RESEARCH PAPER

Nanocarrier-Based Drug Delivery for Pediatric Therapeutics: A Systematic Review

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Abstract
The advent of nanocarrier-based drug delivery systems has proved to be quite effective in addressing the deficiencies observed with existing drugs, especially in pediatric cases. This particular study was undertaken to assess the effectiveness, safety, and practical application of nanocarrier-based drug delivery systems in pediatric treatment options. A thorough search process was carried out in accordance with PRISMA. A total of 140 articles were identified from various database searches, and 10 articles qualified for further analysis based on the set criteria. Liposomal formulations were the most used nanocarriers, followed by lipid nanoparticles and polymeric nanoparticles. These systems demonstrated improved drug bioavailability, sustained release, enhanced therapeutic efficacy, and reduced toxicity compared to conventional formulations. Nanocarriers also showed significant potential in vaccine delivery, gene therapy, oncology, and infectious disease management. Despite promising outcomes, limitations such as small sample sizes, heterogeneity in study design, and limited long-term safety data were identified. The overall risk of bias was moderate across studies. In conclusion, nanocarrier-based drug delivery systems offer substantial advantages in pediatric therapeutics, with strong potential for clinical translation. However, further large-scale, high-quality studies are required to establish their long-term safety and effectiveness.

Keywords: Nanocarriers, Pediatric therapeutics, Lipid nanoparticles, Drug delivery, Liposomes

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Introduction

Drug delivery systems (nanocarriers) have become a revolutionary method in both contemporary therapeutics, especially in overcoming problems related to traditional drug delivery mechanisms. The use of traditional pharmacological interventions is mostly characterized by a low bioavailability, off-target effects, rapid degradation, and tissue non-specificity, which is aggravated by the physiological variation and developmental factors in the pediatric population. More recent breakthroughs in nanotechnology, especially lipid-based and nucleic acid delivery systems, have facilitated accurate and efficient curative measures, such as gene editing and mRNA-based therapies[1].

With the introduction of gene editing in vivo, it has been proven that nanocarriers have the capability of delivering therapeutic constituents to specific tissues. As an example, specialised gene editing methods in treating rare genetic disorders have already demonstrated promising results, underlining the use of the delivery system to obtain specific therapeutic responses[2]. Correspondingly, the use of mRNA to transfect hematopoietic stem cells has made it possible to modify the cells' functionality in vivo, a notable breakthrough in the field of regenerative medicine and gene therapy[3]. Such methods highlight the necessity of an effective delivery system with vehicles that can protect and deliver nucleic acids, as well as enable the intracellular absorption of such acids.

Mechanisms of disease, at the molecular level, have further pointed to the necessity of specific delivery systems. Investigations into ROS-dependent signaling particles, including gasdermin D activation, have brought vital revelations into the inflammatory and cell death activities. Also, the use of vaccine adjuvant formulations such as AS01 has shown how nanoparticle-based formulations can promote an immune response by accurately mediating immune pathways[4]. The control of innate immune activation triggered by the mRNA vaccines is another factor that underscores the dynamics that exist between delivery systems and the initiation of immune responses, in which lipid nanoparticles (LNPs) take a pivotal role in both delivery and activation of the immune response[5].

The use of mRNA vaccines in preventing infectious diseases as lipid nanoparticles has attracted a lot of attention to this group. As an illustration, the immune responses and protection against bacterial infections exhibited by multivalent mRNA-LNP vaccines are versatile compared to their use against viruses only. This has been augmented by mechanistic work, including that of the STING pathway, which has given additional

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information as to how intracellular signaling can be used therapeutically. Simultaneously, pharmacological treatments addressing the inflammatory pathways, such as the inhibition of pyroptosis, can demonstrate the need to consider the development of drug delivery in immune response regulation[7].

Another application of nanocarrier systems is in gene editing and cancer therapy. With this precise delivery of CRISPR-Cas9 parts by lipid nanoparticle, precise genome editing in cancer models has been achieved, with increased therapeutic specificity and reduced systemic toxicity being achieved[9]. Improvements in the design of lipid nanoparticles have triggered the enhancement of the delivery of genome-editing tools as well, and the delivery of CRISPR/Cas9 components across biological barriers has become achievable by using lipid nanoparticles[10]. These developments highlight the growing importance of nanocarriers in enabling next-generation precision medicine.

