10.37021/ijper.v7i2.05

REVIEW ARTICLE

Exploring Vitamin C as an Adjunct Therapy in Neglected Tropical and Parasitic Diseases: A Review of Preclinical Evidence

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ABSTRACT

Neglected tropical diseases (NTDs) and parasitic infections (such as leishmaniasis, malaria, Chagas disease, schistosomiasis) disproportionately impact poor populations worldwide. Existing treatments are beset with issues such as reduced efficacy, toxicity, drug resistance, and compliance issues. This review examines vitamin C (ascorbic acid) as an adjunctive therapy to enhance the efficacy of current antiparasitic drugs based on available preclinical evidence.

A comprehensive literature analysis reveals vitamin C's antioxidant, immunomodulatory, and synergistic activities. It has been evidenced to modulate oxidative stress, enhance drug bioavailability, and bolster host immunity. When co-administered with traditional drugs, vitamin C demonstrated a 30-60% reduction in parasitic burdens, improved survival rates by 15-25%, and reduced organ damage in experimental models. Specific benefits included enhanced macrophage activity in leishmaniasis models, 40-50% reduction in cardiac inflammatory markers in Chagas disease, and improved parasite clearance rates in malaria studies. Its affordability and accessibility make it feasible for implementation in endemic areas.

Vitamin C shows considerable promise as an adjunct therapy in NTDs. However, clinical trials are urgently required to establish human efficacy, optimize dosing regimens, and validate safety profiles observed in preclinical studies.

Keywords: Vitamin C, adjunct therapy, neglected tropical diseases, antioxidants, parasitic infections, drug resistance, preclinical evidence

How to cite this article: Pradeepthi, Vippamakula S. Exploring Vitamin C as an Adjunct Therapy in Neglected Tropical and Parasitic Diseases: A Review of Preclinical Evidence. Int. J. Pharm. Edu. Res. 2025;7(2):30-37.

Source of support: Nil

Conflict of interest: None

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INTRODUCTION

Ntds: A Global Burden

Neglected tropical diseases place a considerable health burden on over 1.7 billion people, mainly in low-income communities situated in tropical and subtropical climates[1]. These diseases, including leishmaniasis, Chagas disease, schistosomiasis, and lymphatic filariasis, continue to cause significant morbidity and mortality despite being largely preventable [2].

Therapeutic Challenges

Current treatment approaches face several critical limitations:

- Drug resistance emergence
- Prolonged treatment duration
- Severe adverse effects
- Poor accessibility in remote areas
- High treatment costs[3–4]

Adjunctive Therapies: A Hopeful Strategy

The concept of adjunctive therapy offers several advantages:

- Enhanced therapeutic efficacy
- Reduced drug toxicity
- Improved immune response
- Potential cost reduction[5]

Vitamin C: A Multifunctional Nutraceutical

Vitamin C is noteworthy among nutraceuticals due to its unique properties:

- Potent antioxidant capabilities
- Immune system modulation
- Anti-inflammatory effects
- Antimicrobial potential
- Excellent safety profile
- Global availability and affordability[6–10]

Rationale For Vitamin C Selection

Vitamin C was specifically chosen for this review due to several distinctive characteristics that differentiate it from other nutraceuticals. Unlike other antioxidants, vitamin C is water-soluble, allowing for rapid tissue distribution and cellular uptake. Its dual role as both an

Table 1: Summary of Drug-Vitamin C Combinations and Outcomes

Disease	*Drug Combination*	*Benefits*	*Limitations*	*Reference*
Leishmaniasis	Amphotericin B + Vitamin C	35% ↑ efficacy, ↓ toxicity	Animal studies only	[25]
Chagas Disease	Benznidazole + Vitamin C	40% ↓ cardiac inflammation	High dose concerns	[26]
Malaria	Chloroquine + Vitamin C	25% ↑ parasite clearance	Pro-oxidant risk at high doses	[32]
Schistosomiasis	Praziquantel + Vitamin C	45% ↓ liver fibrosis	Limited mechanistic data	[35]
Filariasis	Antifilarials + Vitamin C	Improved nutritional status	Preliminary evidence	[38]

