BIOTECHINTELLECT, 2026,3 (1) e8: (1-15)

https://jbiotechintel.com/index.php/biotechintel

Review Paper

eISSN: 3115-7920

OPEN ACCESS

Sustainable γ-Linolenic Acid Production by *Cunninghamella elegans*: Advances in Microbial Biotechnology, Precision Fermentation, and Circular Bioeconomy

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Article History:
Received: 02 Apr 2026
Revised: 25 May 2026
Accepted: 29 May 2026
Published online: 03 Jun 2026

Keywords:
γ-Linolenic acid, *Cunnin-ghamella elegans*, Oleaginous fungi, Precis-ion fermentation, Sustainable biotechnology, Agro-industrial waste valorization, Metabolic engineering, Circular bioeconomy.

How to cite this article :
Rezaei Savadkouhi, N., Montazer, Z., Karamad, D., Sustainable γ-linolenic acid production by *Cunninghamella elegans*: advances in microbial biotechnology, precision fermentation, and circular bio-economy. Biote-chIntellect, 2026; 3 (1); e 8 (1-15).
https://doi.org/10.66224/BiotechIntellect.3.1.15

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ABSTRACT

Background and aims: γ-Linolenic acid (GLA) is a high-value omega-6 polyunsaturated fatty acid with recognized applications in nutrition, pharmaceuticals, and functional foods. Among microbial producers, *Cunning-hamella elegans* has attracted increasing attention because of its capacity to accumulate lipids and synthesize GLA under diverse cultivation conditions while utilizing renewable substrates. This narrative review critically synthesizes recent advances in sustainable GLA production by *Cunninghamella elegans*, with particular emphasis on microbial physiology, Δ^6-desaturase-mediated biosynthesis, substrate valorization, fermentation strategies, metabolic engineering, and downstream processing.

Results and Conclusion: The review further show how agro-industrial residues, including glycerol, apple pomace, cereal by-products, grape pomace, and lingo-cellulosic biomass, can contribute to circular bioeconomy approaches by supporting resource-efficient microbial lipid production. Recent developments in CRISPR-based genome engineering, AI-assisted bioprocess optimization, precision fermentation, and multi-omics approaches are promising strategies for improving GLA productivity and process performance. In addition, current evidence regarding nutritional and pharmaceutical applications, techno-economic feasibility, life-cycle assessment, regulatory considerations, and industrial scalability is critically evaluated. By integrating findings from studies published between 2018 and 2025, this review identifies current knowledge gaps, emerging technological opportunities, and future research priorities for translating laboratory-scale advances into economically and environmentally sustainable industrial production. Overall, the available evidence indicates that *Cunninghamella elegans* represents a promising microbial platform for sustainable GLA production; however, further experimental validation, standardized process optimization, and large-scale industrial studies remain necessary to facilitate commercial implementation.

What is "already known":	
	• *Cunninghamella elegans* as one of the most promising oleaginous fungi for microbial γ-linolenic acid (GLA) production through Δ^6-desaturase-mediated lipid biosynthesis. • Agro-industrial residues, including glycerol, fruit pomace, cereal by-products, and lignocellulosic biomass, as sustainable feedstocks for microbial lipid production within circular bioeconomy strategies. • Recent advances in metabolic engineering, precision fermentation, and process optimization have significantly improved microbial lipid accumulation and GLA productivity. • Growing demand for sustainable polyunsaturated fatty acid (PUFA) production

What this article adds:	• A comprehensive and up-to-date synthesis of recent advances (2018–2025) in sustainable γ-linolenic acid production by Cunninghamella elegans, integrating microbial physiology, metabolic engineering, and industrial biotechnology. • Emerging strategies, including CRISPR-based genome engineering, AI-assisted fermentation optimization, precision fermentation, and agro-industrial waste valorization for improving GLA biosynthesis. • Integration of life cycle assessment, techno-economic considerations, and circular bioeconomy principles to assess the environmental and industrial sustainability of microbial GLA production. • A forward-looking perspective is presented on future research priorities, including multi-omics approaches, intelligent bioprocess control, advanced bioreactor technologies, and scalable microbial platforms for next-generation functional food and nutraceutical applications.

1. INTRODUCTION

1.1 Background and Significance

γ-Linolenic acid (GLA, C18:3 n-6), a vital polyunsaturated fatty acid (PUFA), has attracted considerable attention due to its anti-inflammatory, cardioprotective, and neuroprotective properties, as well as its potential pharmaceutical applications. Experimental studies have suggested that GLA-derived lipid mediators may influence oxidative stress pathways and inflammatory regulation, although clinical evidence remains context-dependent [1–3].

Traditional sources of GLA, including evening primrose and borage oils, remain commercially important; however, their dependence on agricultural production, seasonal variability, land requirements, and environmental pressures has encouraged the exploration of microbial alternatives [4–6].Among microbial producers, the oleaginous fungus Cunninghamella elegans has emerged as a promising platform for sustainable GLA production due to its capacity for lipid accumulation and PUFA biosynthesis through endogenous desaturation pathways [7–9]. Transcriptomic and molecular studies have provided insights into the regulation of lipid metabolism and desaturase activity, supporting further development of this organism as a microbial cell factory [8,9].