Within infectious disease, macrophage-targeted lipid nanoparticle has been shown to confer drug therapy to infected tissues, and enhances treatment in viral pneumonia, among others[11]. In the same manner, innovative delivery systems, such as exosomes, have facilitated tissue-specific delivery of therapeutic RNA molecules, which further contributes to the practice of nanomedicine[12]. The adjuvant mRNA-LNP systems have been used to enhance the efficacy of mRNA vaccines, which work well in stimulating the CD8+ T cell responses and the whole immunization of the body against attenuated viruses or other disease-causing agents[13].

Recent advances in nanocarrier design have been trying to obtain specific delivery to certain tissues and cells. Hematopoietic stem cell genome editing. Bone marrow homing lipid nanoparticles have provided new avenues of therapeutic intervention in hematological disorders by allowing genome editing of hematopoietic progenitor cells[14]. Also, functionalized lipid nanoparticles, which are peptide functionalized, have been shown to penetrate more complicated biological barriers, including the blood-brain barrier, allowing targeted delivery of mRNA to the brain[15]. These developments reveal the possibility of using nanocarriers to cross physiological barriers and achieve precise targeting of therapy.

All of these together indicate that nanocarrier-mediated drug delivery systems have reached the stage where a revolution in biomedical science is expected. The ability to enhance the efficacy of drugs, to identify safety profiles, and to target delivery selectively becomes highly interesting when it comes to pediatric therapy approaches, in which precision and safety become essential. As research continues to advance, it is quite obvious that the combination of nanotechnology and molecular medicine will continue to contribute to personalized treatments.

Methodology

Study Design

This systematic review has been done following PRISMA 2020 guidelines to establish clarity and methodological validity. The objective was to systematically assess the drug delivery system involving nanocarriers for pediatric use concerning its efficacy, safety, and pharmacokinetics. Selection, eligibility assessment, and analysis of research articles were done as per the pre-planned protocol. To ensure an extensive overview of nanocarriers, both clinical and preclinical trials were considered.

Sources of Data and Search Strategy

PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar: Systematic search was conducted. Life cycle: The key terms used were nanocarrier, liposome, lipid nanoparticles, polymeric nanoparticles, pediatrics, and drug delivery. The search terms were modified using the Boolean operators. Only articles published in English were considered for review. Additional articles were located by manually searching through reference lists. The search strategy was designed in a manner to ensure that it was as wide as possible to capture maximum number of articles. All results from the searches were documented.

Eligibility Criteria

PICOS was used to select the studies. This population consisted of pediatric patients aged between neonates and adolescents. Interventions were taken to be nanocarrier-based, including liposomes, lipid nanoparticles, and polymeric nanoparticles. Comparators encompassed the standard treatments or placebo, where necessary. The results were efficacy, safety, pharmacokinetics, and immunogenicity. The inclusion criterion was randomized trials, clinical trials, observational studies, and pertinent preclinical studies. The exclusion criteria were reviews, editorials, and irrelevant studies. This systematic methodology ensured that appropriate and quality research that focused on the objective of the research was included.

Study Selection Process

All discovered records were copied into a reference manager, and the redundant ones were deleted. The screening was done in two phases: title/abstract screening and full-text review. One hundred and forty records were found, and 40 of them were duplicated. The remaining 100 articles were filtered out, and 50 articles were found to be irrelevant. The number of full-text articles evaluated was fifty, and only 42 of them were eliminated using predetermined criteria. Lastly, 10 studies were incorporated in the qualitative synthesis. The selection was done using PRISMA guidelines in order to have a consistent and transparent selection process.

Data Extraction

To ensure consistency, data extraction was done using a standardized form. The variables that were extracted were author, year, study design, population, nanocarrier

type, intervention, comparator, and outcomes. The outcomes were classified based on efficacy, safety, pharmacokinetics, and immunogenicity. Extra information, like study location and time, was tabulated. The systematic comparison was made possible through a methodical comparison of studies. Data mining was done with great attention to quality and exhaustiveness. The approach enabled the systematic synthesis and upheld a valid interpretation of results.

Quality Assessment and Risk of Bias

Appropriate design-specific tools were used to determine the quality of studies. The Cochrane Risk of Bias (RoB 2) tool was used to evaluate randomized trials as well; domains like randomization and outcome reporting were evaluated. The risk of bias was divided into low, moderate, and high. Limitations in blinding and sample size indicated a moderate risk in most studies. This evaluation gave an idea of the validity of evidence and informed analysis of findings.

