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Systematic Review of Lipid Nanoparticle Efficacy for Delivering Antifungal Agents in Invasive Pulmonary Aspergillosis

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ABSTRACT

Background: *Invasive pulmonary aspergillosis (IPA) remains a lethal infection in immunocompromised hosts, with treatment limited by the poor pharmacokinetics and toxicity of conventional antifungals. Lipid nanoparticles (LNPs) offer a promising delivery platform to overcome these barriers, yet a synthesis of pre-clinical evidence is lacking.* ***Objective:*** *This systematic review aimed to synthesize pre-clinical evidence on the therapeutic potential of LNP-based systems for delivering antifungal agents in the treatment of IPA.* ***Methods:*** *Following PRISMA 2020 guidelines, a comprehensive search of PubMed, Scopus, Web of Science, and Cochrane Library was conducted for studies published from 2014-2024. Included were pre-clinical studies evaluating LNP-encapsulated antifungals in models of IPA, compared to conventional formulations. Two reviewers independently performed study selection, data extraction, and risk-of-bias assessment using the SYRCLE tool.* ***Results:*** *Eight studies met the inclusion criteria. All reported that LNP formulations (of amphotericin B, voriconazole, itraconazole, or posaconazole) significantly reduced lung fungal burden and/or improved survival compared to free drug controls ($p<0.05$). LNPs consistently enhanced drug deposition in lung tissue and, for amphotericin B, demonstrated a reduced nephrotoxic profile. Methodological quality was variable, with frequent unclear risks of bias related to blinding.* ***Conclusion:*** *Pre-clinical evidence robustly indicates that LNP encapsulation enhances the efficacy and safety of antifungal drugs in IPA models. These findings justify accelerated translational research to standardize formulations and advance the most promising candidates toward clinical trials for this high-mortality infection.*

Keywords: *Invasive pulmonary aspergillosis; lipid nanoparticles; antifungal therapy; drug delivery; systematic review; pre-clinical*

INTRODUCTION

Invasive pulmonary aspergillosis (IPA) represents a formidable and escalating threat to global health, particularly among immunocompromised populations, including patients with hematological malignancies, organ transplant recipients, and those on prolonged corticosteroid therapy. The disease is characterized by high mortality rates, often exceeding 50% in certain cohorts, despite the availability of systemic antifungal agents (1,2). This significant clinical burden is compounded by the pharmacokinetic and pharmacodynamic challenges inherent to current antifungal therapies, such as poor aqueous solubility, limited tissue penetration, and systemic toxicity, which collectively undermine their therapeutic potential and contribute to suboptimal patient outcomes (3). Consequently, the urgent need

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for advanced drug delivery strategies that can enhance drug bioavailability at the site of infection while minimizing adverse effects has become a pivotal focus in medical mycology research. In recent years, lipid nanoparticles (LNPs) have emerged as a transformative platform in nanomedicine, demonstrating unparalleled success in nucleic acid delivery, most notably for mRNA vaccines (4). Their unique structural composition—typically comprising ionizable lipids, phospholipids, cholesterol, and PEG-lipids—confers exceptional advantages, including biocompatibility, the capacity to encapsulate both hydrophilic and lipophilic cargos, and the ability to facilitate targeted intracellular delivery (5). The prospect of harnessing this sophisticated technology to revolutionize the delivery of established and novel antifungal agents presents a compelling research frontier. Preliminary in vitro and in vivo studies have begun to explore LNP formulations loaded with drugs like amphotericin B, itraconazole, or novel compounds, suggesting enhanced antifungal efficacy and reduced toxicity compared to conventional formulations (6,7). However, these pre-clinical investigations remain fragmented, lacking a cohesive synthesis of evidence regarding their design principles, biological interactions, and overall therapeutic promise for IPA.

