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REVIEW

Microbial carbon utilization for a sustainable future

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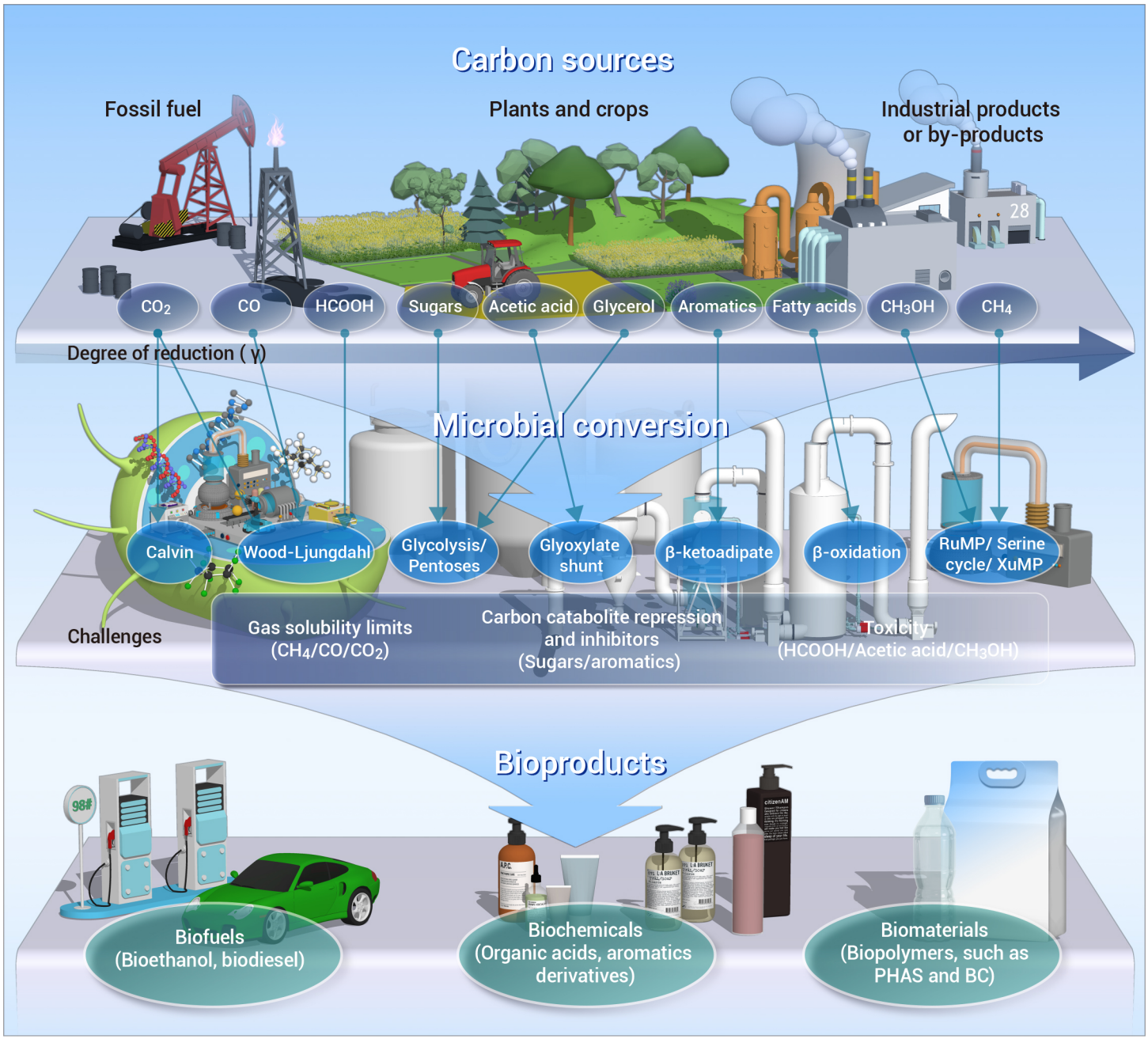
Received: April 16, 2025; Accepted: September 24, 2025; Published Online: September 29, 2025; https://doi.org/10.59717/j.xinn-life.2025.100159

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Microbial carbon utilization is fundamental to green biomanufacturing.
- Enhancing the microbial ability and efficiency is crucial for the development of biomanufacturing.
- Optimizing the ways to obtain carbon sources is an effective strategy to improve environmental benefits.

REVIEW

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Received: April 16, 2025; Accepted: September 24, 2025; Published Online: September 29, 2025; https://doi.org/10.59717/j.xinn-life.2025.100159

Citation: Wang F., Wu T., Wang L., et al. (2025). Microbial carbon utilization for a sustainable future. *The Innovation Life* **3**:100159.

Microbial utilization of diverse carbon sources presents transformative potential for sustainable green biomanufacturing. This review examines ten distinct carbon sources including carbon dioxide, carbon monoxide, formic acid, sugars, aromatic compounds, acetic acid, glycerol, fatty acids, methanol, and methane, with an emphasis on their degree of reduction. We discuss their origins, bioconversion, and practical advantages and limitations, while also evaluating their technical feasibility and sustainability trade-offs. Finally, a comparative life-cycle assessment quantifies the climate impact of microbial utilization of these carbon sources for bioethanol production. Notably, the production of carbon sources contributes the most significant environmental impact, emphasizing the importance of optimizing carbon source acquisition pathways for sustainable green biomanufacturing. The integration of microbial carbon metabolism into biomanufacturing frameworks, enhancement of biorefinery strategies, and collaboration with geographical distributions of various resources emerge as pivotal strategies for advancing circular economies, mitigating climate change, and fostering resource-efficient production systems. This synthesis underscores the critical role of carbon source selection in aligning microbial processes with global sustainability goals.