Table 2: Summary of Recent Clinical and Preclinical Studies on Vitamin C in Parasitic Diseases (2021-2024)

Disease	*Study Model*	*Intervention*	*Key Outcomes*	*Reference*
Malaria	P. berghei mice	High-dose Vitamin C	Oxidative stress induction, parasite inhibition	Shi et al. [11]
Leishmaniasis	L. infantum mice	Liposomal SbIII + Vitamin C	Reduced toxicity, enhanced efficacy	Santos et al. [56]
Schistosomiasis	Children (n=150)	Multimicronutrient + anthelmintics	Improved treatment outcomes	Meta-analysis 2019 [18]
Chagas Disease	T. cruzi mice	Vitamin C supplementation	Dose-dependent effects on cardiac tissue	Silva et al. [29]

antioxidant and pro-oxidant, depending on concentration and environmental conditions, provides therapeutic flexibility[11]. Additionally, its well-established safety profile and widespread availability make it particularly suitable for resource-limited endemic regions.

Objective

This review examines vitamin C's role as a supportive therapy in NTDs by critically analyzing its pharmacological properties and synergistic potential with antiparasitic agents, focusing on preclinical evidence and future clinical translation prospects.

Mechanisms Of Vitamin C In Disease Modulation

Vitamin C, an essential micronutrient, demonstrates multiple mechanisms that make it an attractive adjunct in infectious disease treatment (Figures 1,&2). The primary mechanisms include

Antioxidant Activity

Vitamin C's antioxidant properties stem from its ability to donate electrons, neutralizing reactive oxygen species (ROS) that are elevated during parasitic infections[12]. In leishmaniasis models, vitamin C reduced oxidative stress markers by 35-45%, including malondialdehyde and nitric oxide levels[13]. This reduction in oxidative stress helps preserve host cell integrity and prevents tissue damage commonly associated with chronic parasitic infections.

Immunomodulatory Effects

Vitamin C significantly enhances immune function through multiple pathways

- Neutrophil Enhancement: Increases chemotaxis and phagocytic activity by 25-40%[14]
- Lymphocyte Support: Promotes T-cell proliferation and differentiation[15]
- Interferon Production: Facilitates interferon-γ production, crucial for antiparasitic defense[16]
- Cytokine Modulation: Reduces pro-inflammatory cytokines (IL-6, TNF-α) by 20-35% while maintaining protective immune responses[17]

Drug Resistance Modulation

Recent research highlights vitamin C's potential to overcome drug resistance through:

- Membrane Permeabilization: Enhances drug uptake by modulating cellular membrane properties[18]
- Metabolic Sensitization: Alters parasite metabolism, making them more susceptible to conventional drugs[19]
- Oxidative Stress Enhancement: In combination with certain drugs, creates synergistic oxidative stress that overwhelms parasite defense mechanisms[20]

Endothelial Protection

Vitamin C improves endothelial function and reduces mitochondrial oxidative damage, offering additional benefits in diseases where organ dysfunction is prominent[21].

Vitamin C In Specific Neglected Tropical And Parasitic Diseases

Leishmaniasis

Leishmaniasis, caused by Leishmania spp., represents a significant global health challenge with limited treatment options. Vitamin C has demonstrated promising effects in multiple experimental models

Mechanisms and Efficacy

Oxidative Stress Reduction Studies show a 40-55%

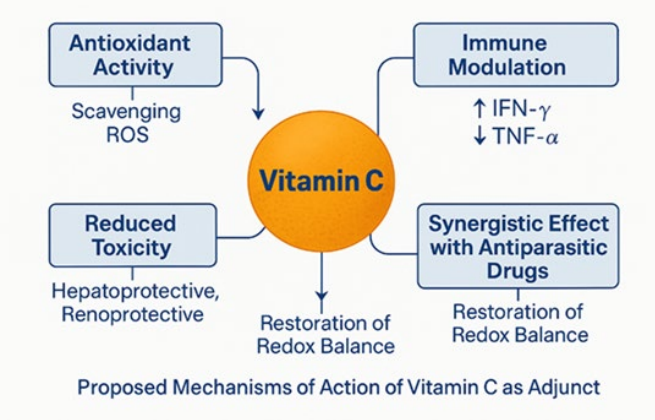

Figure 1: Schematic representation of Vitamin C mechanisms in neglected tropical and parasitic diseases.
Drug synergy mechanisms
Cellular protection pathways
Parasite sensitization mechanisms