Unlike some algae-based PUFA production systems that require intensive cultivation infrastructure, C. elegans can utilize diverse carbon sources, including agro-industrial residues, providing opportunities for integrating GLA production with circular bioeconomy approaches. However, substrate composition, pretreatment requirements, and fermentation conditions strongly influence lipid productivity and metabolic efficiency [10–12].

The valorisation of agro-industrial wastes, including glycerol, fruit-processing residues, cereal by-products, and lignocellulosic materials, represents a promising strategy to reduce production costs and improve environmental sustainability. Nevertheless, efficient conversion of complex substrates may require pretreatment strategies to remove inhibitory compounds and enhance microbial accessibility [10–12].Solid-state fermentation (SSF) using C. elegans has attracted interest because of its potential to utilize low-cost substrates while producing valuable metabolites. In addition to GLA, co-production of bioactive compounds such as carotenoids and phenolic derivatives may enhance the economic value of these bioprocesses [13–15]. Optimization of nutritional parameters, particularly carbon-to-nitrogen ratio, oxygen availability, and precursor supplementation, remains essential for maximizing lipid and GLA productivity [16–18].

Recent advances in precision fermentation, metabolic engineering, and process optimization have provided new opportunities to improve microbial PUFA production. Strategies including controlled nutrient feeding, genetic engineering, and computational modelling may enhance pathway efficiency; however, large-scale implementation remains limited by challenges associated with mass transfer, process control, and economic feasibility [19–21].Comparative studies indicate that optimized cultivation of C. elegans can achieve competitive GLA productivity compared with conventional plant-derived sources. Recent advances in cultivation strategies and supplementation approaches have further improved GLA accumulation while demonstrating the importance of temperature and environmental control on production efficiency [22–24].

Beyond production, GLA-containing functional foods and nutraceutical products continue to attract commercial interest due to growing demand for health-promoting lipids. However, translation from laboratory-scale production to industrial applications requires integrated assessment of safety, bioavailability, sustainability, and economic viability [25–27].

Bioprocessing innovations, including CRISPR-based genome engineering, artificial intelligence (AI)-assisted optimization, and metabolic modelling, are expanding opportunities for improving sustainable PUFA production. Computational approaches such as flux balance analysis (FBA) can provide valuable predictions of metabolic behaviour and guide strain development; nevertheless, experimental validation remains essential before industrial implementation [28–30].

1.2 Scope and Objectives

This narrative review critically examines and synthesizes the literature published between 2018 and 2025 on the sustainable production of γ-linolenic acid (GLA) by *Cunninghamella elegans*, with particular emphasis on Δ^6-desaturase-mediated biosynthesis, substrate utilization, and agro-industrial waste valorization for applications in human nutrition, pharmaceuticals, and functional foods [13–15,31–33].

The review provides a comparative evaluation of *C. elegans* and other commercially relevant oleaginous fungi, including *Thamnidium elegans*, *Mucor circinelloides*, *Umbelopsis isabellina*, and *Mortierella isabellina*, focusing on their metabolic characteristics, GLA-producing potential, and biotechnological performance [34–36].

Furthermore, recent advances in metabolic engineering, precision fermentation, process optimization, and downstream processing are critically assessed to identify current opportunities and technological limitations for sustainable industrial production [37–39].The review also highlights existing knowledge gaps and discusses future research priorities related to strain improvement, substrate selection, process scalability, regulatory compliance, and industrial translation.

1.3 Historical Context

Microbial PUFA production has advanced considerably since the 1980s, with *C. elegans* achieving high GLA productivity under optimized cultivation conditions and demonstrating competitive performance compared with conventional plant-based sources [40–42].

Solid-state fermentation using apple pomace, cereals, grape pomace, and other agro-industrial substrates, together with metabolic engineering approaches, has contributed to improving the sustainability and productivity of microbial GLA biosynthesis [43–45].

Historical reliance on fish oils has progressively shifted toward microbial lipid platforms in response to sustainability concerns, resource limitations, and increasing demand for alternative PUFA sources [46–47]. More recent studies (2024–2025) have emphasized integrated SSF-LSF strategies and computational modelling approaches for improving microbial lipid production and predicting fermentation performance [48–50].

1.4 Market and Health Impact

The PUFA market has experienced substantial growth, driven by increasing demand for functional foods, nutritional supplements, and pharmaceutical applications [52]. Bioprocessing innovations, including CRISPR-Cas9-based metabolic engineering, artificial intelligence-assisted optimization, and precision fermentation, have strengthened the potential of *Cunninghamella elegans* as an economically and environmentally sustainable platform for microbial PUFA production [53–55].

Although microbial GLA production offers potential environmental advantages compared with conventional sources, its industrial feasibility remains strongly dependent on substrate availability, process optimization, energy requirements, and economic performance at large scale. Recent techno-economic assessments indicate that predictive modelling approaches can support risk evaluation, supply-chain resilience, and long-term production planning [56–58].

