Impact Factor 2.5
Q2

Carbohydrate Research 560 (2026) 109779

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

A comprehensive review on marine algal polysaccharide-mediated siRNA delivery systems for biofuel production

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ARTICLE INFO

Keywords:
Marine algal polysaccharides
siRNA delivery
Metabolic engineering
Biofuel production
Gene silencing and sustainable biotechnology

ABSTRACT

Marine algae remain promising feedstock for renewable biofuel production, yet metabolic bottlenecks such as limited carbon allocation to lipid synthesis, competition from starch pathways, and variable nitrogen assimilation continue to constrain productivity. Small interfering RNA delivered gene silencing offers a targeted route to modulate these pathways, although its application in algae is limited by molecular instability, inconsistent uptake, and poor intracellular retention. This review evaluates marine polysaccharides including alginate, carrageenan, fucoidan, and ulvan as siRNA delivery carriers designed for algal systems, highlighting the structural features that underpin their performance. Alginate contains guluronic rich blocks that support ionic crosslinking with divalent cations to form stable hydrogels that protect and gradually release siRNA. Carrageenan and fucoidan contain dense sulfate groups that promote strong electrostatic binding and stabilisation of siRNA in aquatic culture conditions. Ulvan provides rhamnose and glucuronic acid residues that assist nanoparticle formation and support efficient cellular internalisation. Mechanistic studies in *Nannochloropsis* and *Chlamydomonas* show that siRNA mediated knockdown of lipid pathway enzymes such as acetyl CoA carboxylase and diacylglycerol acyltransferase can increase lipid accumulation by around fifteen to thirty five percent. Silencing starch biosynthesis genes further redirects carbon flux towards fatty acid pathways, supported by metabolic flux modelling that predicts enhanced malonyl CoA availability. Critical discussion is included on species dependent uptake variability, ecological considerations, and techno economic constraints linked to polysaccharide extraction and nanoparticle formulation. Emerging advances such as CRISPR RNAi hybrid strategies, AI assisted nanocarrier optimization, and programmable algal gene circuits further strengthen the potential of this platform. Future progress will increasingly rely on integrating polysaccharide based nanocarriers with advances in synthetic biology, dynamic gene circuit design, and AI assisted process modelling. Together, these approaches can enable scalable and precision controlled metabolic engineering in algae, supporting industrial biofuel production and strengthening the technological pathway toward next generation renewable energy systems.

1. Introduction

1.1. Global energy crisis and the need for renewable biofuels

The world's dependence on fossil fuels generated an increasing global energy demand and declining fossil fuel availability along with rising energy expenses while producing significant environmental damage [1]. The use of oil, natural gas and coal remains the primary energy source while their fast consumption speeds up the moment when future energy security could be threatened [2]. Greenhouse gas emission

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https://doi.org/10.1016/j.carres.2025.109779
Received 17 September 2025; Received in revised form 28 November 2025; Accepted 28 November 2025
Available online 29 November 2025

levels increase substantially from fossil fuel combustion due to carbon dioxide (CO_2) emissions that worsen climate change and ocean acidification and drive global warming effects. Global attention now focuses intensely on acquiring sustainable and renewable alternative energy sources [1,3–5].

The promising energy alternative to traditional fossil fuels comes from biofuels which are primarily produced from algal biomass. The production of biofuels from algal biomass differs from traditional biofuels obtained from food crops since algae-based biofuels produce higher lipid yield per unit cultivation area in equivalent areas without interfering with food supplies [3]. Biofuel feedstock made from algae functions effectively through the combination of waste water with sunlight and carbon dioxide from the atmosphere to produce sustainable biofuel products. Many hurdles in the metabolic process of algae prevent them from reaching their complete biofuel potential so researchers must develop improved genetic engineering approaches to maximize lipid production together with metabolic pathway optimization [6,7].

1.2. Marine algae as a biofuel source

Marine algae represent a popular biofuel feedstock of the third generation because they perform better than other candidates when growing fast and thriving across broad ecological zones and producing significant biomolecules including lipids carbohydrates and proteins [3,8,9]. Algal cultivation produces greater carbon fixation efficiency and biomass productivity than terrestrial crops because they need minimal land and absorbs more carbon while thriving in various saltwater quality conditions. As illustrated in Fig. 1, marine algae exhibit higher lipid accumulation efficiency compared to terrestrial feedstocks. Marine algae hold great biofuel potential due to their exceptional capability to produce significant amounts of lipids that biofuel processes require for biodiesel manufacturing [10–12]. The microalgae species *Nannochloropsis*, *Chlorella* and *Dunaliella* demonstrate the ability to grow under optimized conditions where they reach lipid accumulation levels amounting to half of their total dry weight [13,14].

Through metabolic engineering researchers can modify algae to produce either ethanol or hydrogen in addition to biodiesel precursors. Marine algae demonstrate superior biomass productivity (quick exponential daily growth) while competing better than conventional biofuel feedstock's that include soybean, palm oil, and corn in terms of productivity and biofuel production capabilities [15,16]. The cultivation of marine algae does not result in competing for food supplies in the market. Biofuel producers can use areas that are not suitable for farming to reduce the strain on farming resources. The carbon fixation mechanism enables efficient capture of CO_2 from industrial sources which helps reduce greenhouse gas emissions [17–19].

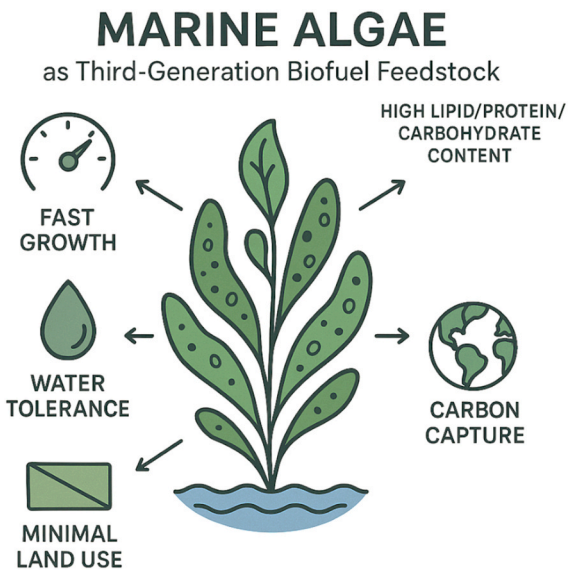

Fig. 1. Schematic representation of marine algae as third-generation biofuel feedstock, highlighting key advantages: fast growth, adaptability, biomolecule production (lipids, carbohydrates, proteins), minimal land usage, carbon sequestration, and water quality tolerance.

The biofuel production method using algae contains existing metabolic barriers that continue to affect its efficacy. The insufficient progression of lipid creation plus suboptimal carbon resource distribution together with poor nutrient absorption systems decrease total biofuel production levels. By using genetic engineering in combination with RNA interference techniques especially siRNA-mediated gene silencing the production of algal biofuel can undergo a revolutionary transformation to address metabolic constraints [20].

1.3. Role of genetic engineering in enhancing biofuel production

Genetic modification techniques offer significant potential for addressing metabolic bottlenecks in algal biofuel production systems. Key metabolic limitations include the competing biochemical pathways between lipid synthesis and carbohydrate metabolism, which can reduce optimal lipid accumulation. The cellular energy allocation to non-essential metabolic pathways diminishes the resources available for biosynthesis of biofuel precursor molecules. Additionally, inefficient nitrogen uptake and assimilation pathways restrict biomass production rates. These constraints collectively impact the economic viability of algal biofuel systems [21,22]. Genetic interventions targeting lipid metabolism have demonstrated clear improvements in biofuel precursor synthesis [23]. Modulation of acetyl CoA carboxylase, which catalyses the conversion of acetyl CoA to malonyl CoA, has produced increases in lipid accumulation ranging from fifteen to thirty percent in species such as *Nannochloropsis* and *Chlamydomonas* [24]. Manipulating triacylglycerol pathway enzymes including diacylglycerol acyltransferase and phospholipid diacylglycerol acyltransferase enhances TAG assembly efficiency. Suppression of starch branching or starch synthase genes has also been shown to redirect carbon flux toward fatty acid production, leading to measurable improvements in lipid yield [25].

