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REVIEW

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Therapeutic potential of chemically modified siRNA: Recent trends

Chelliah Selvam[1] | **Daniel Mutisya**[2] | **Sandhya Prakash**[3] | **Kasturi Ranganna**[1] | **Ramasamy Thilagavathi**[3]

[1]Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Texas Southern University, Houston, TX, USA

[2]Department of Science and Mathematics, Albany State University, Albany, GA, USA

[3]Department of Biotechnology, Faculty of Engineering, Karpagam University, Coimbatore, India

Correspondence
Chelliah Selvam, Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Texas Southern University, Houston, TX, USA.
Email: chelliahs@tsu.edu

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Small interfering RNAs (siRNAs) are one of the valuable tools to investigate the functions of genes and are also used for gene silencing. It has a wide scope in drug discovery through in vivo target validation. siRNA therapeutics are not optimal drug-like molecules due to poor bioavailability and immunogenic and off-target effects. To overcome the challenges associated with siRNA therapeutics, identification of appropriate chemical modifications that improves the stability, specificity and potency of siRNA is essential. This review focuses on the various chemical modifications and their implications in siRNA therapy.

KEYWORDS
chemically modified siRNA, siRNA binding, siRNA therapeutics

1 | INTRODUCTION

RNA interference (RNAi), one of the natural gene regulatory mechanisms in eukaryotes, has become a prominent tool among the research community. It finds tremendous applications in fields such as functional genomics and therapeutics. siRNA (small interfering RNA), a 21–25 nucleotide, double-stranded RNA molecule plays a major role in gene silencing.[1–3] The RNAi machinery involves various components such as sense strand (passenger strand), antisense strand (guide strand), enzymes such as Dicer, Argonaute, and the core part RISC (RNA induced silencing complex). RNAi mechanism was first discovered in the transgenic plant petunia in 1990.[4] Later, Fire and Mello, through their discovery of regulated protein production by mRNA degradation in *Caenorhabditis elegans*, added light to the scientific community and they won the Nobel Prize for the year 2006 in Physiology and Medicine.[1–5]

siRNA is gaining importance as a therapeutic tool for various diseases and disorders such as cancers caused by viruses, hepatitis, and metabolic and genetic disorders because of malfunctioning of genes and unregulated expression. siRNA selectively targets the gene and silences it by inhibiting the protein expression involved in the cell abnormalities. siRNA-based therapeutic molecules for various diseases are under clinical evaluation. Recently, Dar et al.[6] developed specialized databank for chemically modified siRNAs which contains a total of 4,894 chemically modified siRNA sequences. Although siRNA offers surplus significance as a therapeutic tool, it has few detriments which need to be eliminated before its usage as a drug. siRNA has the property of stimulating the innate immunity and may also exhibit non-specific binding. In addition to this, the stability of the duplex is also affected inside the serum and it is difficult for a negatively charged RNA to cross the cell membrane, and hence, the pharmacokinetic profile is affected. The thermodynamic stability and resistance to the nuclease activity need to be improved for