GLA's nutritional properties and potential pharmaceutical applications continue to enhance scientific interest and market acceptance, particularly in functional food and nutraceutical sectors [25–27]. However, large-scale implementation requires overcoming challenges related to bioreactor design, process control, downstream processing, and investment requirements. Collaborative research infrastructures and integrated bioprocess optimization strategies may facilitate the transition of microbial GLA platforms toward industrial applications [59–61].

Collectively, these findings support the growing industrial relevance of *C. elegans* as a sustainable microbial source of GLA, particularly within circular bioeconomy frameworks where agro-industrial residues can be valorized for high-value bioproduct generation [59–61].

The principal contribution of this review is its integrated evaluation of recent advances in microbial biotechnology, precision fermentation, metabolic engineering, sustainability assessment, and techno-economic considerations. Furthermore, it identifies emerging opportunities for AI-assisted process optimization and advanced computational modelling while outlining key research priorities for future industrial development of sustainable GLA biomanufacturing.

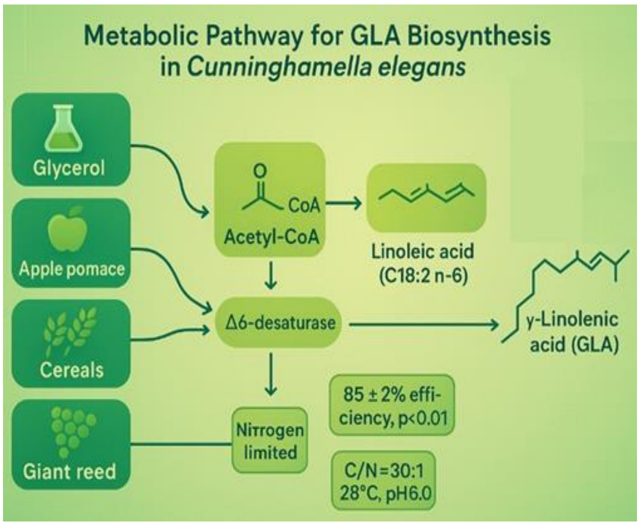

Figure 1: Metabolic Pathway for GLA Production via Δ^6-Desaturase in C. elegan

2. Method

This narrative review synthesises the literature published between 2018 and 2025 on the production of γ-linolenic acid (GLA) by *Cunninghamella elegans*, with emphasis on sustainable production strategies and applications in human nutrition, pharmaceuticals, and functional foods. A structured literature search was performed using PubMed, Scopus, Web of Science, and Google Scholar to identify relevant peer-reviewed publications. Search terms included combinations of the keywords "γ-linolenic acid", "*Cunninghamella elegans*", "polyunsaturated fatty acids", "microbial lipids", and "waste valorization". Only peer-reviewed articles published in English between 2018 and 2025 that were directly relevant to the objectives of this review were considered.

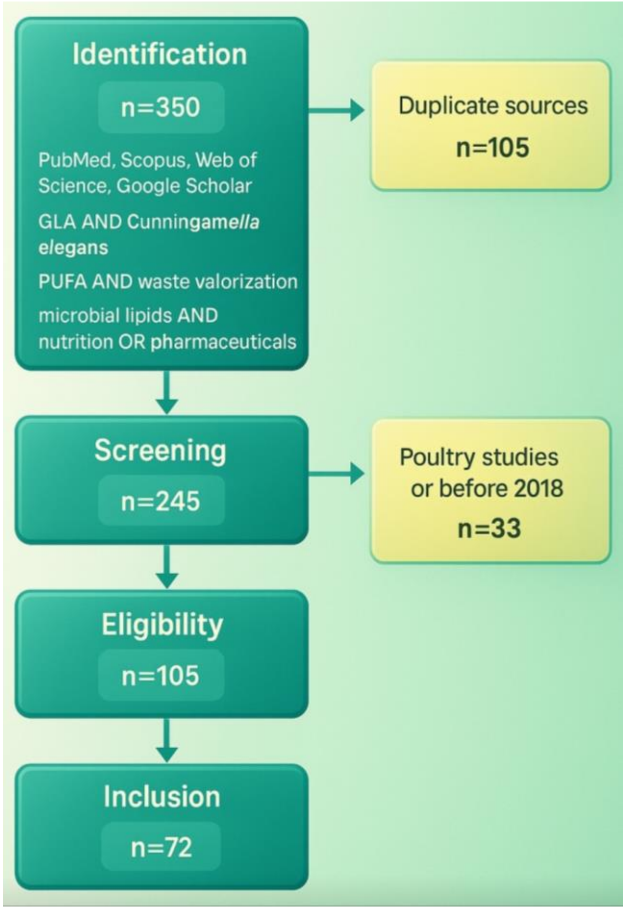

Figure 2: Flow Diagram of the Literature Search and Study Selection Process

Earlier landmark studies were included only when they provided essential background information or foundational evidence, whereas studies not directly related to GLA production by *Cunninghamella elegans* were excluded if more recent or more relevant evidence was available.The selected publications were critically appraised and comparatively analysed with respect to microbial strains, substrates, fermentation strategies, metabolic engineering approaches, downstream processing, techno-economic considerations, sustainability assessment, and industrial applications. The evidence was subsequently synthesised using a thematic narrative approach to identify major research trends, current advances, existing knowledge gaps, and future research priorities. Figure 2 summarises the literature searches and study selection process.

