medicine in the Treatment of Human Parasitic Infections

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Citation: Hermülheim J. (2024) A Review of Orthomolecular Medicine in the Treatment of Human Parasitic Infections. J Orthomol Med. 39.3

ABSTRACT

Parasitic infections pose significant global health challenges, especially in tropical regions, with traditional treatments facing limitations like drug resistance. This review assesses the potential of orthomolecular medicine, particularly high-dose nutrient supplementation, as a novel therapy for parasitic infections. Through a review of 51 studies, we identify a research gap in evaluating orthomolecular interventions at appropriate doses for parasitic infections. Further research is crucial to understand the role of nutrients in treating parasitic diseases and should focus on specific interventions, optimizing protocols, and assessing synergies with conventional therapies. Integrating orthomolecular treatments within public health strategies holds promise for reducing the global burden of parasitic diseases. Addressing limitations such as inadequate studies, meeting dosage criteria, and study design heterogeneity, is essential and can contribute to the development of effective treatment strategies for improved health outcomes.

INTRODUCTION

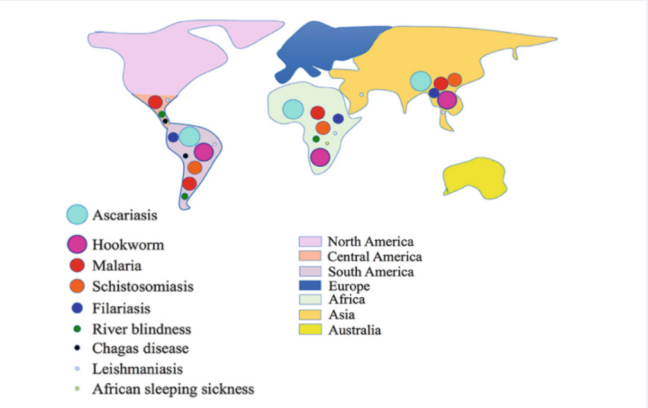
Throughout human evolutionary history, our interaction with both primate ancestors and domesticated animals has resulted in the acquisition of approximately 300 species of parasitic worms (Król et al., 2019) and over 70 species of protozoa (Cox, 2002). Ancient fecal samples have yielded evidence of nearly all known parasites specific to humans (Araújo et al., 2003).

A parasite is an organism that lives in or on another species, known as its host, deriving nutrients at the host's expense, thus causing what is commonly referred to as a parasitic infection (Forman & Maryanti, 2021). Parasitology traditionally limits its focus to protozoa (Imam, 2009), helminths (McVeigh, 2020), arthropods (Di Giovanni et al., 2021), and their vector species, although it is entirely proper from a biological standpoint to classify bacteria, fungi, and viruses as parasites (Bogitsh, Carter, & Oeltmann, 2013).

PARASITIC INFECTIONS: A GLOBAL HEALTH CHALLENGE

Human parasitic infections represent a significant public health burden worldwide, particularly in tropical and subtropical regions (Ung et al., 2021; Bogitsh, Carter, & Oeltmann, 2013). These infections are caused by various protozoa, helminths, and ectoparasites, leading to a range of clinical manifestations from mild discomfort to severe morbidity and mortality (Cox, 2002). Some of the most common parasitic diseases include malaria, schistosomiasis, lymphatic filariasis, soil- transmitted helminthiasis, and leishmaniasis (Ung et al. 2021).

Global Parasitic Disease Epidemiology. Adapted from Nag & Kalita, (2022)



 ISSN 0317-0209

A CLINICAL OVERVIEW OF COMMON PARASITIC DISEASES

Malaria, caused by Plasmodium parasites and transmitted through the bite of infected mosquitoes, remains a major cause of morbidity and mortality worldwide, particularly in sub-Saharan Africa (Bogitsh, Carter & Oeltmann, 2013). Despite significant progress in control efforts, including the distribution of insecticide-treated bed nets and antimalarial drugs, challenges such as insecticide resistance and limited access to healthcare continue to hinder eradication efforts (Ung et al. 2021).

Schistosomiasis, transmitted through contact with contaminated water inhabited by freshwater snails carrying Schistosoma parasites, affects over 200 million people globally, primarily in tropical and subtropical regions (Mutuku, 2020). The disease can lead to chronic complications such as liver and spleen enlargement, bladder cancer, and kidney damage, contributing to the cycle of poverty and economic instability in affected communities (Ung et al. 2021).

Lymphatic filariasis, caused by filarial worms transmitted through the bites of infected mosquitoes, affects over 120 million people worldwide, causing severe disability and disfigurement. The disease can lead to lymphedema, elephantiasis, and hydrocele, significantly impacting the quality of life of affected individuals and imposing a considerable economic burden on endemic countries (Ung et al. 2021).

Soil-transmitted helminthiasis, including infections with roundworms, whipworms, and hookworms, affects over 1.5 billion people globally, particularly in areas with poor sanitation and hygiene practices. These parasites thrive in warm and humid environments and can lead to malnutrition, anemia, and impaired cognitive development, particularly in children (Ung et al. 2021).

