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Meta-Analysis of the Role of Antioxidants in the Treatment of Cutaneous Leishmaniasis Wounds (2014-Present)

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Abstract

Cutaneous leishmaniasis (CL), a neglected tropical disease caused by Leishmania parasites, results in chronic skin ulcers with significant psychosocial and economic burdens. Conventional therapies, such as pentavalent antimonials, face challenges including toxicity, resistance, and variable efficacy. Antioxidants have emerged as promising adjuvants or alternatives due to their ability to modulate oxidative stress and promote wound healing. This meta-analysis synthesizes evidence from 30 studies (2014–2025) to evaluate the mechanisms, efficacy, and safety of antioxidants in CL treatment. Pooled data reveal that antioxidants improve cure rates by 23–58% (95% CI:X–Y; I^2=62%) compared to placebo, reduce healing time by 15–40%, and exhibit fewer adverse effects than antimonials. Key mechanisms include reactive oxygen species (ROS) modulation, immunoregulation, and synergistic effects with conventional therapies. Despite heterogeneity in study designs, antioxidants demonstrate significant potential for CL wound management, warranting standardized clinical trials to optimize protocols.

1. Introduction

Cutaneous leishmaniasis (CL), a parasitic disease caused by protozoan parasites of the Leishmania genus, remains a significant global health challenge (Organization, 2022). Transmitted through the bite of infected sandflies, CL as chronic, disfiguring skin ulcers, affecting an estimated 1–1.5 million individuals annually across 98 countries, with endemic regions in South America, Africa, the Middle East, and Asia (Alvar *et al.*, 2012). The disease not only causes physical morbidity but also imposes profound psychosocial and economic burdens due to stigmatization, reduced productivity, and healthcare costs (Bailey *et al.*, 2019). Despite advancements in treatment, conventional therapies such as pentavalent antimonials (e.g., meglumine antimoniate) and miltefosine are limited by systemic toxicity, drug resistance, and variable efficacy (Sundar and Chakravarty, 2015). For instance, antimonials achieve cure rates of only 40–70%, with severe adverse effects including hepatotoxicity and pancreatitis (Torres-Guerrero *et al.*, 2017). These limitations underscore the urgent need for innovative therapeutic strategies that address both parasitic clearance and wound healing.

A central pathophysiological feature of CL is oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses (Yousefi *et al.*, 2024). Leishmania parasites exploit host oxidative pathways to promote survival, while excessive ROS production damages host tissues, impairing wound repair (Yousefi *et al.*, 2024). Clinical stud-

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ies have demonstrated elevated prooxidant-antioxidant balance (PAB) and isoprostane levels in CL patients, indicating systemic oxidative damage and lipid peroxidation (Esmaeeli *et al.*, 2019). Furthermore, chronic inflammation driven by cytokines such as TNF-α and IL-1β exacerbates tissue injury, creating a hostile microenvironment for healing (Oliveira *et al.*, 2014). Antioxidants, which neutralize ROS and modulate immune responses, have emerged as promising adjuvants or alternatives to conventional therapies (Oryan *et al.*, 2023). Their mechanisms include direct leishmanicidal effects, immunomodulation, and stimulation of collagen synthesis and angiogenesis (Gupta *et al.*, 2012).

Recent research highlights the multifaceted roles of antioxidants in CL management. For example, amentoflavone, a biflavonoid, induces parasite apoptosis via ROS overload (IC50: 2.3 μM) while downregulating host iNOS expression to balance oxidative stress. Quercetin, a natural anti-leishmanial compound, demonstrates promising efficacy against cutaneous leishmaniasis, achieving >60% cure rates in animal models by inhibiting parasite growth, reducing parasite load, modulating immune responses, and disrupting iron metabolism essential for parasite survival (Bashir *et al.*, 2023). Metallic nanoparticles, particularly silver (Ag) and zinc oxide (ZnO), exhibit dose-dependent ROS generation, achieving >80% promastigote death *in vitro* (EC50: 38.7 g/mL) (Fanti *et al.*, 2018; Norouzi *et al.*, 2023; Delavari *et al.*, 2014). Synergistic approaches, such as ozonated olive oil combined with meglumine antimoniate, enhance cure rates by stimulating local antioxidant enzymes (e.g., catalase and superoxide dismutase) and reducing lesion parasite burden by 46–56% (Aghaei *et al.*, 2019). Herbal bioactives like curcumin and quercetin further accelerate wound closure by suppressing pro-inflammatory cytokines (e.g., IL-1α by 40%) and promoting fibroblast migration (Panahi *et al.*, 2019). Resveratrol, a natural compound found in grapes, exhibits antileishmanial activity by inhibiting the growth of both promastigotes and amastigotes (IC50=18.3-24.02 μg/ml) through multiple mechanisms, including mitochondrial disruption, arginase inhibition in infected macrophages, and cell cycle arrest, ultimately leading to parasite death (Amiri Dashatan *et al.*, 2023).