INTRODUCTION

The accelerating impacts of climate change have prompted an urgent reassessment of our reliance on fossil fuels, which are a significant contributor to greenhouse gas emissions.[1-3] The Intergovernmental Panel on Climate Change (IPCC) has emphasized the need for immediate and substantial reductions in carbon dioxide (CO_2) emissions to limit global warming to below 1.5ºC above pre-industrial levels.[4] As fossil reserves diminish and the consequences of their extraction and consumption become increasingly severe, the search for sustainable alternatives is more crucial than ever. Biomanufacturing provides methods to produce fuels and chemicals in a carbon-neutral manner by biological systems.[5] Microorganisms, with their inherent metabolic diversity, offer a sustainable alternative for the production of fuels, materials and chemicals traditionally derived from fossil resources.[6] The biomanufacturing sector has experienced significant breakthroughs in recent years, leveraging microorganisms' ability to convert various carbon sources into value-added products.[7] This development is pivotal in the pursuit of sustainable practices, as it promises to reduce our carbon footprint, mitigate climate change, and promote a circular economy and sustainable future.[8-10]

Biomanufacturing with microbes fundamentally leverages biological systems—such as bacteria, yeast, algae, and their cellular factories—to produce target products from feedstocks at flexible scales. enables the creation of a wide array of chemicals, fuels, materials, and other value-added products through microbial fermentation.[11] This biological approach holds numerous advantages over traditional chemical synthesis, including the reduction of energy consumption and the elimination of harmful byproducts.[8,12] Furthermore, utilizing lignocellulosic biomass, waste, byproducts and other organic materials as feedstocks for biomanufacturing expands the range of accessible carbon sources.[13,14] While the inherent versatility of microbial systems facilitates the development of sustainable production processes that align with circular economy principles.[9,15,16]

Various carbon substrates exhibit significantly different degree of reduction (γ),[17,18] thereby influencing how microorganisms metabolize them and the energy they derive in the process. For instance, the carbon sources with lower degree of reduction, such as CO_2, necessitate higher energy input for activation and conversion into useful products. In contrast, carbon sources with higher degree of reduction, such as glucose, contain greater chemical energy, facilitating energy production and biomass generation. However, the conversion of these less reactive carbon sources into valuable products represents a significant environmental and economic opportunity (Figure 1). Therefore, understanding the degree of reduction of available carbon sources enables researchers to optimize fermentation conditions, maximizing product formation and minimizing waste. This optimization not only enhances the economic feasibility of microbial biomanufacturing but also aligns with the goals of environmental sustainability.

Carbon sources play a central role in microbial bioconversion, directly influencing cell growth, product formation, and energy metabolism. Table S1 provides a comparative overview of ten representative carbon sources used in microbial fermentation processes illustrating the diversity and potential of these substrates. This highlights the trade-offs inherent in carbon source selection—balancing efficiency, scalability, and sustainability—and underscores the need for integrated metabolic engineering and process optimization. The integration of microbial carbon utilization in biomanufacturing offers a sustainable solution to the challenges presented by climate change and the unsustainable consumption of fossil fuels. By leveraging the metabolic capabilities of microorganisms to convert a diverse array of carbon sources into valuable products, we can move towards a more circular and low-carbon economy. The purpose of this review is primarily focused on the research progress in the microbial carbon utilization. We have categorially summarized the microbial utilization of ten carbon sources including their representative sources, microbial chassis, utilization efficiency, products and the advantages and challenges associated with different carbon sources utilization. Finally, we assess the climate change impacts of various carbon utilization strategies employed by microorganisms through comparative life-cycle assessments, and briefly discuss the economic feasibility of different carbon sources.

CARBON DIOXIDE (CO_2)

Overview of CO_2

CO_2 is the most abundant source of carbon on earth, with approximately

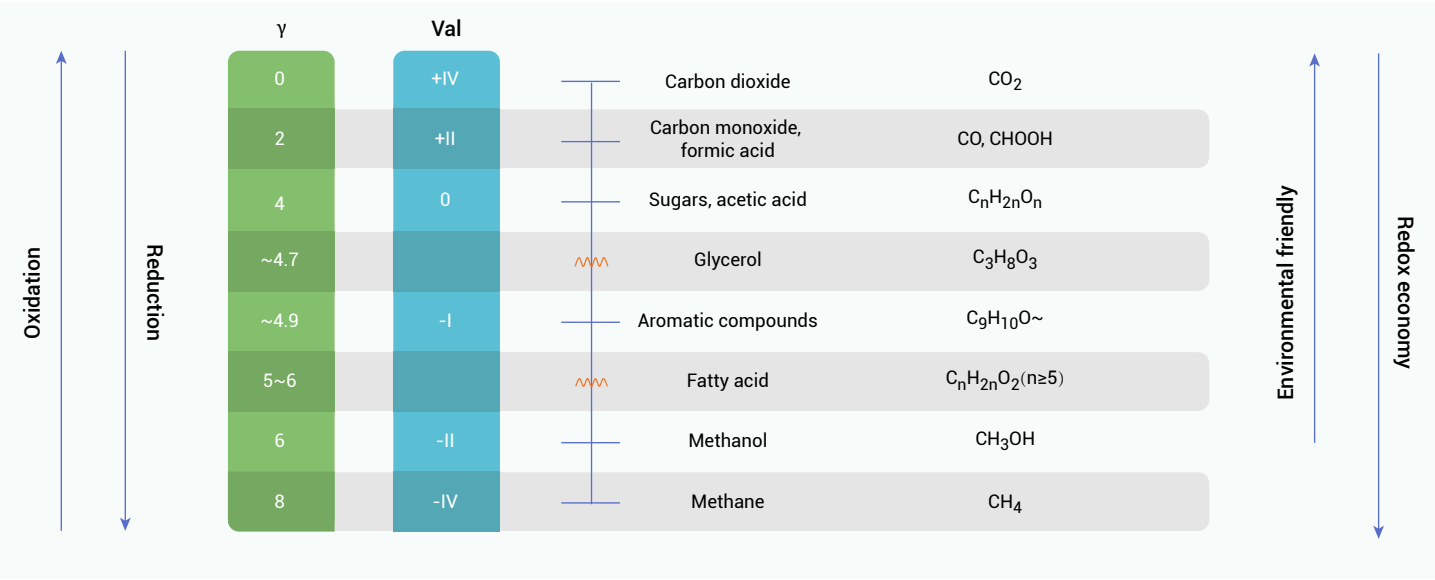

Figure 1. Degree of reduction (γ) and relationships of common carbon sources for microorganisms, Val refers the valence of carbon.