Leishmaniasis, caused by Leishmania parasites transmitted through the bite of infected sandflies, manifests in various clinical forms ranging from cutaneous lesions to visceral involvement, depending on the species of parasite and host immune response. The disease affects millions of people worldwide, with an estimated 350 million people at risk of infection in endemic regions (Ung et al. 2021).

Conventional treatment approaches often rely on antiparasitic drugs, which may be associated with limitations such as drug resistance (Pink et al., 2005), toxicity (Rosenblatt, 1992), and cost (Shahriar, & Alpern, 2020).

Classic antiparasitic drugs, including chloroquine for malaria, metronidazole for amoebiasis, and praziquantel for helminthic infections are extensively discussed in the review by Campbell and Soman-Faulkner (2023).

The World Health Organization (WHO) recognizes 36 antiparasitic drugs as essential, underscoring their critical role in global health initiatives (Arete-Zoe, 2017). Synthetic drugs are commonly used to treat parasitic diseases, but exploring plant-based compounds presents an intriguing avenue for potential advancements in treatment.

A review by Ranasinghe et al. (2023) evaluated 507 plant species, primarily from the Fabaceae, Asteraceae, Combretaceae, and Lamiaceae families, for their antiparasitic effects against gastrointestinal parasites, with a focus on organisms such as Entamoeba histolytica and Giardia duodenalis; ninety-one plant species and thirty-four compounds were identified as demonstrating significant in vitro efficacy against parasites.

Antiparasitic Drugs and Their Targeted Parasites (Campbell and Soman-Faulkner, 2023)

Drug	Targeted parasites
Praziquantel	Cestodes (tapeworms); Trematodes (flukes)
Albendazole	Cestodes (tapeworms); Nematodes (roundworms)
Metronidazole	Entamoeba histolytica (amoebiasis); Giardia lamblia (giardiasis); Sarcoptes scabiei (scabies)
Ivermectin	Onchocerciasis (nematodes); Sarcoptes scabiei (scabies); Pediculus humanus capitis (head lice)

Nutrition significantly influences susceptibility to all parasitic infections (Coop, & Kyriazakis, 1999). Malnutrition, especially protein deficiency, heightens vulnerability and exacerbates conditions such as hookworm infection – leading to anemia, weight loss, abdominal swelling, and mental fatigue (Bogitsh, Carter, & Oeltmann, 2013).

Poor nutrition not only increases susceptibility to parasitic infections but also can be both a consequence and exacerbating factor of infection-induced malnutrition. Onchocerciasis, the second leading infectious cause of blindness, affects 20 million people, mainly in tropical Africa, with another 120 million at risk. Caused by Onchocerca volvulus, it leads to "river blindness" and severe dermatitis, resembling vitamin A deficiency symptoms , suggesting a possible competition for or interference with vitamin A metabolism in the host (Bogitsh, Carter, & Oeltmann, 2013). De Gier et al. (2014) analyzed 37 studies on Helminth infections and micronutrients in school-age

children and found that helminth infections correlate with decreased serum retinol but not ferritin levels in children, concluding that further research on other micronutrients is needed.

THE POTENTIAL ROLE OF ORTHOMOLECULAR MEDICINE IN ADDRESSING PARASITIC INFECTIONS

Orthomolecular medicine, as defined by Pauling in 1968, focuses on restoring and maintaining health through the administration of substances naturally present in the body. The aging process, often accelerated by factors like free radical exposure (Migliore & Coppedè, 2009), inflammation (Bektas, et al, 2018), and toxic exposures (Dutta, et al., 2023), can be slowed or reversed through orthomolecular therapy, alongside addressing health issues (Carter, 2019).

Orthomolecular medicine can potentially contribute to the One Health approach by emphasizing optimal nutrition and natural substances to boost immune function, support host resistance, and reduce parasite burden in both humans and animals, thus complementing efforts to control parasitic diseases while promoting overall health and well-being. Global aging poses a multifaceted challenge within the One Health paradigm. Aging, influenced by a multitude of interconnected factors such as bio-genetics, environment, and socioeconomic forces, not only manifests internal vulnerabilities like frailty and comorbidities but also external challenges such as social isolation and financial strain, collectively rendering the elderly population more susceptible to infections, including parasitic infections (Forman & Maryanti, 2021).

Scientific studies increasingly support the therapeutic and preventive benefits of high doses of nutrients. Vitamins C and E, beta-carotene, B-complex vitamins, and coenzyme Q10 have demonstrated positive effects on health and longevity at doses exceeding the Recommended Dietary Allowance (RDA). Although mineral requirements, such as magnesium, zinc, and chromium, are closer to the RDA, supplements beyond dietary intake levels may still be necessary for disease prevention, treatment, and slowing the aging process (Carter, 2019).

Orthomolecular medicine offers a potential alternative therapy for parasitic infections. By restoring health through the administration of natural substances present in the body (Hemat, 2004), orthomolecular medicine can address underlying health issues while slowing the aging process (Carter, 2019). High-dose nutrient supplementation, a cornerstone of orthomolecular therapy, (Cathcart, Cott & Foster 2014) has shown promising therapeutic and preventive benefits in various health conditions. However, its efficacy in treating parasitic infections at orthomolecular doses remains largely unexplored.