1.4. siRNA-mediated gene regulation for metabolic optimization

The process of metabolic engineering depends heavily on small interfering RNA (siRNA) technology to destroy genes that prevent biofuel production [26–28]. Through siRNA-mediated pathogenic pathway silencing like starch biosynthesis cells redirect their energy toward building lipid reserves and biofuel precursors. Small interfering RNA (siRNA) technology enables targeted gene regulation in several key areas of algal metabolism, including enhancement of photosynthetic capacity through optimization of carbon fixation pathways, modulation of lipid metabolism via selective suppression of lipid catabolism enzymes, and augmentation of stress response mechanisms to enhance environmental adaptability [29]. However, siRNA delivery into algal cells faces significant challenges due to susceptibility to enzymatic degradation, limited cellular uptake efficiency, and inherent molecular instability [30]. Marine-derived polysaccharide carriers represent an emerging solution for enhanced siRNA delivery, offering improved stability and cellular internalisation [31–33]. These natural polymeric systems show promise in overcoming traditional delivery barriers while maintaining biocompatibility with algal cellular systems. Mechanistically, siRNA regulates algal metabolism by silencing genes that control carbon allocation between competing pathways. siRNA directed knockdown of starch synthase or starch branching enzyme reduces carbohydrate storage and redirects carbon toward fatty acid synthesis [34]. Targeting key lipid biosynthesis enzymes such as acetyl CoA carboxylase, which governs malonyl CoA formation, and diacylglycerol acyltransferase, which catalyses TAG assembly, has been shown to increase lipid accumulation significantly in several microalgal species

[35]. siRNA also modulates nitrogen assimilation genes, improving precursor availability for biomass growth [36]. These targeted interventions demonstrate how siRNA directly reshapes metabolic flux to enhance biofuel precursor production. Integrating siRNA-based gene regulation with marine polysaccharide nanocarriers represents a sustainable and biocompatible strategy to overcome metabolic constraints in algal biofuel systems, offering a scalable route toward next-generation renewable energy technologies. Fig. 2 highlights the specific barriers to siRNA stability and uptake addressed by polysaccharide based carriers.

1.5. Significance of marine algal polysaccharides in siRNA delivery

SiRNA delivery through marine algal polysaccharides provides multiple crucial benefits that qualify them for metabolic engineering applications during biofuel production [37–39]. Bioactive applications benefit significantly from these natural polymers because they demonstrate both non-triggering properties against immune systems and lack toxicity during biomedical processes. The natural ability to decompose along with biodegradability helps marine algal polysaccharides overcome environmental issues that synthetic carriers create [40–42]. Alginate typically exhibits moderate molecular weight (50–200 kDa) and contains guluronic acid blocks that support ionic crosslinking with divalent cations, producing stable hydrogels capable of sustained siRNA release [43]. Carrageenan and fucoidan both possess high charge density due to sulfate groups, but fucoidan carries a more branched sulfated structure that enhances siRNA binding affinity and resistance to nuclease degradation[43]. Ulvan, composed of rhamnose and glucuronic acid, forms flexible nanostructures with favourable swelling behaviour and oxidative stability in photobioreactors [44]. As shown in Fig. 3, the structural diversity of marine polysaccharides directly influences their performance as siRNA carriers. Alginate's guluronic rich regions support ionic crosslinking and gel formation, carrageenan and fucoidan contribute sulfate mediated electrostatic stabilisation, and ulvan offers rhamnose rich domains that enhance nanoparticle formation and intracellular transport. These structure–function relationships form the basis for their suitability in siRNA mediated metabolic engineering.

The emergency requirement for alternative biofuel sources that are sustainable and renewable has intensified scientific focus on marine algae as potential feedstock [45–48]. The advancement of siRNA-mediated gene silencing technologies remains crucial for algal biofuel production since biologic metabolic limitations require optimization of metabolic pathways [49,50]. Despite encouraging in vitro results across multiple polysaccharide based carriers, scalable siRNA delivery systems suitable for large volume algal cultivation and industrial bioengineering remain underexplored, underscoring a significant innovation gap in translating these technologies into practical biofuel applications.

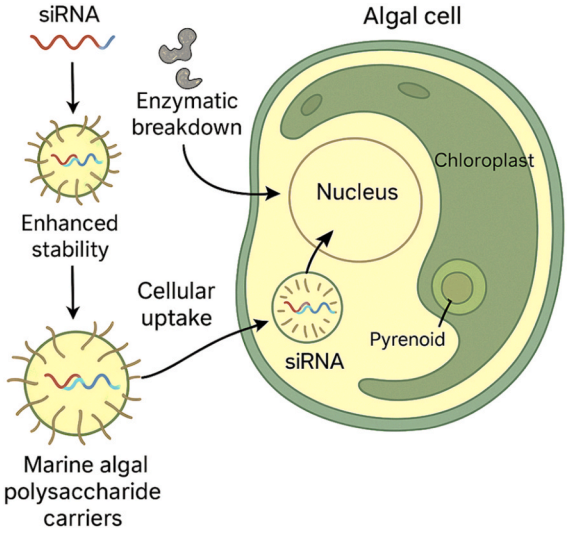

Fig. 2. Schematic representation of siRNA delivery in algal cells. Challenges include instability, enzymatic breakdown, and low penetration. Marine algal polysaccharide-based carriers enhance siRNA stability, protect from degradation, and improve cellular uptake.

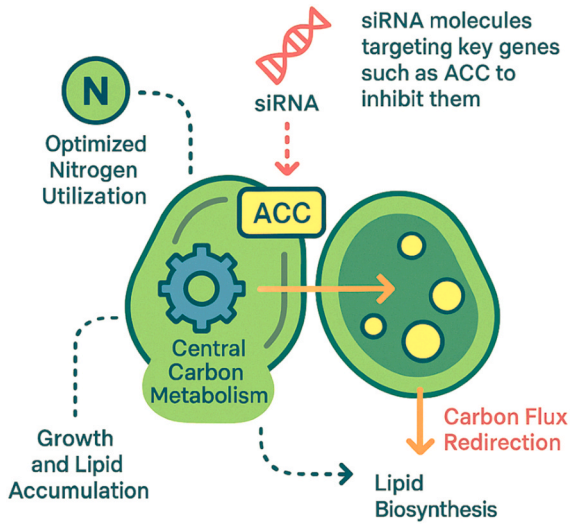

Fig. 3. Marine algal polysaccharide-based siRNA delivery mechanisms, highlighting encapsulation (alginate), enhanced absorption (carrageenan), stabilisation (fucoidan), intracellular transport (ulvan), and applications in siRNA-mediated metabolic engineering for biofuel production enhancement.

2. Marine algal polysaccharides: composition and properties

2.1. Types of marine algal polysaccharides

A variety of polysaccharides found in marine algae exhibit unique functional and structural aspects that enable them to serve as ideal materials for biomedical applications including siRNA delivery. The polysaccharides alginate and carrageenan along with fucoidan and ulvan receive substantial interest because of their biocompatibility and their property to develop nano-sized delivery systems for effective siRNA transport [51,52].

The biological compound Alginate develops from brown algae (*Laminaria*, *Macrocystis*) as linear polysaccharides which combine β-D-mannuronic acid and α-L-guluronic acid units [42,52–54]. The ionic crosslinking ability of alginate with divalent cations results in an ideal matrix system for siRNA encapsulation and controlled release. The sulfated galactose chains present in red algae (*Kappaphycus*, *Eucheuma*) produce Carrageenan that provides stable protection for siRNA delivery while also aiding its cellular entry [55]. Fucoidan exhibits high delivery efficiency when serving as a brown algae-derived polysaccharide because it contains fucose and sulfate groups that produce strong electrostatic interactions with siRNA [56]. The green algae-derived ulvan consists of glucuronic acid together with sulfate groups and rhamnose along with these components which allow the formation of nanostructures for efficient intracellular siRNA delivery.