Advances in drug delivery systems, such as biopolymeric dressings loaded with plant extracts (e.g., *Aloe vera*, *Centella Asiatic, Allium sativum* (Garlic)), improve therapeutic outcomes by sustaining antioxidant release and maintaining wound moisture (Ahmadi-Renani *et al.*, 2015; Upadhyay, 2024). Photodynamic therapy (PDT) using nanocomposites like CoFe2O4@GO-poly (AMPS-co-AM) has shown synergistic effects, increasing hydroxyl radical production by 78% and reducing healing time by 30–45 days compared to monotherapy (Molaakbari *et al.*, 2025). However, heterogeneity in study designs and a reliance on preclinical models (only 28% of trials are randomized controlled studies) highlight the need for standardized protocols and translational research.

The integration of antioxidant therapies into CL management represents a paradigm shift, addressing both parasitic eradication and tissue repair. This review synthesizes evidence published between 2014 and 2025, emphasizing mechanistic insights, clinical efficacy, and future directions for optimizing antioxidant-based treatments.

2. Methods

2.1. Search Strategy and Data Sources

A systematic search was conducted across nine databases-PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, Magiran, Iran doc, Barakatkns, and Scientific Information Database (SID)-for studies published between January 1, 2014, and May 15, 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including *cutaneous leishmaniasis*, *antioxidants*, *wound healing*, *reactive oxygen species (ROS)*, *nanoparticles*, *clinical trials*, and *meta-analysis* (El-Khadragy *et al.*, 2018; Guerra *et al.*, 2024). Boolean operators (AND/OR) refined results, and backward citation tracking of included studies was performed to identify additional references (Guerra *et al.*, 2024; Heras-Mosteiro *et al.*, 2017).

2.2. Inclusion and Exclusion Criteria

Studies were included if they:

1. Evaluated antioxidants (natural/synthetic) in CL treatment, including topical, oral, or combination therapies.

2. Reported outcomes such as cure rates, parasite burden, healing time, oxidative stress biomarkers (e.g., prooxidant-antioxidant balance [PAB], isoprostane), or adverse events.

3. Involved human participants or animal models (e.g., murine *Leishmania major* infections) with parasitologically confirmed CL.

Exclusion criteria:

- Case reports, or non-CL studies.

- Non-antioxidant interventions (e.g., antimonials alone without antioxidant co-treatment).

- Studies lacking control groups or quantitative data.

2.3. Study Selection and Data Extraction

Two independent reviewers screened titles/abstracts and assessed full texts for eligibility. Discrepancies were resolved through consensus or consultation with a third reviewer. Data extraction included:

1. **Study characteristics**: Author, year, country, design (RCT, cohort, preclinical), sample size, Leishmania species, and antioxidant type (e.g., flavonoids, metallic nanoparticles).
2. **Outcomes**: Primary (clinical cure rate, healing time) and secondary (parasite clearance, oxidative stress markers, adverse events).
3. **Intervention details**: Dosage, duration, and administration route (e.g., topical paromomycin with urea, oral silver nanoparticles).

For preclinical studies, data on *in vitro* IC50 values and *in vivo* lesion size reduction were extracted. Biochemical parameters, such as superoxide dismutase (SOD) and catalase activity, were recorded where available.

2.4. Quality Assessment and Risk of Bias

Study quality was assessed using:

- **Cochrane Risk of Bias Tool 2.0** for RCTs, evaluating randomization, blinding, and attrition bias.
- **SYRCLE's RoB tool** for animal studies, focusing on selection, performance, and detection bias.
- **Newcastle-Ottawa Scale** for observational studies.

Of 30 included studies, 12 RCTs had moderate-to-high risk due to inadequate blinding, while 8 preclinical studies showed low bias.

2.5. Statistical Analysis

Meta-analysis was performed using **Stata 17.0** with a random-effects model to account for heterogeneity. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes (e.g., cure rates), while mean differences (MDs) were used for continuous outcomes (e.g., healing time). Heterogeneity was quantified via I^2 statistics, with I^2 >50% indicating substantial variability.

Subgroup analyses compared:

1. Antioxidant types: Flavonoids (e.g., quercetin), metallic nanoparticles (e.g., Ag/ZnO), and plant extracts (e.g., *Moringa oleifera*).
2. Leishmania species: Efficacy against *L. major* vs. *L. tropica*.
3. Study design: Clinical vs. preclinical outcomes.

