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Nanocarriers: A New Paradigm for the Treatment of Cutaneous Leishmaniasis

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ABSTRACT

Background: Cutaneous leishmaniasis (CL) remains a neglected tropical disease with significant psychosocial and economic impacts, primarily affecting resource-limited regions. Current chemotherapies, including pentavalent antimonials, amphotericin B, and miltefosine, are plagued by systemic toxicity, poor bioavailability, emerging drug resistance, and inadequate targeting of intracellular *Leishmania* amastigotes within macrophages. Nanomedicine has emerged as a new strategy to overcome these limitations by repurposing existing drugs through advanced delivery systems. This review comprehensively examined the application of various nanocarrier platforms, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, and metallic nanoparticles for the treatment of CL. These systems function by leveraging passive targeting via the enhanced permeability and retention (EPR) effect at lesion sites and active targeting through innate macrophage phagocytosis. Key advantages include enhanced drug solubility, prolonged circulation, improved bioavailability, reduced systemic toxicity, and increased intracellular drug accumulation. The clinical success of liposomal amphotericin (AmBisome®) exemplifies the potential of nanomedicine, offering high efficacy with minimal nephrotoxicity. Topical applications of SLNs/NLCs show promise for non-invasive treatment, while polymeric and metallic nanoparticles enable controlled release and multimodal therapy. Despite these advancements, challenges related to scalability, regulatory approval, long-term stability, and affordability in endemic regions remain. Future directions include the development of ligand-functionalized "smart" nanoparticles, combination therapies, and plant-based nanoformulations. Nanomedicine represents a paradigm shift in CL treatment, bridging the gap between drug efficacy and clinical applicability through precision targeting and enhanced therapeutic outcomes.

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Introduction

Cutaneous leishmaniasis (CL), a disfiguring and stigmatizing skin disease caused by protozoan parasites of the *Leishmania* genus [1], represents a persistent and neglected global health challenge. Endemic primarily in tropical and subtropical regions, it places a severe burden on over 70 countries, with millions of new cases estimated annually [2]. The disease manifests as chronic skin ulcers, nodules, or plaques that, while rarely fatal, lead to permanent scarring, social exclusion, and significant psychological distress, perpetuating cycles of poverty in affected communities [3].

For decades, the clinical management of CL has relied on a limited and archaic arsenal of chemotherapeutic agents primarily pentavalent antimonials, amphotericin B, miltefosine, and paromomycin [4]. However, this standard pharmacopeia is fraught with severe and often prohibitive limitations. Treatment with pentavalent antimonials requires prolonged, painful parenteral administration and is associated with significant cardiotoxicity and hepatotoxicity [5]. The potent amphotericin B, while effective, carries a high risk of dose limiting nephrotoxicity [6]. Furthermore, the emergence and escalation of parasite resistance to first-line drugs, coupled with the inherently poor bioavailability and inadequate targeting of these therapeutics to the intracellular parasite sanctuaries within macrophages, have created a therapeutic impasse. This therapeutic challenge urgently requires innovative strategies that go beyond conventional drug design and pave the way for an effective role for nanomedicine against this ancient disease.

Nanotechnology offers a paradigm shift in this landscape, moving beyond the discovery of novel drug molecules to instead re-engineer existing anti-leishmanial agents into sophisticated, targeted delivery systems [7]. By addressing the fundamental pharmacological flaws of these drugs, the field unlocks their latent potential. The core principle involves the encapsulation of therapeutic cargo within nanoscale carriers typically ranging from 1 to 1000 nanometers [8]. These nanoparticles are expertly designed to deliver their cargo directly to infected macrophage cells while simultaneously protecting healthy tissues from exposure [9]. This targeted approach collectively achieves what conventional therapy cannot: a dramatic enhancement of therapeutic efficacy at the precise site of infection, a drastic reduction of systemic and organ-specific toxicity, and a powerful multipronged mechanism that holds immense promise for overcoming established drug resistance.

This review aimed to comprehensively analyze and synthesize the current landscape of nanomedicine as a novel therapeutic strategy for CL. It sought to to elucidate the fundamental mechanisms, including enhanced permeability and retention (EPR) at lesion sites and innate macrophage targeting, that enable nanocarriers to overcome the critical limitations of conventional chemotherapy—namely systemic toxicity, poor bioavailability, and emerging drug resistance. Furthermore, this review provides a critical evaluation of the major nanocarrier platforms: Liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, and metallic nanoparticles detailing their unique advantages, mechanisms of action, and the preclinical and clinical evidence supporting their efficacy. Finally, the study aimed to identify prevailing challenges in manufacturing, regulation, and accessibility, while outlining future research directions for the development of next-generation, smart nanotherapeutics to combat this neglected tropical disease.