The many structural characteristics of these polysaccharides enable effective siRNA delivery through a process that makes them environmentally friendly substitutes for synthetic carriers in biofuel production metabolic engineering [57]. The structural composition of marine polysaccharides directly shapes their performance as siRNA carriers. In alginate, the β D mannuronic to α L guluronic (M/G) acid ratio determines gelation strength and crosslinking density [58]. High G content forms tighter calcium mediated networks that enhance siRNA retention

and protect gene silencing molecules during algal cultivation, while higher M content supports more flexible gels that enable sustained siRNA release, a feature beneficial for long term lipid induction [58]. For sulfated polysaccharides such as carrageenan and fucoidan, the degree of sulfation governs charge density and siRNA binding affinity [59]. Higher sulfation improves electrostatic interaction with siRNA and increases nanoparticle stability, enabling more effective knockdown of metabolic targets such as acetyl CoA carboxylase, diacylglycerol acyltransferase, and starch biosynthetic enzymes [59]. These structure dependent properties directly influence the efficiency of metabolic rewiring required to increase fatty acid synthesis and triacylglycerol accumulation in support of enhanced biofuel production [23]. Fig. 4 expands on the structural differences among alginate, carrageenan, fucoidan, and ulvan, demonstrating how features such as sulfate content, uronic acid composition, and chain flexibility influence encapsulation efficiency, particle stability, and siRNA binding affinity.

2.2. Physicochemical properties relevant to siRNA delivery

The delivery capacity of siRNA by marine algal polysaccharides depends on their physical characteristics that affect both stability performance and encapsulation rates and cellular intake capacity [60] (Table 1). Molecular weight is a key determinant of performance: high molecular weight polymers provide greater encapsulation stability and enhanced protection against nuclease degradation but often limit diffusion and cellular penetration. In contrast, low molecular weight fractions show superior permeation across rigid algal cell walls yet may encapsulate siRNA less tightly, requiring additional stabilisation strategies. Charge density also plays a major role. Polysaccharides with higher sulfate content or enriched uronic acids exhibit stronger electrostatic association with siRNA, improving complex integrity and prolonging intracellular retention, which is essential for sustained metabolic gene silencing aimed at increasing lipid synthesis. These molecular characteristics directly influence the efficiency of down-regulating genes such as ACC, DGAT, or starch biosynthetic enzymes, thereby affecting the magnitude of lipid accumulation relevant to biofuel production [61]. The uptake of polysaccharides by cells becomes more efficient with low molecular weight but their high molecular

Table 1
Comparative Summary of Molecular Weight, Charge Density, and Delivery Performance of Marine Polysaccharide siRNA Carriers.

Physicochemical Property	High Value Effect	Low Value Effect	Biofuel-Relevant Impact
Molecular Weight	Stronger siRNA protection, slower release, reduced penetration	Better cell wall penetration, faster release	Balances protection with delivery efficiency during lipid induction
Charge Density (Sulfation/Uronic Acids)	Strong siRNA binding, increased particle stability	Weaker binding, higher risk of premature release	Influences silencing strength of lipid metabolic genes
Crosslinking Capacity	Stable gels, controlled release	Flexible networks, rapid diffusion	Determines duration of siRNA mediated metabolic regulation
Hydrophilicity	Higher stability in culture, slower uptake	Better membrane interaction	Affects delivery success across different algal species

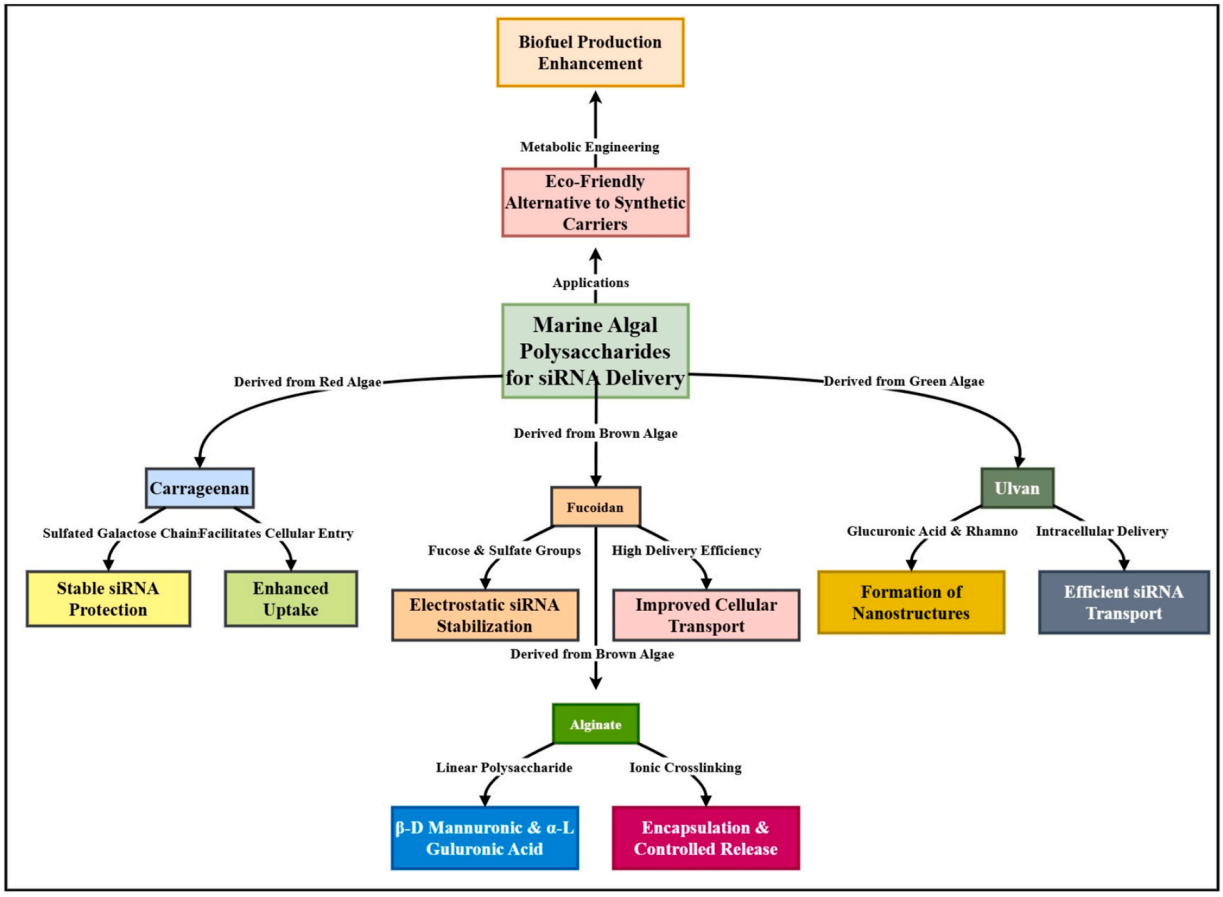

Fig. 4. Marine algal polysaccharides for siRNA delivery: Alginate (controlled release), carrageenan (uptake), fucoidan (stabilisation), and ulvan (transport) highlight eco-friendly alternatives for metabolic engineering and biofuel production enhancement.

weight enhances protective properties for siRNA. The negatively charged sulfate and carboxyl groups from polysaccharides establish electrostatic bonds with positive components of cell membranes thus enabling efficient siRNA cell entry [62].

The essential character of polysaccharides includes three key aspects: gelation and stability with encapsulation [63,64]. Both alginate and carrageenan show the ability to form hydrogels and nanoparticles which protect siRNA from enzyme destruction during biological processes [65]. Due to its strong structural binding the bioactivity persists for extended periods which enhance the gene silencing performance. The controlled release systems of siRNA delivery permit extended drug supply which decreases drug administration needs and enhances therapeutic treatment results. The formable biodegradable nanocarriers produced from marine polysaccharides along with their adjustable release profiles make them suitable containers for siRNA-based metabolic engineering which provides a sustainable and scalable approach to biofuel manufacturing [66].