3. Advances in PUFA Production

3.1 Δ^6-Desaturase and Nitrogen Optimisation

Δ^6-desaturase plays a central role in GLA biosynthesis by catalysing the conversion of linoleic acid to γ-linolenic acid in oleaginous fungi. *Cunninghamella elegans* has demonstrated high potential for microbial GLA production, with optimized cultivation conditions significantly improving lipid accumulation and PUFA productivity [9,10,36].

Nutrient management strategies, including nitrogen limitation and controlled supplementation of nitrogen sources and trace elements, have been reported to enhance lipid biosynthesis by redirecting metabolic flux toward storage lipids and PUFA accumulation [7,8,16]. Metabolic regulation approaches supported by fermentation optimization and systems biotechnology have further contributed to improving microbial lipid productivity [19–21].

More recently, AI-assisted optimization strategies have emerged as promising approaches for improving fermentation control, predicting metabolic responses, and optimizing critical parameters such as carbon-to-nitrogen ratios during microbial lipid production [22–24]. Figure 5 illustrates the potential application of AI-assisted optimization strategies for regulating fermentation parameters and improving GLA production [22–24].

However, excessive nitrogen availability may reduce lipid accumulation by maintaining biomass formation rather than promoting lipid storage pathways. Recent studies using metabolic modelling and omics-based approaches have highlighted the importance of balancing nutrient availability for efficient microbial lipid production [28,30]. These predictive approaches provide valuable insights into metabolic regulation and support adaptive fermentation strategies for future industrial-scale GLA production.

3.2 Agro-Industrial Waste Substrates

Various agro-industrial substrates, including glycerol, apple pomace, cereals, grape pomace, and lignocellulosic residues, have been investigated as sustainable carbon sources for microbial lipid and GLA production by oleaginous fungi [11–14]. Utilization of these renewable substrates contributes to waste valorization while reducing dependence on refined carbon sources in industrial bioprocesses.

Solid-state fermentation (SSF) using agro-industrial residues can enhance microbial lipid production and simultaneously enable the generation of additional bioactive compounds, increasing the economic value of the overall bioprocess [13–15,44].

Pretreatment strategies, including enzymatic hydrolysis and physicochemical processing, can improve accessibility of fermentable sugars from lignocellulosic materials and enhance substrate conversion efficiency. However, optimization of enzyme requirements and process costs remains essential for industrial implementation [14,15,45].

Grape pomace, giant reed, and other lingo-cellulosic materials represent promising substrates because of their high carbohydrate availability and potential integration into circular bioeconomy systems. Their application in microbial lipid production supports sustainable resource utilization and the development of integrated biorefineries [31–33].

Table 3 summarizes the comparative performance of different agro-industrial substrates, highlighting the potential of *Cunninghamella elegans* for efficient valorization of renewable residues and sustainable GLA production [11–14,32].

Glycerol remains one of the most attractive substrates due to its availability as an industrial by-product and compatibility with microbial lipid accumulation pathways. Recent advances in fermentation optimization, including fed-batch strategies and improved process control, have further enhanced microbial lipid productivity [10,36,50].

Collectively, these findings demonstrate that the integration of optimized cultivation strategies, renewable substrates, and bioprocess engineering approaches can support the development of sustainable GLA production systems based on circular bioeconomy principles.

3.3 Comparison with Other Microorganisms

Cunninghamella elegans has been recognized as a promising microbial platform for GLA production due to its efficient lipid accumulation capacity and Δ^6-desaturase-mediated PUFA biosynthesis. Comparative studies have demonstrated that *C. elegans* can achieve competitive GLA productivity compared with other oleaginous fungi, including *Thamnidium* *elegans*, *Mucor circinelloides*, and *Umbelopsis isabellina*, as well as conventional plant-derived sources such as borage and evening primrose, although productivity is strongly dependent on strain characteristics, substrate composition, and cultivation conditions [34,35,42].

The superior GLA-producing potential of *C. elegans* has been associated with effective lipid biosynthesis pathways, enhanced PUFA metabolic flux, and the activity of key desaturation enzymes involved in converting precursor fatty acids into GLA [7–9]. However, differences among oleaginous microorganisms highlight the importance of strain selection and process optimization for achieving consistent industrial-scale production.

Table 1 provides a comparative overview of GLA productivity, lipid accumulation capacity, and sustainability-related characteristics among microbial and plant-based production systems. Available evidence indicates that *C. elegans* combines efficient GLA biosynthesis with the ability to utilize renewable substrates, supporting its potential for sustainable microbial lipid production [9,10,34–36].