Data Synthesis

Because of the heterogeneity of study design and results, a meta-analysis was not done. The synthesis of qualitative narratives was carried out. The studies were categorized according to the type of nanocarrier, therapeutic use, and results. Trends and patterns were determined in studies to evaluate effectiveness and safety. Analysis was done with the help of graphical representations. The synthesis aimed at comparing nanocarrier systems and their clinical effect. This method guaranteed the systematic interpretation and tolerated the variability between studies.

Results

Study Selection

The process of selecting the studies was performed in line with the PRISMA guidelines 2020, and the flow chart of included studies is presented in the PRISMA diagram. One hundred and forty records were found after the first stage, 125 records were found in the electronic databases, and 15 records were found after screening of references through manual screening. Following the deletion of 40 duplicates, 100 studies were left to be screened on titles and abstracts.

At the stage of screening, 50 records were eliminated as they were not relevant to the research question. The rest of the 50 full-text articles were evaluated to be eligible. Out of this, 42 studies failed to make the cut after careful consideration, mainly because their interventions or results are not relevant to the study, or the study design and type of publication are not suitable. Finally, 10 studies passed the inclusion criterion and were included in the qualitative synthesis. The PRISMA flow diagram of the study selection is presented in Figure 1.

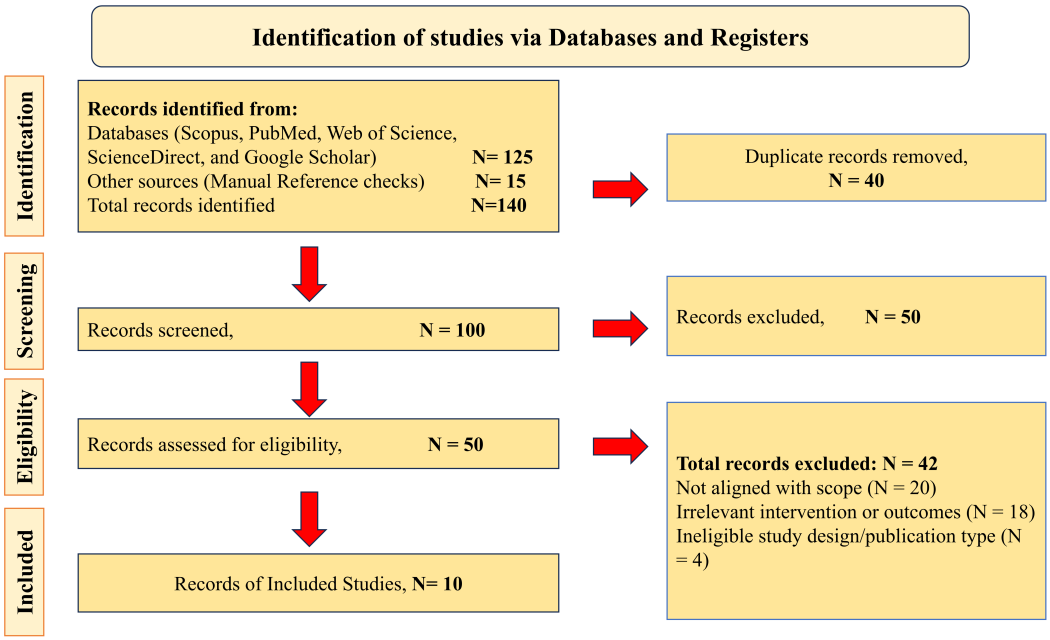

Figure 1: PRISMA Flow Diagram of Study Selection

Study Characteristics

The last data set consisted of 10 studies with diverse designs containing randomized controlled trials, phase I-III clinical trials, observational cohort studies, cross-sectional analyses, and preclinical studies. The papers differ in terms of sample size, population, and therapeutic focus based on the multidisciplinary aspect of nanocarrier-based drug delivery research. A majority were pediatric (inclusive of neonates, children, and adolescents) studies, but there were fewer studies used to give mechanistic or translational information on nanocarrier systems. The clinical trials were carried out in a variety of

settings, both in hospitals and multicenter studies. Table 1 provides a summary of the study features of the included studies.