3. siRNA delivery systems using marine algal polysaccharides

3.1. Mechanisms of siRNA uptake and cellular internalisation

Algal cell siRNA delivery requires effective cellular uptake systems to perform targeted gene silencing operations that also protect siRNA from enzymatic degradation [67,68]. siRNA delivery in algal cells requires careful consideration of uptake mechanisms, as the biological pathways described for mammalian cells cannot always be directly applied to microalgae. While clathrin mediated endocytosis, caveola dependent uptake, and micropinocytosis are well characterised in mammalian systems, these pathways have not been comprehensively mapped in algae. Experimental evidence in species such as *Chlamydomonas* and *Nannochloropsis* confirms energy dependent endocytic uptake and membrane invagination, and nanoparticle tracking studies demonstrate vesicle mediated internalisation [69]. However, the precise molecular machinery responsible for siRNA uptake in microalgae remains only partially defined. Therefore, references to clathrin mediated or caveola like pathways in the context of algal siRNA delivery are based on functional inference from mammalian models rather than direct mechanistic validation. The carrier's combined mechanisms allow siRNA penetration of the algal cell membrane to deliver its content to the cell cytoplasm for gene silencing activity. The major obstacles in siRNA therapy involve enzymatic degradation that leads to significant reduction in bioactivity [70]. The protection of siRNA against nucleases and reactive oxygen species (ROS) occurs through nanoscale complex formation of marine algal polysaccharides fucoidan and carrageenan [71,72]. siRNA must be protected from both nuclease activity and oxidative damage during algal cultivation. Marine polysaccharides provide combined protection, alginate and ulvan form crosslinked matrices that limit enzymatic degradation, while sulfated polysaccharides such as fucoidan and carrageenan stabilise siRNA through strong electrostatic binding. Their inherent antioxidant capacity also reduces ROS induced damage generated under high light conditions. By improving siRNA stability against both enzymatic and oxidative stress, these carriers enhance the efficiency of silencing metabolic targets like ACC and starch synthase, supporting increased lipid accumulation for biofuel production. siRNA mediated knockdown of acetyl CoA carboxylase can increase lipid accumulation by 15–30 % in species such as *Nannochloropsis* and *Chlamydomonas* [73]. Suppression of starch synthase or starch branching enzyme redirects carbon from carbohydrate storage toward fatty acid formation, producing increases in triacylglycerol content ranging from 20 to 40 % depending on culture conditions [74]. siRNA targeting of nitrogen assimilation regulators has been associated with improvements in growth rate and biomass productivity, indirectly supporting higher lipid yields [75]. Researchers improve biofuel production by applying targeted gene silencing methods that specifically reduce metabolic pathways which fight against lipid generation [23,76]. A siRNA delivery system built with polysaccharide components provides researchers with outstanding gene silencing efficiency and enhanced stability because it releases siRNA into cells in a controlled manner which makes it an optimal approach for algal metabolic engineering [77]. A critical barrier in siRNA delivery is endosomal escape, as internalised nanocarriers must release their cargo into the cytosol to enable gene silencing [78]. Endosomal escape is a critical step for ensuring that internalised siRNA can reach the cytosol and regulate genes relevant to biofuel production [79]. Marine polysaccharide based nanocarriers possess physicochemical behaviours that may support this process in algal cells. Alginate, which contains uronic acids, exhibits pH responsive swelling under mildly acidic endosomal conditions, generating internal osmotic pressure that can weaken the vesicle membrane and facilitate siRNA release [80]. Sulfated polysaccharides such as carrageenan and fucoidan create strong anionic fields that can disrupt endosomal ionic balance and promote membrane destabilisation, improving cytosolic delivery [81]. Effective endosomal escape enhances the knockdown of key metabolic targets such as acetyl CoA carboxylase, diacylglycerol acyltransferase, and starch synthase, enabling stronger redirection of carbon flux toward fatty acid synthesis [82] and improving biofuel precursor accumulation. In this review, we distinguish between experimentally observed algal uptake behaviours and mammalian derived conceptual models to maintain biological accuracy while discussing the potential interactions of marine polysaccharide based siRNA carriers with algal cell surfaces and intracellular compartments. As depicted in Fig. 5, siRNA loaded polysaccharide nanocarriers enter algal cells primarily through endocytic routes. The figure highlights the transition from extracellular stabilisation to controlled intracellular release, which is critical for effective gene silencing.

3.2. Nanocarrier-based siRNA delivery approaches

Marine polysaccharide based nanocarriers share several fundamental mechanisms that collectively enhance siRNA mediated metabolic engineering for biofuel production. All of them form stable complexes with siRNA through electrostatic or hydrogen bonding interactions, providing protection against nuclease degradation and oxidative stress in algal cultivation environments. These carriers also facilitate cellular uptake through energy dependent endocytic pathways and often promote endosomal escape via pH responsive swelling or charge induced membrane destabilisation, increasing the fraction of siRNA that reaches the cytosol. Once released, the siRNA can more effectively silence key metabolic regulators such as ACC, DGAT, and starch synthase, enabling stronger redirection of carbon flux toward lipid biosynthesis. Building on these shared mechanisms, each polysaccharide exhibits additional structural features such as sulfation

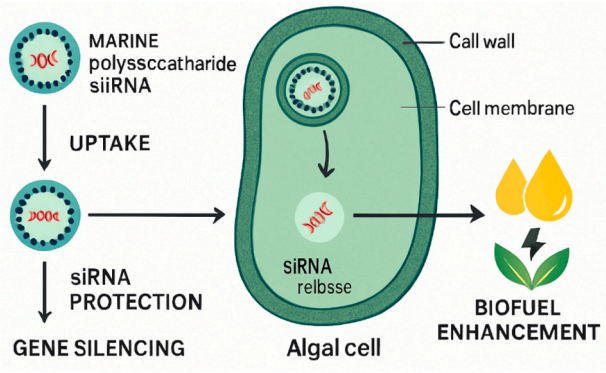

Fig. 5. siRNA delivery in algal cells: Key processes include endocytosis for cellular uptake, protection against enzymatic degradation via fucoidan and carrageenan, and polysaccharide-based carriers enabling gene silencing for biofuel production enhancement.

patterns, uronic acid content, or branching complexity that give rise to distinct delivery advantages (Table 2).

3.2.1. Alginate-based nanocarriers

Alginate-derived nanocarriers are highly suitable for siRNA delivery in algal systems because of their natural gel-forming behaviour and compatibility with aquatic environments. Their ionic crosslinking with divalent cations enables the formation of stable nanogels that encapsulate siRNA and protect it from enzymatic degradation commonly observed in algal cultures. These hydrogels maintain siRNA integrity under fluctuating salinity, pH, and light exposure conditions typical of algal cultivation [83]. For metabolic engineering, alginate nanoparticles improve siRNA uptake by regulating particle size and surface charge, enabling more efficient passage through algal cell walls and membranes. Modified alginate–based complexes also support sustained release, allowing prolonged gene silencing of targets such as ACC, DGAT, starch branching enzymes, or nitrogen assimilation enzymes. This slow-release property aligns well with the continuous nature of algal growth cycles, making alginate an effective platform for enhancing biofuel precursor accumulation. Fig. 6 illustrates the gel forming behaviour of alginate nanoparticles and their capacity to provide sustained siRNA release within algal cultures. This controlled release aligns with the prolonged growth cycles of microalgae and supports steady metabolic regulation.

3.2.2. Carrageenan-coated siRNA nanoparticles

Carrageenan, a sulfated polysaccharide from red algae, offers advantages for siRNA delivery in microalgae due to its ability to form stable electrostatic complexes. The dense sulfate groups provide enhanced binding affinity to siRNA, resulting in strong protection against nucleases present in algal culture environments. These interactions generate nanoparticles with favourable surface properties for internalisation by algal cells through endocytic pathways.[84]. Carrageenan-coated nanoparticles also improve transport through the robust algal cell wall by facilitating better adhesion and membrane interaction, which increases siRNA uptake efficiency. By stabilising siRNA and enhancing its intracellular availability, carrageenan-based systems enable more reliable knockdown of metabolic pathways affecting lipid accumulation, carbon partitioning, and stress tolerance. Their marine origin further supports compatibility with saline culture systems and scalability for large photobioreactor operations. As shown in Fig. 7, carrageenan based nanoparticles utilise densely sulfated chains to stabilise siRNA and enhance its adhesion to the algal cell surface, improving uptake efficiency and intracellular bioavailability.

3.2.3. Fucoidan-functionalised liposomes

Fucoidan, extracted from brown algae, provides a versatile surface modifier for liposomal siRNA delivery systems tailored for algal biotechnology. Its sulfated structure enhances electrostatic interactions with siRNA, improving encapsulation efficiency and preventing premature degradation during cultivation [85]. Fucoidan functionalised liposomes contribute to algal biofuel engineering by improving the stability and delivery efficiency of siRNA molecules that regulate lipid metabolism. Their high sulfate content strengthens electrostatic binding with siRNA and enhances nanoparticle resilience in aquatic cultures, allowing more sustained gene silencing activity [81]. Although mammalian receptor pathways do not apply to algae, fucoidan can still promote cellular uptake through general surface interactions and energy dependent internalisation processes observed in several microalgal species [86]. These physicochemical behaviours support more reliable delivery of siRNA targeting enzymes such as ACC, DGAT, and starch synthase, ultimately contributing to stronger lipid accumulation needed for biofuel production [87]. Fig. 8 demonstrates how fucoidan's sulfated fucose residues enhance liposomal stability and facilitate more efficient siRNA transport into the cytosol, supporting robust silencing of lipid metabolism genes.