The immune response to parasites involves a complex interplay of defense mechanisms. Nitric oxide (NO) plays a crucial role by targeting cysteine proteases essential for parasite life cycles and host-parasite interactions (Ascenzi et al., 2003). Histones, known for DNA regulation, also act as key mediators of host defense, triggering inflammatory responses and directly combating parasites (Hoeksema et al., 2016).

Additionally, a robust IFN-γ response in humans indicates effective pro-inflammatory action against parasites (Artavanis-Tsakonas et al., 2003). Despite variations among parasite groups, common immune reactions are activated upon infection, involving pattern recognition, inflammatory signaling, effector molecule expression, antigen presentation, and establishment of adaptive immune responses, contributing to infection control (Buchmann, 2022). This orchestrated immune response highlights the host's intricate mechanisms to combat parasitic challenges.

Huemer (2006), while exploring the orthomolecular ramifications of chronic renal disease, highlights the importance of mega doses of vitamins B6, B12, folate, and trimethyl glycine (betaine) in increasing nitric oxide levels by inhibiting homocysteine. Short-term supplementation with 750 mg of vitamin E leads to increased production of the T helper 1 cytokine IFN-gamma (Malmberg et al., 2002; Saul, 2003).

The effectiveness of vitamin C to enhance the innate immune response is well established (Hoang et al, 2020), and high-dose vitamin C showed a non-significant trend towards increased cell- mediated immune responses in healthy elderly individuals (Goodwin et al, 1983). According to Mikirova (2020), continuous ascorbate infusions may stimulate histone function, potentially influencing gene expression.

Recent clinical trials indicate that vitamin A supplementation reduces morbidity and mortality in various infectious diseases, while studies in animal models and cell lines highlight its significant role in immunity, including modulation of mucins and keratins expression, lymphopoiesis, apoptosis, cytokine expression, antibody production, and the function of immune cells such as neutrophils, natural killer cells, monocytes, macrophages, T lymphocytes, and B lymphocytes (Semba, 2007; Ash, 2011).

The intricate interplay between molecular targets and nutrient interactions underscores the plausibility of these interventions in effectively combating human parasitosis. Orthomolecular medicine, focusing on high-dose nutrient supplementation, potentially offers an adjuncive therapy for parasitic infections, but its efficacy remains largely unexplored in this context.

ORTHOMOLECULAR INTERVENTIONS

In addition to the molecularly targeted interventions of vitamins A, B, C, and E, several nutrients have emerged as promising candidates in clinical trials for combating parasitic infections and their complications.

Iron

Iron supplementation is recommended to address potential anemia associated with infections caused by Ancylostoma duodenale and Necator americanus, even before diagnosis or treatment initiation (Kucik, Martin, & Sortor, 2004).

Zinc

Kucik, Martin, and Sortor (2004) showed that parasites are better able to survive in zinc-deficient hosts compared to well-nourished hosts. Zinc deficiency, affects gut immunity, prolonging parasite survival (Scott & Koski, 2000). Further, zinc supplementation, particularly with zinc gluconate, has shown promising evidence of reducing Plasmodium falciparum-mediated febrile episodes in malaria (Overbeck, Rink, & Haase, 2008). Kotepui et al. (2023) conducted a systematic review on the impact of daily oral zinc supplementation, either alone or in combination with other nutrients, on malaria risk. They found no significant effect of zinc alone but suggested a potential benefit when combined with other micronutrients. This underscores the necessity for larger studies to clarify the effects of multi-nutrient supplementation on malaria risk.

Folate

Clinical trials investigating folate's impact on malaria progression have primarily focused on antimalarial drug efficacy rather than direct folate intake, making it challenging to disentangle the specific effects of folate supplementation on malaria risk (Nzila, Okombo, & Hyde, 2016).

Vitamin B1

Vitamin B1 (thiamine) deficiency reduces resistance to parasitic infestations in rats, highlighting its crucial role in immune function against helminth infections (Watt, 1944). Children who did not meet the recommended intake for thiamin had a higher prevalence of infection with Trichuris trichiura suggesting a potential association between thiamin deficiency and susceptibility to parasitic infections (Papier et al., 2014).

Vitamin B12

Layden et al. (2018) conducted a review on the interplay of neglected tropical diseases (NTDs) and vitamin B12 (cobalamin) highlighting the scarcity of literature and the need for future prospective studies to establish the role of vitamin B12 in NTD etiology and potential clinical significance.

Vitamin C

Vitamin C exhibits potent antiparasitic effects against Trypanosoma cruzi, potentially through a pro-oxidant mechanism, making it a promising candidate for Chagas' disease treatment (Puente et al., 2018). Klenner (1954) suggests the use of high-dose intravenous vitamin C, alongside para- aminobenzoic acid, for treating trichinosis, advocating daily injections of four to twelve grams of vitamin C for non-responsive patients due to its roles in antibody formation and detoxification.

