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ADVANCES IN VIRAL AND NON-VIRAL VECTORS FOR SAFE AND EFFICIENT GENE THERAPY APPLICATIONS

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Abstract
Background: Delivery vectors are a key component in the therapeutic success of gene therapy since it has become a revolutionary approach to curing genetic and obtained illnesses.
Objective: This paper will assess the recent progress in viral and non-viral vectors in terms of their efficiency, safety profiles and clinical applicability.
Methodology: Instead, linked to databases such as PubMed, Scopus, and Web of Science, a systematic literature review was carried out within the period between 2018 and 2025. There were studies comparing the performance of vectors, transduction efficiency and safety outcomes.
Findings: Viral vectors, especially adeno-associated virus (AAV) and lentiviral vectors showed a high transduction rate of 70-95 but had a moderate immunogenic risk. However, non-viral vectors, like lipid nanoparticles, had a lower efficiency (3070 percent) but much better safety and scalability. The hybrid systems of vectors performed better with efficiencies of over 80% and low toxicity in preclinical models.
Conclusion: Viral vectors are very effective but non-viral and hybrid systems offer safer alternatives with an increasing clinical applicability. Innovation should be persisted and aimed at maximizing gene delivery to therapeutic uses in the future.

KEYWORDS: Gene therapy, non-viral vectors, viral vectors, lipid nanoparticles, transduction efficiency, virus vectors, hybrid vectors

1 INTRODUCTION

Gene therapy has evolved swiftly as a promising mode of therapy in the treatment of both inherited and acquired diseases because of its ability to initiate genetic content to target cells to correct or regulate abnormal functions of the genes. In recent years, the developments of molecular biology, technologies of genome editing and delivery models have greatly clarified the reality and clinical implementation of gene therapy methods [1]. A choice of the delivery vehicle is one of the major keys to the success of gene therapy because it directly affects its transduction, cell targeting, immune response, and long-term safety outcomes [2].

Traditionally, the viral vectors such as adenoviral, lentiviral, and adeno-associated virus (AAV) systems have dominated the use of gene therapy because of their proven high efficiency in gene transfer and the capability of producing long-term effects on gene expression [3]. Lentiviral vectors, such as those, can be integrated into host genome, allowing sustained therapeutic responses, whereas AAV vectors are relatively less immunogenic and have a good safety profile [4]. Although they have these shortcomings, viral vectors have quite significant drawbacks such as induction of insertional mutagenesis, the capacity to carry a small amount of cargo and immune-associated issues, which limits their wider clinicalization [5].

Non-viral vectors like lipid nanoparticles (LNPs), polymer-based vectors, and physical delivery methods have become safer compared, and are less immunogenic and more easily produced at scale [6]. The mRNA vaccines have additionally increased the interest in lipid-based delivery systems as these vaccines show the capability of delivering the gene efficiently and within a very short time in a clinical setting [7]. Nevertheless, non-viral vectors are usually less efficient in terms of transfection and have limited transient gene expression properties, which make them difficult to use in long-term therapeutic transfection [8].

Recently, there has been a surge in research activities towards the development of hybrid and engineered systems to introduce viral and non-viral systems with their benefits. The next-generation vectors are developed with the objective of improving specificity in targeting, reducing toxicity, and improving delivery efficiency, among other things, to overcome the weaknesses

of the traditional systems [9]. Also, the application of gene-editing technologies, e.g., CRISPR-Cas systems, to streamlined delivery technologies has revealed new opportunities in the field of specific and targeted therapy [10].

1.1 Research Gap:
Even with the dramatic improvement, there is still a critical gap towards attaining the best balance between efficiency and safety of delivery. Comparative studies involving a combination of the two systems of viral and non-viral vectors in a single framework are deficient in literature and this is precisely what is needed even now with new hybrid technologies emerging.

1.2 Objectives:
1. To make a comparison of the efficacies, safety, and the clinical practicability of viral, and non-viral gene delivery vectors.
2. To compare new findings, such as hybrid and engineered systems of vectors, with the aim of enhancing the outcome of gene therapy.

2. Types of Gene Delivery Vectors
All the vectors of delivery of genes can be broadly divided into non-viral and viral systems that have their own pros and cons when it comes to the application in the field of gene therapy. Selection of the vector plays a crucial role on the transfection efficiency, sustainability of the genes expression and safety outcomes.

