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Microbiology PERSPECTIVE

Mass production of microbial protein using low-value materials

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Received: July 13, 2025; Accepted: December 15, 2025; Published Online: January 7, 2026; https://doi.org/10.59717/j.xinn-life.2026.100200

Citation: Chen Z., Deng J., Han P., et al. (2026). Mass production of microbial protein using low-value materials. *The Innovation Life* **4**:100200.

Global demand for protein now exceeds 200 million tonnes annually and is projected to rise to around 280 million tonnes by 2050. Meeting this demand requires diversifying protein sources beyond conventional animal- and plant-based products. Microbial proteins offer a promising alternative to traditional food and feed sources by reducing dependence on conventional agricultural systems and mitigating the environmental impacts of livestock farming. However, large-scale production of microbial proteins is currently hindered by the scarcity of cost-effective raw materials and the lack of efficient bioconversion technologies. This paper outlines strategies to accelerate the near-term scale-up of microbial proteins using low-value carbon sources. These include establishing feedstock databases, engineering robust strains for crude substrate utilization, and integrating advances in metabolic and process engineering. We further emphasize the importance of pilot- and demo-scale validation, regulatory streamlining, and cross-sector collaboration to enable sustainable and economically viable industrial deployment.

ACCESSIBLE LOW-VALUE RAW MATERIALS

Lignocellulosic biomass and carbon dioxide (CO_2) have garnered significant attention as feedstocks for bioconversion. However, given the current challenges in achieving market viability and the extensive literature on the topic, this paper does not focus on reviewing these materials. Here, we characterize low-value raw materials as those that are utilizable by microorganisms, are abundantly available, and have projected or current prices lower than glucose on an equivalent molar carbon basis. These materials primarily contain methanol, acetate, and glycerol, followed by methane, formic acid, and ethanol.

Methanol, primarily sourced from fossil fuels, is produced at a global capacity of approximately 90 million tons annually, with 65% derived from natural gas and the remainder from coal (Figures 1A-B). Given its abundance and low cost, waste methanol from fossil sources represents a promising carbon feedstock for microbial bioconversion into value-added products. Although renewable methanol derived from green hydrogen and captured CO_2 remains economically less competitive, the tightening of sustainability regulations in Europe is expected to enhance its competitiveness.[1] Methanol exhibits exceptional energetic efficiency in microbial processes, achieving 80–90% conversion efficiency under anaerobic conditions via acetogens and up to 50% efficiency under aerobic conditions through the ribulose monophosphate cycle, both surpassing the efficiency of H_2/CO_2 or CO, and other C1 feedstocks.[2] Given its sustainable source and high energetic efficiency, methanol is a crucial feedstock for microbial protein production.

Acetate is produced globally at a substantial scale, with approximately 12.9 million metric tons annually. Conventional acetate synthesis predominantly relies on chemical methods such as methanol carbonylation and hydrocarbon oxidation, which account for over 80% of total production (Figure 1B). Industrial waste acetate has recently gained attention as an underutilized yet readily available carbon source for microbial protein production, enabling near-term opportunities for waste valorization. In parallel, harnessing *Acetobacter* species to produce acetate from food waste, lignocellulosic biomass, and CO_2/H_2 offers a promising and environmentally friendly alternative, although its large-scale application may require further efforts.

Crude glycerol, a glycerol-rich aqueous solution containing 60–85% (w/w) glycerol, is primarily generated as a by-product during biodiesel production. For every 10 metric tons of biodiesel synthesized, approximately 1 metric ton of crude glycerol (approximately 90% purity, w/w) is generated.[3] In 2023, global biodiesel production reached about 5 million metric tons, resulting in the production of around 0.5 million metric tons of crude glycerol. According to data from the World Bioenergy Association, the majority of this crude glycerol is sourced from major biodiesel-producing regions, including Indonesia, the EU, Brazil, the USA, and China. Additional glycerol-containing by-products are also generated in other oleochemical and bioethanol production units. The utilization of crude glycerol for microbial protein production offers a valuable and sustainable alternative to its conventional sources (Figures 1A-B).