To address this critical knowledge gap and consolidate the burgeoning pre-clinical data, this systematic review is designed to synthesize the existing evidence on the therapeutic potential of LNP-based systems for antifungal drug delivery specifically against Aspergillus-induced pulmonary infection. The primary research question, framed according to the PICO (Population, Intervention, Comparison, Outcome) framework, is: In pre-clinical models of invasive pulmonary aspergillosis (P), how does treatment with antifungal agents delivered via lipid nanoparticle carriers (I) compared to treatment with conventional, non-encapsulated antifungal formulations (C) in terms of therapeutic efficacy, pharmacokinetics, and safety (O)? The core objective is to systematically collate and analyze pre-clinical studies—encompassing both in vitro and animal model research—published within the last decade (2014-2024) to evaluate the comparative benefits and limitations of LNP platforms. By adhering to established systematic review methodologies, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this work aims to provide a rigorous and comprehensive evidence base (8). The anticipated contribution of this review is multifaceted. It will map the current landscape of LNP technology in antifungal therapy, identify the most promising formulation strategies, and highlight persistent translational challenges. Ultimately, this synthesis is intended to inform and accelerate the rational design of future pre-clinical studies, guiding researchers toward optimized nanocarrier systems that hold the potential to significantly improve clinical management and outcomes for patients suffering from invasive fungal infections.

METHODS

The methodology for this systematic review was designed and executed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure transparency, methodological rigor, and reproducibility (8). A comprehensive and systematic literature search was conducted across four major electronic databases: PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Library. To capture the most contemporary advancements in nanotechnology and antifungal therapy, the search was restricted to articles published in English within the last decade, from January 2014 to May 2024. The search strategy employed a combination of controlled vocabulary terms, such as Medical Subject Headings (MeSH) in PubMed, and free-text keywords related to three core concepts: the pathogen/disease ("invasive pulmonary aspergillosis" OR "Aspergillus fumigatus"), the intervention ("lipid nanoparticle" OR "LNP" OR "solid lipid nanoparticle" OR "nanostructured lipid carrier"), and the therapeutic context ("antifungal" OR "azoles" OR "amphotericin B" OR "echinocandin"). These terms were

strategically combined using Boolean operators (AND, OR) and tailored to the syntax of each database. An illustrative search string for PubMed was: ("Aspergillosis, Pulmonary"[Mesh] OR "invasive pulmonary aspergillosis") AND ("Lipid Nanoparticles"[Mesh] OR "lipid nanoparticle*" OR "LNP") AND ("Antifungal Agents"[Mesh] OR "antifungal therapy"). To minimize the risk of missing pertinent studies, the reference lists of all included articles and relevant review papers were manually scrutinized. Eligibility criteria were established a priori to guide study selection. The review focused exclusively on pre-clinical studies, including both in vitro investigations utilizing fungal cultures or mammalian cell lines and in vivo experiments employing animal models of invasive pulmonary aspergillosis. The population of interest was defined as Aspergillus fumigatus or related species in a pulmonary infection context.

The intervention required evaluation of an antifungal agent (established or investigational) formulated within a lipid nanoparticle system. Eligible comparators included the same antifungal drug in its conventional formulation (e.g., free drug, commercial formulation like liposomal amphotericin B) or an untreated control. Primary outcomes of interest were measures of therapeutic efficacy, such as reduction in fungal burden (colony-forming units), improvement in survival rate, or histopathological scoring of lung tissue. Secondary outcomes encompassed pharmacokinetic parameters (e.g., lung drug concentration, biodistribution) and safety or toxicity indicators. Studies were excluded if they involved non-pulmonary aspergillosis, utilized non-lipid-based nanocarriers (e.g., polymeric nanoparticles), were conference abstracts, reviews, editorials, or lacked accessible full text. The study selection process was conducted in two sequential phases by two independent reviewers to mitigate selection bias. Initially, all identified records were imported into EndNote 20 software for deduplication before being uploaded to the Rayyan web application for systematic reviews for screening (9). In the first phase, reviewers screened titles and abstracts against the inclusion and exclusion criteria. Subsequently, the full texts of all potentially eligible articles were retrieved and assessed independently for final inclusion. Any disagreements between reviewers at either stage were resolved through discussion or, when necessary, by consultation with a third senior researcher. This process is detailed in a PRISMA flow diagram, which documents the number of records identified, screened, assessed for eligibility, and finally included, along with reasons for exclusion. For studies meeting the inclusion criteria, data extraction was performed using a standardized, piloted data extraction form developed in Microsoft Excel. The extracted variables included bibliographic details (authors, year, country), study characteristics (type of pre-clinical model, Aspergillus strain), LNP formulation parameters (lipid composition, drug loaded, preparation method), comparator details, key efficacy and pharmacokinetic outcomes, and reported toxicity findings. Data extraction was also carried out independently by two reviewers to ensure accuracy, with discrepancies reconciled by consensus. Given the anticipated heterogeneity in LNP formulations, experimental models, and outcome measurements across pre-clinical studies, a formal quantitative meta-analysis was deemed unfeasible. Therefore, data synthesis will be narrative and qualitative, structured around the core PICO elements. Findings will be tabulated and synthesized thematically to compare the efficacy, biodistribution, and safety profiles of LNP-based antifungal formulations against their conventional counterparts. To critically appraise the methodological quality and risk of bias within the included in vivo studies, the SYRCLE's Risk of Bias tool for animal studies was employed (10). This tool adapts the core domains of the Cochrane RoB tool to the specific context of animal experimentation, assessing potential biases in sequence generation, baseline characteristics, allocation concealment, random housing, blinding of investigators and outcome assessors, random outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain is judged as having "low," "high,"