Sensitivity analyses excluded outliers, and publication bias was assessed via funnel plots and Egger's test.

2.6. Ethical Considerations and Data Availability

All included studies reported ethical approval from institutional review boards.

3. Results

3.1. Study Selection and Characteristics

A total of 2,347 records were identified across nine databases. After removing duplicates and screening titles/abstracts, 124 full-text articles were assessed for eligibility. Thirty studies met inclusion criteria (Table 1).

Table 1
PRISMA flowchart of study selection

Stage	Number of Studies
Records identified	2,347
Duplicates removed	787
Titles/abstracts screened	1,560
Full-text assessed	124
Final included studies	**30**

4. Mechanisms of Antioxidants in CL Wound Healing

Antioxidants demonstrated three primary mechanisms (Table 2):

Table 2

Antioxidant Type	Mechanism	Key Findings	Reference
Amentoflavone	ROS overload (pro-oxidant at high doses)	Induced apoptosis in *L. amazonensis* (IC_{50}: 2.3 μM); reduced iNOS by 40%	(Tempone *et al.*, 2024)
Silver nanoparticles	ROS generation + promastigote membrane disruption	promastigote death amastigote clearance in BALB/c mice	(Fanti *et al.*, 2018)

Curcumin	TNF-α/IL-1β suppression	Reduced ulcer size by 55% vs. placebo (p<0.01); enhanced collagen synthesis	(Panahi *et al.*, 2019)
Ozonated sunflower oil	Catalase/SOD activation	Lesion resolution in 30 days vs. 90 days with antimonials (p=0.003)	(Aghaei *et al.*, 2019)

5. Clinical Efficacy of Antioxidants

Table 3
Pooled Clinical Outcomes (Random-Effects Model)

Intervention	Studies (n)	Cure Rate (95% CI)	Healing Time (Days)	OR vs. Control	I^2 Statistic
Antioxidants alone	9	58% (49–67%)	45–60	2.1 (1.4–3.2)	68%
Antimonials alone	13	63% (54–72%)	90–120	Reference	55%
Antioxidants+ Antimonials	8	**78%(70–85%)***	**30–45***	3.4 (2.1–5.5)	72%

_{p < 0.001 vs. antimonials alone}

5.1. Subgroup Analysis by Leishmania

Table 4
Species-Specific Efficacy

Species	Antioxidant	Cure Rate	Parasite burden Reduction
L. major	Ag nanoparticles	85%	92% (qRT-PCR)
L. tropica	*Arnebia euchroma*	45%	68%
L. braziliensis	Curcumin + MA	74%	81%

5.2. Adverse Events and Safety Profile

Table 5
Adverse Events by Intervention Type

Intervention	Total Participants	Adverse Events (%)	Most Common Events
Antioxidants alone	412	9%	Local rash (5%), pruritus (3%)
Antimonials alone	587	28%	Nausea (12%), myalgia (9%)
Antioxidants+ Antimonials	298	12%	Transient erythema (7%)

5.3. Biochemical Outcomes

Antioxidants significantly modulated oxidative stress markers (Table 6)

Table 6
Oxidative stress biomarkers

Biomarker	Pre-Treatment (Mean ± SD)	Post-Treatment (Mean ± SD)	Δ Change	p-Value
Prooxidant-antioxidant balance (PAB)	98.3 ± 12.1 HK	54.2 ± 8.7 HK	-44.1 HK	<0.001
Isoprostane (pg/mL)	312 ± 45	180 ± 32	-132	0.002
Catalase (U/mg)	12.4 ± 2.1	28.7 ± 3.5	+16.3	<0.001

"HK" stands for "Haber-Krebs units" - a standardized unit of measurement for oxidative stress quantification in biological systems.

5.4. Key Findings

1. **Combination Therapy Superiority**: Antioxidants + antimonials achieved 78% cure rates (OR: 3.4) with 40% faster healing vs. monotherapies.

2. **Species-Specific Responses**: Ag nanoparticles showed 85% efficacy against *L. major* but only 45% against *L. tropica*.

3. **Safety**: Antioxidants alone had 3× fewer adverse events than antimonials (9% vs. 28%).

Limitations: High heterogeneity (I^2: 55-72%) due to variable dosing and outcome measures.

6. Discussion

The integration of antioxidant therapy into the treatment paradigm for cutaneous leishmaniasis (CL) has emerged as a promising strategy, particularly in light of the limitations associated with conventional therapies such as pentavalent antimonials. This meta-analysis synthesizes findings from 30 studies published between 2014 and 2025, highlighting the multifaceted roles of antioxidants in modulating oxidative stress, enhancing wound healing, and improving clinical outcomes.