Vitamin D

Vitamin D deficiency is associated with increased susceptibility to infectious diseases, including tuberculosis and Leishmania parasitic infections, while sufficient levels have been shown to enhance immune responses against pathogens such as Mycobacterium tuberculosis and Campylobacter jejuni (Zughaier, Lubberts, & Bener, 2020). Vitamin D has potential as an adjunctive therapy in parasitic diseases like leishmaniasis, owing to its modulation of inflammation and wound healing pathways (Ramos-Martínez et al., 2015).

Arachidonic Acid

Arachidonic acid (ARA) has shown potent schistosomicidal effects by inducing parasite death through excessive hydrolysis of sphingomyelin (SM) and has demonstrated efficacy in both in vitro and in vivo studies against Schistosoma mansoni and Schistosoma haematobium infections (Tallima, Hanna, & El Ridi, 2020).

RESEARCH GAP AND OBJECTIVES

The evidence supporting the efficacy of orthomolecular medicine in treating human parasites remains limited and inconclusive. This review seeks to systematically evaluate the available literature to elucidate the role of orthomolecular interventions in the management of human parasitic infections.

Orthomolecular interventions can enhance host immune responses, inhibiting parasite growth. Research supporting the therapeutic and preventive benefits of high doses of nutrients exists, but their efficacy in treating parasitic infections at the appropriate doses remains uncertain.

While our analysis encompassed a comprehensive search of relevant studies, it is noteworthy that not a single study meeting the criteria for orthomolecular dosing was identified. This absence of empirical data underscores a critical gap in our understanding of the potential efficacy of such interventions in this context.

Despite this limitation, our review provides valuable insights into the current state of research and highlights the need for further investigation into the use of orthomolecular medicine as a therapeutic approach for parasitic infections. By elucidating existing gaps in the literature, our study aims to inform future research endeavors and contribute to the advancement of effective treatment strategies for parasitic diseases.

Parasitic Infections & Orthomolecular Approaches: PubMed Search Terms

Human Parasitic Infections	Orthomolecular Terms
Malaria	Orthomolecular Medicine
Schistosomiasis	Vitamins
Giardiasis	Minerals
Lymphatic Filariasis	Antioxidants
Soil-transmitted Helminthiasis	
Leishmaniasis	

METHODS

A meticulous search strategy was implemented using PubMed, a renowned biomedical database, to identify relevant literature on orthomolecular medicine's efficacy in treating human parasitic infections published up to December 2023. The search query covered two domains: human parasitic infections, and orthomolecular medicine. Terms for parasitic infections like malaria, schistosomiasis, and giardiasis were included to ensure comprehensive coverage. Similarly, terms for orthomolecular medicine, such as vitamins, minerals, and antioxidants, were selected to encapsulate its essence.

Boolean operators, namely OR and AND, were strategically utilized to refine the search and delineate logical relationships between terms. The resulting query, "(malaria OR schistosomiasis OR giardiasis) AND (orthomolecular medicine OR vitamins OR minerals OR antioxidants)," aimed to retrieve articles at the intersection of these domains. This systematic approach aimed to compile literature for a comprehensive review, providing insights into the role of orthomolecular medicine in combating human parasitic infections.

The initial search yielded 1,281 results, which were subsequently narrowed down to 51 through abstract analysis.

LITERATURE REVIEW METHODOLOGY

The exclusion of a significant number of studies from the initial search results can be attributed to the fact that many of them focused on pharmaco- or toxicomolecular interventions rather than orthomolecular medicine or the specific nutrients (vitamins, minerals, antioxidants) mentioned in the search criteria. Therefore, studies that did not align closely with the targeted interventions or topics were omitted during the abstract analysis phase, resulting in a smaller subset of relevant studies.

Studies were included if they met the following criteria:

1. original research articles evaluating the efficacy of orthomolecular interventions (e.g., vitamin supplementation, mineral therapy) in treating human parasitic infections
2. inclusion of clinical outcomes such as parasite clearance, symptom resolution, and adverse effects
3. availability of sufficient data to calculate effect sizes or odds ratios.
4. publication date spanning several decades, from the late 1960s to December 2023.

Studies were excluded if they were reviews, case reports, or animal studies. Excluding reviews, case reports, and animal studies from the analysis ensures the review focuses solely on high-quality, original research, thereby maintaining rigor by prioritizing studies with larger sample sizes, rigorous methodologies, and direct applicability to human populations in evaluating the efficacy of orthomolecular interventions for human parasitic infections.