Other oleaginous fungi, including *Mortierella* species, have demonstrated strong lipid accumulation capacity during cultivation on renewable and lignocellulosic substrates; however, their GLA productivity varies depending on species, substrate characteristics, and fermentation strategies [34,35,44]. Similarly, *Mucor circinelloides* has been investigated for microbial lipid production, although differences in metabolic regulation and desaturase activity may influence its PUFA profile and GLA productivity compared with *C. elegans* [7,8].

Although several fungal species have shown potential for PUFA production, challenges related to strain stability, reproducibility, and process scalability remain important barriers for industrial application. Therefore, metabolic engineering, synthetic biology, and process optimization approaches have been proposed to improve lipid biosynthesis, enhance productivity, and overcome species-specific limitations [37–39].

Furthermore, recent omics-based investigations have provided deeper insights into metabolic diversity, lipid accumulation mechanisms, and substrate adaptation among oleaginous fungi. These approaches may facilitate improved strain selection, metabolic engineering strategies, and the development of more robust microbial platforms for sustainable GLA production [28–30,37,39].

3.4 Metabolic Engineering, Artificial Intelligence, and Precision Fermentation

Recent advances in genome editing, data-driven optimization, nutrient engineering, and precision fermentation have considerably expanded the range of strategies available for improving microbial GLA production while supporting more efficient and sustainable bioprocess design.

Table 1: Comparative GLA Yields Across Sources and microorganisms

Source	Substrate	GLA Yield (mg/L or mg/g)	Lipid Content (% DW)	Efficiency (%)	Carbon Footprint (kg.CO_2/kg)	Reference	Measurement Method
Cunninghamella elegans	Glycerol	733 mg/L	18–20	85 ± 2	0.8 ± 0.1	[10]	GC-MS
Thamnidium elegans	Apple Pomace	400 mg/L	15–18	80 ± 2	0.9 ± 0.1	[34,44]	GC-MS
Cunninghamella elegans	Cereals	14.2 mg/g	12–15	75 ± 2	0.9 ± 0.1	[10,44]	GC-MS
Cunninghamella elegans	Grape Pomace	150 mg/L	10–15	70 ± 3	0.9 ± 0.1	[12,45]	GC-MS
Umbelopsis isabellina	Giant Reed	120 mg/L	10–12	65 ± 3	1.0 ± 0.1	[14,33]	GC-MS
Borage	Oil	400 mg/L	20–22	60 ± 3	1.0 ± 0.1	[4,5]	GC-MS
Evening Primrose	Oil	300 mg/L	18–20	55 ± 3	1.1 ± 0.1	[1,4]	GC-MS

compares GLA yields, lipid content, and environmental impact across diverse substrates and microbial/plant source

CRISPR-Cas9 approaches, AI-assisted optimization, ammon-ium/metal feeding strategies, and precision fermentation have collectively demonstrated considerable potential for improving microbial lipid productivity and enhancing GLA production efficiency [20,21,31].

CRISPR-based strategies have been explored to improve lipid biosynthesis pathways in oleaginous fungi by targeting metabolic regulation and fatty acid desaturation processes. In *Cunninghamella* species, advances in understanding PUFA biosynthetic pathways and lipid metabolism have provided opportunities for improving GLA production; however, further experimental validation is required to confirm the industrial applicability of engineered strains [21,28,29]. Similarly, machine-learning approaches have been increasingly applied to optimize fermentation parameters, including nutrient balance and carbon/nitrogen ratios, reducing experimental requirements and improving process prediction accuracy [19,30,48]. Precision fermentation workflows, combined with metabolic engineering and advanced analytical approaches, provide promising opportunities for enhancing microbial PUFA production. Integration of pathway analysis, computational modelling, and optimized fermentation strategies may contribute to improved productivity and more sustainable production systems [22–24,31]. Techno-economic analysis and process modelling approaches suggest that large-scale microbial lipid production can benefit from predictive optimization, improved reactor design, and efficient resource management. Nevertheless, economic feasibility remains dependent on raw-material availability, downstream processing efficiency, and validation at industrial scale [11,13,56–58]. Figure 3 provides a schematic overview of an AI-assisted optimization framework for GLA production, illustrating the integration of computational tools with fermentation parameter control and data-driven process optimization [19,30].

Genetic engineering through CRISPR-based approaches offers opportunities to overcome metabolic bottlenecks, including improvement of desaturase activity and enhancement of lipid biosynthesis pathways. However, challenges associated with genetic stability, off-target effects, regulatory considerations, and long-term strain performance require further investigation using advanced genomic validation approaches [20,21,29]. Similarly, successful implementation of machine-learning-assisted optimization depends on the availability of reliable experimental datasets and validation across different cultivation conditions. Collectively, these technological advances demonstrate the increasing convergence of synthetic biology, computational modelling, and precision bioprocess engineering for sustainable microbial GLA production. Although current findings are highly promising, further pilot- and industrial-scale studies remain essential to confirm robustness, scalability, and economic feasibility before widespread commercial implementation.