Collective Strengths of Nanocarrier Systems

The superiority of nanomedicines in treating CL stems from a convergence of beneficial properties shared across different nanocarrier platforms [10]. Firstly, their minute size allows them to passively accumulate at the site of the skin lesion through the EPR effect, a phenomenon where the inflamed and leaky vasculature of the ulcer permits nanoparticles to extravasate and be retained. This localized delivery ensures a high drug concentration exactly where it is needed.

More importantly, the innate biology of the infection plays directly into the hands of nanotherapy [11]. The *Leishmania* parasite resides and multiplies inside host macrophages [12]. Nanocarriers, regardless of their specific composition, are naturally recognized and phagocytosed (engulfed) by these very same macrophages. This built-in active targeting mechanism ensures that the drug-loaded nanoparticles are delivered with exquisite precision to the primary disease reservoir, dramatically increasing intracellular drug levels and overwhelming the parasites.

Furthermore, encapsulation within a nanocarrier provides profound pharmacokinetic advantages [13]. The drug is protected from premature degradation in the bloodstream, its solubility is often enhanced (a key benefit for poorly soluble drugs, like amphotericin B), and it can be released in a controlled, sustained manner. This maintains a therapeutic concentration at the target site for extended periods, reducing dosing frequency and

improving patient compliance. Crucially, by packaging toxic drugs, nanocarriers minimize their exposure to sensitive organs, like the heart and kidneys, thereby decoupling efficacy from toxicity—a fundamental breakthrough in the treatment of CL [14] (Table 1).

A United Front of Nano Platforms Against a Common Foe

The nanomedicine arsenal against CL is diverse, with each platform contributing its unique strengths to a unified goal.

Liposomes, spherical vesicles made of phospholipid bilayers, are the most clinically advanced category [15]. Their greatest success story is liposomal amphotericin B (marketed as AmBisome®). By encasing the highly nephrotoxic amphotericin B within a lipid shell, the drug's affinity for human cholesterol is masked, preventing kidney damage [16]. Simultaneously, the liposome directs the payload to macrophage ergosterol-rich parasite membranes, making it devastatingly effective [17]. This same liposomal strategy has been successfully applied to the toxic antimonial drugs, with studies showing that nanoencapsulation can enhance their efficacy several hundredfold while completely avoiding the cardiotoxicity that plagues their conventional use.

SLNs and NLCs represent a particularly promising avenue for CL, especially for topical application [18]. Composed of biocompatible solid lipids, these systems are ideal for crafting creams or gels designed to be applied directly to skin lesions. Their lipidic nature enhances adhesion to the skin and promotes penetration into the deeper dermal layers where infected macrophages reside. Research has demonstrated that topical formulations of amphotericin B or paromomycin loaded into SLNs/NLCs achieve significantly higher cure rates in animal models than conventional ointments, which often suffer from poor skin permeability [19]. This approach promises a powerful, noninvasive, and localized treatment option that could revolutionize outpatient care.

Polymeric Nanoparticles, crafted from biodegradable materials, like PLGA, excel in providing controlled release [20]. These polymers slowly degrade within the body, providing a steady, long-term trickle of the encapsulated drug, whether it is amphotericin B, miltefosine, or others. This sustained release profile ensures continuous exposure of the parasites to therapeutic drug levels, which is crucial for achieving a complete cure and potentially mitigating the development of resistance. For a drug like miltefosine, which has teratogenic risks and gastrointestinal side effects, encapsulation could allow for lower, safer oral doses while improving targeting to macrophages.

Beyond mere drug delivery, metallic nanoparticles, particularly silver (AgNPs) and gold (AuNPs), introduce a dual mechanism of action [21]. AgNPs possess intrinsic anti leishmanial properties, capable of disrupting parasite membranes and generating lethal reactive oxygen species [22]. They can be used alone or as synergistic carriers for conventional drugs. AuNPs, easily functionalized with drugs and targeting ligands, serve as efficient and inert platforms to enhance drug delivery and cellular uptake [23].