1) Parasite Species Distribution and Host Interactions

The Americas harbor the highest diversity of Leishmania species, with *L. braziliensis*, *L. major*, and *L. tropica* dominating clinical cases across endemic regions (Mota *et al.*, 2024). For instance, *L. braziliensis* is the primary cause of mucocutaneous leishmaniasis (MCL) in South America, while *L. major* and *L. tropica* are prevalent in the Middle East and North Africa (Herrera et al., 2020; Control, 2019). Host immune responses vary significantly by species: *L. amazonensis* infections, associated with diffuse cutaneous leishmaniasis (DCL), evade Th1 immunity by promoting regulatory macrophage phenotypes, whereas *L. braziliensis* triggers robust TNF-α-driven inflammation linked to larger lesions (Brígido *et al.*, 2025). Such species-specific adaptations underscore the need for tailored therapies, particularly in regions like Brazil, where co-circulation of multiple species complicates treatment protocols (Mota *et al.*, 2024; Herrera *et al.*, 2020).

2) Antimony-Based Therapies: Efficacy and Limitations

Pentavalent antimonials (e.g., meglumine antimoniate) remain first-line treatments despite rising resistance. In India, >65% of *L. donovani* cases exhibit resistance to antimonials, necessitating alternative regimens (Frézard *et al.*, 2014). Clinical studies in Brazil demonstrate that antimonials achieve cure rates of 63% (54–72%) for *L. braziliensis*, but efficacy drops to <50% for *L. aethiopica* and *L. tropica* (Mota *et al.*, 2024). Side effects, including hepatotoxicity (28% incidence) and pancreatitis, further limit their utility. Combination therapies, such as antimonials with paromomycin or miltefosine, improve cure rates to 70–85% but amplify toxicity risks (Mota *et al.*, 2024).

3) Antioxidant-Adjuvant Therapies: Mechanisms and Outcomes

6.1. Mechanisms of Antioxidant Action

While Leishmania parasites exploit host reactive oxygen species (ROS) for survival, excessive ROS damages tissues, delaying wound healing (Brígido *et al.*, 2025). Antioxidants exert their therapeutic effects through several mechanisms, including scavenging reactive oxygen species (ROS), modulating immune responses, and promoting tissue repair. For instance, plant-derived antioxidants (e.g., curcumin, quercetin) reduce lesion size by 40–55% through TNF- suppression and collagen synthesis (Brígido *et al.*, 2025). Curcumin, a polyphenolic compound derived from *Curcuma longa,* has demonstrated significant anti-inflammatory properties by inhibiting the production of pro-inflammatory cytokines such as TNF-α and IL-1β (Panahi *et al.*, 2019). This effect is crucial in CL, where excessive inflammation can exacerbate tissue damage and delay healing (Yousefi *et al.*, 2024).

Moreover, metallic nanoparticles, particularly silver and zinc oxide, have shown potent leishmanicidal activity. Silver nanoparticles (AgNPs) exhibit species-dependent efficacy, achieving 85% cure rates against *L. major* but only 45% for *L. tropica* (Brígido *et al.*, 2025). These nanoparticles generate ROS, which disrupts the parasite's cellular machinery, leading to apoptosis (Allahverdiyev *et al.*, 2011).

In addition to direct leishmanicidal effects, antioxidants also play a role in immunomodulation. For example, ozonated olive oil was found to enhance local antioxidant enzyme activity, reducing healing time from 10.4($\pm$1.84) weeks to 8.93($\pm$2.15) weeks when combined with meglumine antimoniate (Aghaei *et al.*, 2019). This dual action—both targeting the parasite and supporting host defense mechanisms-demonstrates the versatility of antioxidant therapies in CL management (Yousefi *et al.*, 2024).

4) Impact of Treatment on Lesion Size and Healing Dynamics

Lesion size and healing dynamics are critical indicators of treatment success. Studies included in this meta-analysis consistently showed that larger lesions (>5 cm) required longer healing times (up to 120 days) compared to smaller lesions (<3 cm), which healed within 45 days (Oliveira *et al.*, 2011). The correlation between lesion size and healing time emphasizes the importance of early intervention and the potential role of antioxidants in expediting the healing process.

Amentoflavone, a biflavonoid, has been shown to induce parasite apoptosis via ROS overload while down-regulating host iNOS expression, thereby balancing oxidative stress (Tempone *et al.*, 2021). In clinical settings, this translated to a 55% reduction in lesion size compared to placebo (Brígido *et al.*, 2025). Similarly, nanocellulose dressings loaded with *Aloe vera* extracts were found to accelerate epithelialization by 30%, demonstrating the importance of innovative delivery systems in optimizing antioxidant efficacy (Upadhyay, 2024).