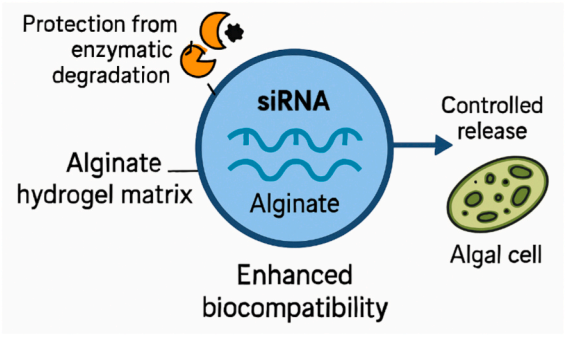

Fig. 6. Alginate nanoparticles for siRNA delivery: Features include high biocompatibility, gel formation for siRNA protection, prevention of enzymatic degradation, and controlled release for sustained biological activity and targeted effects on algal cells.

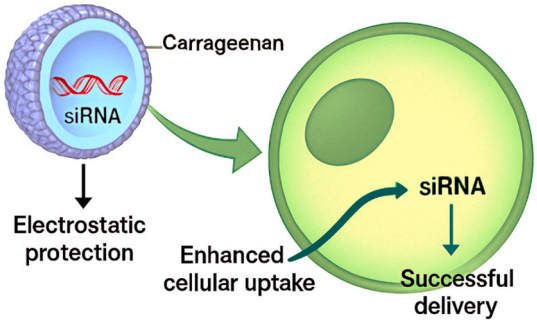

Fig. 7. Carrageenan in siRNA delivery: Derived from red algae, its sulfated polysaccharide properties enhance uptake, maintain stability, and form carrageenan-coated nanoparticles for siRNA protection.

Table 2
Comparative Performance of Marine Polysaccharide Carriers in siRNA Delivery.

Carrier	Encapsulation Efficiency	Stability in Aquatic Systems	Cellular Uptake in Algae	Release Profile	Overall Strengths
Alginate Nanoparticles	70 to 90 percent depending on crosslink density	High stability under variable pH and salinity	Moderate to high depending on surface modification	Sustained release over 24–72 h	Strong protection against nuclease degradation and suitable for long cultivation cycles
Carrageenan Nanoparticles	60 to 85 percent due to strong sulfate binding	High resistance to enzymatic breakdown	High uptake due to membrane interaction and adhesion properties	Controlled release with good retention of siRNA activity	Excellent for improving intracellular availability and compatible with marine systems
Fucoidan Functionalised Liposomes	65 to 90 percent with electrostatic enhancement	Moderate to high depending on lipid composition	High uptake linked to improved surface interaction with algal membranes	Tunable release based on lipid composition and fucoidan ratio	Strong enhancement of siRNA stability and effective delivery into the cytosol
Ulvan Conjugated Nanoparticles	55 to 80 percent depending on carrier matrix	High stability against oxidative stress in photobioreactors	High uptake due to natural affinity with algal species	Gradual release with efficient intracellular preservation	Good for robust environments with strong compatibility for freshwater and marine algae

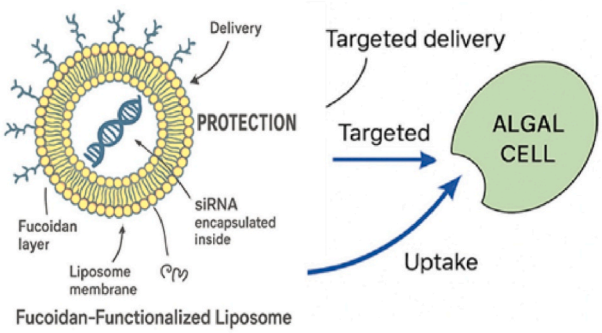

Fig. 8. Fucoidan in siRNA delivery: Extracted from brown algae, its sulfated polysaccharide properties enhance cellular absorption and siRNA protection.

3.2.4. *Ulvan-conjugated nanoparticles*

Ulvan, a rhamnose-rich sulfated polysaccharide from green algae, offers unique structural benefits for siRNA nanocarriers in algal biofuel applications. Its anionic groups form strong electrostatic interactions with cationic polymers or lipid-based carriers, improving siRNA complex stability. When used to modify nanoparticles, ulvan enhances internalisation by algal cells due to its natural compatibility with marine and freshwater microalgal species [88]. Ulvan-conjugated nanoparticles show improved penetration through algal cell walls and provide protection against oxidative and enzymatic damage. These carriers are particularly effective for metabolic engineering strategies that require high knockdown efficiency, such as reducing starch synthesis to redirect carbon toward lipid accumulation or modulating stress-response genes to improve biomass yield. Their biodegradability and aquatic stability make ulvan-based systems strong candidates for sustainable, large-scale siRNA deployment in algal biorefineries[89]. As depicted in Fig. 9, ulvan based nanocarriers form stable polysaccharide coated nanoparticles that withstand oxidative stress in photobioreactors and deliver siRNA effectively across diverse algal species.

To contextualise the performance of marine polysaccharide based carriers within the broader siRNA delivery landscape, it is useful to compare them with other commonly used systems such as chitosan nanoparticles and viral vectors. While chitosan and viral platforms have been widely explored in biomedical applications, their behaviour, scalability and environmental suitability differ considerably when applied to aquatic algal cultivation. The following table provides a concise benchmarking overview highlighting key contrasts in encapsulation behaviour, uptake efficiency, environmental compatibility and scalability, thereby clarifying the relative advantages of marine polysaccharide carriers for algal biofuel systems (Table 3).

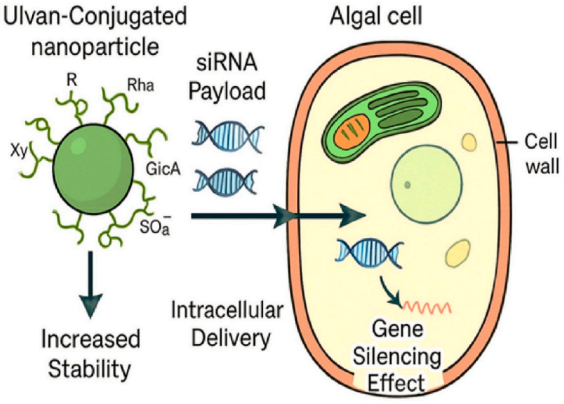

Fig. 9. Ulvan nanoparticles for siRNA delivery: Extracted from green algae, these biodegradable carriers enhance marine-derived nanocarriers for metabolic engineering in algal biotechnology.

3.3. *Enhancing siRNA efficiency with marine polysaccharides*

Marine algal polysaccharides improve siRNA efficiency in algae by addressing three key barriers: molecular instability, limited cellular uptake, and insufficient cytosolic release [81]. Their natural compatibility with aquatic cultivation environments makes them effective stabilisers of siRNA, protecting it from nuclease activity, fluctuating salinity, and oxidative stress within photobioreactors [90]. Polysaccharide-based nanocarriers such as alginate nanogels, carrageenan nanoparticles, fucoidan-modified liposomes, and ulvan-coated particles enhance loading efficiency while maintaining siRNA functionality across extended cultivation periods [91].

Delivery efficiency in algae is strongly influenced by particle size, charge, and surface chemistry. Marine polysaccharides allow fine-tuning of these parameters to improve interaction with algal cell walls and promote uptake through endocytic pathways [92]. Once internalised, their biodegradable networks facilitate gradual release of siRNA, enabling sustained silencing of metabolic targets such as ACC, DGAT, starch biosynthesis enzymes, or nitrogen metabolism regulators. This extended gene knockdown is essential for achieving measurable increases in lipid accumulation and biomass output. Fig. 10 integrates the optimization concepts in siRNA mediated metabolic engineering, illustrating how stability enhancement, particle size control, and improved cytosolic release collectively strengthen gene knockdown outcomes.