37.41 billion tonnes emitted from fossil fuel combustion and industrial processes in 2024.[19] Rather than being perceived solely as a pollutant, third-generation biorefineries aim to convert CO_2 into fuels and chemicals.[20] Significant sources of CO_2 for microbial carbon utilization include atmospheric CO_2, industrial waste gases, and biogas (Figure 2). Although atmospheric CO_2, which constituting 0.04 vol.%, is abundant, it remains underutilized, posing challenges for autotrophic cell growth. Increasing CO_2 levels through direct air capture (DAC) presents a potential solution, albeit with significant cost and energy requirements.[21] Nevertheless, the conversion of CO_2 into valuable products through microbial processes, particularly via microalgae and cyanobacteria to produce sugars or carbohydrates, shows considerable promise.[22] Industrial waste gases generated from cement, iron and steel production, and chemical manufacturing release substantial amounts of CO_2, typically ranging from 10 to 40 vol.%, making them suitable for culturing autotrophic cells.[23] Notably, ethanol fermentation plants emit nearly pure CO_2, highlighting the potential for capture and reuse.[24] For example, a plant in the United States emitted 25.9 million tons of CO_2 in 2008, illustrating this opportunity.[25] Current developments are integrating bioprocessing with industrial emissions by channeling flue gases into microbial bioreactors to produce substances such as ethanol.[26,27] Furthermore, the carbon in CO_2 is in its highest oxidation state with lowest degree of reduction. Thus, all functionalization processes must be reductive. The Gibbs free energy (ΔG) changes of CO_2 reductive reactions are generally positive, necessitating the input of various forms of energy.[28] However, the utilization of CO_2 from diverse sources contributes to sustainable biomanufacturing, mitigates greenhouse gas emissions, and promotes a circular economy and carbon neutrality.

Microbial CO_2 utilization

The CO_2 fixation pathways employed by various microbial species can be broadly categorized into two categories: natural pathways and synthetic pathways. Natural pathways have evolved over millions of years, whereas synthetic pathways have been engineered through biotechnological advancements to improve efficiency and yield. Previous reviews have comprehensively examined the key enzymes, reactions and their mechanisms, the CO_2 fixation rates, as well as the applications of seven natural CO_2 fixation pathways and twelve synthetic CO_2 fixation pathways.[20,22,28-36] Furthermore, metabolic engineering strategies has been employed to convert CO_2 into bioproducts including biofuels, organic acids, fatty acids[37] and pharmaceuticals in bacteria,[38,39] yeast,[40] cyanobacteria and microalgae.[41] Additionally, emerging microbial electrosynthesis systems facilitate the fixation of CO_2 into valuable biocommodities via electrochemical pathways supported by microbial activities. This approach not only reduces the energy requirements for CO_2 capture but also generates energy through the process of biomethanation, presenting a sustainable solution for CO_2 capture and utilization.[42]

Advantages and challenges of CO_2 utilization

The application of microbial processes to convert CO_2 into valuable products represents a promising and innovative approach for mitigating climate change and fostering a sustainable future. One of the primary advantages of microbial CO_2 utilization is its potential to reduce greenhouse gas, thereby addressing the urgent need to combat global warming. By harnessing these natural processes, we can create circular carbon economies that recycle CO_2, transforming a greenhouse gas into a valuable resource rather than a waste. Moreover, microbial CO_2 utilization processes often operate under mild conditions, necessitating significantly less energy compared to traditional chemical catalysis, which typically demands high temperatures and pressures. The biological approach is also more environmentally benign, as it minimizes the use of toxic chemicals and the generation of hazardous byproducts.

Nevertheless, microbial CO_2 utilization faces several challenges (Figure 2). Economic viability remains a significant obstacle, as the costs associated with microbial conversion technologies are still relatively high. The efficiency of CO_2 conversion into target products is frequently limited by the metabolic capabilities of the microorganisms involved. The rates of CO_2 fixation and product synthesis are generally lower than those achieved through chemical processes. Additionally, capturing CO_2 from the atmosphere is both cost- and energy-intensive. Another challenge lies in the scalability of microbial CO_2 utilization systems. While lab-scale demonstrations have shown promise, transitioning these technologies to industrial applications requires overcoming both technical and economic barriers. Furthermore, integrating CO_2 capture and utilization with existing industrial processes presents engineering and logistical complexities. Finally, the economic and environmental impacts of large-scale microbial CO_2 utilization systems need to be thoroughly assessed to ensure their sustainability.

CARBON MONOXIDE (CO) AND FORMIC ACID (HCOOH)

Overview of CO and formic acid

CO has emerged as a promising feedstock in biomanufacturing processes due to its potential as a sustainable carbon source for the production of valuable bio-based materials and chemicals. This otherwise toxic gas, primarily derived from syngas—a mixture of H_2, CO, and CO_2—presents an attractive candidate as it can be produced from various feedstocks, including agricultural residues, municipal solid waste, and fossil fuels.[43] Moreover, CO is found in significant quantities in flue gases from industrial operations such as steel manufacturing or oil refining, where its capture and utilization not only mitigate greenhouse gas emissions but also contribute to principles of circular economy principles by transforming waste into valuable bioproducts (Figure 3).

