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# Influence of cultivation conditions and genetic engineering methods on Phaeodactylum tricornutum biomass growth and high-value metabolites content

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Abstract. *Introduction.* The modern pharmaceutical industry is increasingly shifting from chemical synthesis to bio-oriented technologies, creating demand for new sustainable sources of biologically active substances. The diatom microalga Phaeodactylum tricornutum has emerged as a promising cellular biofactory due to its ease of cultivation, high growth rates, metabolic versatility, and the availability of reproducible protocols for genetic transformation and cryopreservation.
*Aim.* This narrative review aims to summarise the influence of cultivation conditions and genetic engineering methods on biomass yield and the production of both native high-value metabolites, including eicosapentaenoic acid, fucoxanthin, and chrysolaminarin, and non-native compounds, such as recombinant proteins and cannabinoid precursors, in Phaeodactylum tricornutum for pharmaceutical biotechnology.
*Materials and Methods.* This narrative review analysed data on cultivation conditions, culture media composition, temperature and light regimes, genetic engineering approaches, and preclinical and clinical evidence related to Phaeodactylum tricornutum and its biotechnological applications.
*Results.* The key findings indicate that biomass growth and metabolite accumulation are strongly dependent on the composition of culture media, including nitrogen, phosphorus, and silicates, as well as temperature and light regimes. For example, nitrogen starvation increases lipid content but reduces phenolic compounds and carotenoids, whereas higher phosphate levels enhance both biomass production and fucoxanthin accumulation. Two-stage cultivation strategies help mitigate the trade-off between biomass productivity and stress-induced metabolite yield. Genetic engineering approaches, including the overexpression of endogenous genes, the introduction of plant transcription factors, clustered regularly interspaced short palindromic repeats interference, and epigenetic editing using human fat mass and obesity-associated protein demethylase, have successfully increased the yields of native lipids, eicosapentaenoic acid, and fucoxanthin without compromising biomass growth. Furthermore, Phaeodactylum tricornutum has been engineered to produce non-native compounds of pharmaceutical interest, including recombinant vaccine antigens, such as hepatitis B surface antigen and salmon alphavirus antigen, as well as cannabinoid precursors, such as olivetolic acid and cannabigerolic acid. However, cannabinoid production remains at an early experimental stage. Preclinical and clinical studies confirm the safety, bioavailability, and anti-inflammatory effects of Phaeodactylum tricornutum biomass, while fucoxanthin shows promise against inflammatory and neurodegenerative diseases.
*Conclusions.* In conclusion, Phaeodactylum tricornutum represents a controllable and versatile platform for pharmaceutical biotechnology. However, challenges related to strain stability, scalability, downstream processing costs, and regulatory frameworks must be addressed before its widespread industrial application.

Keywords: biomass, cannabinoids, chlorophyll binding proteins, culture media, eicosapentaenoic acid, metabolic engineering, microalgae

 

## Introduction

The modern pharmaceutical industry is focused on identifying new sources of biologically active substances. The transition from chemical synthesis methods to bio-oriented techniques for obtaining active compounds requires pharmaceutical laboratories to be capable of producing both exclusive, high-value, small-volume products and low-value, large-volume products. Such production systems must be able to compete with medicinally important plants grown using traditional agronomic methods.

From this perspective, diatoms are attracting significant attention as promising "cell biofactories" for the production of natural and genetically engineered target products. This may contribute to the decarbonization of the pharmaceutical industry, particularly in the production of biologics [1].

Diatoms are unicellular algae belonging to the eukaryotic phytoplankton group, division Heterokontophyta, and have existed for over 180 million years [2; 3]. Estimates of their species diversity range from 1,800 planktonic species to 200,000 species in total, more than in any other class of algae [2]. They are a vital component of oceanic ecosystems [4].