While methanol, acetate, and glycerol are primary substrates for microbial protein production, methane, formate, and ethanol also merit consideration. Methane, the simplest and most abundant hydrocarbon, constitutes 70–90% of natural gas. Global proven natural gas reserves were estimated at 7,537.7 trillion cubic feet by 2024, sufficient to meet current demand for the next 50 years. Additionally, methane can be sourced from biogas, with global production growing at a 3% annual rate to reach 4.3 billion cubic feet per day in 2023 (Thunder Said Energy). Approximately 1.3 billion tons of food, nearly one-third of global production, is lost or wasted annually. This highlights the potential of anaerobic digestion of food waste to produce biogas, thereby providing sustainable feedstocks for microbial protein production. While current ethanol production primarily depends on corn and sugarcane, lignocellulosic ethanol and ethanol derived from one-carbon sources present attractive substitute as feedstocks for microbial protein production. Moreover, formate, produced as a byproduct of chemical and energy processing, has the potential to serve as a scalable raw material for large-scale microbial protein synthesis.

Beyond carbon sources, nitrogen and energy are critical determinants of production costs. In microbial protein production, nitrogen-related expenses typically account for less than one-fifth of carbon-related costs. However, utilizing waste resources can further reduce nitrogen input costs. For example, nutrient-rich wastewater from legume processing and biogas slurry can serve as highly cost-effective nitrogen sources, enhancing the economic viability of microbial protein production. Renewable energy, particularly solar photovoltaic and wind power, is poised to dominate global electricity generation. By 2030, these sources are projected to supply over 50% of global electricity demand, with their combined levelized cost of energy expected to undercut fossil fuels, even without subsidies.

TECHNICAL REQUIREMENTS

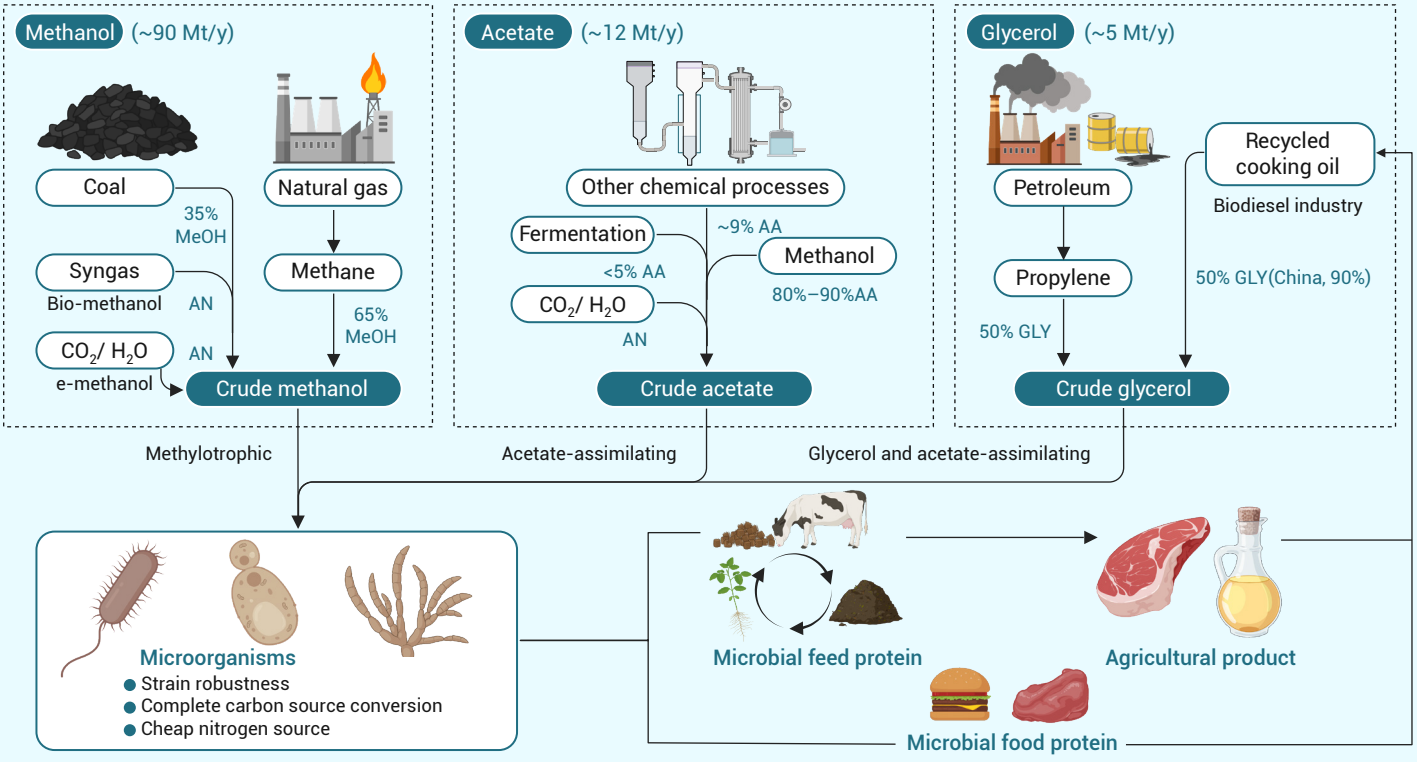
Microbial proteins remain more expensive than plant-based proteins but are already comparable to, or even cheaper than, animal-derived proteins.[4] Further improvements in feedstock utilization and reductions in process engineering costs could enhance their competitiveness even more. The use of crude materials offers a promising strategy to reduce production costs by 10–30% compared with pure feedstocks. However, their complex composition, comprising diverse fermentable carbon sources and various fermentation inhibitors, creates significant technical challenges. In light of these challenges, the development of microbial strains capable of efficiently converting mixed carbon sources and withstanding high-stress environments is paramount. Notably, compounds such as methanol and acetate are inherently cytotoxic at moderate concentrations. When combined with other inhibitory substances present in crude raw materials, they can severely hinder microbial fermentation performance. While glycerol itself is non-cytotoxic, crude glycerol typically contains acetate, further complicating its utilization. In addition, synergistic toxicity and catabolite repression in mixed-carbon