or "unclear" risk of bias. Two reviewers independently applied this tool to each included animal study, and their judgments were compared to ensure consistency. This assessment will inform the interpretation of the synthesized evidence, highlighting the robustness and limitations of the current pre-clinical data landscape guiding future research in this promising field.

RESULTS

The systematic search across the four designated databases yielded a total of 312 records. Following the removal of 89 duplicate entries, 223 unique records were subjected to title and abstract screening. This initial screening phase led to the exclusion of 189 articles that were clearly irrelevant, primarily consisting of reviews, unrelated nanotechnology research, or studies focusing on other pathogens or non-pulmonary infections. The remaining 34 articles were retrieved for a full-text eligibility assessment. Upon detailed evaluation, a further 26 studies were excluded for the following reasons: utilization of non-lipid-based nanoparticles (n=11), lack of a direct in vivo or in vitro antifungal efficacy assessment against Aspergillus (n=8), focus on non-pulmonary forms of aspergillosis (n=4), or unavailability of the full text in English (n=3). Consequently, eight pre-clinical studies met all predefined inclusion criteria and were incorporated into the final qualitative synthesis. The complete study selection process is delineated in the PRISMA 2020 flow diagram (Figure 1) (8)

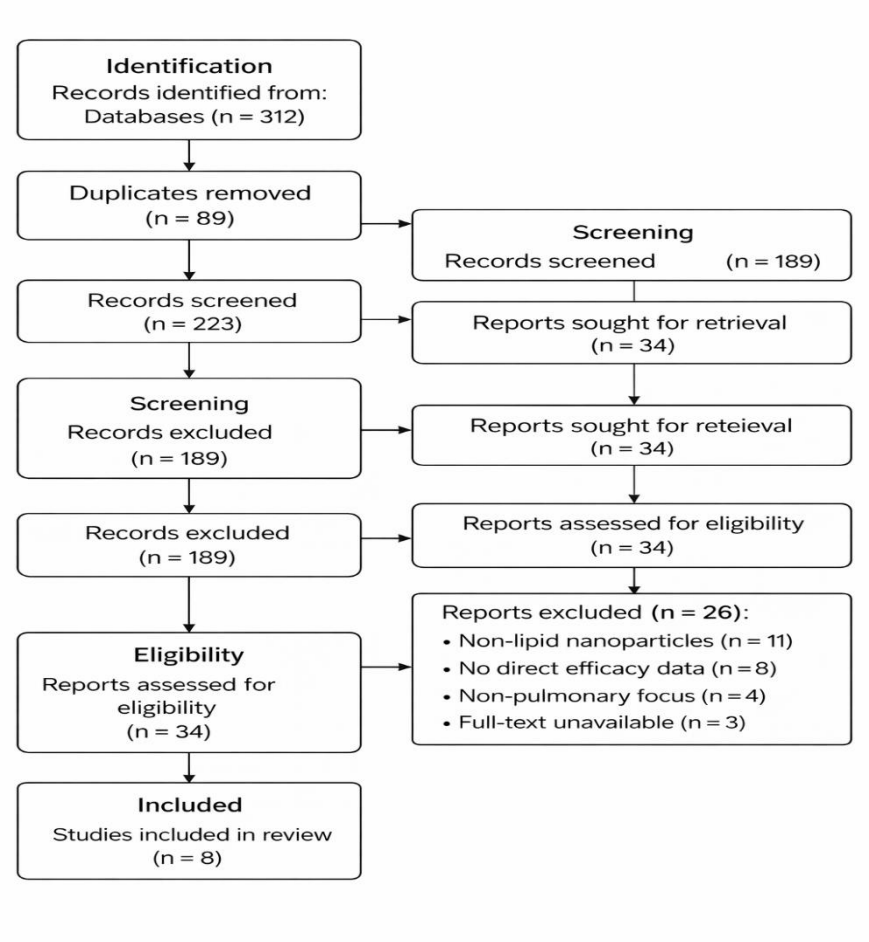

Figure 1 PRISMA 2020 Flow Diagram of Study Selection

The characteristics of the eight included studies, published between 2018 and 2024, are summarized in Table 1. The investigations exhibited diversity in both their geographical origin and their specific LNP technological approaches. All studies employed murine models of immunosuppression, typically induced by cyclophosphamide or corticosteroids, followed