Table 1: Characteristics of Included Studies

Study (Author et al.)	Design	Population	Nanocarrier Type	Intervention	Comparator	Key Outcomes	Main Findings
Bonuccelli et al.[16]	Double-blind RCT	Children (1–6 yrs)	Liposome	Liposomal melatonin	Placebo	Sleep latency	Faster sleep onset; improved bioavailability
Walter et al.[17]	Phase 1–3 RCT	Children (5–11 yrs)	LNP	mRNA COVID-19 vaccine	Placebo	Efficacy, immunogenicity	90.7% efficacy; strong immune response
Farag et al.[18]	RCT	Preterm infants	Liposomal system	Bovine colostrum (LDS)	Standard feeding	ROP, CRP, growth	Reduced ROP; anti-inflammatory effect
Meryk et al.[19]	Retrospective cohort	Pediatric leukemia	Liposome	Liposomal amphotericin B	Fluconazole	IFIs, toxicity	Reduced infections; improved tolerability
Nielsen et al.[20]	Phase 1 trial	Adults (vaccine study)	Liposomal adjuvant	PAMVAC vaccine	—	Safety, immunogenicity	Safe, functional antibody response
Alameh et al.[22]	Preclinical study	Animal models	LNP	mRNA-LNP vaccine	Control	Immune response	Strong humoral and cellular immunity
Tirotta et al.[23]	Phase 3 trial	Children (6–17 yrs)	Liposome	Liposomal bupivacaine	Bupivacaine HCl	PK, safety	Sustained release; safe plasma levels
Cooper et al.[24]	Phase I/II trial	Pediatric AML	Liposome	CPX-351	Standard therapy	Response rate	High remission; manageable toxicity
Feng et al.[25]	Cross-sectional	Pediatric oncology trials	Liposomes	Multiple drugs	—	Trial design	Limited high-quality RCTs
Lv et al.[26]	Preclinical study	Animal/infection models	Polymeric nanoparticles (PLGA)	Lum/Ce6@PLGA	Control	Anti-infection, inflammation	Dual anti-inflammatory and antimicrobial effect

Types of Nanocarrier Systems

Three major types of nanocarrier systems were evaluated through the included literature review: liposomes, lipid nanoparticles (LNPs), and polymeric nanoparticles. Liposomal systems turned out to be the most widely studied because of their versatile application in medicine. Liposome-based drug delivery was considered as promising because of the benefits concerning the encapsulation of drugs and their sustained delivery from cells. The use of liposomes was demonstrated to be helpful not only in oncology and antifungal treatment but also in anesthesia and neurological applications. LNPs turned out to be useful for delivering mRNAs and were found to promote intracellular delivery of nucleic acids effectively along with strong immune responses and safety features.

Polymeric nanoparticle systems, specifically PLGA, were examined in preclinical research. Polymeric nanoparticles, or PLGAs, were found to have reactive nature to pathological microenvironments and were considered effective to achieve targeted drug delivery due to their multiple benefits, including antimicrobial and anti-inflammatory effects. The types of nanocarriers are shown in Figure 2 below.