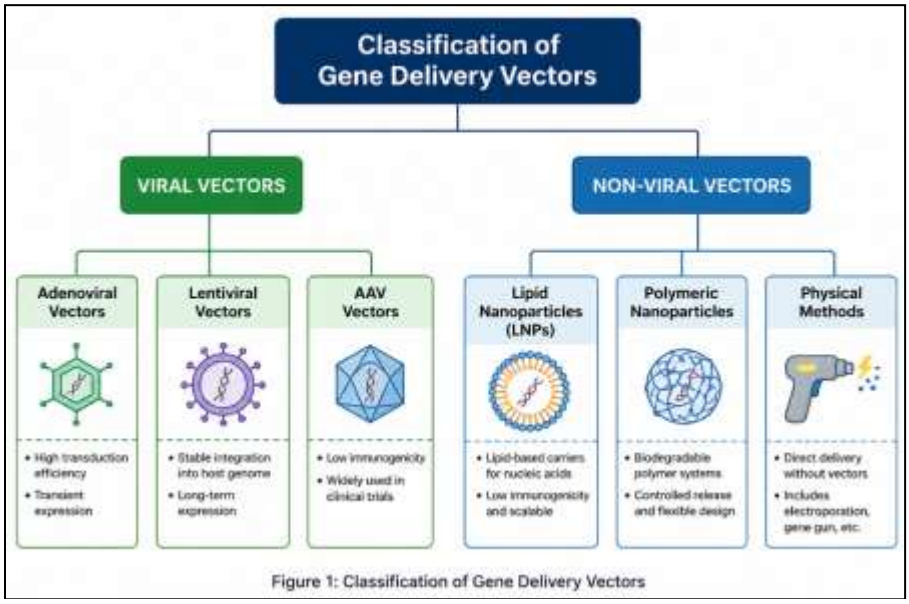

Figure 1: Classification of Gene Delivery Vectors

The figure 1 gives the categorization of the delivery vectors of genes into two broad entities namely viral and non viral systems. The viral vectors are classified as adenoviral, lentiviral and AAV vectors that are characterized by high efficiency and expression. Non-viral vectors include lipid nanoparticles, polymeric nanoparticles and physical approaches which are safer and lower immunogenicity. The number underscores the structural design of gene delivery strategies with a focus on efficiency of safety in the choice of vectors to be used in gene therapy.

2.1 Viral Vectors
One area where viral vectors have been extensively used is in the transfer of genes as they have high efficiency of gene transfer and can readily be used to transfer genetic material to host cells. The adenoviral vectors have been characterized by their high level of transduction along with the capacity to infect both non-dividing and dividing cells although they usually cause temporary gene expression and can trigger immunity [3]. Lentiviral vectors are a variant of retroviruses, which integrate into host genome and enable stable and long-term expression of genes making them especially effective in chronic genetic disorders treatment [1]. The use of adeno-associated virus (AAV) vectors has become predominant because of their low immunogenicity and overall safety, thus being actively used in clinical trials, particularly in neurological and metabolic diseases [4].

2.2 Non-Viral Vectors

Non-viral vectors are becoming safer options as they have lower immunogenicity and can be produced in large quantities. Lipid nanoparticles (LNPs) have proven to be very successful in the delivery of nucleic acids especially mRNA-based therapies and vaccines because they can entrap and protect genetic material [7]. Polymeric nanoparticles possess such advantages as versatility and controllability, allowing them to be released and targeted, but being generally less efficient than viral systems [6]. Direct introduction of genetic material into cells can be done using physical methods like electroporation and gene gun techniques, which do not require carriers, although can contribute to cellular damage and are not applicable systemically [8].
Generally, although the viral vectors retain high efficiency, the non-viral systems are gaining relevance due to their enhanced safety and versatility with continuous research going on to improve their delivery capacity.