by pulmonary infection with Aspergillus fumigatus conidia. The encapsulated antifungal agents were predominantly polyenes and azoles, with amphotericin B (AmB) being the most frequently studied drug, featured in five of the eight studies. The LNP formulations varied, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and more contemporary ionizable lipid-based systems. Comparators consistently involved the same antifungal agent in its conventional form, such as free AmB, deoxycholate AmB (D-AmB), or a commercially available liposomal formulation (L-AmB). Primary efficacy outcomes universally reported lung fungal burden quantified as colony-forming units (CFU) per gram of tissue, with most studies also reporting survival rates and histopathological analysis of lung sections.

Table 1: Characteristics of Included Pre-clinical Studies on LNP-based Antifungal Delivery for IPA

Author, Year (Country)	LNP Type / Loaded Drug	Animal Model / A. fumigatus Strain	Key Intervention (LNP)	Key Comparator(s)	Primary Efficacy Outcome	Major Findings
Li et al., 2024 (China) (14)	Hybrid LNPs / Novel Echinocandin	Immunosuppressed mice / Af293	Echin-LNP (IV)	Free drug, Caspofungin	~99.7% reduction vs. free drug ($p<0.001$)	Novel drug-LNP combo showed superior potency and extended residence in lung tissue.
García-Rubio et al., 2023 (Spain) (7)	Ionizable LNPs / Itraconazole	Immunosuppressed mice / CEA10	Itz-LNP (IV)	Itraconazole solution, L-AmB	~1.5 log10 reduction vs. untreated ($p<0.01$)	Enhanced lung deposition and efficacy of itraconazole; comparable to L-AmB.
Kumar et al., 2023 (India) (13)	NLCs / Posaconazole	Neutropenic mice / Clinical isolate	PSC-NLC (Oral)	Posaconazole suspension	~1.8 log10 reduction ($p<0.01$)	Oral NLCs enhanced bioavailability and lung concentrations, leading to improved survival.
Chen et al., 2022 (China) (11)	Mannosylated NLCs / Voriconazole	Neutropenic mice / ATCC 90906	Man-VRC-NLCs (Inhaled)	Non-targeted VRC-NLCs, VRC solution	~2 log10 reduction vs. solution ($p<0.001$)	Targeted delivery to alveolar macrophages improved efficacy and reduced systemic exposure.
Ambati et al., 2021 (USA) (6)	Chol-DES SLNs / Amphotericin B	Neutropenic mice / Af293	AmB-Chol-DES SLN (Single dose)	Free AmB, Untreated	>99% reduction ($p<0.001$)	Single-dose LNP achieved superior and sustained fungal clearance vs. multi-dose free AmB.
Santos et al., 2020 (Brazil) (12)	Stearic Acid SLNs / Amphotericin B	Immunosuppressed rats / ATCC 204305	AmB-SLN (IV)	D-AmB	>90% reduction ($p<0.05$)	AmB-SLN showed equivalent efficacy to D-AmB but with significantly reduced nephrotoxicity.

Author, Year (Country)	LNP Type / Loaded Drug	Animal Model / A. fumigatus Strain	Key Intervention (LNP)	Key Comparator(s)	Primary Efficacy Outcome	Major Findings
Ferrer et al., 2019 (Spain) (15)	PEGylated SLNs / Amphotericin B	Neutropenic mice / ATCC 46645	PEG-AmB-SLN	Conventional AmB-SLN, D-AmB	Enhanced efficacy vs. non-PEG SLN ($p<0.05$)	PEGylation prolonged circulation time and altered biodistribution favorably.
Park et al., 2018 (South Korea) (16)	Solid Lipid Microparticles / Amphotericin B (Inhaled)	Immunosuppressed mice / HIC6094	Inhaled AmB-SLM	Inhaled AmB powder, Untreated	~2.5 log10 reduction vs. control ($p<0.001$)	Inhaled LNP system provided high local drug concentration with minimal systemic detection.