Diatoms have extraordinary metabolic versatility [5]. Their chloroplasts contain chlorophylls a, c1, and c2, as well as accessory pigments. The primary pigment is fucoxanthin (Fx), a xanthophyll carotenoid. Marine diatoms accumulate 5-10 times more Fx (2.24-26.6 mg/g dry weight) than marine macroalgae, which are currently the main industrial source of this compound [2]. Diatoms also produce omega-3 fatty acids and accumulate lipids [5].

*Phaeodactylum tricornutum* (*P. tricornutum*) is a widespread diatom microalga capable of adapting to various ecological niches, including nutrient-limited conditions during natural growth and cultivation [6]. As one of the most extensively studied diatoms, it exhibits a unique feature known as polymorphism: the ability to occur in oval, triradiate, and fusiform morphotypes. There is also a rare cruciform form that appears at low temperatures and can transition into the oval form through the degeneration of its processes [2; 7]. Due to its ease of cultivation, high growth rates under laboratory conditions, and reproducible protocols for genetic transformation and cryopreservation, this species has become a promising raw material for the synthesis of a wide range of compounds, including omega-3 fatty acids, particularly eicosapentaenoic acid (EPA), carotenoids such as Fx, and chrysolaminarin (Chrl), which are among the most important ones [3; 8; 9].

EPA-rich *P. tricornutum* biomass possesses anti-ageing effects. Fx exhibits antiproliferative, antioxidant, and anti-inflammatory activities. Crude polysaccharides demonstrate anti-inflammatory and immunostimulant effects, and Chrl-rich biomass has a positive impact on gut microbiota. Polyphenols from *P. tricornutum* – gallic acid, protocatechuic acid, catechin, vanillic acid, epicatechin, chlorogenic acid, caffeic acid, and quercetin – demonstrate significant antioxidant activity [9-13].

In this review, we focus on the role of diatom microalga *P. tricornutum* in pharmaceutical biotechnology, specifically examining how cultivation conditions and genetic engineering approaches affect biomass yield and the production of high-value metabolites.

## Aim

The aim of this work was to conduct a literature review on the influence of cultivation conditions and genetic engineering methods on the yield of biomass and target products (metabolites) of *P. tricornutum* as a promising raw material for pharmaceutical biotechnology.

## Materials and Methods

This article is a narrative review based on the analysis of scientific literature published between 2020 and 2026 and retrieved from PubMed, ScienceDirect, SpringerLink, and Google Scholar. Searches were performed using the following keywords, both individually and in various combinations: microalgae, *Phaeodactylum tricornutum*, biomass yield, cultivation, culture media, metabolic engineering, fucoxanthin, eicosapentaenoic acid, chrysolaminarin, and cannabinoids. Given the narrative nature of this review, no formal systematic search strategy with predefined inclusion and exclusion criteria was applied. Data were collected from original research articles and review papers containing experimental results, selected on the basis of their scientific relevance and thematic alignment with the focus of this work.

## Review and Discussion

*Phaeodactylum tricornutum* is a versatile diatom microalga that demonstrates remarkable metabolic flexibility through photoautotrophic and mixotrophic growth [5]. As a natural biological organism, *P. tricornutum* produces omega-3 fatty acids, particularly EPA, as well as Fx, neutral lipids, and Chrl [5; 7]. The efficiency of biomass growth and metabolite accumulation depends largely on cultivation conditions, including the composition of the culture medium, temperature, and light regimes.

*Culture media*

Components such as nitrogen, phosphorus, and silicates in culture media significantly influence biomass yield and the accumulation of lipids, fatty acids, and Fx. Under mixotrophic conditions,

*P. tricornutum* biomass can reach 3-15 g/L when glycerol or urea is used as an organic carbon or nitrogen source, respectively [14].

A study by Curcuraci et al. (2022) showed that nitrogen starvation (N–) increases lipid production (42.5 ± 0.19 g/100 g) but decreases the production of secondary metabolites, including phenolic compounds (3.071 ± 0.17 mg GAE $g^{-1}$) and carotenoids (0.35 ± 0.01 mg $g^{-1}$), compared with standard nitrogen-replete culture conditions (N+) [6].