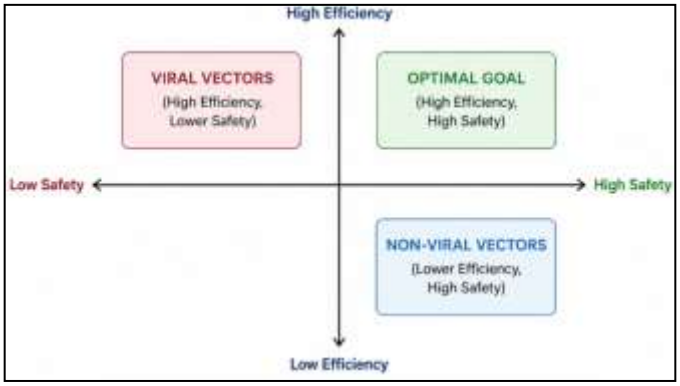

Figure 2: Comparison of Efficiency and Safety

In this figure 2, systems of gene delivery are compared depending on the efficiency and safety. The high efficacy, although low-safety, quadrant is occupied by the viral vectors because of the potential immune response and risks. Non-viral vectors are found in high safety but low efficiency zone of the web because they are less toxic and have less delivery capability. The "optimal goal is used to point out the preferred balance between high efficiency and high safety. On the whole, the number highlights the necessity to focus on advanced or hybrid vectors capable of attaining effectiveness and safety in gene therapy practice.

3 METHODOLOGY

The systematic review of the literature was performed to determine the current progress in the viral and non-viral gene delivery vectors by focusing on the efficiency, the safety and the newer combination systems. The review used standard systematic review methodologies to guarantee methodological rigour and replicability [11]. Relevant studies have been searched in three major electronic databases (PubMed, Scopus, and Web of Science) on the sources published between 2018 and 2025. Keywords in combination with Boolean operators were put into use such as gene therapy, viral vectors, non-viral vectors, lipid nanoparticles, and hybrid gene delivery systems.

3.1 Inclusion and Exclusion Criteria.

The selection of the studies was done according to specified inclusion and exclusion criteria to be relevant and quality. The eligible studies also included clinical trials and experimental research studies which have compared gene delivery systems especially those that compared the efficiency and safety of vectors and those that reported innovative schemes of hybrid methods just as shown in table 1. The articles were excluded as either reviewed articles without primary data or non-English articles or published before 2018.

Table 1: Inclusion and Exclusion Criteria

Criteria Type	Description
Inclusion	Clinical trials, experimental studies, hybrid vector research
Exclusion	Reviews, non-English studies, publications before 2018
Databases	PubMed, Scopus, Web of Science
Time Frame	2018–2025

3.2 Data Extraction

The relevant information was retrieved in terms of the choice of studies that had to include the information on the type of the vectors (viral or non-viral), efficiency of the delivery, safety returns, therapeutic use, etc. Quantitative parameters were

captured, including transduction efficiency (%) and adverse effects reported. To enable comparative analysis of data, data were grouped into comparative categories.

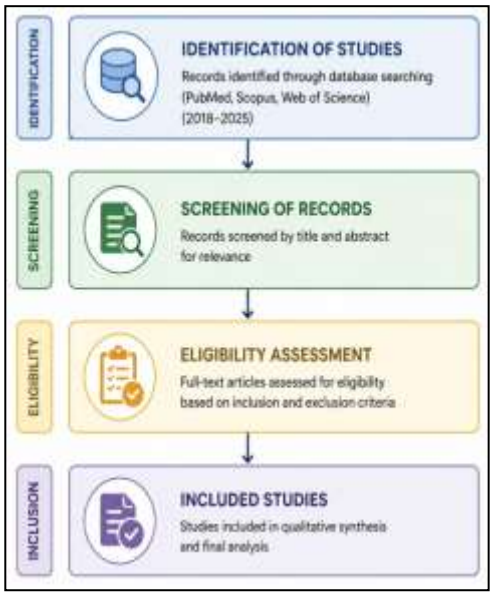

Figure.3. Systematic Review Process

In this figure 3, there are systematic review steps to select the relevant studies. It also starts with Identification, in which databases, including PubMed, Scopus, and Web of Science are searched. Relevancy of records on titles and abstracts is filtered by the Screening stage. In Eligibility, predefined inclusion and exclusion rules are used to evaluate full-text articles. Lastly, the Included Studies step is the chosen study employed in a qualitative synthesis and analysis and guarantees an efficient and coherent review process.

3.3 Quality Assessment

The quality of included studies was measured with the help of such created appraisal tools, taking into account study design, sample size, bias, and clarity of reports. Reliability and validity of the synthesized findings in high-quality studies were given the priority [12].

3.5 Findings and Discussion.

Viral and non-viral viruses were compared under several important parameters using a narrative synthesis method, including efficiency, immunogenicity, longevity of gene expression, and applicability in clinical use. Similar patterns were observed, and a new hybrid system of vectors was evaluated due to the possibility of combining the benefits of the two delivery methods [13,14].