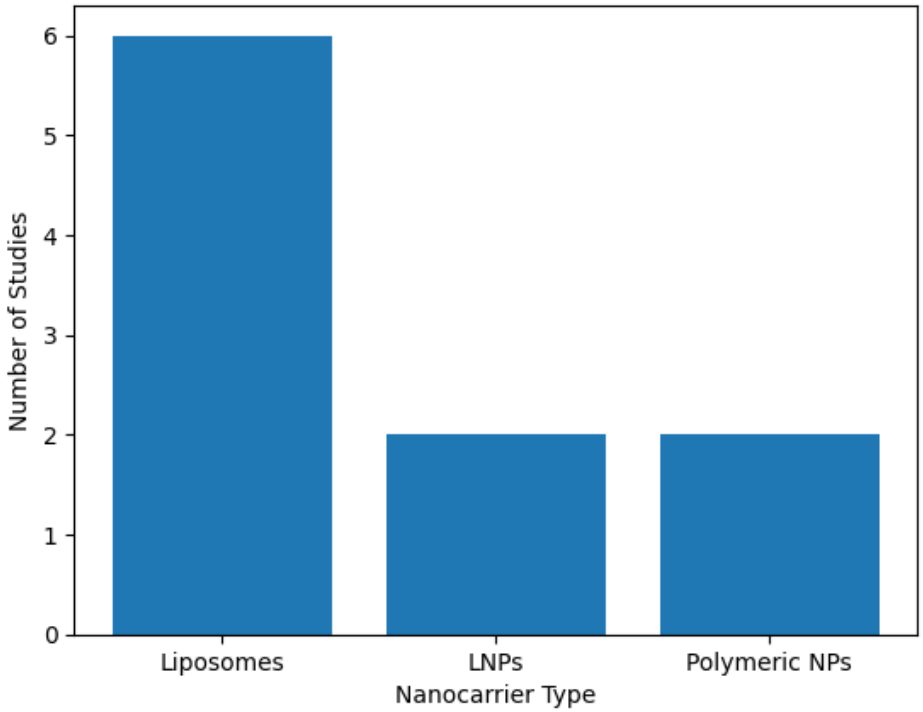

Figure 2: Distribution of Nanocarrier Types

Therapeutic Applications

Therapeutic areas represented by the included articles were diverse. Among the most prominent were oncology cases wherein the liposome-delivered chemotherapy was noted to have an increased therapeutic effect and reduced systemic toxicity in the case of children suffering from leukemia. Another area of importance was that of infectious disease and immunization when LNP-based mRNA vaccines proved to have high efficacy and induce a strong immune response. Liposomes used for antifungal treatment were more well-tolerated and associated with fewer adverse reactions compared to conventional treatments. Neonatology uses of liposomes included their use as a delivery mechanism for supplementary nutrition and prevention of retinopathy of prematurity. Other uses involved postoperative pain management and neurology treatment as a means of illustrating the extensive scope of application of the nanocarrier system in treating children. Study design representation is given in Figure 3.

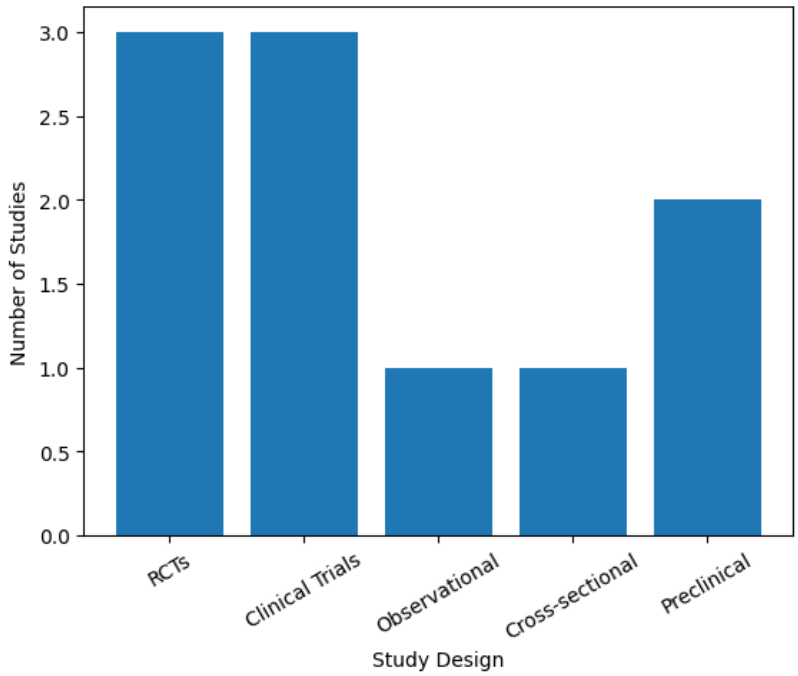

Figure 3: Study Design Distribution

Clinical Outcomes

From the studies reviewed above, nanocarrier-based drug delivery systems produced beneficial clinical and pharmacological performance across all of the studies. Drug bioavailability enhancement is another rather common event that facilitates better therapeutic effects despite lower doses. Drug delivery that was characterized by its delay and slowness was observed particularly in liposomal formulations, resulting in higher effectiveness and reduced dosing frequency. Drugs The pharmacokinetics study has also demonstrated more consistent plasma concentration of drugs as well as delay of their maximum concentration in the body, thus lowering the risk of toxicity.

In general, safety was observed as a favorable factor in clinical trials. There were more nanocarrier-based treatments whose incidence rate and severity of adverse effects were lower compared to those of conventional preparations. In the case of analgesics administration, there was an increased pain-relieving effect of liposomal preparations combined with an excellent safety profile. When it came to vaccine development, LNPs facilitated an immunogenic response including humoral and cellular reactions. Such findings confirm the potential of nanocarrier-based approaches to the regulation of vaccines in adolescents. Domains of outcome assessed are provided in Figure 4.