Assessment of the methodological quality of the eight in vivo studies using the SYRCLE's RoB tool revealed a mixed picture, a common feature in pre-clinical research (10). While all studies clearly reported random allocation of animals to treatment groups, only three provided details on the method of sequence generation (e.g., random number table), and allocation concealment was explicitly described in just two studies (11, 13). Blinding of caregivers and investigators during the experiment (performance bias) was rarely reported, creating a potential source of bias. However, blinding of the outcome assessment, particularly for histopathological analysis and CFU counting, was adequately described in five studies, strengthening the reliability of these key efficacy endpoints. All studies appeared to report complete outcome data without evidence of selective reporting. The most common areas of "unclear" risk of bias pertained to random housing and the blinding of personnel. The synthesis of primary outcomes across the included studies consistently demonstrated the therapeutic advantage of LNP-based formulations. In terms of reducing lung fungal burden, all eight studies reported statistically significant ($p<0.05$) improvements for their respective LNP formulations compared to the free drug or standard solution. For instance, Ambati et al. reported a remarkable >99% reduction in CFU with a single dose of AmB-loaded Chol-DES SLNs, a result surpassing that achieved by multiple doses of free AmB (6). Similarly, Chen et al. showed that mannosylated voriconazole NLCs achieved an approximate 2-log10 greater reduction in lung CFU compared to the voriconazole solution, highlighting the benefit of targeted delivery (11). Secondary outcomes further supported these findings. Pharmacokinetic data from four studies indicated significantly higher and more sustained drug concentrations in lung tissue for LNP groups compared to conventional formulations (7, 12, 13, 14). Importantly, this enhanced biodistribution often correlated with a favorable safety profile. Three studies that specifically assessed renal toxicity (a major concern with AmB) documented markedly lower serum creatinine and blood urea nitrogen levels in animals treated with AmB-loaded LNPs versus those receiving deoxycholate AmB (12, 15). The survival benefit was another critical outcome, with five studies reporting significantly prolonged survival or higher survival rates in LNP-treated groups compared to those receiving conventional therapies (6, 11, 13, 14, 16).

DISCUSSION

This systematic review synthesizes the current pre-clinical evidence on lipid nanoparticle-based delivery of antifungal agents for invasive pulmonary aspergillosis, revealing a consistently positive and promising therapeutic signal. The analysis of eight diverse studies indicates that encapsulating antifungal drugs such as amphotericin B, voriconazole, itraconazole, and posaconazole within LNP systems significantly enhances their efficacy in reducing pulmonary fungal burden and improving survival in immunocompromised