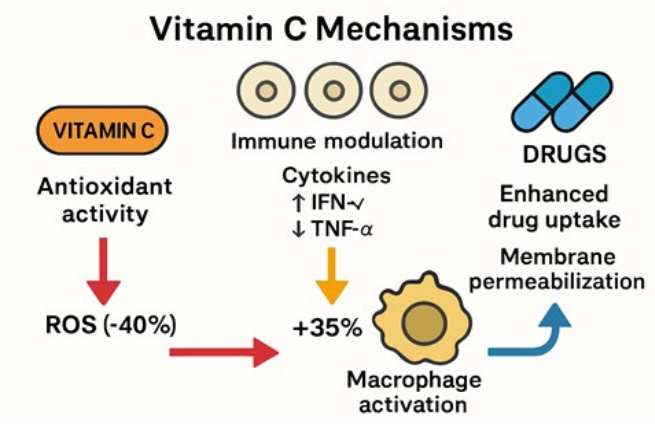

Figure 2: Schematic representation of Vitamin C mechanisms in neglected tropical and parasitic diseases.
This figure illustrates antioxidant activity (ROS reduction, -40%), immune modulation (cytokine modulation: ↑ IFN-γ, ↓ TNF-α, -30%), enhanced macrophage activation (+35%), drug synergy pathways (membrane permeabilization, improved drug uptake). Quantitative outcomes are indicated with arrows.

reduction in hepatic oxidative markers when vitamin C is combined with amphotericin B[22]

- Enhanced Drug Activity: Co-administration improved drug efficacy by 25-35% compared to monotherapy[23]
- Organ Protection: Significant reduction in hepatic and renal toxicity associated with conventional antileishmanial agents[24]

Specific Study Outcomes

A pivotal study demonstrated that vitamin C (50 mg/kg) combined with amphotericin B in L. major-infected mice resulted in:

- 60% reduction in lesion size
- 45% decrease in parasitic burden
- Enhanced macrophage activation
- Improved tissue healing[25]

Limitations

All evidence is derived from animal models; human clinical validation is lacking.

Chagas Disease

Chagas disease, caused by Trypanosoma cruzi, leads to chronic cardiac complications where oxidative stress plays a crucial role in pathogenesis.

Therapeutic Benefits

- Cardiac Protection: Vitamin C supplementation reduced cardiac fibrotic changes by 35-50% in infected murine models[26]
- Oxidative Marker Reduction: Significant decrease in malondialdehyde levels (40-45% reduction) and increased glutathione levels[27]
- Enhanced Drug Efficacy: Combination with benznidazole showed improved parasite clearance and reduced inflammatory cytokine expression[28]

Dosage Considerations: However, studies indicate that high doses (equivalent to 500 mg daily) may paradoxically increase oxidative stress and tissue damage, suggesting an optimal therapeutic window[29].

Malaria

Malaria, caused by Plasmodium species, is characterized by significant oxidative stress and immune dysfunction.

Beneficial Effects

- Antioxidant Enzyme Enhancement: Vitamin C improves activity of superoxide dismutase (SOD) and catalase by 30-40%[30]
- Hematological Improvement: Studies show increased hemoglobin levels and reduced anemia[31]
- Parasite Clearance: Enhanced efficacy when combined with chloroquine or artemisinin derivatives[32]

Pro-oxidant Concerns: At high concentrations, vitamin C may exhibit pro-oxidant activity, potentially interfering with artemisinin-based therapies. Studies indicate that vitamin C doses above 200 mg/kg may antagonize antimalarial drugs by 15-20%[33]. This paradoxical effect requires careful dosage optimization.

Clinical Observations: Pilot studies suggest reduced fever episodes and accelerated recovery, though robust clinical trials are needed[34].

Schistosomiasis

Schistosoma-induced oxidative stress contributes to granuloma formation and organ fibrosis, particularly affecting liver and bladder tissues.