The collective evidence from in vitro and in vivo studies presents a compelling case: nanomedicine is not merely an incremental improvement but a fundamental advancement in the treatment of CL. by collectively addressing the critical trifecta of poor targeting, high toxicity, and emerging resistance, nanocarriers have breathed new life into existing drugs [24].

The path forward, while promising, requires overcoming challenges in scalable manufacturing, regulatory approval for complex nanomedicines, and ensuring affordability and access in endemic regions. Future research will likely focus on "smart" nanocarriers with surface ligands for even more precise targeting, combinations of multiple drugs within a single nanoparticle to combat resistance, and the exploration of natural plant-derived compounds encapsulated for enhanced efficacy [25] (Table 2).

Discussion

The reviewed article compellingly argues that nanomedicine represents a paradigm shift in the treatment of CL, moving beyond incremental improvements to offer a fundamental redesign of therapeutic strategy. This discussion will expand upon the article's core themes, integrating evidence from related research to provide a critical analysis of the strengths and weaknesses of each nanocarrier system, the challenges ahead, and the future trajectory of the field.

The article correctly identifies the core failures of conventional CL chemotherapy: Systemic toxicity, poor bioavailability, and inadequate targeting. The premise that nanocarriers can collectively solve these issues is strongly supported by the literature. The concept of using nanocarriers as "Trojan horses" is particularly apt, as it encapsulates the dual strategy of passive targeting via the EPR effect and active targeting through innate mac-

Table 1. Key advantages of nanocarrier systems for treating CL

Advantage	Mechanism & Benefit
Passive targeting via EPR effect	The small size of nanoparticles allows them to accumulate at the skin lesion site through the leaky vasculature, ensuring a high local drug concentration.
Built-in active targeting	Nanocarriers are naturally phagocytosed by macrophages, the very host cells where the *Leishmania* parasite resides, delivering drugs directly to the infection reservoir.
Enhanced pharmacokinetics & safety	Encapsulation protects drugs from degradation, enhances solubility, and allows for controlled, sustained release. It also minimizes drug exposure to sensitive organs (e.g. kidneys, heart), thereby reducing toxicity.

rophage phagocytosis. As Maeda emphasize, the EPR effect, while sometimes debated in oncology, is highly relevant to the inflamed, vascularized microenvironment of CL lesions, ensuring preferential nanoparticle accumulation [26, 27].

The assertion that this approach "decouples efficacy from toxicity" is the cornerstone of the nanomedicine argument for CL. This is not merely theoretical; it is clinically validated by the success of liposomal amphotericin B (AmBisome®). The article accurately highlights its role as a landmark achievement. Studies have consistently shown that AmBisome® achieves high cure rates in CL, including in cases refractory to antimonials, with a dramatically improved safety profile, effectively eliminating the nephrotoxicity associated with conventional amphotericin B deoxycholate [28]. This single product validates the entire nanomedicine approach for parasitic diseases.

Critical analysis of nanocarrier platforms

Liposomes: As stated, they are the most clinically advanced platform. Their biocompatibility (composed of natural phospholipids and cholesterol) and ability to encapsulate both hydrophilic (in the aqueous core) and hydrophobic (within the lipid bilayer) drugs are major advantages [29]. The success with antimonials, as referenced, is notable. For instance, Doroud et al. demonstrated that liposome-encapsulated meglumine antimoniate was over 700 times more effective than the free drug in a murine model of CL [30]. Long-term stability can be an issue, with potential for drug leakage and phospholipid degradation upon storage (fusion, aggregation, and hydrolysis). Scalability and cost of good manufacturing practice (GMP) production remain significant hurdles for wider application beyond AmBisome®. Their relatively rapid clearance by the mononuclear phagocyte system (MPS) can sometimes limit circulation time, though this is an advantage for macrophage-targeted diseases, like CL.

SLNs & NLCs: This article correctly identified their immense promise for topical therapy. Their solid matrix provides superior stability compared to liposomes and allows for controlled drug release. Their occlusive effect on the skin enhances hydration and drug penetration, a key factor for treating skin lesions. Pinto et al. showed that paromomycin-loaded NLCs in a gel formulation significantly enhanced drug penetration into the skin layers and improved efficacy against *L. major* in mice compared to a free drug solution [31]. A potential drawback is low drug loading capacity due to the crystalline structure of the solid lipid. Drug expulsion can occur during storage as the lipid matrix undergoes polymorphic transitions. The feasibility of large scale production using high pressure homogenization is established, but ensuring batch-to-batch reproducibility of particle size and drug encapsulation efficiency remains a critical challenge for translation.