A Estimation of microbial protein production cost based on different carbon substrates

Substrate	Recent price in China ($/tonne)	Average purity(%)	Example microorganisms	Average SCP content (DCW%)	$Y_{protein/substrate}$ (g/g)	Substrate cost ($/kg protein)	Data source
Glucose	355–455	≥90	*Pichia pastoris*	51.60	0.18	1.97–2.81	10.1016/j.bej.2008.09.020
			Pleurotus ostreatus	44.80	0.22	1.61–2.30	10.1039/D2FB00058J
			Cupriavidus necator	69.00	0.32	1.11–1.58	10.1016/j.jbiotec.2024.04.009
Methanol	270–327	≥99	*P. pastoris*	50.60	0.22	1.23–1.50	10.1186/s12934-023-02198-9
			P. pastoris (engineered)	67.21	0.31	0.87–1.07	10.1186/s13068-023-02428-7
			Enterobacter aerogenes	58.00	0.31	0.87–1.07	10.1002/bit.260290310
Acetate	370–469	≥99	*P. pastoris*	45.00	0.20	1.85–2.37	
			C. necator	46.00	0.23	1.61–2.06	10.1016/j.biortech.2020.124021
			Methylobacterium extorquens	82.00	0.35	1.06–1.35	
Crude glycerol	170–213	60-80	*P. pastoris*	50.20	0.24	0.89–1.48	10.1016/j.bej.2008.09.020
			Yarrowia lipolytica	47.20	0.20	1.06–1.78	10.1016/j.biortech.2013.03.010
			Wickerhamomyces anomalus	33.00	0.26	0.82–1.37	10.5433/1679-0375.2019v40n2p179

Note: 1. Given regional and temporal variability in substrate prices, the substrate cost for protein production can be recalculated accordingly.
2. Microbial protein production costs were calculated based on $Y_{protein/substrate}$ as the core reference, excluding costs related to energy, nitrogen sources, water, and other process-associated inputs.