Formic acid is gaining recognition as an appealing microbial feedstock. It

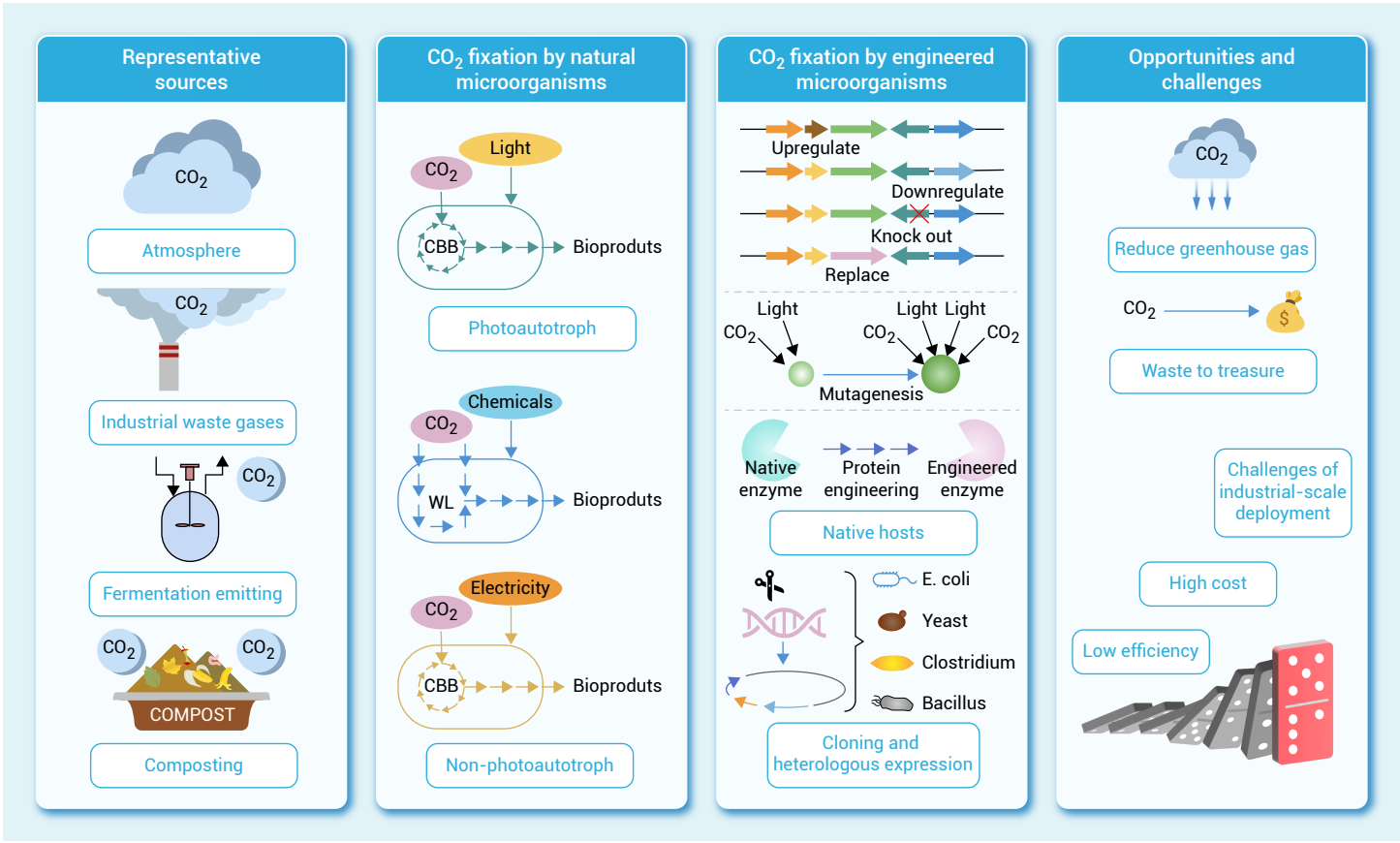

Figure 2. Microbial CO_2 fixation.

can be readily obtained from CO_2, CO or waste gases via chemical, photo- and electro-chemical catalysts,[44,45] offering a cost-effective and sustainable alternative.[46] Additionally, formic acid can be produced from biomass, offering a renewable alternative to fossil resources.[45,47] Recent advancements in biotechnological innovations have also enabled the microbial fermentation of formic acid derived from the anaerobic digestion of organic waste, positioning it as a sustainable, carbon-neutral feedstock (Figure 3).

Microbial CO and formic acid utilization

Research on microbial CO conversion predominantly focuses on strict anaerobic bacteria.[48] These microbes primarily utilize CO dehydrogenase (CODH) to oxidize CO into CO_2 and transfer electrons to acceptors, allowing for producing multi-carbon products via the Wood-Ljungdahl pathway.[49] *Acetobacterium*, for example, possess CODH and employ the complete Wood-Ljungdahl pathway, resulting in CO_2 and acetate as end products of CO oxidation.[50] A study of *Clostridium ljungdahlii* revealed that CO served as the preferred carbon and electron source for growth and alcohol production.[51] Despite these findings, aerobic processes present thermodynamic and low-cost advantages, particularly in CO oxidation, which generates higher free energy and more complex products. *Hydrogenophaga pseudoflava* and *Oligotropha carboxidovorans* are examples of aerobic microorganisms capable of syngas utilization, demonstrating CO-oxidizing capacity and metabolic versatility, and engineered *H. pseudoflava* has even been shown to produce sesquiterpenes.[52,53] Innovations in synthetic biology may enhance CO fixation and optimize metabolic pathways for better product yields.[54] To date, there have been no successful reports of engineered *Escherichia coli* utilizing CO as a carbon source for biosynthesis. However, modifications targeted at CO_2 utilization may offer valuable insights and guidance.[55] The products derived from CO include valuable chemicals and fuels, contributing to sustainability and addressing CO emissions linked to industrial processes while promoting renewable energy production and biochemical feedstocks.