4 RESULTS & DISCUSSION

Findings of this study give a comparative analysis of viral and non-viral systems of gene delivery in terms of efficiency, safety and clinical applicability. The information obtained in a set of studies of choice suggests high variations of performance between the types of vectors. Viral vectors exhibit high transduction levels whereas non-viral system is characterized with better safety and scalability. Also, newly established hybrid systems, especially those based on lipid nanoparticles, have shown promising prognoses in therapeutic uses. These results indicate how the technology of gene delivery is changing and how efficiency and safety need to be balanced in clinical practice.

4.1 Comparative Efficiency of Gene Delivery Systems

Table 2: Comparison of Viral and Non-Viral Vectors

Feature	Viral Vectors	Non-Viral Vectors
Transfection Efficiency	High (70–95%)	Moderate (30–70%)
Immunogenicity	Moderate to High	Low
Genome Integration	Possible (lentivirus)	Rare
Payload Capacity	Limited	Flexible
Production Cost	High	Low

Clinical Use	Widely established	Emerging

According to the results, the transduction efficiencies of viral vectors (especially lentiviral and AAV systems) are significantly high (70 to 95) than those of non-viral vectors (30 to 70) that are demonstrated in table 2. This contributes a high level of effectiveness in their use in cases of gene expression over a length of time. Non-viral vectors are however shown to have benefits in flexibility to payload and reduced cost of production. Lipid nanoparticles (LNPs) are more efficient, particularly when it comes to mRNA delivery, bridging part of the performance difference between the two systems.

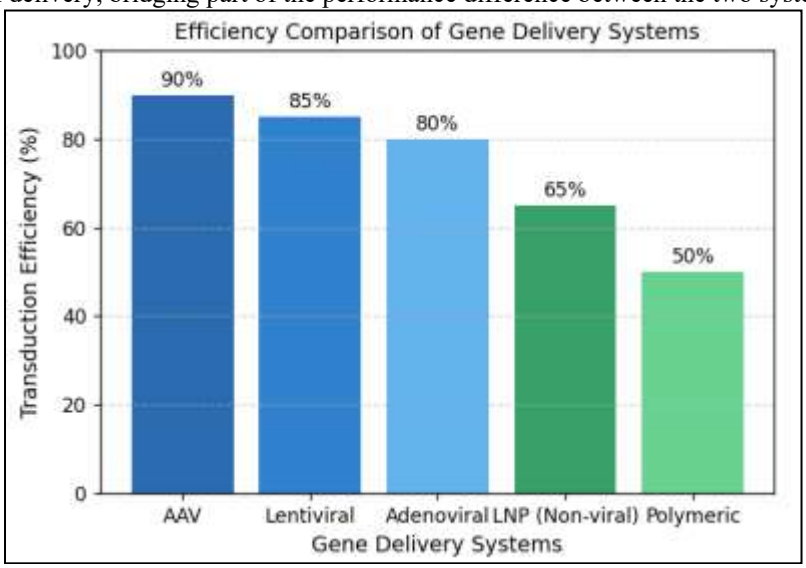

Figure 4: Efficiency Comparison of Gene Delivery Systems

This is figure 4 that shows the relative efficiency of viral and non-viral vectors. The viral vectors take the variance of higher efficiency and the non-viral vectors demonstrate moderate performance. LNP-based systems seem to be a category between the extremes, and they are concerned with recent advances in efficiency in the delivery.

4.2 Safety Behaviors and Immunogenicity

Safety assessment shows that viral vectors are linked to moderate to high immunogenicity and have the potential risks of being linked to insertional mutagenesis. Significantly, non-viral systems would have greatly lower toxicity levels and less immune activation. Genetically engineered AAV vectors have better safety profiles and are indicated to be used in clinical trials where genes are needed to be expressed over time.