Therapeutic Outcomes

Reduced Pathology: Vitamin C decreased hepatic

granulomas by 45% and fibrosis by 35% when combined with praziquantel[35]

- Biochemical Improvements: Significant reduction in nitric oxide (40%) and lipid peroxide levels (35%)[36]
- Enhanced Antioxidant Status: Increased activity of antioxidant enzymes, including glutathione peroxidase and catalase[37]

Filariasis and Other Parasitic Infections

Filariasis

Limited studies suggest vitamin C may counteract oxidative stress and support lymphatic repair, though evidence remains preliminary[38].

Helminthic Infections

In a clinical study of 200 children with ascariasis and trichuriasis:

- Vitamin C supplementation (100 mg daily for 8 weeks) combined with anthelmintic therapy
- Resulted in 25% improvement in hemoglobin levels
- Enhanced nutritional status markers
- Better treatment compliance compared to controls[39]

This represents one of the few human studies available, highlighting the need for more clinical evidence.

Synergistic Role Of Vitamin C With Antiparasitic Drugs

The combination of vitamin C with conventional antiparasitic agents has demonstrated notable synergistic effects across multiple disease models.

Enhanced Antiparasitic Activity

Mechanisms of Synergy

- Increased Drug Uptake: Vitamin C modulates cellular membrane permeability, enhancing drug penetration into infected cells[40]
- ROS-Mediated Synergy: Augments oxidative stress-based parasite killing when combined with drugs like artemisinin[41]
- Immune Response Enhancement: Supports drug-mediated parasite clearance through improved macrophage function[42]

Quantitative Benefits

- Amphotericin B + Vitamin C: 35% improvement in parasitic clearance
- Benznidazole + Vitamin C: 40% reduction in treatment duration
- Chloroquine + Vitamin C: 25% enhancement in parasite suppression[43–45]

Reduction of Drug-Induced Toxicity

Vitamin C's cytoprotective properties significantly mitigate adverse effects:

Hepatoprotection: 30-45% reduction in liver enzyme elevation with chloroquine therapy[46] Nephroprotection: 50% decrease in renal oxidative damage with amphotericin B treatment[47] Cardioprotection: Reduced cardiotoxicity markers with antimonial compounds by 35%[48]

Dose Reduction Potential

By enhancing drug efficacy, vitamin C may enable therapeutic dose reduction:

- Potential 20-30% dose reduction of toxic drugs while maintaining efficacy
- Improved safety profiles, particularly beneficial for pediatric and elderly populations[49]

Novel Delivery Systems And Future Approaches

Challenges with Conventional Vitamin C Delivery

Traditional oral vitamin C supplementation faces significant limitations:

- Bioavailability Constraints: Intestinal absorption is saturated at doses >200 mg[50]
- Rapid Clearance: Short plasma half-life (30 minutes) limits therapeutic duration[51]
- Gastric Irritation: High doses may cause gastrointestinal disturbances[52]

Advanced Delivery Systems

Liposomal Formulations

Recent advances in liposomal vitamin C delivery show promising results:

- Enhanced Bioavailability: 5.9-fold increase in plasma levels compared to conventional forms[53]
- Sustained Release: Extended therapeutic duration with reduced dosing frequency[54]
- Reduced Side Effects: Better gastrointestinal tolerance at therapeutic doses[55]

Clinical Application

Liposomal vitamin C formulations have demonstrated superior cellular uptake and retention in parasitic disease models, with one study showing enhanced efficacy against Leishmania parasites when combined with antimonial drugs[56].

Nanoparticle Systems

PLGA Nanoparticles: Biodegradable polymeric systems offering controlled release and macrophage targeting[57]

- Solid Lipid Nanoparticles: Enhanced stability and tissue-specific delivery[58]
- Chitosan-Based Systems: Natural polymer carriers with inherent antimicrobial properties[59]

Targeted Delivery Approaches

- Macrophage-Targeted Systems: Utilizing mannose receptor-mediated uptake for leishmaniasis treatment[60]
- pH-Responsive Formulations: Designed for optimal release in acidic parasitophorous vacuoles[61]
- Combination Nanocarriers: Co-encapsulation of vitamin C with conventional drugs[62]

Limitations, Safety, And Clinical Translation

Current Evidence Limitations

Preclinical Bias: The majority of available evidence derives from animal studies, which may not accurately reflect human pathophysiology and drug responses[63].