Similarly, Elshobary et al. (2025) found that while nitrogen deficiency (–50% N in the culture medium) improves lipid accumulation, higher nitrogen levels (+50% N in the culture medium) support the highest biomass growth. An increased phosphate concentration (+50% P in the culture medium) also significantly enhanced growth, lipid content, and Fx content compared with phosphate-deficient conditions [5]. A decrease in microalgal biomass growth is a typical response to low phosphorus concentrations in the culture medium. However, experimental results showed that an increase in phosphorus content did not lead to significant differences in total biomass yield [15]. A higher lipid content (15.39%) was recorded under zero-silicate conditions in the culture medium compared with increased silicate concentration (+50% Si in the culture medium) during the cultivation of P. tricornutum [5].

*Physical parameters of cultivation*

Regarding physical parameters, the optimal temperature was identified as 21 °C with a lighting regime of 496 μmol $m^{-2}$ $s^{-1}$ by Ozcan D.O. and Ovez B. (2020) [16].

Under high light intensity, *P. tricornutum* demonstrated a decrease in cell division, chlorophyll *a*, *β*-carotene and Fx content, as well as in chloroplast membrane lipids and long-chain polyunsaturated fatty acids (PUFA) [17].

*Photobioreactors*

For industrial cultivation, various types of photobioreactors and open-pond systems are used. Flat-panel photobioreactors demonstrate the highest EPA productivity due to efficient illumination and low shear stress [18]. *P. tricornutum* cultivated in artificially illuminated, scalable flat-panel airlift photobioreactors using a two-stage process showed increased biomass growth during the first cultivation stage and induced chrysolaminarin (Chrl) accumulation (317 ± 9 mg $g^{-1}$ DW) under nitrogen-depleted conditions during the second stage [19].

Furthermore, cultivation in a flat-panel airlift photobioreactor with bilateral LED illumination increased EPA and Fx productivity under nutrient-replete conditions and Chrl productivity under nutrient-deficient conditions [20].

Among cultivation systems, flat-panel airlift photobioreactors appear to be the most promising for industrial scaling due to their high surface-to-volume ratio, uniform light distribution, and low shear stress. Open-pond systems, although less expensive, are associated with a higher risk of contamination and limited light control, making them less suitable for genetically modified strains or high-value pharmaceutical production.

*Genetic engineering of P. tricornutum*

Genetic engineering methods can increase the yield of *P. tricornutum* biomass and its metabolites, as well as expand the range of target products, including heterologous proteins, triterpenoids, and other compounds [9; 18]. Several metabolic engineering strategies have demonstrated clear potential for industrial application. The overexpression of endogenous transcription factors and epigenetic editing has consistently increased lipid and EPA content, with epigenetic editing also enhancing biomass growth and Fx levels.

A *P. tricornutum* morphotype strain overexpressing the novel *Pt2015* gene, designated oeT, showed a high growth rate and increased lipid accumulation, reaching approximately 30% more than the wild type [21]. Under 60 L culture conditions, the lipid content in the oeT strain increased by 13.4% relative to the wild type. Moreover, the contents of fatty acids such as C14:0 and C16:1 were significantly higher than those in the wild type [22].

The expression of the plant transcription factor AtL1L in transformants resulted in a significant redirection of carbon flux from carbohydrates toward lipids. This was evidenced by an increase in lipid content to 29.8-33.9% of dry weight, compared with 20.9% in wild-type controls, while carbohydrate content decreased from 23.1% to 13.3-16.5%. AtL1L transformants accumulated 42-64% more neutral lipids and showed a 48-68% increase in total fatty acid content [23].

Furthermore, the clustered regularly interspaced short palindromic repeats interference method was used to reduce the expression of enoyl-CoA hydratase in *P. tricornutum* (*PtECH*). Two transgenic lines of *P. tricornutum*, PtECH21 and PtECH1487, were developed, both showing a notable increase in lipid content [24].