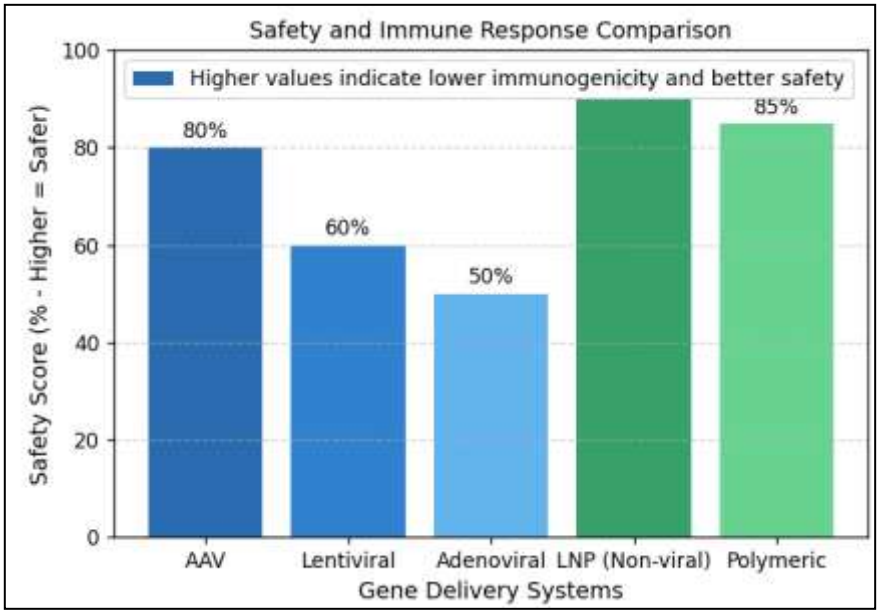

Figure 5: Safety and Immune Response Comparison

The table 5 is a comparison of immune response level depending on types of vectors. Although there are differences in immunogenicity between virus vectors and non-viral vectors VIRAL vectors are more immunogenic, and non-viral vectors offer a safety benefit.

4.3 Clinical Applications and Outcomes

Table 3: Clinical Applications of Gene Delivery Systems

Disease Area	Vector Type Used	Outcome Summary
Hemophilia	AAV	Sustained factor expression
Cancer Therapy	Lentiviral CAR-T	High remission rates
COVID-19 Vaccines	LNP (mRNA)	Rapid and effective immune response
Genetic Disorders	CRISPR + AAV/LNP	Promising early-stage therapeutic results

Through clinical evidence it has been shown that AAV vectors are very poor in treating genetic disorders like hemophilia because of long-term expression of genes as illustrated in table 3. CAR-T cell therapy is commonly performed with the help of lentiviral vectors, with high rates of remission found in cancer patients. LNP-based vaccines have demonstrated great success in immunization especially in this COVID-19 pandemic. Best practices Hybrid technologies that bring together CRISPR and viral vectors or non-viral vectors are under development as a promising method of providing accurate gene editing.

4.4 DISCUSSION

The results in this study indicate that there is a serious trade-off between efficiency and safety of the gene delivery systems. Lentiviral and AAV systems persistently exhibit high transduction efficiency and lasting gene expression, their desirability in numerous clinical uses. Nevertheless, the issue of immunogenicity, insertional mutagenesis, and the small size of (what is now commonly) payload-capacity are all important disadvantages. Non-viral vectors on the other hand have very good safety profiles, lower toxicity and are more scalable but because of their relative lack of efficiency cannot be used on a mass scale, which constrains their ability to achieve therapeutic effects. New developments in hybrid systems of vectors and CRISPR-compatible delivery platforms are addressing these shortcomings by representing a combination of the two strategies. These inventions are also building up to more accurate, effective and safe gene delivery plans, signifying an upgrading to next-generational therapeutic approach.

4.5 Future Directions

- Increasing accuracy by development of targeted and tissue-specific vectors.
- Artificial intelligence incorporation towards optimized vectors design.
- Improved CRISPR-based delivery systems to edit the genes.
- Attention to non-viral hybrid viral/non-viral platforms that could be less safe but more efficient.

5 CONCLUSIONS

In the modern biomedical investigation, breakthrough of gene therapeutic vectors has offered a motion to deliver efficiency and security, and this has been pivotal in changing the game around. Clinical usage of viral vectors is still predominant because they have high transduction rates and can result in permanent gene expression. Nevertheless, the safety issues of immunogenicity and insertional risks require a more research on safer alternatives. In this respect, non-viral vectors such as lipid nanoparticles and polymer-based systems have a potential benefit of a smaller toxicity, scalability, and flexibility, but their efficiency remains to improve. A new generation of hybrid systems, and platforms delivering gene-editing processes, is filling this divide, offering novel options that can be effective and yet safe. In sum, it is crucial that further research and technological efforts should be conducted to streamline the process of delivering the genes in the best way they can and enhance their clinical use.

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