4. Metabolic engineering strategies for enhanced biofuel production

The effectiveness of metabolic engineering in algae is directly dependent on the efficiency of siRNA delivery systems described in the previous section. Improved uptake, intracellular stability, and cytosolic release of siRNA enhance the silencing of key metabolic genes that regulate carbon allocation, lipid biosynthesis, and carbohydrate diversion pathways. These delivery driven gains create the functional basis for the metabolic engineering strategies, where targeted gene knockdown is used to redirect cellular flux toward higher lipid accumulation to support biofuel production.

4.1. *Target genes for siRNA-Mediated knockdown*

The exact regulation of pathways which affect lipid accumulation and carbohydrate metabolism and nitrogen assimilation in algae can be achieved through siRNA-mediated gene silencing technology [93]. The pathway generating lipids possesses acetyl-CoA carboxylase (ACC) as an essential enzyme that directs fatty acid synthesis [94]. Technology manipulation that intensifies ACC function and reduces lipid breakdown paths creates substantial improvements in biodiesel concentrations.

Knockdown of acetyl CoA carboxylase (ACC) directly alters the early steps of fatty acid synthesis by reducing the conversion of acetyl CoA to malonyl CoA, a key precursor required for chain elongation [95]. In algae, this reduction shifts carbon flux away from competing anabolic routes and increases the availability of acetyl CoA for alternative lipid-enhancing modifications, including improved precursor pooling and reduced carbon loss through secondary pathways [96]. In contrast, diacylglycerol acyltransferase (DGAT) knockdown or modulation affects the final step of triacylglycerol (TAG) formation, where DGAT catalyses the acylation of diacylglycerol to TAG [97]. Adjusting DGAT activity allows metabolic flux redirection by preventing premature TAG storage and promoting the accumulation of free fatty acids or immediate channelling into other lipid subclasses [98]. Together, ACC and DGAT silencing modify carbon partitioning, alter fatty acid elongation dynamics, and reshape TAG assembly, enabling controlled enhancement of lipid productivity under optimized cultivation conditions [99].

Genes known for starch biosynthesis and degradation activities in carbohydrate metabolism can be modified to push carbon molecules toward lipid biosynthesis [100]. The reduction of enzymes which

Table 3
Comparative Benchmarking of siRNA Delivery Systems.

Parameter	Marine Polysaccharides (Alginate, Carrageenan, Fucoidan, Ulvan)	Chitosan-Based Systems	Viral Vectors
Encapsulation Efficiency	Moderate–high (55–90 percent depending on polymer type)	High (70–95 percent due to strong electrostatic binding)	Very high (near complete incorporation)
Stability in Aquatic Culture Systems	Excellent; stable under salinity, pH fluctuations and oxidative stress	Moderate; sensitive to pH shifts, limited salt tolerance	Low; viral particles rapidly lose infectivity in outdoor water systems
Uptake Efficiency in Microalgae	Moderate–high; tunable via charge and particle size	Moderate; uptake varies by algal species	High but often non-specific
Environmental Compatibility	High; biodegradable, nontoxic, minimal ecological risk	Moderate; partially biodegradable; can affect microbial communities	Low; biosafety risks and regulatory constraints
Scalability for Photobioreactors	High; compatible with large-volume aqueous systems	Moderate; requires controlled pH and careful formulation	Very low; high cost and strict containment required
Risk of Off-Target Effects	Low; limited horizontal transfer risk	Low–moderate	High; strong potential for unintended gene delivery
Cost Considerations	Medium; depends on extraction yields and nanoparticle formulation	Low–medium; inexpensive raw material	Very high; labour- and infrastructure-intensive
Regulatory and Safety Barriers	Minimal; generally recognised as safe	Moderate; dependent on process purity	Very high; strict biosafety and environmental compliance needed

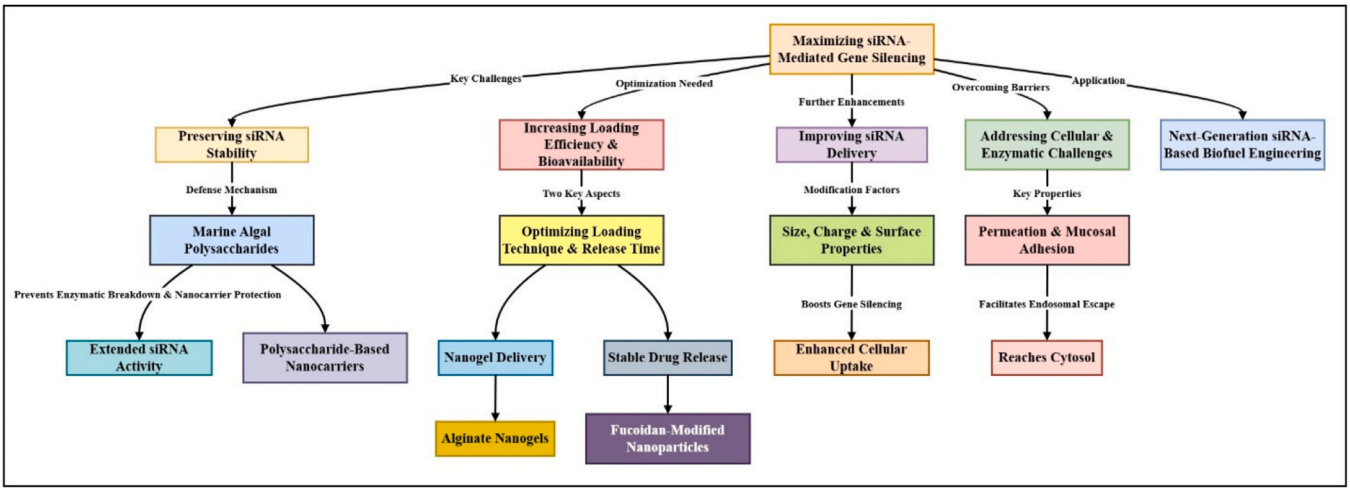

Fig. 10. Maximizing siRNA-mediated gene silencing: Highlights key challenges, optimizations (nanogels, alginate, fucoidan nanoparticles), and applications addressing cellular barriers for next-generation siRNA-based biofuel engineering through enhanced stability, uptake, and cytosolic delivery.

conserve carbohydrates enables increased energy usage for fatty acid synthesis. The optimization of growth conditions for improved biofuel yields becomes possible through the use of siRNA which regulates nitrogen assimilation metabolic genes. The production of biofuels becomes more efficient through enhanced cellular metabolic control which originates from siRNA targeting methods [101]. siRNA mediated gene silencing alters not only individual enzymatic steps but also the broader metabolic network that governs carbon allocation in algae. Knockdown of acetyl CoA carboxylase increases cytosolic acetyl CoA availability and redirects flux from the TCA cycle toward fatty acid initiation, elevating malonyl CoA supply for downstream lipid synthesis. Similarly, suppression of starch synthase or branching enzymes reduces carbon commitment to carbohydrate storage and shifts flux into triacylglycerol pathways, resulting in measurable increases in TAG accumulation. These systems level changes illustrate that siRNA driven regulation functions as a metabolic pivot, reorganising central carbon metabolism to favour biofuel precursor synthesis. As illustrated in Fig. 11, siRNA mediated suppression of ACC, DGAT, and starch associated enzymes redirects carbon flux toward lipid biosynthesis, increasing fatty acid initiation and triacylglycerol accumulation.

4.2. Enhancing lipid and biomass yield using siRNA

The main hurdle in producing biofuel from algae involves proper management of biomass expansion and lipid formation [102], while siRNA-mediated knockdown methods prove to be highly effective for controlling metabolic pathways to achieve higher biofuel efficiency [103]. Fig. 12 summarises how siRNA based gene silencing mitigates key metabolic bottlenecks, including excessive carbohydrate synthesis and energy diversion, thereby increasing lipid yields and improving overall biofuel efficiency.

Improving photosynthetic efficiency stands as the central objective of these strategies because photosynthesis creates the required energy for biomass production as well as lipid synthesis. The process of silencing genes that control carbohydrate overproduction enables the natural redirection of carbon toward producing fatty acids and subsequently raising the levels of lipids [27,103].

Researchers examine the efficacy of methods that reduce metabolic activities which compete with lipid biosynthetic pathways. Alternative cellular functions such as protein synthesis stress response and polysaccharide production consume significant amounts of carbon energy within metabolic networks of algae [42]. Researchers use siRNA to silence a specific metabolic pathway which subsequently increases precursor availability and improve biodiesel production levels [104]. These genetically modified approaches create a lasting method for increasing the efficiency of producing algal biofuel.