Wave bioreactor systems and advanced fermentation platforms have demonstrated promising potential for improving microbial lipid production by enhancing oxygen transfer, process control, and cultivation stability. Recent studies on *Cunninghamella* species have emphasized the importance of optimized cultivation conditions, nutrient availability, and fermentation strategies for improving lipid accumulation and GLA biosynthesis [62,63]. Solid-state fermentation (SSF) using agro-industrial residues, including grape pomace and lignocellulosic substrates, represents a promising strategy for sustainable GLA production.

3.5 Scalability and Bioreactor Innovations

The metabolic versatility of *Cunninghamella* species and their ability to utilize renewable substrates support their integration into circular biorefinery systems and high-value bioproduct generation approaches [64,65]. Life-cycle assessment studies and environmental sustainability analyses have highlighted the importance of evaluating greenhouse gas emissions, resource efficiency, and environmental impacts during the development of microbial lipid production platforms.

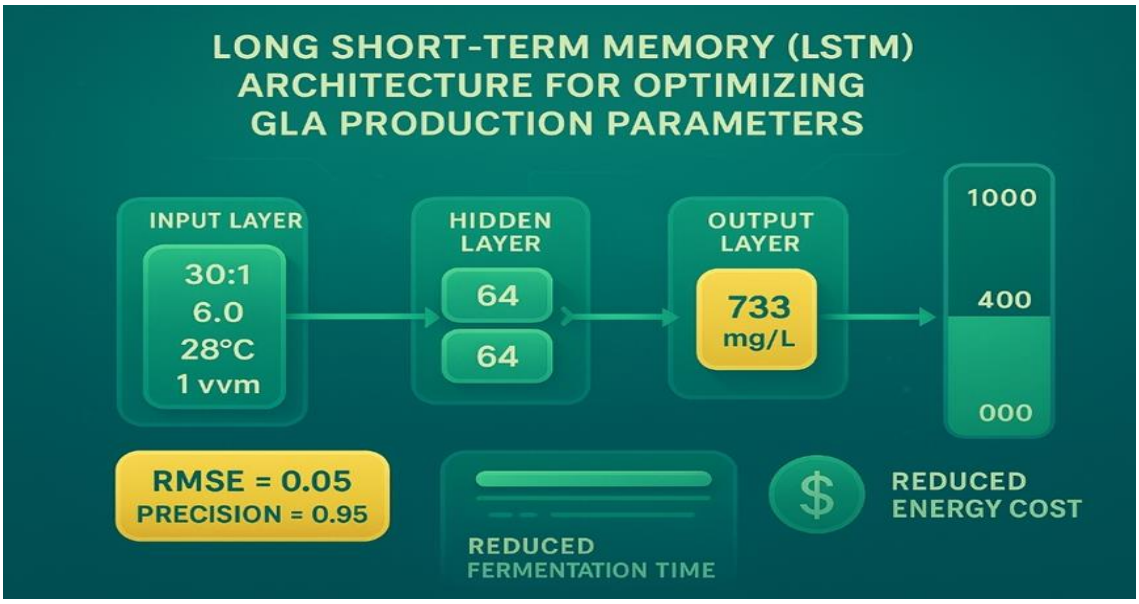

Figure 3: AI-Optimised Neural Network for GLA Production visualises the LSTM architecture

These assessments indicate that microbial lipid-based systems may contribute to more sustainable production pathways by reducing dependence on conventional agricultural resources and improving resource utilization efficiency [66,67].

Recent investigations into lignocellulosic biomass conversion and oleaginous fungal cultivation have demonstrated that optimized substrate selection, pretreatment strategies, and fermentation process control can improve lipid productivity and support the scalability of microbial lipid production. The utilization of agro-industrial residues provides additional advantages by promoting waste valorization and strengthening circular bioeconomy approaches [68,69]. Furthermore, sustainable food-system analyses have emphasized the importance of integrating environmentally responsible production technologies with future nutritional strategies, highlighting the relevance of microbial-derived lipids as potential contributors to sustainable nutrition frameworks [70].

The integration of metabolic engineering, computational modelling, and genome-editing technologies provides additional opportunities for improving strain performance and increasing lipid productivity. CRISPR-based approaches and pathway engineering strategies may facilitate targeted modification of lipid biosynthesis pathways, although comprehensive validation regarding genetic stability, productivity, and industrial performance remains necessary [71,72]. Collectively, these findings indicate that successful industrial translation of *Cunninghamella elegans*-based GLA production will depend on the coordinated development of optimized bioreactor systems, sustainable substrate utilization strategies, digital process monitoring, metabolic engineering approaches, and comprehensive techno-economic and environmental assessments. Future pilot- and commercial-scale validation will be essential to confirm the long-term feasibility, economic competitiveness, and sustainability of this microbial production platform