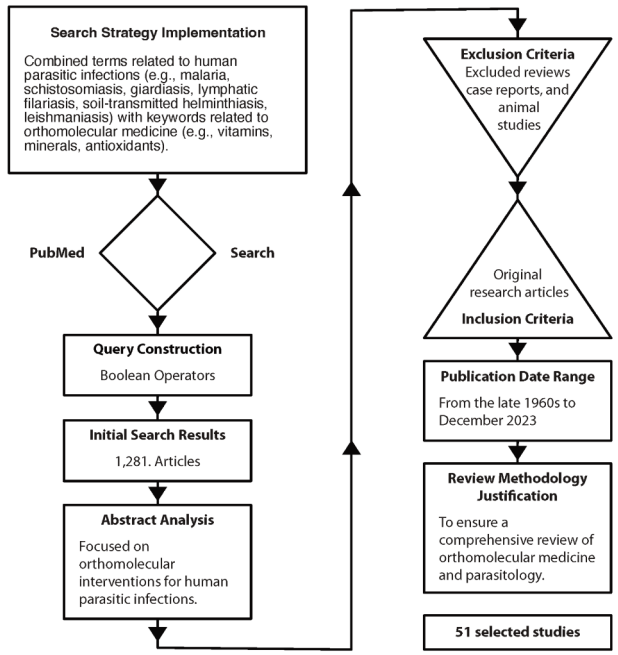
Addressing potential bias in the review process itself involved several strategies to mitigate publication bias and selective outcome reporting. These include utilizing multiple databases to minimize publication bias, conducting thorough manual searches of reference lists, registering the review protocol to enhance transparency and reduce selective outcome reporting, and employing sensitivity analyses to assess the impact of potential bias on the review findings, ensuring a comprehensive and unbiased synthesis of the evidence.

The extended timeframe from the 1960s to December 2023 was chosen to capture the historical development of research in both orthomolecular medicine and parasitology, ensuring a comprehensive review of the field. The choice of the 1960s as the timeframe for parasitology is justified by its embeddedness in a longer historical context of continuous discovery and formalization, interdisciplinary nature of this research, and significant technological advancements during that era (Roberts, L. S., 2004).

A comprehensive search of relevant literature was conducted to evaluate the efficacy of orthomolecular interventions in treating human parasitic infections.

The review included original research articles meeting specific criteria related to orthomolecular interventions and clinical outcomes.

PubMed Search Strategy



RESULTS

The analysis of the 51 selected studies revealed a diverse spectrum of research focused on nutritional interventions for human parasitic infections. Among these studies, the distribution of research varied across different nutrients and interventions.

Nutrient and Intervention Analysis for Parasitic Infections: Study Counts

Nutrient/Intervention	Number of Studies
Iron	16
Vitamin A	10
Multivitamin	8
Zinc	7
Vitamin C	2
Archaidonic Acid	2
Vitamin B1 Vitamin B12 Folate Vitamin D NAC	1 each

The tables in the appendix provide a comprehensive listing of the studies included in the review, organized by specific micronutrients, allowing for easy reference and examination of the primary research contributing to the analysis.

Iron

In 16 studies conducted between 1984 and 2021 investigating the effects of iron supplementation on various parasites, involving a total of 11,565 participants, the average dosage for iron supplementation administered across studies was approximately 48.75 mg.

Vitamin A

In 9 studies conducted between 1999 and 2020 investigating the effects of vitamin A supplementation on various parasites, involving a total of 8,364 participants, the dosage for vitamin A supplementation administered across studies varied, ranging from 2,500 IU to 200,000 IU, with dosing frequency ranging from single doses to every three months.

Multivitamin

The 8 studies conducted between 2003 and 2019 investigating the effects of multivitamin supplementation on various parasites, involving a total of 13,844 participants, supplementation varied widely in composition and format, including unspecified combinations of iron, zinc, and calcium, vitamin B complex, vitamins C and E, as well as lipid-based nutrient supplements and micronutrient powders, with frequencies ranging from daily intake to weekly sachets.

Zinc

In the 6 studies conducted between 1969 and 2016 investigating the effects of zinc supplementation on various parasites, involving a total of 1,918 participants, supplementation ranged from daily doses of 10 mg to 60 mg of zinc sulfate or zinc methionine, with dosing frequency varying from daily intake to bi-weekly administration. These studies were targeting parasites such as Schistosoma hematobium, Ascaris lumbricoides, Giardia intestinalis, Entamoeba histolytica/E. dispar, malaria, cutaneous leishmaniasis, and helminths/protozoa.

Vitamin C

In the 2 studies conducted in Uganda in 2013 and Ghana in 2015 investigating the effects of vitamin C supplementation on parasites, involving a total of 2,983 participants, supplementation dosages ranged from 66 mg to 180 mg, administered via mango juice as a drink. These studies targeted schistosomes, malaria, and hookworm.

Arachidonic Acid

In the 2 studies conducted in Egypt in 2014 and 2015 investigating the effects of arachidonic acid supplementation on Schistosoma mansoni, involving a total of 334 participants, supplementation dosages ranged from 10 mg/kg to 396 mg.

CRITERIA FOR ORTHOMOLECULAR DOSING

Hoffer (1976) defined a megadose as a dosage of 800 International Units (IU) or more of vitamin E per day, exceeding the Recommended Daily Allowance (RDA) of 33.3 IU by approximately 24 times. Megavitamin or orthomolecular doses were therefore defined as nutrient supplementation exceeding twenty times the recommended dietary allowances (RDAs) or daily intakes (RDIs) established by authoritative bodies such as the Institute of Medicine (IOM) or the World Health Organization (WHO).