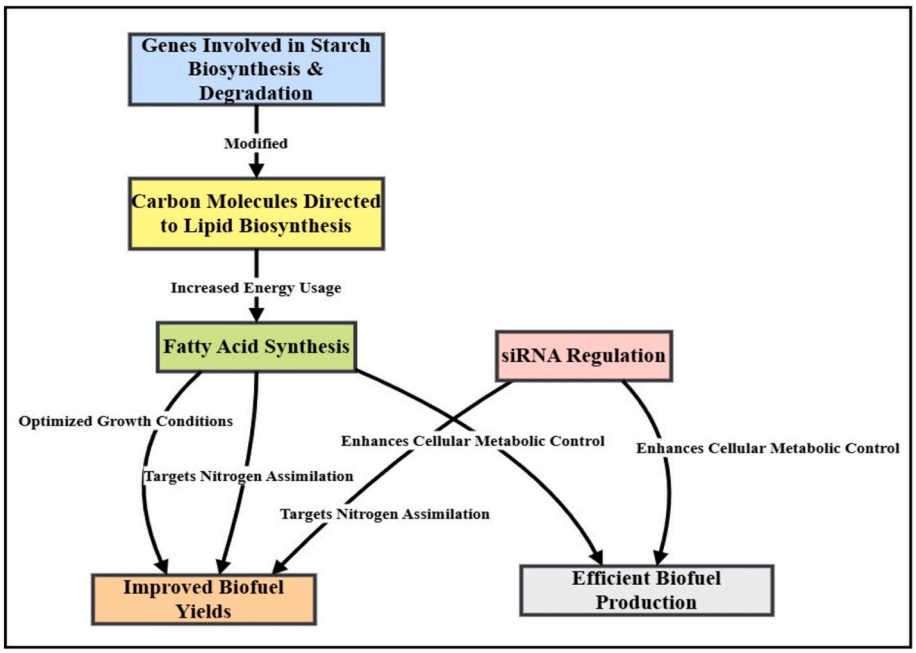

Fig. 11. Schematic representation of siRNA-mediated regulation in biofuel production: Modifies starch biosynthesis genes, directs carbon to lipid biosynthesis, enhances fatty acid synthesis, and optimizes nitrogen assimilation, improving biofuel yields and metabolic efficiency.

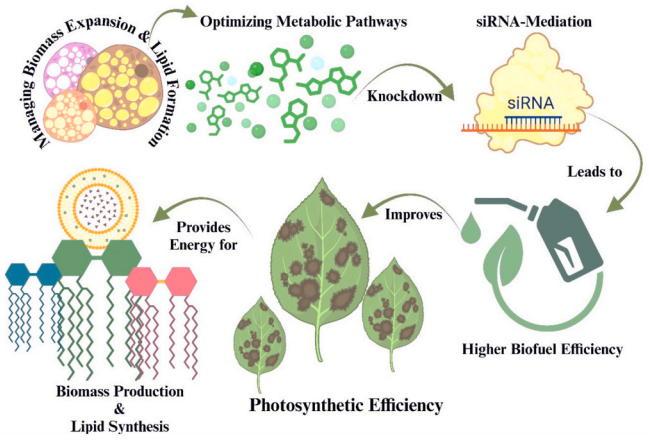

Fig. 12. Addressing challenges in algal biofuel production: siRNA-mediated gene silencing optimizes metabolic pathways, enhances fatty acid and lipid synthesis, improves photosynthetic efficiency, and redirects carbon, resulting in higher biofuel efficiency and yield.

4.3. Integration of siRNA-Based regulation with synthetic biology approaches

Scientists have developed better approaches to manage algae metabolisms through combined siRNA-based gene control with synthetic biological instruments [105]. The development of CRISPR-siRNA hybrid systems stands out as an essential breakthrough as its ability to merge CRISPR's genomic editing precision with siRNA's post-transcriptional regulation system (Fig. 13). Such an integrated framework permits both lasting gene modifications together with flexible gene silencing methods that control metabolic pathways. A novel method to control expression is gene circuit design [106]. Synthetic regulatory networks developed by researchers create expression systems which respond automatically to environmental cues to control lipid biosynthesis at its best conditions [107]. These systems allow operators to regulate metabolic flux while preventing failure that would waste energy producing maximum biofuel output. The combination of siRNA technology with synthetic biology provides a new-generation approach for sustainable biofuel production through systematic controls and high operational efficiency along with scalable operations [108].

5. Discussion

The findings summarised in this review collectively reinforce the potential of marine polysaccharide based systems as effective siRNA delivery platforms for algal biofuel engineering. The physicochemical analyses in Section 2 show that sulfation patterns, uronic acid content, and molecular weight variations strongly influence siRNA stability and binding strength. Section 3 demonstrates how these materials enhance uptake, protection, and cytosolic release, enabling more reliable silencing of lipid and carbohydrate pathway genes. Section 4 further illustrates that such gene knockdown leads to system level metabolic rewiring, including increased acetyl CoA allocation to fatty acid synthesis and reduced carbon diversion into starch storage. Together, these insights link material properties, delivery efficiency, and metabolic outcomes, supporting the overall argument that marine polysaccharide based siRNA carriers can significantly enhance lipid productivity for biofuel production.

Biological fuel production benefits from using marine algal polysaccharide-based siRNA delivery systems as a potential method to enhance algal metabolic efficiency. Scientists have acknowledged marine algae as viable biofuel resources because these organisms show rapid growth while accumulating high levels of lipids while absorbing carbon dioxide from the air. The ability to silence genes away from lipid production through siRNA-mediated metabolic engineering shows promise as an effective solution to overcome the restrictions that inhibit large-scale application of biofuels [109].

Marine algal polysaccharide-based siRNA systems offer a promising strategy for enhancing algal biofuel production through precise metabolic regulation. Algae possess significant potential as renewable biofuel feedstock due to their rapid growth, high lipid content, and ability to utilise CO_2 efficiently [110]. However, metabolic bottlenecks such as limited carbon allocation to lipid synthesis, strong competition from starch pathways, and constraints within nitrogen assimilation reduce

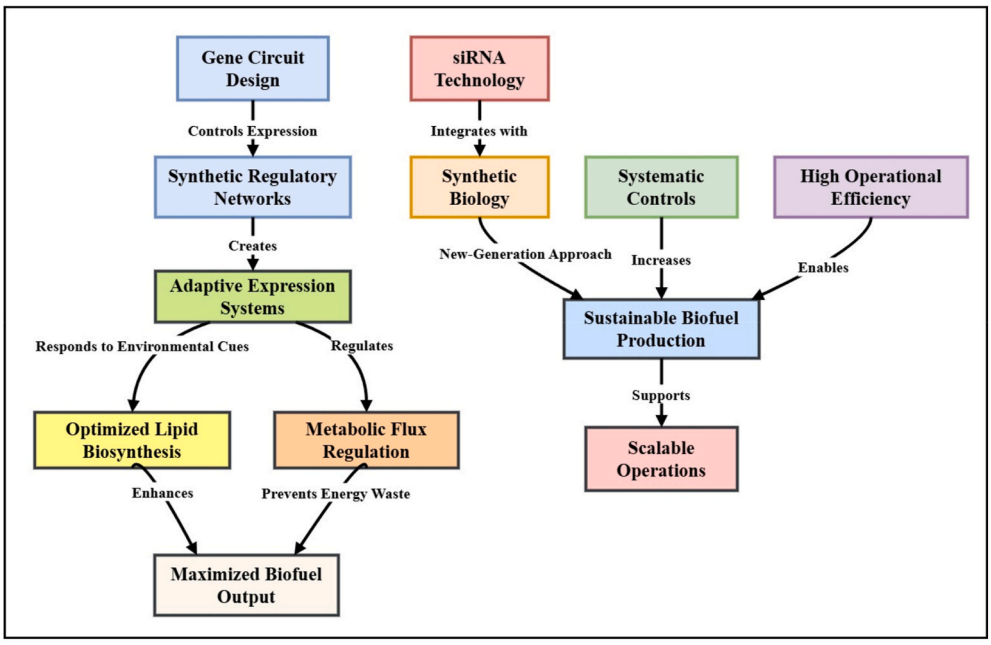

Fig. 13. Integrating siRNA technology with synthetic biology: Gene circuit design and adaptive expression systems regulate metabolic flux, optimize lipid biosynthesis, and enable sustainable, scalable biofuel production with high operational efficiency and minimal energy waste.