B Accecible raw materials & technology demands



C Organizational model

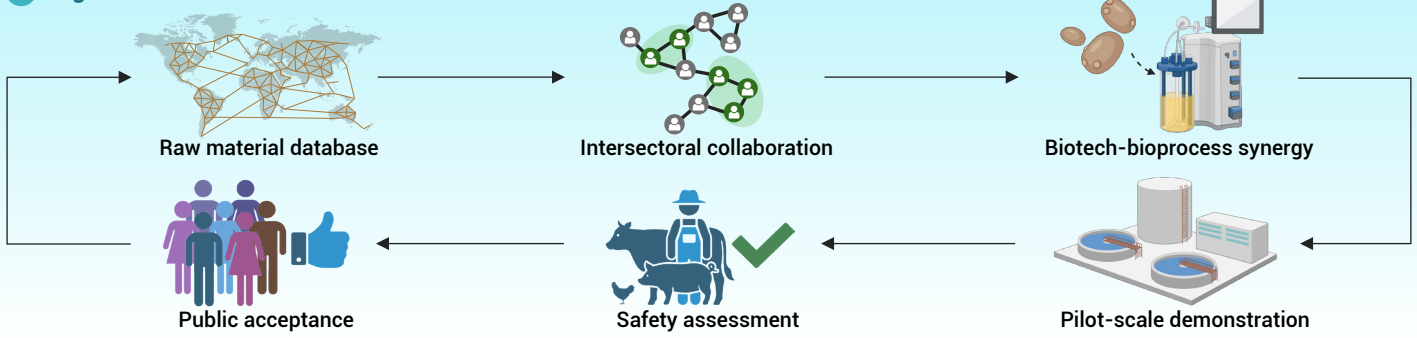


Figure 1. Strategy for mass production of microbial protein using low-value materials (A) Estimation of microbial protein production cost based on different carbon substrates; (B) Accessible raw materials and technology demands to support large-scale microbial protein production; (C) Organizational models for achieving sustainable microbial protein manufacturing in the future. AN, almost negligible; MeOH, methanol; AA, acetate; GLY, glycerol. Mt/y, million metric tons per year.

systems can significantly impact fermentation. For example, methanol induces oxidative and formaldehyde stress. Co-substrates such as glucose, glycerol, or ethanol, when combined with methanol, can affect methanol pathway gene expression and alter protein yields.[5]

To tackle these issues, modern genetic modification and directed evolution techniques provide effective approaches for enhancing microbial strain robustness and substrate conversion efficiency. For instance, iterative directed evolution successfully increased methanol tolerance of the methy-

lotrophic yeast *Pichia pastoris* from 4% (m/v) to 10%.[6] Extensive research has demonstrated the potential of microorganisms in utilizing crude glycerol to synthesize organic acids or proteins. However, a particularly promising avenue lies in the direct conversion of glycerol and acetate mixtures derived from biodiesel production, which could further reduce microbial protein production costs. Among the microbial candidates, *Kluyveromyces marxianus* stands out for its ability to metabolize both glycerol and acetate to produce microbial protein. Recognized as a safe microorganism under food and feed regulations, this yeast offers potential for large-scale applications. Enhancing its tolerance to raw materials and improving its conversion efficiency could significantly facilitate industrial-scale production. Furthermore, metabolic pathway reconstruction to enhance carbon atom economy holds promise for achieving protein yields that surpass conventional theoretical limits.[7]

While genetic and metabolic strategies can enhance microbial strain performance, the economic viability of microbial protein production also critically depends on process engineering. Key aspects include feedstock pretreatment, feeding strategies, and overall process control. Feedstock pretreatment can improve conversion efficiency but often increases costs, highlighting the need for economically viable approaches. One promising strategy is to tailor pretreatment methods to the tolerance of specific microbial strains. Feeding strategies and process control are equally important. In the presence of inhibitory compounds, tailored feeding provides a direct and cost-effective means to alleviate repression. Furthermore, the low carbon concentrations in crude feedstocks often necessitate large fermentation volumes, emphasizing the potential benefits of feedstock concentration or the use of continuous or semi-continuous fermentation processes.[8] In any case, overall cost-effectiveness should remain a key consideration when designing process engineering strategies.