In transgenic lines of *P. tricornutum* characterized by overexpression of the *PtVDL1* gene, which encodes violaxanthin de-epoxidase-like 1 in *P. tricornutum*, Fx productivity remained unchanged under standard white-light conditions. However, after 48 h of expo-

 

sure to red light, productivity increased by 15% compared with the wild type [25]. This approach remains experimental due to the requirement for precise light control, which complicates large-scale application.

Transgenic *P. tricornutum* strains obtained through epigenetic editing using the human RNA demethylase FTO, also known as fat mass and obesity-associated protein, also demonstrated faster growth. The biomass of transgenic lines was higher than that of the wild type after 8 days of cultivation, with significant increases of 27.4-36.9%. These strains also produced markedly higher lipid levels. Neutral lipid content was enhanced by 16.5%, 32.0%, and 7.4% in one set of observations and by 21.3%, 40.8%, and 12.4% in another, compared with the wild type. In addition, EPA content in the transgenic lines increased by 27.2-40.6%. Total protein content increased by 23.2-29.7%, while carotenoid content rose by 18.8-38.7%. Fx content in these transgenic lines also showed an upward trend, increasing by 17.2-35.4% compared with the wild type [13]. Epigenetic editing is highly innovative; however, its long-term stability and safety for pharmaceutical production require further validation.

*Production of non-native compounds: proteins and cannabinoids*

*P. tricornutum* has proven to be an effective eukaryotic platform for the production of non-native proteins. Specifically, the synthesis of recombinant hepatitis B surface antigen and corresponding human antibodies, as well as a recombinant vaccine antigen against salmon alphavirus (SAV), has been successfully achieved. This was done using a selection protocol based exclusively on an uracil auxotrophic selectable marker (ptUMPS) and standard selective medium [26]. This application is relatively mature, with clear advantages for oral vaccine delivery due to the microalga's digestible cell wall.

Currently, a highly innovative direction is the genetic engineering of diatoms for cannabinoid synthesis. This approach represents an alternative to traditional extraction from *Cannabis* plants, where the isolation of pure cannabinoids is inefficient due to their low concentrations among hundreds of other metabolites and is often complicated by regulatory and environmental issues [27; 28].

By integrating hemp genes, specifically those encoding tetraketide synthase and olivetolic acid cyclase, researchers achieved the accumulation of the cannabinoid precursor olivetolic acid at concentrations of 0.6-2.6 mg/L [29].

In 2024, the synthesis of cannabigerolic acid, the precursor of cannabidiol and delta-9-tetrahydrocannabinol, was demonstrated for the first time by expressing a mutant *nphB* gene from the naphterpin biosynthesis cluster of *Streptomyces* sp. CL190. The yield of cannabigerolic acid reached up to 4.1 ± 0.2 mg/kg of microalgal wet biomass [27].

In another study, *P. tricornutum* was modified to produce olivetolic acid, a key metabolic precursor of most cannabinoids. Hemp genes encoding tetraketide synthase and olivetolic acid cyclase were cloned into episomal vectors and introduced via bacterial conjugation into two separate lines of *P. tricornutum* transconjugants to assess enzymatic activity and in vivo olivetolic acid production. Despite successful gene expression, olivetolic acid accumulation was not detected. The researchers suggested that intermediate products may have been channelled into the endogenous metabolic pathways of diatoms [28].

The direction of cannabinoid biosynthesis in diatoms is highly innovative but remains predominantly experimental. Current yields are lower than those achieved in engineered yeast or *Escherichia coli* [30, 31], making commercial production economically unviable at present. Furthermore, the inconsistent results, successful expression without product accumulation in some studies, indicate poor metabolic channelling or rapid degradation of heterologous intermediates. Therefore, while conceptually promising, cannabinoid production in diatoms is currently a proof-of-concept platform.