For example, megavitamin doses of vitamin C were considered to be doses exceeding 2000 milligrams per day. Studies administering nutrients at or below these threshold doses were excluded from further analysis.

Safety Considerations

Critics of orthomolecular treatment express concerns about the potential risks associated with high-dose nutrient supplementation, highlighting that such doses may lead to adverse effects or interactions with medications, posing safety risks to patients (Hoffer, 1983).

Prousky (2013) extensively discussed the adverse effects of orthomolecular medicine, highlighting that Orthomolecular Medicine Therapy (OMT) is generally not associated with physiological dependence, withdrawal symptoms, or

Orthomolecular Doses Compared to Recommended Daily Allowances for Various Nutrients in Intervention Studies

Nutrient	RDA (Adult Males)	Orthomolecular Dose (x20)	Employed as or approximating Orthomolecular Intervention by
Iron	8 mg/day	160 mg/day	Stoffel, von Siebenthal, Moretti, & Zimmermann, 2020 – Against Anemia
Vitamin A	900 mcg/day	18,000 mcg/day	Dollimore et al., 1997 – Infants with Measles
Vitamin B1	1.2 mg/day	24 mg/day	Brenner, 1982 - Children with hyperkinesis
Folate (B9)	400 mcg/day 600 mcg/day for pregnant women	8 mg/day 12 mg/day	Murphy et al., 2021 (4 mg) – Pregnant Women
Vitamin B12	2.4 mcg/day	48 mcg/day	Toole, 2002 (400 mcg) - Nondisabled Stroke Victims
Vitamin C	90 mg/day	1,800 mg/day	Choi et al., 2017 (2000 mg) - Korean Women for fatigue recovery
Vitamin D	600 IU/day	12,000 IU/day	Holick, 2002, 2003 (10.000 IU) – Obese and normal weight individuals without apparent additional health challenges
Zinc	11 mg/day	220 mg/day	Pataracchia, 2010 (120 mg) - Middle-aged Females (56 years old) with Chronic Depression
NAC	Not applicable	1200 mg / day	Nur et al., 2012 – Sickle cell patients

long-term harm, although there are instances where excessive doses of micronutrients can lead to adverse reactions. These adverse effects include hepatotoxicity and neurotoxicity, particularly with high doses of Vitamin B3/B6; however, it is emphasized that such adverse effects are usually self-limited and reversible upon reducing or discontinuing the dosage. Additionally, the therapeutic indexes (TIs) of orthomolecules tend to be extremely large, suggesting that the amount needed to produce a therapeutic effect is significantly lower than the amount needed to produce a lethal effect, thus implying a relatively low risk of mortality associated with OMT.

The table "Orthomolecular Doses Compared to Recommended Daily Allowances for Various Nutrients in Intervention Studies" lists studies in which high doses of the aforementioned nutrients were safely administered to human populations.

Orthomolecular interventions may exert their effects through various molecular pathways, including immune modulation, antioxidant activity, and direct inhibition of parasite growth.

The included studies investigated a variety of nutritional interventions, including vitamin A, vitamin C, vitamin D, zinc, and selenium, alone or in combination with conventional antiparasitic drugs. However, it is important to note that none of the studies reached the orthomolecular doses mentioned earlier in the analysis.

The absence of studies meeting orthomolecular doses for parasitic infections is a significant limitation of the review. Despite conducting a comprehensive search and analysis of relevant literature, no studies were found that specifically evaluated the efficacy of orthomolecular interventions at doses considered orthomolecular for treating parasitic infections.

DISCUSSION

The following limitations have several implications for the review findings:

1. Lack of Direct EvidenceThe absence of studies meeting orthomolecular doses means that there is a dearth of direct evidence supporting the effectiveness of orthomolecular interventions in treating parasitic infections. Without studies specifically designed to investigate this question, it is challenging to draw firm conclusions about the efficacy of orthomolecular medicine in this context.
2. Uncertainty Regarding Optimal DosagesOrthomolecular medicine emphasizes the use of high-dose nutrient supplementation to restore optimal physiological functioning. However, without studies evaluating the efficacy of orthomolecular doses for parasitic infections, it remains unclear what dosage levels are most effective in combating these diseases. This uncertainty hinders the ability to develop evidence-based treatment guidelines or recommendations in the field of orthomolecular medicine for parasitic infections.
3. Potential Overlooked Benefits or RisksStudies investigating orthomolecular interventions at lower doses may still provide valuable insights into their potential benefits or risks in treating parasitic infections. However, by focusing solely on studies meeting orthomolecular doses, the review may overlook relevant findings that could inform clinical practice or future research directions.
4. Implications for Future ResearchThe absence of studies meeting orthomolecular doses underscores the need for further research in this area. Future studies should aim to evaluate the efficacy of orthomolecular interventions at doses considered orthomolecular specifically for parasitic infections. This would help fill the existing gap in the literature and provide more robust evidence to guide clinical decision-making.

While the absence of studies meeting orthomolecular doses for parasitic infections limits the ability to draw definitive conclusions, it highlights the need for continued research efforts to explore the potential role of orthomolecular medicine in treating these diseases.