Polymeric nanoparticles (e.g. PLGA): This article accurately highlights their excellence in providing sustained and controlled release, thanks to the tunable degradation rate of polymers, like PLGA. This is crucial for maintaining therapeutic drug levels within macrophages over days or weeks, reducing dosing frequency. This platform is highly versatile for surface functionalization (e.g. with ligands, like mannose to actively target macrophage mannose receptors). For instance, mannosylated PLGA nanoparticles loaded with amphotericin B showed significantly higher uptake in macrophages and superior anti leishmanial activity compared to non-targeted particles [32]. The potential cytotoxicity of polymer degradation products is a concern that requires thorough investigation. Although PLGA is approved by the US Food and Drug Administration (FDA), the safety profile of its acidic monomers (lactic and glycolic acid) at the high local concentrations achieved by degrading nanoparticles must be monitored. Furthermore, the synthesis process often involves organic solvents, which must be completely removed to meet regulatory standards, complicating scalable production.

Table 2. Nano platforms used in the treatment of CL

Nano Platform	Key Features & Applications
Liposomes	- Spherical phospholipid vesicles; the most clinically advanced. - Example: Liposomal amphotericin B (AmBisome®) masks drug toxicity and targets macrophage parasites. - Can be applied to antimonial drugs, enhancing efficacy and avoiding cardiotoxicity.
SLNs/NLCs	- Composed of biocompatible solid lipids; ideal for topical creams/gels. - Enhance skin adhesion and penetration to reach infected dermal layers. - Topical formulations (e.g. amphotericin B, paromomycin) show higher cure rates than conventional ointments.
Polymeric nanoparticles	- Crafted from biodegradable materials (e.g. PLGA). - Excel in providing controlled, sustained drug release for long-term therapy. - Can encapsulate drugs, like miltefosine to potentially lower doses and reduce side effects.
Metallic nanoparticles	- Introduce a dual mechanism of action. - Silver Nanoparticles (AgNPs): Have intrinsic anti-leishmanial properties (disrupt membranes and generate ROS). - Gold nanoparticles (AuNPs): Serve as inert, efficient platforms that can be functionalized with drugs and targeting ligands.

Metallic nanoparticles (silver & gold): This study correctly notes their dual mechanism of action. AgNPs have demonstrated potent intrinsic leishmanicidal activity by disrupting mitochondrial function and generating ROS [33]. AuNPs are excellent, inert platforms for functionalization. This platform carries the greatest regulatory and safety concerns. The long-term biodistribution, potential for accumulation in organs, and chronic toxicity of metallic ions (especially silver) are poorly understood and represent major barriers to clinical translation [14]. The synthesis must be meticulously controlled to ensure precise size, shape, and monodispersity, as these factors heavily influence biological activity and toxicity. Their potential environmental impact also requires consideration.

Regulatory agencies, like the FDA and European Medicines Agency (EMA) have frameworks for nanomedicines, but the complexity of characterizing nanoparticles (size distribution, surface charge, drug release kinetics, and stability) makes the approval process more demanding than for conventional drugs. Demonstrating equivalence between batches is particularly challenging.

Access and Affordability: The core burden of CL lies in low resource settings. The high cost of AmBisome®, while justified by its production complexity, limits its use in endemic regions. Future development must prioritize cost-effective synthesis using scalable techniques, such as microfluidics, and locally sourced, affordable materials to ensure equitable access. The future directions outlined are appropriate. “Smart” nanocarriers with stimuli-responsive release (e.g. pH-sensitive release in the phagolysosome) are an active area of research [34]. Combination therapy within a single nanoparticle (e.g. co-delivering a chemotherapeutic agent and an immunomodulator) holds immense promise for synergistic effects and overcoming resistance, as suggested by this article.

Challenges and potential drawbacks of nanocarrier systems

While nanocarriers offer a revolutionary approach to treating CL, it is imperative to acknowledge and address their potential drawbacks and inherent risks. A primary concern is the toxicity of nanocarrier components themselves. For instance, cationic lipids or polymers, while enhancing cellular uptake, can induce cytotoxic effects and inflammatory responses by disrupting cell membranes [35]. The long-term fate and potential organ accumulation of non-biodegradable components, particularly in metallic nanoparticles, like silver (AgNPs) and gold (AuNPs), raise significant safety concerns. Chronic exposure to AgNPs has been linked to hepatotoxicity and bioaccumulation, necessitating rigorous toxicological profiling [36].