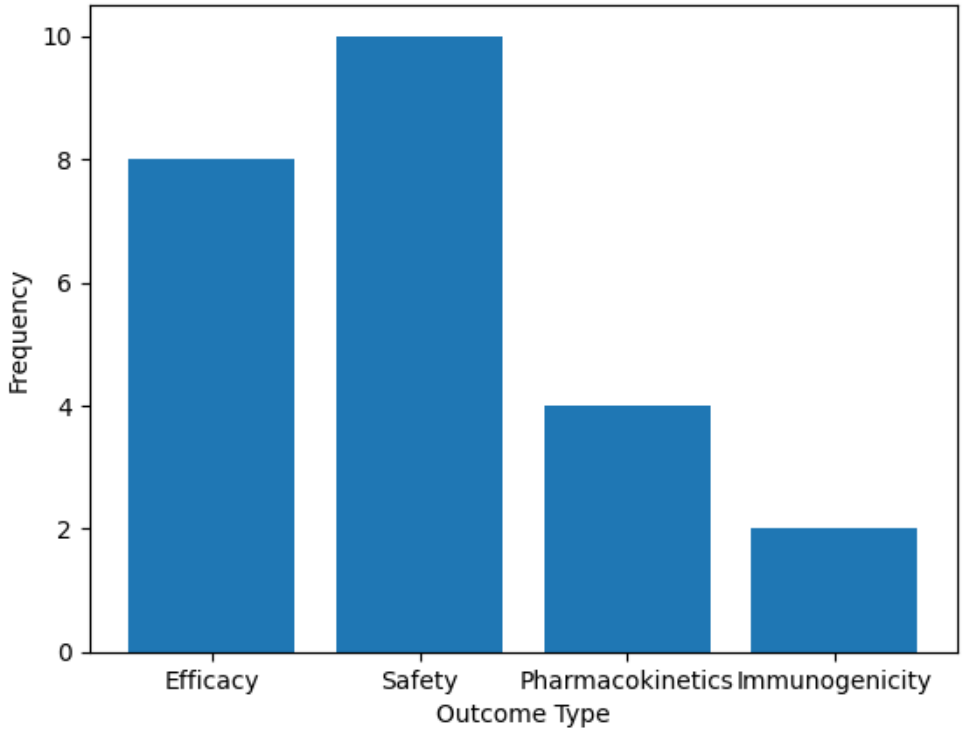

Figure 4: Outcome Domains Assessed

Comparative Effectiveness

Analytical comparisons between studies revealed that the use of nanocarriers as drug delivery platforms invariably performed better in relation to traditional drug delivery methods. Liposomal drugs were found to be less toxic and better tolerated than the non-liposomal analogs. In oncology, liposomal chemotherapeutics were found to have better response rates and reduced off-target effects.

Liposomal bupivacaine had a prolonged effect in maintaining the pain over standard preparations in analgesic studies. In the same manner, LNP-based vaccines were very effective in the prevention of infectious diseases, much higher than the placebo groups. These data demonstrate the capability of nanocarrier systems to increase therapeutic index to a greater extent of efficacy and reduce adverse effects. Figure 5 illustrates the relative efficiency of the nanocarrier.

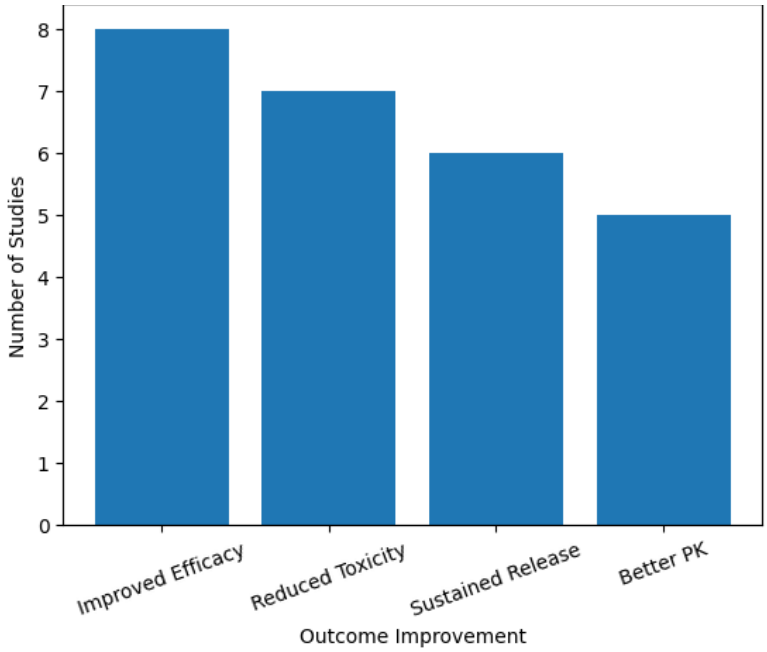

Figure 5: Comparative Effectiveness of Nanocarrier Systems

Quality Assessment and Risk of Bias

The quality of methodology used in the studies included varied. The methodological quality of randomized controlled trials and phase III studies was moderate to high, and there was satisfactory randomization and outcome assessment. This was hindered by the small sample size of early-stage clinical trials and observational studies and the possible presence of selection bias. Registry and cross-sectional analysis indicated an insufficiency of study design, such as the absence of randomization and reporting of missing results. The preclinical tests were insightful in understanding the mechanisms, but inherently constrained by their own direct clinical utility. In general, the evidence base was moderate, and stronger and larger-scale randomized controlled trials to enhance the reliability of findings were required. Table 6 includes the summary of the risk of bias of the included studies.