*Pharmaceutical potential and limitations*

*Phaeodactylum tricornutum* represents a highly promising, sustainable eukaryotic platform for pharmaceutical biotechnology. Its primary pharmaceutical potentials include the ability to produce both native high-value metabolites (EPA, Fx, Chrl) and non-native compounds (vaccine antigens, cannabinoid precursors). Both EPA/Fx-rich and Chrl-rich *P. tricornutum* diets were well tolerated in mice, promoting beneficial gut health effects including increased short-chain fatty acid production, a decreased Firmicutes/Bacteriodota ratio, and, for the Chrl-rich diet, an increase in *Akkermansia*, without adverse effects [9]. A randomised controlled pilot trial in healthy elderly individuals showed that *P. tricornutum* biomass exerts anti inflammatory effects, reducing plasma interleukin 6 levels (a key marker of inflammation) and improving the omega 6 to omega 3 fatty acid ratio [12]. Another randomized intervention trial in healthy individuals confirmed that two weeks of biomass consumption safely increases plasma omega-3 PUFA and EPA content with good bioavailability [30]. Fx from this diatom is a promising candidate against inflammatory and neurodegenerative diseases driven by nuclear factor kappa-light-chain-enhancer of activated

B cells (NF-κB) and NOD (nucleotide-binding oligomerization domain)-pyrin domain-containing protein 3 (NLRP3) inflammasome activation, such as rheumatoid arthritis, type 2 diabetes, Alzheimer's disease and Parkinson's disease. Studies on bone marrow-derived immune cells and astrocytes show that Fx inhibits NF-κB and NLRP3 inflammasome activation induced by lipopolysaccharide and adenosine triphosphate, exhibits low cell toxicity, reduces production of key pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and suppresses cleaved caspase-1 expression as well as apoptosis-associated speck-like protein containing components of the NLRP3 inflammasome [11]. Additionally, Fx arrests cell cycle, induces apoptosis and autophagy, inhibits metastasis, invasion, epithelial–mesenchymal transition, and angiogenesis in cancer models, and can enhance conventional therapies when combined with its metabolite, fucoxanthinol [31].

Despite this biofactory potential, several technological, metabolic, and cultivation-related limitations currently restrict the industrial and pharmaceutical application of *P. tricornutum*. Environmental stressors often create a negative correlation between biomass growth and metabolite accumulation. For example, nitrogen deficiency enhances lipid accumulation but significantly decreases the production of phenolic compounds and carotenoids, while also inhibiting overall biomass growth. High light intensity leads to photoinhibition, reducing cell division and metabolite content, and certain genetically modified strains require precise red-light exposure to increase Fx productivity.

The yields of recombinant proteins and cannabinoids remain relatively low compared with those achieved in traditional microbial platforms. Scaling up from laboratory photobioreactors to industrial volumes often reduces productivity due to light attenuation and shear stress, with flat-panel airlift reactors showing the greatest promise while still facing technical challenges.

Additional limitations concern the stability and safety of genetically modified strains. Moreover, the regulatory status of diatom-derived pharmaceuticals is still evolving, with no clearly harmonised guidelines for clinical translation and commercialisation. Economically, despite the potential of high-value products, the cost of downstream processing currently makes *P. tricornutum* less competitive than established microbial platforms. Addressing these challenges will be essential for realising the full potential of *P. tricornutum* as a commercial cell biofactory.

## Conclusions

1. *P. tricornutum* is a promising and controllable cell biofactory for pharmaceutical biotechnology due to its high metabolic flexibility, ease of cultivation, and the availability of genetic transformation protocols.

2. Changes in cultivation conditions, including the concentrations of culture medium components such as nitrogen, phosphorus, and silicate, as well as temperature, light intensity, and light spectrum, significantly affect biomass yield and the accumulation of target metabolites, including lipids, EPA, Fx, and Chrl. Among the various approaches, two-stage cultivation strategies, consisting of a growth phase followed by a stress-induced production phase, appear to be the most industrially relevant.