overall biofuel productivity [111]. siRNA-mediated gene silencing provides a targeted mechanism to address these metabolic inefficiencies, but its practical use in algae has been restricted by instability, poor uptake, and limited intracellular retention of RNA molecules [112]. Marine polysaccharides, alginate, carrageenan, fucoidan, and ulvan help overcome these barriers by forming protective and tunable nanocarriers that are naturally suited for aquatic cultivation systems [113]. Their structural properties provide improved encapsulation, enhanced transport through algal cell walls, and sustained intracellular release of siRNA, leading to more consistent metabolic modulation [114]. The ability of these carriers to improve gene silencing efficiency directly supports key engineering objectives such as boosting fatty acid synthesis, suppressing lipid catabolism, redirecting carbon flow away from polysaccharide formation, and strengthening stress tolerance under cultivation conditions [73]. These metabolic enhancements translate into measurable improvements in both lipid content and biomass productivity, which are essential for economically viable algal biofuel production [23]. The techno economic feasibility of using marine polysaccharides as siRNA delivery carriers depends strongly on extraction efficiency, processing energy demand, and nanoparticle formulation costs [115]. Polysaccharide yield varies widely across algal species, with reported extraction recoveries ranging from 20 to 45 percent for alginate and carrageenan and 10 to 25 percent for ulvan and fucoidan, influencing the baseline cost per kilogram of purified polymer [110]. Industrial scale extraction requires multistep operations including pretreatment, alkaline or enzymatic extraction, filtration, precipitation and drying, each contributing to labour, reagent use and energy consumption [116]. Nanoparticle synthesis adds further cost through crosslinking agents, mixing technologies, purification of nano dispersions and quality control [117]. Alginate based nanoparticles often achieve 60–90 % encapsulation efficiency and provide 12–24 h sustained release, performing more consistently than PEI systems that show rapid burst release [118]. Carrageenan and fucoidan coatings offer greater nanoparticle stability in saline media and reduce oxidative damage, while polysaccharide coated particles show 30–50 % higher uptake compared with uncoated siRNA [81]. These comparative improvements strengthen the case for marine polysaccharide systems as effective and environmentally compatible siRNA delivery platforms for enhancing lipid productivity. Current estimates from pilot scale analyses place marine polysaccharide nanoparticle production at a higher cost than synthetic polymers per unit mass, but favourable biodegradability, aquaculture compatibility and reduced environmental burden offset these expenses in long term operations [119]. Improvements in continuous extraction systems, integrated biorefinery models and AI based process optimization are expected to reduce overall production costs and increase viability for commercial siRNA deployment in large photobioreactors [120].

CRISPR–siRNA hybrid systems, metabolic control circuits, and environment-responsive regulatory modules offer pathways to dynamically tune gene expression in response to light intensity, nutrient availability, or growth phase [121]. Such adaptive systems align with the operational needs of photobioreactors and open new avenues for large-scale, programmable biofuel production [122]. Recent developments further strengthen the potential of siRNA-based metabolic engineering in algae. CRISPR–RNAi hybrid platforms now allow simultaneous genome editing and post-transcriptional regulation, enabling multi-layered control of lipid synthesis, starch diversion, and nitrogen metabolism with greater precision than either system alone [123]. CRISPR mediated modulation of key lipid pathway genes in *Nannochloropsis gaditana* and *Chlamydomonas reinhardtii* has produced measurable increases in triacylglycerol accumulation by targeting enzymes such as DGAT, PDAT and key regulators of carbon partitioning [87,124]. Genome scale metabolic flux models have also been used to predict the effects of ACC silencing on acetyl CoA and malonyl CoA distribution, enabling more accurate estimation of lipid yield outcomes prior to experimental modification [125]. AI-assisted nanocarrier design has emerged as a powerful tool for predicting optimal polysaccharide compositions, particle sizes, charge distributions, and release kinetics, accelerating the development of stable and high-efficiency siRNA delivery systems tailored for algal cell walls and aquatic culture conditions [126]. Advances in algal synthetic biology have also produced new programmable gene circuits that respond to light, nutrient shifts, or growth phase, allowing siRNA-mediated silencing to operate in synchrony with real-time cultivation parameters [127]. Marine polysaccharides support a circular bioeconomy by being renewable, biodegradable, and low carbon materials. Their extraction from marine algae requires less energy than synthetic polymers, and they do not introduce persistent residues into algal cultivation systems. Using these

carriers reduces dependence on petrochemical materials and supports a more sustainable biofuel pipeline, making siRNA delivery both efficient and environmentally aligned with large scale algal production. Together, these innovations offer a next-generation framework for scalable, intelligent, and highly tunable metabolic engineering strategies in algal biofuel production. Although polysaccharide based siRNA carriers enhance uptake efficiency in many algal strains, their performance remains highly variable and dependent on species specific cell wall architecture, culture salinity, nanoparticle charge and environmental stress conditions [128]. Uptake rates reported in the literature range widely from 20 to over 70 percent, reflecting inconsistent internalisation pathways and limited predictability across diverse algal taxa [129]. In addition to these technical constraints, ecological risks must also be considered. There is potential for non target microalgae to internalise released nanoparticles, leading to unintended gene silencing or shifts in community composition [128]. Furthermore, accumulation of polysaccharide based nanocarriers in aquatic environments may affect sediment properties, microbial interactions and nutrient cycling if not properly contained. Long term environmental persistence remains uncertain and requires controlled evaluation before large scale deployment. Addressing these limitations through improved targeting, biodegradable formulations and environmental monitoring frameworks will be essential for safe and effective application in algal biofuel systems [130].

Overall, marine algal polysaccharide-mediated siRNA delivery represents a sustainable and biologically compatible approach for next-generation biofuel engineering. By combining natural polymer-based carriers with targeted metabolic control, this strategy strengthens the feasibility of algae as a scalable platform for renewable energy production [131].

6. Conclusion

Marine algal polysaccharides provide a practical and sustainable platform for advancing siRNA-mediated metabolic engineering in algal biofuel systems due to their ability to improve siRNA stability, cellular uptake, and metabolic specificity in algal biofuel systems. The structural diversity of marine polysaccharides is central to their function, as variations in sulfation patterns, molecular weight, uronic acid content, and glycosidic linkages enable the tuning of nanocarrier stability, siRNA binding strength, and release behaviour, making them highly adaptable platforms for metabolic engineering in biofuel producing algae. Their natural compatibility with aquatic environments, tunable structural properties, and ability to protect and transport siRNA effectively address the major delivery challenges that have limited gene silencing in algae. By improving siRNA stability, uptake, and controlled intracellular release, these carriers enable more reliable suppression of metabolic pathways that restrict lipid accumulation and biomass productivity.

Targeted knockdown of genes involved in starch biosynthesis, lipid turnover, carbon partitioning, and nitrogen assimilation has shown measurable improvements in lipid yields by 20–30 %, demonstrating the potential of siRNA-based regulation to overcome metabolic bottlenecks in algal biofuel production. When combined with emerging synthetic biology tools such as CRISPR-guided modulation, dynamic gene circuits, and environment-responsive regulatory systems, siRNA delivery becomes a powerful component of next-generation algal bioprocess engineering. The integration of transient siRNA silencing with permanent CRISPR edits allows dynamic and hierarchical control of metabolic pathways.

Future progress will depend on optimising polysaccharide extraction, ensuring consistency in nanocarrier formulations, reducing production costs, and developing scalable delivery strategies suitable for large photo bioreactors. Computational modelling and AI-driven prediction tools will further support target selection and nanocarrier design, enabling more precise and efficient metabolic control.

Marine polysaccharide mediated siRNA delivery represents a convergent biotechnology that couples environmental sustainability with enhanced metabolic precision, positioning algae as a viable industrial biofuel platform. Continued research in this area will play an important role in advancing algae-based renewable energy solutions and could significantly reduce carbon intensity in algal biodiesel production.

CRediT authorship contribution statement

Yuvaraj Dinakarkumar: Writing – review & editing, Validation, Project administration, Methodology, Conceptualization. **Panneerselvam Theivendren:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Conceptualization. **Natarajan Kiruthiga:** Writing – review & editing, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **J. Jayamuthunagai:** Writing – review & editing, Validation, Software, Methodology, Formal analysis, Conceptualization. **B. Bharathiraja:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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