There could be several potential reasons for the absence of studies meeting orthomolecular doses for parasitic infections including but not limited to, lack of research focus, safety concerns, regulatory hurdles, limited funding and the complexity of parasitic infections.

CONCLUSION

While orthomolecular interventions, particularly vitamin supplementation, have shown promise in other health conditions, their efficacy in treating human parasitic infections remains uncertain due to the lack of direct evidence.

Clinicians may default to conventional antiparasitic drugs, which have established efficacy but may also be associated with limitations such as drug resistance and toxicity. In the absence of evidence supporting orthomolecular interven-

treatments that could complement or enhance conventional therapy.

Future studies should aim to fill this gap in the literature by evaluating the effectiveness of orthomolecular medicine specifically for parasitic infections. Additionally, research efforts should focus on optimizing intervention protocols, exploring potential synergistic effects with conventional therapies, and assessing long-term outcomes and cost-effectiveness.

High-dose nutrient supplementation, while potentially beneficial, may also pose risks of adverse effects, drug interactions, and unintended consequences. Moreover, the use of orthomolecular therapy raises questions regarding patient autonomy, informed consent, and equitable access to treatment. Addressing these ethical considerations is essential to ensure the responsible and ethical implementation of orthomolecular interventions in clinical practice.

Integrating orthomolecular approaches into existing public health strategies may offer a promising avenue for combating human parasitic infections and reducing the global disease burden. In alignment with the One Health approach, the integration of orthomolecular medicine holds potential to address parasitic infections by emphasizing optimal nutrition and the therapeutic use of natural substances, thereby supporting the interconnected health of humans, animals, and ecosystems.

REVIEW LIMITATIONS

The primary limitation of this review is the absence of studies meeting orthomolecular doses for parasitic infections, which precludes definitive conclusions regarding the efficacy of orthomolecular interventions in this context. Additionally, the variability in study designs, population characteristics, and outcome measures among the included studies may introduce heterogeneity and limit the generalization of findings.

Publication bias may also have influenced the results, as studies reporting positive outcomes are more likely to be published. Furthermore, the quality of evidence ranged from moderate to low, primarily due to methodological limitations such as inadequate blinding, incomplete outcome data, and risk of bias. Lastly, the potential interactions between orthomolecular interventions and conventional treatments were not systematically assessed, which could impact treatment efficacy and safety.

DISCLOSURE STATEMENT

Some data were unavailable at the time of publication (DUATOP). The conclusions drawn in this manuscript are based on the available data.

The **APPENDIX** appears below the references.

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Appendix

Authors	Year	Country	Participants	Dosage	Parasite	Effect size
Iron studies						
Olsen et al.	2000	Kenya	231 children 181 adults	60 mg iron bi-weekly	Schistosoma mansoni	0.38 (0.18 – 0.80)
Glinz	2015	Ivory Coast	41	3 mg ferrous sulfate 50 µg ferrous citrate I.V.	Afebrile malaria, Hookworm	OR 0,38
van Hensbroek et al.	1995	Gambia	600	Not specified	Falciparum malaria	
Brabin et al.	2017	Burkina Faso	1954 women	60 mg	Malaria	OR 0.2667
Ayoya et al.	2012	Malawi	406	Praziquantel and Iron	S. haematobium	OR 3.04
Mwanakasale	2009	Zambia	240	weekly ferrous sulphate 200 mg	S haematobium	At 9 months: Male: OR = 0.71 (95% CI: 0.51, 1.00) Female OR = 0.83 (95% CI: 0.58. 1.18)
Olney et al.	2013	Zanzibar	247	Iron (12.5 mg) + folic acid (50 µg) (FeFA) with or without zinc (10 mg)	Malaria	5–9 months olds OR 23.51
Gies et al.	2018	Burkina Faso	980	60 mg iron and 2.8 mg folic acid / week	Malaria	P. falciparum parasitemia in the iron and folic acid group OR 1.0
Gies et al.	2021	Burkina Faso	180	Weekly periconceptional iron supplementation	Malaria	OR 1.3 (0.5–3.3)