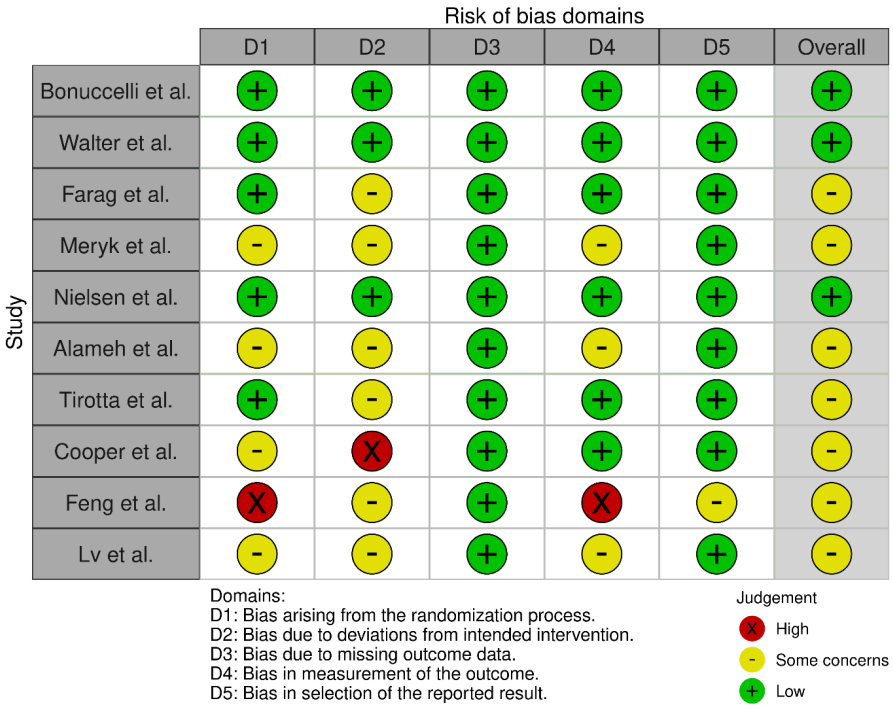

Figure 6: Risk of Bias Summary

The overall data points out that drug delivery systems that use nanocarriers have extensive benefits in clinical intervention in children. Liposomal formulations are the most developed or most validated systems, and show an increase in pharmacokinetics, efficacy, and safety. LNP systems have also become an incredibly promising platform to administer the vaccine, especially the mRNA-based therapeutic. Polymeric nanoparticles are an exciting field of innovation that can provide the potential of targeted and responsive drug delivery. Despite these innovations, the variability of study systems and scarcity of large-scale trials in childhood underscore the necessity of additional studies to conclusively determine the clinical utility and safety of nanocarrier-based systems in the long-term. The literature continues to endorse the extensive incorporation of nanotechnology in pediatrics and holds imminent effects in terms of enhancing the quality of treatment in a broad spectrum of diseases.

Discussion

The use of nanocarrier-based drug delivery systems has shown a lot of advancement in enhancing therapeutic precision, especially in complicated diseases that need to be treated through a localized treatment. Recently, the design of lipid nanoparticles (LNPs) like acid-degradable derivatives has significantly improved endosome avoidance and intracellular release efficacy of the mRNA, leading to a higher therapeutic effect in models of cancer and caries biology[26]. Concurrently, development of nanoparticles through artificial intelligence has facilitated optimization of physicochemical characteristics, driving to the offer of enhanced targeting and delivery efficacy, specifically in pulmonary gene treatment[27]. These innovations underline the transition to the rational and data-driven design of nanocarriers.

Another important innovation has been the capability to tune the immune reactions with nanocarriers. An example of this is the improved immunomodulatory effect of immunomodulatory cytokines like IL-12 in response to mRNA-delivery systems, which has been reported to induce tissue-specific immunity with very high effectiveness[28]. Likewise, nanocarrier-mediated chemotherapeutic agent delivery, including ultrasound-responsive liposomal doxorubicin, has shown the capability to induce immunity in innate immunity, such as cGAS-STING, signaling to promote antitumor immunity[29]. The above results highlight the dual application of nanocarriers in immune modulation and the delivery of drugs.