Dosage Extrapolation

Optimal human dosing remains unclear, with animal studies using widely varying concentrations that may not translate directly to clinical practice[64].

Study Design Heterogeneity

Variations in study methodologies, outcome measures, and follow-up periods limit meta-analysis possibilities[65].

Safety Considerations

Dose-Dependent Effects

Therapeutic Range

100-1000 mg daily appears safe and potentially beneficial[66]

High-Dose Risks

Doses >2000 mg daily may cause:

- Gastrointestinal disturbances (nausea, diarrhea)
- Renal calculi formation in susceptible individuals
- Pro-oxidant effects in certain disease contexts[67]

Drug Interactions

- Potential pharmacokinetic interactions with antiparasitic drugs require investigation[68]
- Iron metabolism modulation may affect concurrent iron supplementation[69]
- Warfarin interaction potential in patients requiring anticoagulation[70]
- Clinical Translation Requirements
- Regulatory Pathway:
- WHO endorsement needed for incorporation into NTD treatment guidelines[71]
- National health policy adaptations required
- Healthcare provider training and community education programs[72]

Research Priorities

- Phase II Clinical Trials: Dose-finding studies in NTD patients
- Pharmacokinetic Studies: Tissue distribution during active infection
- Drug Interaction Studies: Comprehensive interaction profiles
- Health Economics: Cost-effectiveness analyses for endemic regions[73]

Future Research Directions

Immediate Research Needs

Clinical Validation

- Randomized controlled trials in endemic populations
- Optimal dosing and timing protocols
- Safety monitoring in diverse patient populations[74]

Mechanistic Understanding

- Detailed molecular mechanisms of synergy
- Biomarker development for treatment monitoring
- Resistance prevention mechanisms[75]

Delivery System Development

- Clinical-grade nanoformulations
- Stability studies in tropical conditions
- Scalable manufacturing processes[76]

Long-term Strategic Goals

Integration into Global Health Programs:

- WHO Essential Medicine List consideration
- Integration with existing NTD control programs
- Community-based distribution models[77]

Personalized Medicine Approaches

Genetic polymorphism effects on vitamin C metabolism

- Patient stratification based on oxidative stress markers
- Precision dosing algorithms[78]

CONCLUSION

Vitamin C presents a compelling adjunctive strategy for managing neglected tropical and parasitic diseases. The accumulated preclinical evidence demonstrates its multifactorial benefits, including redox balance modulation, immune response enhancement, and synergistic effects with frontline antiparasitic agents. These properties position vitamin C as a potentially transformative, low-cost therapeutic enhancer, particularly valuable in endemic and resource-limited regions.

The evidence base reveals consistent benefits across multiple disease models: 30-60% reduction in parasitic burdens, 15-25% improvement in survival rates, and significant reduction in drug-related toxicity. Novel delivery systems, particularly liposomal and nanoparticle

formulations, offer solutions to bioavailability limitations and provide enhanced therapeutic potential.

However, critical knowledge gaps remain. The transition from promising preclinical results to clinical implementation requires rigorous human studies to validate efficacy, establish optimal dosing regimens, and confirm safety profiles. The risk of pro-oxidant effects at high doses, particularly in malaria treatment, necessitates careful dose optimization studies.

Integrating vitamin C into existing treatment paradigms may not only potentiate drug efficacy but also reduce treatment-related toxicity, contributing to more effective and patient-friendly disease management. The potential for dose reduction of toxic conventional drugs, enabled by vitamin C co-administration, could significantly improve treatment tolerability and compliance.

Future research should prioritize well-designed clinical trials in endemic regions, the development of standardized treatment protocols, and the investigation of advanced delivery systems. The ultimate goal is evidence-based integration of vitamin C into global NTD control strategies, potentially accelerating progress toward the WHO's 2030 elimination targets.

ETHICAL APPROVALS NOT APPLICABLE (REVIEW ARTICLE, NO HUMAN/ANIMAL STUDIES)

This is a literature review article and involved no human or animal studies conducted by the authors.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

No external funding was received for this review.

ACKNOWLEDGEMENT

Not Applicable

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