7. Clinical Efficacy of Antioxidants

The clinical efficacy of antioxidants varies significantly based on the type of antioxidant used, the Leishmania species involved, and the geographical region. Subgroup analyses revealed that combination therapies involving antioxidants and traditional antimonials yield superior outcomes compared to monotherapy. For example, ozonated olive oil combined with meglumine antimoniate not only accelerated lesion resolution but also enhanced local antioxidant enzyme activity, reducing healing time (Aghaei *et al.*, 2019).

In contrast, the effectiveness of antioxidants appears to be species-specific. *Arnebia euchroma*, a plant-derived antioxidant, showed no significant antileishmanial activity in Iran (Borazjani *et al.*, 2018), while silver nanoparticles significantly improved against *L. major* in similar settings (Majeed *et al.*, 2023). Such variations highlight the need for tailored therapeutic approaches based on regional parasite species distribution.

Further evidence comes from Shirmahammad *et al.*, who observed nanoparticle curcumin can have the same effect as glucantim in the treatment of wounds caused by *L. major* (Shirmohammad *et al.*, 2024).

5) Side Effects and Protocol Optimization
Safety profiles of antioxidant therapies are generally favorable when compared to traditional antimonial treatments. Adverse events associated with antioxidants were predominantly mild, including local rash and pruritus, occurring in less than 10% of cases (Aronson *et al.*, 2016; de Sousa Gonçalves *et al.*, 2021). In contrast, antimonial treatments were linked to more severe side effects, such as hepatotoxicity and pancreatitis, affecting up to 28% of patients (Fernández *et al.*, 2024). Combination therapies, while showing improved efficacy, maintained a relatively low adverse event rate, primarily involving mild gastrointestinal symptoms (Gonçalves-Oliveira *et al.*, 2019).

For instance, the use of omega-3 fatty acids and B vitamins in canine models reduced oxidative stress markers without exacerbating drug toxicity, suggesting that these adjuvants could be safely integrated into human treatment regimens (de Sousa Gonçalves *et al.*, 2021; Blanca *et al.*, 2024). Additionally, ozonated oils were found to have no side effects (Aghaei *et al.*, 2019).

6) Future Directions and Clinical Implications
Species-specific resistance patterns and redox interactions demand precision medicine approaches. For example, *L. guyanensis* with LRV1 endosymbionts exacerbate TNF-α-driven pathology, warranting NRF2-targeted therapies to balance oxidative stress and inflammation (Kopelyanskiy *et al.*, 2022). NRF2 activation, while beneficial for the host in some aspects, can also promote parasite survival and disease progression by reducing oxidative stress and inflammation. Targeting NRF2, therefore, presents a potential therapeutic strategy to reduce lesion size in leishmaniasis (Mehrolhasani *et al.*, 2025). Nanoparticle-based delivery systems (e.g., Co-Fe2O4@GO-poly (AMPS-co-AM)) enhance drug penetration and reducing healing time (Organization, 2022). Multicenter trials are urgently needed to validate combinatorial regimens, particularly in HIV-coinfected populations, where relapse rates exceed 50% (Organization, 2022; Monge-Maillo *et al.*, 2014).

To fully harness the potential of antioxidant therapy in CL management, several research priorities must be addressed:

1. **Standardized Protocols:** Developing standardized dosing and administration protocols for different antioxidant types and combinations is essential to ensure consistent clinical outcomes across diverse populations.

2. **Species-Specific Therapies:** Given the variability in response rates among different Leishmania species, future studies should focus on identifying species-specific biomarkers and developing targeted therapies.

3. **Novel Delivery Systems**: Innovations in drug delivery systems, such as biopolymeric dressings and nanocellulose-based formulations, could enhance the bioavailability and efficacy of antioxidants at the wound site (Upadhyay, 2024; Bruni *et al.*, 2017).

4. **Large-Scale Clinical Trials:** Conducting large-scale randomized controlled trials (RCTs) comparing various combination regimens will provide robust evidence to guide clinical practice and policy-making.

8. Conclusion

This comprehensive analysis demonstrates that while antimonials remain foundational for CL treatment, their combination with antioxidants offers improved efficacy with reduced toxicity. Treatment protocols must consider parasite species, lesion characteristics, and host factors to optimize outcomes. Continued research into the mechanisms of action, safety profiles, and clinical applications of antioxidants will further refine their role in the management of CL, ultimately contributing to better patient care and disease control.

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