In addition to conventional methods, green technologies present innovative pathways for microbial protein production by sustainably transforming CO_2 into platform compounds such as methanol, formic acid, and ethanol.[9] These green resources, similar to petrochemical materials, possess mixed fermentable carbon sources and fermentation inhibitors. Therefore, the successful integration of bioprocessing with chemical feedstocks, along with advancements in their utilization and fermentation tolerance, is crucial. An engineered *P. pastoris* strain in a 300-L pilot fed-batch using methanol, achieved 63.37 g DCW/L with 50.6% protein (w/w DCW), estimating on-bioreactor production costs of 8.16 USD/kg protein.[10] Enhancing pilot-scale research efforts will further solidify the foundation for large-scale applications.

ORGANIZATIONAL MODEL

To enable the large-scale application of microbial proteins while ensuring cost reduction and enhancing market competitiveness, a structured approach is essential (Figure 1C). (1) Addressing information asymmetry: A fundamental barrier to optimizing microbial protein production lies in the asymmetry of information regarding available raw materials. Conducting comprehensive surveys of raw material availability and establishing a centralized database can provide stakeholders with the necessary insights to make informed decisions. (2) Balancing raw material use: To prevent overreliance on specific raw materials and ensure sustainable growth, balance the competitive use of resources by industry associations and government initiatives is crucial. (3) Intersectoral collaboration: The success of microbial protein production relies on collaboration across multiple sectors, including chemical, biology, feed, and food processing. In 2024, Solar Foods entered a partnership with Fazer to commence commercial-scale production of Solein, a microbial protein synthesized from CO_2 and hydrogen, and to drive its market introduction. Solein-containing products have already been featured at the "Taste the Future" snack bar in Singapore. Such cross-sector collaborations help bridge technical, regulatory, and market barriers and thus accelerate the scale-up and adoption of microbial protein solutions. (4) Synergy of biotechnology and biochemical engineering: Biotechnological tools enhance the performance of microbial strains for synthesizing ideal proteins from raw materials. Biochemical engineering provides strategies for optimizing fermentation processes. The mutual feedback between these two fields facilitates a systematic resolution of challenges in microbial protein production, particularly at pilot-scale and beyond. (5) Regulatory and safety considerations: Proactive safety assessments and streamlined regulatory approval processes facilitate the commercialization of microbial protein. (6) Consumer acceptance: Scientific and proactive communication strategies help address misconceptions and foster public confidence in microbial protein products. Educating consumers on the environmental and nutritional merits of microbial protein promotes adoption and cultivates a favorable market environment.

OUTLOOK

To advance large-scale microbial protein production, effective conversion of low-value materials is essential. The feasibility of current raw materials heavily depends on production scale, supply chain economics, and technological capabilities. Most existing studies have focused on pure substrates and small-scale demonstrations. Future progress will require research on mixed or raw substrates, coupled with pilot-scale validation to enhance industrial relevance. Interdisciplinary collaboration among bioengineering, chemical engineering, and food technology will be critical to overcoming these challenges. The growing adoption of renewable energy, particularly solar power, offers opportunities to reduce energy costs in microbial fermentation. Additionally, leveraging the environmental benefits of microbial systems to convert sustainable feedstocks into proteins supports global efforts to mitigate greenhouse gas emissions. Ongoing advances in this field present a near-term opportunity to produce low-cost microbial proteins from raw materials containing conventional platform compounds, such as methanol, acetate, and glycerol.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Strategic Priority Research Program of the Chinese Academy of Sciences (XDC0110303), and by the Taishan Scholars Program (tsqn202408308). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Shi'an Wang and Dong Li conceived the idea. Shi'an Wang, Zhihang Chen, Jiajun Deng and Peijie Han prepared the manuscript. Zhihang Chen prepared the figure. Shi'an Wang and Dong Li revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.