Formic acid serves as both a terminal electron donor and a carbon source for various anaerobic microorganisms. Three native metabolic pathways are related to microbial formic acid utilization including the Wood-Ljungdahl (reductive acetyl-CoA) pathway, serine cycle, and reductive glycine pathway.[56] Despite the natural occurrence of formic acid-utilizing microorganisms, their growth rates are typically slow and their efficiency is limited. To address these challenges, ten synthetic formate-assimilation pathways have been constructed, and synthetic biology and metabolic engineering techniques have been employed to develop strains with enhanced formic acid utilization capabilities.[56] For instance, *E. coli* has been genetically modified and evolved to assimilate formic acid through the reconstruction of the tetrahydrofolate cycle and reverse glycine cleavage.[57-61] Notably, an engineered *Vibrio natriegens* has been developed as a microbial platform for efficient formic acid conversion by rewiring the serine cycle and the TCA cycle, demonstrating the capability to produce 29.0 g/L of indigoidine and consume 165.3 g/L of formate within 72 hours.[62] The improvement of the strain's tolerance to formic acid and the exploration of genetically engineered strains would be further enhancing the yield and selectivity of desired products from formic acid.

Advantages and challenges of CO and formic acid utilization

CO utilization can synergistically develop with hydrogen energy (Figure 3).[63-66] Microbial CO utilization offers a viable strategy for mitigating industrial CO emissions and valorizing industrial waste gases, both of which significantly contribute to climate change and the circular economy.[67] Despite these advantages, there are several challenges that must be overcome to fully realize the potential of microbial CO utilization. One of the primary challenges is the low efficiency of CO bioconversion by natural microbial strains resulted from the toxicity of CO and its intermediates, and the strict anaerobic process, which often results in low product yields and high production costs. Despite the substantial potential for CO utilization, aerobic syngas-converting bacteria remain inadequately characterized compared to their anaerobic counterparts.[53] Additionally, the toxicity and explosiveness of CO render it a less suitable carbon feedstock.[68] Another challenge is that the scale-up of laboratory processes to a commercially viable level presents significant technical and economic hurdles.

Microbial utilization of formic acid presents a myriad of advantages that

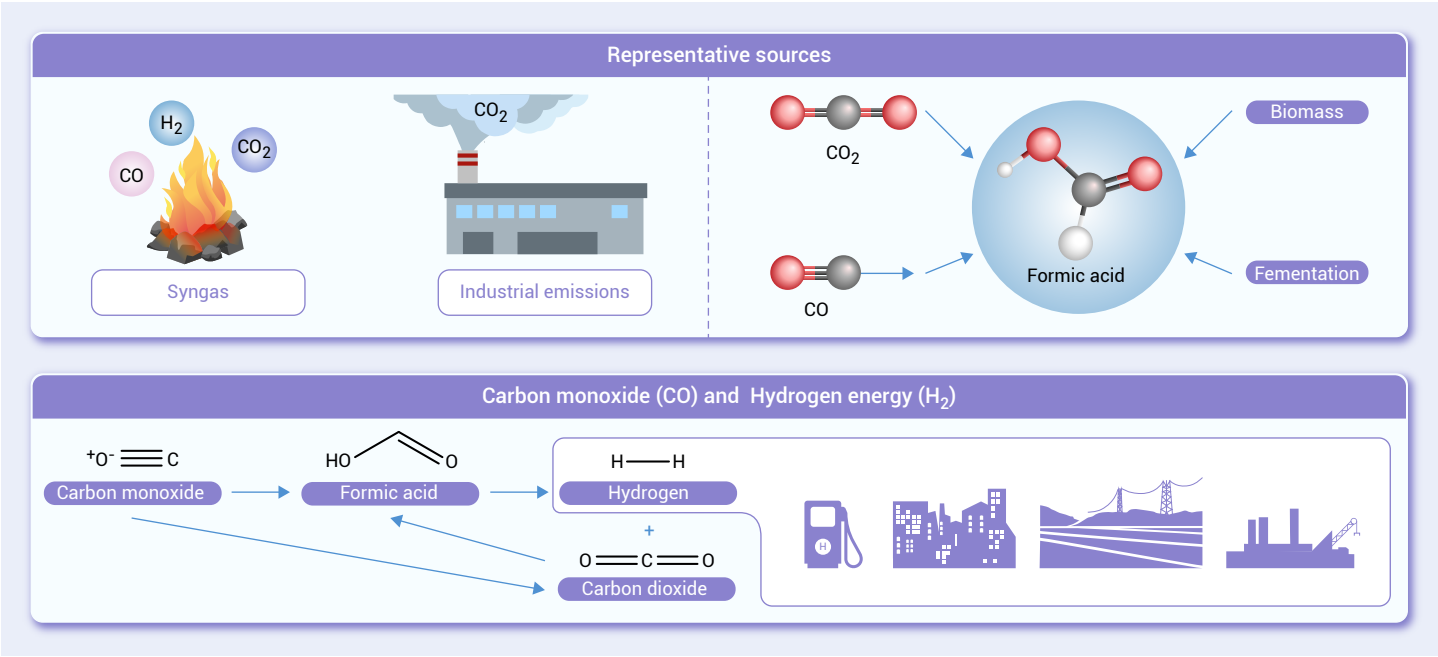

Figure 3. Microbial carbon monoxide (CO) and formic acid utilization.

make it a compelling avenue for sustainable development. The liquid form of formic acid facilitates easier storage and handling compared to gaseous alternatives, making it a practical C1 gases equivalent carbon source.[69] Its high energetic efficiency allows for superior bioconversion into valuable products.[68] Furthermore, formic acid contributes to carbon capture and conversion strategies, thereby providing the dual benefit of reducing greenhouse gas emissions while producing useful products.[70] Notably, certain microorganisms possess unique enzymatic systems capable of efficiently converting formic acid into hydrogen gas.[71,72] However, one of the main challenges is the relatively low efficiency and rate of formic acid uptake and conversion by microorganisms, attributed to its cellular toxicity.[69] Enhancing the metabolic pathways and tolerance of microorganisms to formic acid is therefore crucial for improving the overall process efficiency.[62] Additionally, the scalability of microbial formic acid utilization processes to an industrial level remains a significant challenge, requiring further optimization of bioreactor designs and process engineering.