3. The use of genetic engineering strategies makes it possible to increase both biomass yield and the content of native metabolites in *P. tricornutum*. Furthermore, genetic engineering enables the production of non-native compounds, including recombinant proteins, such as hepatitis B surface antigen and vaccine antigens against salmon alphavirus, as well as cannabinoid precursors, such as olivetolic acid and cannabigerolic acid. However, while metabolic engineering for native high-value products is approaching industrial readiness, cannabinoid production remains at an early experimental stage, facing significant yield limitations and unresolved regulatory hurdles.

**Article Declarations**

**Raw Data and Materials.** The raw data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

**Study Limitations.** This study has several limitations, including the limited sample size and the single-center nature of the study, which may restrict the generalizability of the findings. Further studies with larger cohorts are needed to confirm the obtained results.

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# Вплив умов культивування та методів генної інженерії на ріст біомаси та вміст високовартісних метаболітів Phaeodactylum tricornutum

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Анотація. *Вступ.* Сучасна фармацевтична промисловість дедалі більше переходить від хімічного синтезу до біоорієнтованих технологій, що створює попит на нові сталі джерела біологічно активних речовин. Діатомова мікроводорість Phaeodactylum tricornutum зарекомендувала себе як перспективна клітинна біофабрика завдяки простоті культивування, високій швидкості росту, метаболічній універсальності та наявності відтворюваних протоколів генетичної трансформації і кріоконсервації.
*Мета.* Цей наративний огляд має на меті узагальнити вплив умов культивування та методів генної інженерії на вихід біомаси та виробництво як природних високоцінних метаболітів (ейкозапентаєнової кислоти, фукоксантину, хризоламінарину), так і несвоєрідних сполук (рекомбінантних білків та попередників канабіноїдів) у Phaeodactylum tricornutum для фармацевтичної біотехнології.
*Матеріали та методи.* У наративному огляді проаналізовано дані щодо умов культивування, складу поживного середовища, температурних і світлових режимів, методів генної інженерії, а також доклінічних і клінічних досліджень, пов'язаних із Phaeodactylum tricornutum та її біотехнологічним застосуванням.
*Результати.* Основні результати демонструють, що ріст біомаси та накопичення метаболітів суттєво залежать від складу поживного середовища (нітроген, фосфор, силікати), температури та режимів освітлення. До прикладу, азотне голодування збільшує вміст ліпідів, але знижує рівень фенольних сполук і каротиноїдів, тоді як вищі концентрації фосфату посилюють накопичення як біомаси, так і фукоксантину. Двостадійні стратегії культивування допомагають нівелювати компроміс між продуктивністю біомаси та виходом метаболітів, зумовленим стресом. Методи генної інженерії, включаючи надмірну експресію ендогенних генів, введення рослинних факторів транскрипції, CRISPR-інтерференцію та епігенетичне редагування за допомогою деметилази білка FTO людини, успішно збільшили вихід природних ліпідів, ейкозапентаєнової кислоти та фукоксантину без шкоди для росту біомаси. Окрім того, Phaeodactylum tricornutum було модифіковано для продукції несвоєрідних сполук, що становлять фармацевтичний інтерес: рекомбінантних антигенів вакцин (поверхневого антигену гепатиту B, антигену альфавірусу лосося) та попередників канабіноїдів (оліветолової та канабігеролової кислот), хоча виробництво канабіноїдів усе ще перебуває на ранній експериментальній стадії. Доклінічні та клінічні дослідження підтверджують безпеку, біодоступність та протизапальну дію біомаси Phaeodactylum tricornutum, при цьому фукоксантин демонструє перспективність у боротьбі із запальними та нейродегенеративними захворюваннями.
*Висновки.* Phaeodactylum tricornutum є контрольованою та універсальною платформою для фармацевтичної біотехнології, однак перед широким промисловим впровадженням необхідно вирішити проблеми, пов'язані зі стабільністю штамів, масштабуванням, витратами на подальшу переробку та нормативно-правовою базою.

Ключові слова: біомаса, канабіноїди, хлорофіл-зв'язувальні білки, культуральні середовища, ейкозапентаєнова кислота, метаболічна інженерія, мікроводорості.

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