Appendix continued

Authors	Year	Country	Participants	Dosage	Parasite	Effect size
Seshadri et al.	1984	India		20 mg elemental iron	E. histolytica and G. lamblia	N/A
Akenzua	1985	Nigeria	112	50 mg Iron I.M. / week	Malaria	OR 0.583
Gara et al.	2010	Nigeria	82	Iron (2 mg/kg/day) plus Folate (5 mg/day)	Plasmodium malaria	Mean Febrile Illnesses (3 months) OR 1.54
Leenstra et al.	2009	Kenya	279	120 mg Iron / week Vitamin A 25.000 IU	Malaria	Odds of parasitemia OR≈6.98
Parul et al.	2009	Pakistan	6288	Iron (120 mg) and folic acid (400 µg)	Geohelminths and malaria	OR at Visit 1: 1.64
Tomashek et al.	2001	Tanzania	215	Thrice-weekly oral iron and folic acid	Malaria and Helminths	OR Group II vs. III ≈0.962
Bresnahan	2014	Zambia	181	Iron rich Food	Malaria	DUATOP
Vitamin A studies						
Rosado et al.	2009	Mexico	584	45,000 IU every 2 months	Giardia duodenalis, Ascaris lumbricoides and Entamoeba spp.	DUATOP
Long et al.	2007	Mexico	707 children	vitamin A every 2 months	G. lamblia E. histolytica A. lumbricoides	DUATOP
Villamor et al.	2003	Tanzania	546 children	4 x200 000 IU over 8 months	Malaria parasitaemia	DUATOP
Shankar	1999	Papua New Guinea	239	200000 IU every three months	Plasmodium falciparum	DUATOP
Sondo	2020	Burkina Faso	1059	Vitamin A + PlumpyDoz™ + Zinc	Malaria	DUATOP
Al-Mekhlafi et al.	2014	Malaysia	250	200,000 IU (x1)	Soil-transmitted helminths	DUATOP
Darling et al.	2017	Tanzania	2500	2,500 IU Vitamin A, 25 mg Zinc	Placental malaria	DUATOP
Owusu-Agyei et al.	2013	Ghana	200 Children	2x 100,000- 200,000 IU, Zinc 10 mg daily	Malaria	DUATOP
Abbeddou et al.	2017	Burkina Faso	2435 children	400 µg of vitamin A 10 mg of zinc, 6 mg of iron	Malaria	DUATOP
Zeba et al.	2008	Burkina Faso	74 children	1 dose of 200,000 IU vitamin A & 10 mg zinc, six times a week for ½ year	Plasmodium falciparum	DUATOP

Appendix continued

Authors	Year	Country	Participants	Dosage	Parasite	Effect size
Multivitamin studies						
Gibson	2003	Malawi	281	Iron, zinc, calcium	Malaria	DUATOP
McDonald et al.	2015	Tanzania	2400	Vitamin B complex, vitamins C and E, and zinc	Malaria	DUATOP
Suchdev et al.	2016	Kenya	1062 children	0.9 Multivitamin sachets/wk	Malaria	DUATOP
Suchdev et al.	2012	Kenya	1063 children	Sprinkles MNP	Malaria	DUATOP
Chandrasiri et al.	2015	Malawi	1,009 pregnant women	Lipid-based nutrient supplement, multiple micronutrients, or iron and folic acid	Malarial antibody responses	DUATOP
Siekmann et al.	2003	Kenya	555 school aged children	Meat (60-85 g/d)	Malaria	DUATOP
Aimone et al.	2017	Ghana	1943 children	Micronutrient powders containing vitamins and minerals	Malaria	DUATOP
Ercumen et al.	2019	Bangladesh	5551 Women	Lipid-based nutrient supplements	Helminths	DUATOP
Zinc studies						
Carter et al.	1969	United Arab Republic	90	60 mg $ZnSO_4 \cdot 7H_2O$	Schistosoma hematobium	DUATOP
Srinivasan et al.	2016	Mexico	800	20 mg Zinc methionine; Vitamin A every 2 months	Ascaris lumbricoides, Giardia intestinalis, and Entamoeba histolytica/E. dispar	
Saaka et al.	2009	Ghana	Not specified	Not specified	Malaria	DUATOP
Guzman-Rivero et al.	2015	Bolivia	29 (14 verum)	45mg/day	Cutaneous leishmaniasis	DUATOP
Grazioso et al.	1993	Guatemala	130	10 mg of zinc per day for 120-150 days	Helminths and protozoa	DUATOP
Shankar et al.	2000	Papua New Guinea	274 preschool children (136 verum)	10 mg elemental zinc given 6 days a week for 46 weeks	Plasmodium falciparum	DUATOP
Müller et al.	2001	Burkina Faso	685	12,5 mg Zinc	Symptomatic falciparum malaria	DUATOP
Vitamin B1						
Mayxay et al.	2014	Laos	314	10 mg/day	Plasmodium falciparum malaria	DUATOP
Vitamin B3						
Ajayi et al.	1991	Africa	28	50 mg	Malaria	DUATOP
Vitamin B12						
Shield, et al.	1981	Papua New Guinea	345	12.9 mg/day	Necator americanus	DUATOP

Appendix continued

Authors	Year	Country	Participants	Dosage	Parasite	Effect size
Folate						
Mbaye et al	2006	Gambia	1,035	500-1,500 mcg/day	Plasmodium falciparum	DUATOP
Vitamin C						
Muhumuza	2013	Uganda	2,833	180 mg from Mango Juice	Schistosomes	DUATOP
Egbi	2015	Ghana	150 children	66 mg from 200 ml of a drink	Malaria Hookworm	
Vitamin D						
Snyman et al.	1997	59		Calcitriol 1 µg	Schistostomah aematobium	DUATOP
N-Acetyl Cysteine (NAC)						
Magalhães et al.	2022	Brazil	60	Three doses of 600 mg/day	Visceral leishmaniasis	DUATOP
Arachidonic Acid						
Barakat et al.	2015	Egypt	268	396 mg	S. mansoni	
Selim et al.	2014	Egypt	66	10 mg/kg	S. mansoni	