SUGARS AND AROMATIC COMPOUNDS

Overview of sugars and aromatic compounds

Sugars serve as critical and common carbon sources for fermentation processes in biomanufacturing, enabling diverse microbial pathways that convert these substrates into valuable biofuels, chemicals, and materials.[73] The fermentable sugars include monosaccharides such as glucose, xylose, fructose, and galactose, as well as disaccharides like sucrose and lactose, all of which can be derived from various abundantly available natural resources. The main source of these sugars is plant biomass, which encompasses sugar crops (such as sugarcane, sugar beet, and sugar sorghum), starchy crops (such as corn and cassava) and cellulose-rich materials (such as energy crops, agricultural residues and wood) (Figure 4A).[74,75] However, sugar crops and starchy crops are principally cultivated for the production of sugar and starch to feed a growing population. By-products of sugar processing has been proved an efficient and very low-cost carbon source for microbial fermentation (like molasses). Furthermore, sugars offer the flexibility of being sourced from renewable and sustainable feedstocks, reducing reliance on fossil fuels and promoting a circular economy.[76]

Aromatic compounds, characterized by their stable ring-like structures and rich functionalization potential, constitute a diverse and promising category of carbon sources for microbial fermentation. These compounds are prevalent in various natural and anthropogenic environments, and can be derived from several representative sources, including lignin, which is a major component of plant biomass and an abundant and underutilized byproduct of the forestry and paper industries (Figure 4A).[77,78] Other notable sources include industrial effluents from petrochemical processes, and coal tar, which mainly relate to microbial environmental remediation rather than biomanufacturing.[79] Therefore, these sources are not discussed further. As the most accessible and least costly source for biomass, lignin, an intriguing candidate due to its renewable property and abundant storage on earth is discussed in detail.

Microbial sugars and aromatic compounds utilization

The primary pathways for microbial sugar utilization are well-studied glycolysis, the pentose phosphate pathway, and the tricarboxylic acid (TCA) cycle, also known as the Krebs cycle. Sugar fermentation can be used to produce almost all bioproducts including pharmaceuticals, biofuels, chemicals, materials, and food ingredients.[80] Fermentative microorganisms exhibit varied sugar utilization capabilities, each adapted to specific substrates and conditions, thus enabling product specificity and yield optimization. For example, *E. coli* can utilize a broader range of sugars, including pentoses like xylose and arabinose.[81] Additionally, the metabolic engineering of these strains can enhance product titers and expand substrate utilization, including pentose sugars derived from lignocellulosic biomass. In additional, co-utilizing sugars provide an alternative approach for efficient biosynthesis.[82] However, the major limitation is the presentation of carbon catabolite repression (CCR) wherein the expression of functions related to the utilization of secondary carbon sources and the activities of the corresponding enzymes are diminished when glucose is present (Figure 4B).[83,84]

Microbial pathways for the utilization of aromatic compounds typically involve their conversion into central metabolic intermediates through catabolic processes, enabling subsequent fermentation (Figure 4C).[79] Key enzymatic steps are catalyzed by a variety of enzymes such as dioxygenases, dehydrogenases, and transferases, which facilitate the breakdown of the aromatic ring and subsequent functional group modifications.[85] For example, the utilization of aromatic compounds involves their uptake via specific transporters like MolK in *Xanthomonas citri*, followed by NAD+-dependent enzymatic conversion into hydroxycinnamic acids and hydroxybenzyl aldehyde derivatives through a unique metabolic pathway.[86] Strains such as engineered *Saccharomyces cerevisiae*, *E. coli*, *Pseudomonas putida* and *Rhodococcus* have also been extensively studied for their ability to metabolize a wide range of aromatic hydrocarbons, with products ranging from short-chain organic acids to valuable industrial precursors such as biofuels and bioplastics.[87,88]

Advantages and challenges of sugars and aromatic compounds utilization

The development and use of sugars as carbon sources have a long history for the production of bioproducts. One of the primary advantages is the ability