Application in cardiovascular and neurological systems: Delivery of nucleic acids via lipid nanoparticles has also demonstrated potential applications in both cardiovascular and neurological applications. The therapeutic flexibility of these systems has been observed with improved tissue repair and functional recovery observed in the case of systemic administration of LNPs to deliver mRNA to injured myocardium, foundational to the repair of its function and volume in patients with damaged myocardium, which is always assumed to pose limitations on using such systems[30]. There have also been high-throughput screening platforms, allowing nanoparticle formulations that can penetrate the blood-brain barrier, overcoming one of the central nervous system drug delivery MMs. Such developments represent the improved ability of nanocarriers to defeat biological barriers.

Still, nanocarrier technology has been promoted with the help of gene editing applications. CRISPR-Cas9 ribonucleoproteins have demonstrated capable delivery in vivo using lipid nanoparticles in order to gene edit a clinically relevant target, such as pulmonary tissues, which have been contained in a liquid form, and lipid nanoparticles have made this possible[31]. Equally, targeted gene expression in pancreatic B cells with macrophage-like delivery dynamics of mRNA via ionizable lipid nanoparticles has shown great potential in identifying a new therapeutic approach to metabolic diseases and diabetes[31]. The role of nanocarriers in precision gene therapy is growing, as depicted by these advancements.

Besides the delivery of nucleic acids, the nanocarriers have also been investigated in combination and disease targeting therapies[32]. Ferroptosis-regulated bio-nanocomplexes containing therapeutic agents, including pitavastatin and resveratrol, are effective in preventing atherosclerosis by regulating ferroptosis-related pathway[33,34]. Moreover, nanocarrier systems that replicate a natural immune response, like STING activation, have shown a higher tumor response upon selective activation of tumor-suppressive pathways[35]. The strategies present opportunities in multifunctional nanocarriers to deal with complicated disease pathways.

Nanocarriers have also been of interest in immunotherapy and treatment of allergy. Experimental allergies prevented and treated with allergen-specific mRNA -LNP systems have induced targeted immune tolerance to prevent and treat experimental allergies[36]. Nevertheless, even with these encouraging trends, a number of obstacles still exist such as nanoparticle stability that should be improved, biodistribution, and immune compatibility. Extensive studies of nanomedicine have determined the main limitations, namely biological barriers, complexity in manufacturing, and inconsistency in clinical translation[37,38].

Nanocarrier-based gene editing applications are also emerging, and have provided potential in the treatment of genetic disorders. CRISPR-Cas9 systems of delivery, such as those used to treat monogenic and digenic hearing loss, have shown efficacy, and this point illustrates how the nanocarrier can be used in controlling disease through precision medicine, as demonstrated by nanocarriers[39]. Such results highlight the role of ongoing investigation in designing nanoparticles and methods of their delivery.

In general, the literature suggests that nanocarrier-based systems have the potential to provide a great benefit in sessions of targeted therapy, pharmacological response to therapy, and immune response to therapy[40]. Nevertheless, issues surrounding safety, scalability, and long-term impacts are also critical factors to consider. Ongoing studies aiming at the refinement of nanoparticle design, large-scale clinical trials, and long-term safety analysis are necessary to maximize the potential of nanoparticle-based therapeutics in medicine.

Conclusion

Nanocarrier-based drug delivery systems have proved themselves to be a valuable innovation in modern medicine, showing more effectiveness, efficiency, and safety than conventional methods. This was made possible through the involvement of lipid nanoparticles, liposomes, and other nanocarrier techniques that allowed for the delivery of various therapeutic drugs like nucleic acid, small molecule, and protein. These technologies were able to overcome many biological barriers, improve bioavailability, and deliver therapeutic substances to their targets. This review highlights the growing importance of nanocarriers in both clinical and translational settings, particularly in the treatment combinations of pediatrics. The recent advancements in nanoparticles' design, immunomodulation, and gene-editing have further stressed the advantages of these approaches concerning complex and untreatable diseases of the eyes. However, problems associated with the safety and scaling up of technology still remain. It is necessary for the current scientific efforts to focus on the implementation of large-scale clinical trials, standardizing preparations of nanocarriers and conducting safety tests. In order for the nanocarrier drug delivery system to become truly effective, additional innovation is required.

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