Furthermore, the very mechanism that enables targeted delivery—recognition and uptake by the MPS—can also be a limitation. Rapid clearance of nanocarriers by the liver and spleen can reduce their circulation time and bioavailability at the target site, potentially diminishing therapeutic efficacy [37]. The complexity of large-scale manufacturing presents another significant hurdle. Ensuring batch-to-batch reproducibility in terms of particle size, polydispersity index, drug loading efficiency, and sterility is far more challenging and costly than for conventional drugs, which can impact both regulatory approval and final product affordability [38]. Finally, despite their targeting capabilities, off-target effects and unpredictable immune reactions, such complement activation-related

pseudoallergy (CARPA), have been reported with some liposomal formulations, underscoring the need for comprehensive preclinical safety evaluation [39].

Addressing these challenges is paramount for the successful clinical translation of nanomedicines for CL. Future work must focus on optimizing the biocompatibility and biodegradability of materials, developing strategies to evade MPS clearance and establishing scalable, cost-effective GMP production processes to ensure these advanced therapies can reach the endemic regions that need them most.

Limitations in study designs

Many in vitro studies utilize promastigotes or axenic amastigotes, which do not fully replicate the intracellular environment within human macrophages. Furthermore, most in vivo studies employ rodent models infected with a single *Leishmania* species, which may not accurately reflect the complex immune response and variable pathology seen in human CL caused by different species. Variable and Incomplete Efficacy in Humans: The clinical efficacy of nanocarriers in human CL, outside of liposomal amphotericin B, remains variable and often incompletely characterized. While AmBisome® has set a high benchmark, results for other nanoformulations have been mixed. For instance, topical paromomycin formulations, even in nanocarriers, like SLNs, have shown variable cure rates in clinical trials, often influenced by factors, such as lesion chronicity, parasite species, and patient immune status [40]. This variability highlights that nanocarriers are not a universal panacea; their success depends on optimizing the formulation for the specific clinical presentation of CL. Furthermore, many clinical reports focus on short-term cure rates, with long-term follow-up data on relapse and scar quality remaining scarce for most emerging nanotherapies.

Critical unresolved challenges: Beyond the challenges of manufacturing and cost, several critical scientific and safety hurdles remain inadequately solved. The long-term biodistribution and chronic toxicity of many nanocarrier components, particularly non-biodegradable polymers and metallic nanoparticles, are poorly understood. The potential for off-target accumulation in organs, like the liver and spleen, even with targeting ligands, raises concerns about delayed adverse effects. Moreover, the propensity of some nanocarriers to activate the complement system (e.g. CARPA reaction) or induce a pro-inflammatory response can undermine their safety profile [41]. Finally, the regulatory pathway for these complex products is still maturing. Demonstrating rigorous characterization, batch-to-batch consistency, and the absence of novel, nanoparticle-specific toxicities presents a formidable barrier that has slowed the clinical advancement of many otherwise promising nanoformulations [42].

Conclusion

In conclusion, nanocarriers present a promising alternative strategy for the treatment of CL, offering potential solutions to key limitations of conventional drugs, such as systemic toxicity, poor bioavailability, and insufficient targeting of intracellular parasites. By repurposing existing therapeutics within platforms, like liposomes, lipid nanoparticles, and polymeric nanoparticles, this approach aims to enhance drug delivery through passive accumulation at lesion sites and innate uptake by infected macrophages. The clinical success of liposomal amphotericin B provides a compelling proof of concept for the potential of this strategy. However, the translation of nanomedicine from promising concept to widespread clinical reality faces considerable challenges. Issues of scalable manufacturing, long-term stability, regulatory pathways for complex formulations, and ultimate affordability in endemic regions remain significant hurdles. Future research efforts will be crucial to address these barriers and to further explore the development of targeted ligand-functionalized systems, combination therapies, and plant-based nanoformulations. While substantial work remains, nanomedicine offers a valuable and evolving approach that could contribute to more effective and accessible treatments for CL.

Ethical Considerations

Compliance with ethical guidelines

This article is a review paper with no human or animal sample.

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Authors contribution's

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Conflict of interest

The authors declared no conflict of interest.

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