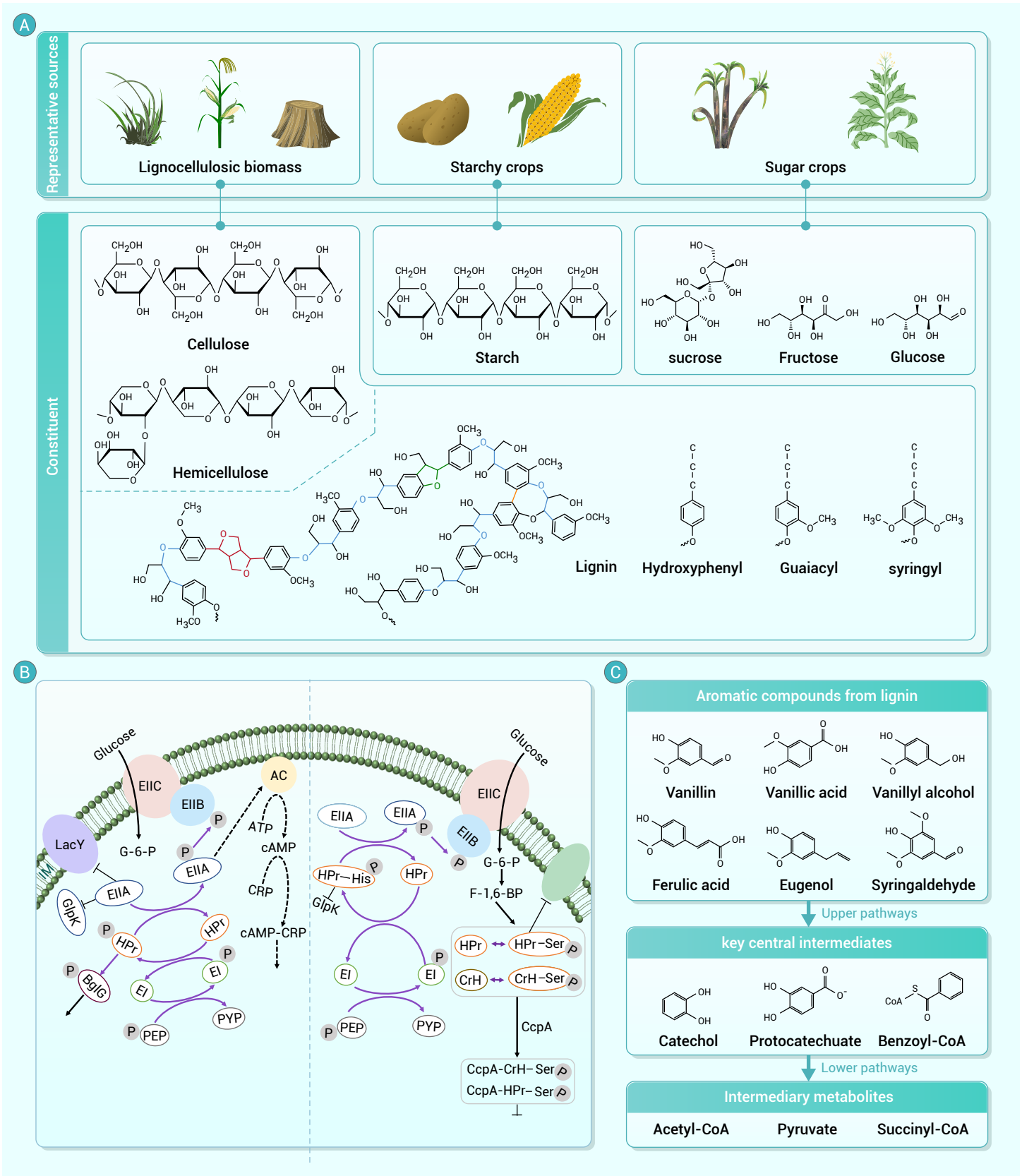

Figure 4. Sugars and aromatic compounds as fermentation carbon sources (A) The representative sources sugars and lignin-derived aromatic compounds. (B) Carbon catabolite repression (CCR). Glu-6-P: glucose-6-phosphate, F-1,6-BP: fructose-1,6-bisphosphate, AC: adenylate cyclase, cAMP: cyclic adenosine monophosphate, CRP: cAMP receptor protein, PEP: phosphoenolpyruvate, HPr: Histidine protein, PYR: pyruvate, Ser: serine. The purple arrows show phosphate transfer. (C) The transformation of aromatic compounds by microorganisms.

of microbes to efficiently convert a diverse range of sugars into valuable bioproducts, which represents a sustainable and mature process for biomanufacturing with microorganisms.[89] And this process can be used to reduce reliance on fossil fuels and mitigate environmental impacts due to the operation under mild conditions.[82] However, challenges remain that must be addressed to reduce costs for commercial viability. The low economic bene-

fits mainly derived from the inefficient simultaneous consumption of mixed carbon sources,[90,91] competing with food and the high cost of hydrolysis of lignocellulosic biomass due to the recalcitrance of their structure.

Microbial conversion of lignin-derived aromatics into bioproducts aligns with the principles of sustainability, offering a renewable alternative to petrochemical-based feedstocks. One notable advantage lies in lignin's abundance as a byproduct of the pulp and paper industry, as well as from agricultural residues.[92] Moreover, the conversion of lignin-derived aromatic compounds into valuable bioproducts, such as biofuels, bioplastics, and specialty chemicals, can drive a circular economy by transforming waste materials into economically viable products. However, several challenges impede the efficient microbial conversion of lignin-derived aromatic compounds to bioproducts. The complexity and heterogeneity of lignin structure result in the complexity and irregularity of lignin-derived aromatic compounds obtained through chemical hydrolysis, further hindering microbial utilization processes.[87] Additionally, the inhibitory effects of certain lignin-derived aromatic compounds on microbial growth and fermentation processes can lead to decreased overall yields and productivity. Moreover, the scale-up of microbial fermentation processes remains a critical challenge, as laboratory-scale successes do not always translate effectively to industrial scales.

ACETIC ACID

Overview of acetic acid

Acetic acid, a simple yet pivotal organic compound, has emerged as a noteworthy feedstock for fermentation processes in the realm of biomanufacturing, given its versatility and sustainability potential.[93] Traditionally, it is derived from methods such as methanol carbonylation, ethylene oxidation, aldehyde oxidation, and alkane oxidation, which together account for approximately 85% of global acetic acid production.[94] Additionally, the conversion of lignocellulosic materials stands out as a prime candidate, with agricultural residues and dedicated energy crops providing a sustainable route for large-scale production.[95] Furthermore, acetic acid can be obtained through the aerobic or anaerobic fermentation.[96,97] Acetic acid bacteria, which can produce acetic acid from ethanol, are well-known for commercial production of vinegar.[93] Notably, acetogens like *Moorella thermoacetica*, can catalyze the direct fixation of CO and CO_2 to synthesize acetic acid, aligning with the goals of carbon neutrality and enhanced sustainability in modern biomanufacturing.[98]