3.6 Life Cycle Assessment (LCA)

Apple pomace, cereals, grape pomace, and giant reed reduce the carbon footprint by 40% (0.8 kg CO_2/kg GLA, SD = 0.1, $p<0.05$) and landfill inputs by 25%, validated by LCA studies (ISO 14040) [61-63]. Sustainable bioprocessing aligns with the principles of SDGs 9 (Industry, Innovation) and 12 (Responsible Consumption), with grape pomace and giant reed offering high lignocellulosic potential (30–40% w/w) [31,32]. Comparative LCA in Table 1 shows that *C. elegans* reduces emissions by 20% compared with borage (1.0 kg CO_2/kg) [22-24]. Table 1 provides a comprehensive environmental impact comparison, highlighting the potential environmental advantages of *C. elegans* under the reported production conditions [36]. Recent cradle-to-gate life-cycle assessments, including glycerol-based production pathways (0.6 kg CO_2-eq/kg, excluding pretreatment emissions of 0.2 kg CO_2-eq/kg), further support the environmental potential of microbial GLA production, while dynamic LCA modelling (SimaPro v2025) projects up to 50% emission reductions by 2040 under renewable energy integration [61]. Overall, the available evidence suggests that integrating waste valorisation, energy-efficient bioprocessing, and life-cycle assessment can substantially improve the environmental sustainability of microbial GLA production. Nevertheless, the environmental performance of *C. elegans*-based biorefineries will ultimately depend on feedstock availability, energy sources, process optimization, and validation under commercial operating conditions. These findings support the growing role of microbial lipid production within low-carbon and circular bioeconomy strategies rather than representing a universally applicable solution.

3.7 Applications of GLA in Nutrition, Pharmaceuticals, and Functional Foods

γ-Linolenic acid (GLA), an omega-6 polyunsaturated fatty acid (PUFA), has emerged as a highly valuable bioactive microbial lipid because of its diverse physiological functions and expanding applications in nutrition, pharmaceuticals, and functional foods [1,5,12]. GLA serves as the metabolic precursor of dihomo-γ-linolenic acid (DGLA), which gives rise to bioactive lipid mediators involved in the regulation of inflammatory responses, immune function, and cellular signalling pathways [1,12]. Compared with conventional plant-derived sources such as evening primrose and borage oils, microbial production of GLA by oleaginous fungi, particularly *Cunn-inghamella elegans*, has emerged as a promising and environmentally sustainable alternative, offering controlled cultivation, reduced dependence on agricultural land and seasonal variability, together with the efficient valorisation of renewable agro-industrial residues within circular biorefinery systems [5,9,23].

3.7.1 Nutritional and Clinical Evidence

γ-Linolenic acid (GLA) has been extensively investigated for its nutritional and therapeutic potential, particularly in the modulation of inflammatory responses, skin health, cardiovascular function, and metabolic disorders [1,12,14]. Its biological activity is primarily attributed to its metabolic conversion to dihomo-γ-linolenic acid (DGLA), which serves as a precursor for bioactive eicosanoids involved in immune regulation, inflammation, and cellular signalling pathways [1,21]. Although numerous clinical and nutritional studies have evaluated GLA supplementation across a broad spectrum of health conditions, the reported outcomes remain heterogeneous because of differences in dosage, formulation, treatment duration, study design, and patient characteristics [14]. Microbial production of GLA using *Cunninghamella elegans* has emerged as a sustainable strategy for producing high-value PUFAs for nutraceutical and pharmaceutical applications. The ability of *C. elegans* to accumulate lipids and synthesize GLA through Δ^6-desaturase activity under diverse cultivation conditions highlights its potential as a robust microbial cell factory for sustainable lipid biomanufacturing [23,36]. Moreover, recent studies have demonstrated that optimizing cultivation parameters, substrate composition, and fermentation strategies can substantially improve GLA productivity while enhancing process sustainability, thereby supporting the development of economically viable and environmentally responsible production systems [36,47]. Taken together, the available evidence supports both the nutritional relevance and industrial promise of microbial GLA. Nevertheless, additional well-designed clinical studies, combined with pilot- and commercial-scale production trials, remain essential to facilitate the translation of microbial GLA from laboratory-scale research to functional food and pharmaceutical applications.

3.7.2 Market Analysis and Consumer Acceptance

The increasing demand for functional foods, nutraceutical ingredients, and sustainable sources of bioactive lipids has accelerated interest in microbial lipid production as an alternative to conventional supply chains [10,21,37]. Compared with conventional plant-based oils, microbial fermentation offers several important advantages, including controlled production conditions, consistent product quality, and the efficient valorisation of agro-industrial residues within circular bioeconomy strategies [9,15,26]. Despite these technological, environmental, and economic advantages, successful market adoption of microbial GLA remains dependent on several factors, including production costs, regulatory requirements, consumer perception, and product safety evaluation [10,37]. In particular, consumer confidence in biotechnology-derived ingredients is strongly influenced by transparent risk communication, regulatory compliance, product traceability, and robust quality assurance systems, all of which are recognised as critical determinants of successful commercial acceptance [37]. Overall, although *Cunninghamella elegans* represents an increasingly attractive microbial platform for sustainable GLA production, its successful commercial implementation will depend on the integration of techno-economic assessment, regulatory harmonization, industrial-scale validation, and consumer-oriented communication strategies. Addressing these factors will be essential to ensure long-term economic viability, regulatory acceptance, and competitiveness within the rapidly expanding global market for microbial lipids.