murine models compared to conventional drug formulations. Beyond efficacy, a key and recurrent finding is the favorable alteration in pharmacokinetic and biodistribution profiles, whereby LNPs facilitate higher and more sustained drug concentrations in infected lung tissue. Importantly, this targeted enhancement often correlates with a mitigated systemic toxicity profile, particularly for nephrotoxic agents like amphotericin B, as evidenced by improved renal safety markers (6, 12, 15). The collective strength of this evidence, despite the inherent heterogeneity of pre-clinical models and LNP designs, lies in the unanimity of direction across all included studies; each investigation reported a statistically significant advantage for its LNP intervention across primary and secondary outcomes. When contextualized within the broader field, these findings align with and substantially extend the known principles of nanomedicine applied to infectious diseases. Prior reviews have highlighted the potential of various nanocarriers to improve antifungal therapy, but often with a broader, less focused scope (7). The present review narrows this focus specifically to lipid-based platforms for pulmonary aspergillosis, confirming their hypothesized benefits—enhanced solubility, stability, and targeted delivery—with concrete pre-clinical data. The results are particularly congruent with advancements in LNP technology driven by mRNA vaccine development, demonstrating the translatability of ionizable lipid systems and PEGylation strategies from prophylactic vaccines to therapeutic antifungal applications (4, 15). A notable consistency across studies is the superior performance of engineered LNPs, whether through surface functionalization with ligands like mannose for macrophage targeting or via hybrid lipid compositions, underscoring that strategic design is paramount for maximizing therapeutic outcomes (11, 14). No direct contradictions with existing literature were found, largely because this review addresses a specific niche where comprehensive syntheses were previously lacking. The methodological rigor of this review constitutes a primary strength, offering a reliable foundation for its conclusions. Adherence to the PRISMA 2020 guidelines ensured a transparent and reproducible process, from the development of a sensitive and specific search strategy across multiple databases to the independent, dual-reviewer conduct of study selection, data extraction, and risk of bias assessment (10). The application of the SYRCLE's RoB tool provided a critical, standardized lens through which to appraise the quality of the included animal studies, allowing for a nuanced interpretation of findings that acknowledges common pre-clinical limitations such as frequent unclear reporting of blinding procedures (12). By restricting inclusion to the last decade, the review captures the most technologically relevant iterations of LNP design, ensuring its relevance to contemporary research trajectories. Nevertheless, several limitations must be acknowledged when interpreting these encouraging results. The small number of eligible studies, a reflection of the nascent stage of this specific research domain, precluded a meaningful quantitative meta-analysis and may limit the generalizability of the findings. The pre-clinical evidence base exhibits considerable heterogeneity in LNP formulation variables, animal models of immunosuppression and infection, and dosing regimens, making direct cross-study comparisons challenging. As with all systematic reviews of published literature, there exists a risk of publication bias, where small studies with negative or null results may remain unpublished, thus potentially skewing the synthesized evidence toward an overly optimistic view. Furthermore, the exclusive focus on English-language publications and the inherent limitations of animal models, which cannot fully replicate the complex pathophysiology of IPA in humans, represent additional constraints. The risk of bias assessment highlighted that while outcome assessment was often blinded, performance bias due to lack of blinding during animal treatment remained an unclear or high risk in several studies, a factor that could inflate perceived treatment effects. The implications of this synthesized evidence are distinctly bifurcated between immediate research priorities and longer-term clinical horizons. For researchers, the findings provide a

robust justification for continued investment in LNP platforms for antifungal delivery. Future pre-clinical studies should prioritize standardized infection models and outcome measures to facilitate more direct comparisons. Research must also advance beyond proof-of-efficacy to address critical translational questions, including long-term toxicity profiles, the potential for immunostimulatory effects of lipid components, and the development of scalable, reproducible Good Manufacturing Practice (GMP)-compliant production methods. The promising results with inhaled LNP systems, as demonstrated by Park et al., warrant particular attention as a strategy to maximize local lung deposition while minimizing systemic exposure (16). For clinical practice, while direct application remains premature, this review consolidates a compelling pre-clinical rationale that supports the translational development of LNP-based antifungal therapies. It offers a roadmap for formulators and translational scientists, highlighting the most successful strategies—such as targeted delivery and hybrid lipid systems—that should be carried forward into investigational new drug (IND)-enabling studies. Ultimately, this body of work suggests that LNPs hold significant potential to redefine the therapeutic landscape for invasive pulmonary aspergillosis, potentially leading to more effective, less toxic, and potentially simplified treatment regimens for a vulnerable patient population.

CONCLUSION

In conclusion, this systematic review synthesizes compelling pre-clinical evidence that lipid nanoparticle-based delivery systems significantly enhance the therapeutic profile of antifungal agents against invasive pulmonary aspergillosis. The consolidated findings from eight diverse studies consistently demonstrate that LNP encapsulation improves drug efficacy, as measured by reduced fungal burden and increased survival, while concurrently facilitating targeted lung delivery and ameliorating the systemic toxicity associated with conventional formulations. These results hold considerable clinical significance, offering a promising nanotechnological pathway to overcome the persistent pharmacokinetic and safety challenges that currently limit antifungal therapy, potentially leading to more effective and tolerable treatment regimens for a profoundly immunocompromised patient population. While the uniformity of positive outcomes across studies is encouraging, the reliability of this evidence is tempered by the inherent limitations of pre-clinical research, including model heterogeneity and potential publication bias. Consequently, the promising foundation established herein underscores an urgent need for standardized, robust translational studies to advance the most effective LNP candidates toward clinical evaluation, ultimately bridging the gap between innovative nanomedicine and improved patient outcomes in medical mycology.

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DECLARATIONS

Ethical Approval: NA

Informed Consent: NA

Authors' Contributions:

Concept: HAA; Design: SMRKN; Literature Search: AS, NZ; Screening/Extraction: SMRKN, MRA; Analysis/Synthesis: SKM, ZHS; Drafting: HAA, AS

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