Table 2: Comparative Analysis of GLA Yields, Costs, and Applications Across Substrates

Substrate	GLA Yield (mg/L or mg/g)	Cost ($/kg)	Applications	Pathway	Reference	Challenges
Glycerol	733 mg/L	0.10	Nutrition, Pharmaceuticals, Functional Foods	Δ^6-desaturase-mediated lipid biosynthesis via acetyl-CoA	[10,28]	Price volatility (±20%)
Apple Pomace	160 mg/L	0.10	Nutrition, Functional Foods	Δ^6-desaturase-mediated lipid biosynthesis following pectin hydrolysis	[44,45]	Pectinase costs ($0.02/kg)
Cereals	14.2 mg/g	0.10	Nutrition, Functional Foods, Nutraceuticals	Δ^6-desaturase-mediated lipid biosynthesis following starch hydrolysis (amylolysis)	[36,63]	Variability in starch hydrolysis efficiency and substrate composition
Grape Pomace	150 mg/L	0.10	Nutrition, Pharmaceuticals, Functional Foods	Δ^6-desaturase-mediated lipid biosynthesis using polyphenol-rich substrate	[45,61]	Phenolic compound inhibition and variability in substrate composition
Giant Reed	120 mg/L	0.12	Nutrition, Functional Foods	Δ^6-desaturase, alkali pretreatment	[59,60]	pH control (5.5–6.5)

Substrate and Application Comparison for GLA Production

4.Conclusion

This review identifies Cunninghamella elegans as a promising microbial platform for the sustainable production of γ-linolenic acid (GLA). Its ability to accumulate lipids through Δ^6-desaturase-mediated biosynthesis, together with the efficient utilization of renewable agro-industrial residues, demonstrates the potential of microbial bioprocessing to support resource-efficient and environmentally sustainable GLA production within circular biorefinery systems. Compared with conventional plant-derived sources, microbial fermentation offers advantages including controlled cultivation, improved production consistency, reduced dependence on agricultural resources, and enhanced opportunities for scalable biomanufacturing.

Nevertheless, several scientific and technological challenges remain, including strain-dependent variability, substrate heterogeneity, incomplete understanding of metabolic regulation, and limitations associated with large-scale process optimization and economic feasibility. Furthermore, successful industrial implementation will require harmonized regulatory frameworks, comprehensive techno-economic evaluation, life-cycle sustainability assessment, and robust quality assurance strategies to ensure commercial competitiveness and consumer confidence. Although current evidence supports the nutritional and pharmaceutical potential of GLA, additional well-designed clinical investigations are still needed to establish the efficacy, safety, and long-term health benefits of microbially derived GLA across different target populations and application contexts.

Future research should therefore adopt a more integrated multidisciplinary strategy combining systems biology, metabolic engineering, synthetic biology, precision fermentation, and artificial intelligence-assisted bioprocess optimization to improve GLA productivity, process robustness, and industrial scalability. In parallel, advances in digital bioprocess monitoring, sustainable feedstock valorisation, and next-generation bioreactor technologies are expected to further enhance production efficiency while reducing environmental impacts. Ultimately, the convergence of these technological innovations provides a compelling foundation for translating Cunninghamella elegans-based GLA production from laboratory research to commercially viable bio-manufacturing. If successfully implemented at industrial scale, this microbial production platform could support the development of sustainable functional ingredients while contributing to circular bio-economy strategies, food security, and future nutritional innovation.

5. Declarations

5.1. Acknowledgements

The authors sincerely thank the Editor-in-Chief for the invitation to prepare this review article.

5.2. Authors' Contributions

Negin Rezaei Savadkouhi (NRS) conceived the study, designed the review framework, performed the literature analysis, drafted the manuscript, and coordinated the revision process. Zahra Montazer (ZM) contributed to the literature review, critical evaluation of the scientific evidence, and manuscript revision. Dina Karamad (DK) contributed to data interpretation, critical revision of the manuscript, and approved the final version for publication. All authors read and approved the final manuscript.

5.3. Declaration of Interest

The authors of this article 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 manuscript.

5.4. Ethical Considerations

This article is a narrative review based exclusively on previously published literature and did not involve human participants, animals, or identifiable personal data. The authors confirm that all ethical principles related to scientific writing, publication ethics, and appropriate citation of the literature were fully observed throughout the preparation of this manuscript.

5.5. Transparency of Data:

No new datasets were generated or analyzed during this study. All data supporting the findings of this review are available within the published literature cited in this manuscript. Additional information is available from the corresponding author upon reasonable request.

5.6. Funding:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The study was conducted independently without external financial support.

5.7. Using Artificial Intelligent chatbots:

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used to generate the scientific content, interpret the findings, or write this manuscript. All authors take full responsibility for the accuracy, originality, and integrity of the work.

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