Microbial acetic acid utilization

Acetic acid can be metabolized by a variety of microorganisms, including microalgae, fungi, and bacteria, primarily through the glyoxylate shunt and less frequently via the ethylmalonyl-CoA pathway or the methylaspartate cycle (Figure 5A). These pathways facilitate the assimilation of acetate into cellular biomass and other compounds by converting it into acetyl-CoA, which has been elaborated in several outstanding review papers.[93,95,99-101] Efficient acetate-utilizing strains such as *Acetobacter* and *Clostridium* species are particularly well-studied for their capabilities in converting acetic acid into valuable products like ethanol, butanol, biosurfactants, and biopolymers.[93] The main issue with microorganisms using acetic acid as a carbon source is the toxicity of acetic acid. However, acetic acid bacteria occupy a distinctive niche in acetic acid metabolism due to their exceptional tolerance to acetic acid, enabling them to thrive in environments containing approximately 100 g/L of acetate. This remarkable capability highlights their significant potential for utilization.[93,102] Meanwhile, the study about toxicity mechanism of acetic acid provides further strategies for microbial acetic acid utilization (Figure 5B). In addition, recent advances in synthetic biology and artificial intelligence have enabled the engineering of microbial strains to optimize these pathways further, improve yield and productivity, and expand the range of target products (Figure 5C).[101,103-105]

Advantages and challenges of acetic acid utilization

The integration of microbial acetic acid utilization not only contributes to waste valorization strategies but also supports the development of circular economy models, creating a sustainable platform for bio-based production processes in the future. One of the primary advantages is the versatility of acetic acid as a carbon source. It is a simple and readily available metabolite that can be utilized by a wide range of microorganisms, allowing for the exploitation of diverse feedstock, thereby facilitating a circular economy.[100] Additionally, the conversion of acetic acid by microbes can yield valuable bioproducts, including butyrate and other short-chain fatty acids, which have numerous applications in pharmaceuticals, food products, and as biofuels and can serve as alternatives to fossil fuels.[93] On the flip side, challenges remain in optimizing microbial strains for efficient acetic acid utilization due to the inhibitory effect of acetic acid on microbial growth, which can reduce growth rates and limit product concentrations.[99] Moreover, the low energy content of acetic acid compared to other carbon sources like glucose or glycerol necessitates careful energy and redox balancing.[99] Additionally, metabolic pathways can be complex and often require fine-tuning to enhance the yield and productivity from acetic acid. Addressing these challenges is crucial for the development of sustainable and economically viable microbial processes that utilize acetic acid.

GLYCEROL

Overview of glycerol

Glycerol, also known as glycerin or propane-1,2,3-triol, is a versatile and valuable feedstock for fermentation processes in biomanufacturing.[106] It is a colorless, odorless, and viscous liquid that serves as a key component in various industrial applications, including the production of biofuels, chemicals, and pharmaceuticals.[107] Glycerol is predominantly derived from the hydrolysis of fats and oils, a byproduct of soap industries, which has led to an increased surplus of crude glycerol.[108] Moreover, this biodiesel-derived glycerol, although often of lower purity, offers a sustainable and cost-effective alternative to virgin glycerol, which is traditionally sourced from vegetable oils and animal fats.[109] Glycerol can also be obtained from the chemical synthesis involving the reduction of propylene oxide, but this method is less common due to the environmental and economic impact.[110] In addition to these sources, glycerol can also be produced by microbial fermentation (Figure 6A).[111,112]

Microbial glycerol utilization

The utilization of glycerol as a feedstock for microbial fermentation is particularly promising due to its high degree of reduction, which makes it an ideal substrate for the production of reduced chemicals and fuels.[113] Furthermore, the exploration of glycerol utilization by various microorganisms, including *S. cerevisiae*, *E. coli*, *Clostridium*, *Klebsiella*, *Enterobacter* and *Yarrowia lipolytica*, has opened up new avenues for the efficient conversion of this renewable resource into value-added products, contributing to a more sustainable future in biomanufacturing.[108,114-116] The pathways for microbial glycerol utilization are primarily divided into reductive and oxidative branches (Figure 6B). The reductive pathway converts glycerol into 1,3-propanediol under low oxygen conditions. The oxidative pathway changes glycerol into intermediates that enter glycolysis, producing various metabolic products such as 2,3-butanediol, ethanol, acetoin, lactic acid, and acetic acid.[117] Key enzymes in glycerol metabolism include glycerol kinase (GK), which phosphorylates glycerol to glycerol-3-phosphate (G3P), a crucial step in the oxidative pathway. GK is part of the FGGY carbohydrate kinase family and is essential for glycerol uptake and metabolism. Other important enzymes are glycerol dehydratase and the oxidoreductases involved in the reductive pathway.[118] The products derived from microbial glycerol utilization contribute to a range of industrial applications, from food and pharmaceuticals to biomaterials and energy production, highlighting the significance of microbial glycerol utilization in creating a sustainable future.

Advantages and challenges of glycerol utilization

The advantages and challenges of microbial glycerol utilization are multifaceted, reflecting the complex interplay between biotechnological potential and practical constraints. Advantages of microbial glycerol utilization are primarily centered on sustainability and the conversion of a waste product into valuable resources.[119] This process not only reduces waste but also contributes to a circular economy by transforming a low-value byproduct into high-value chemicals that are biodegradable and environmentally friendly.[120] Moreover, the additional reducing power of glycerol supports the use of more oxidized substrates by microorganisms than glucose and offers advantages in the production of various bulk chemicals.[120] Additionally, the use of crude glycerol as a feedstock can potentially lower the production costs by up to 50%, given that the feedstock price constitutes a significant portion of the total production cost. Furthermore, the metabolic engineering of microorganisms allows for the optimization of glycerol utilization pathways, enhancing the efficiency of converting glycerol into desired products.[121] However, one of

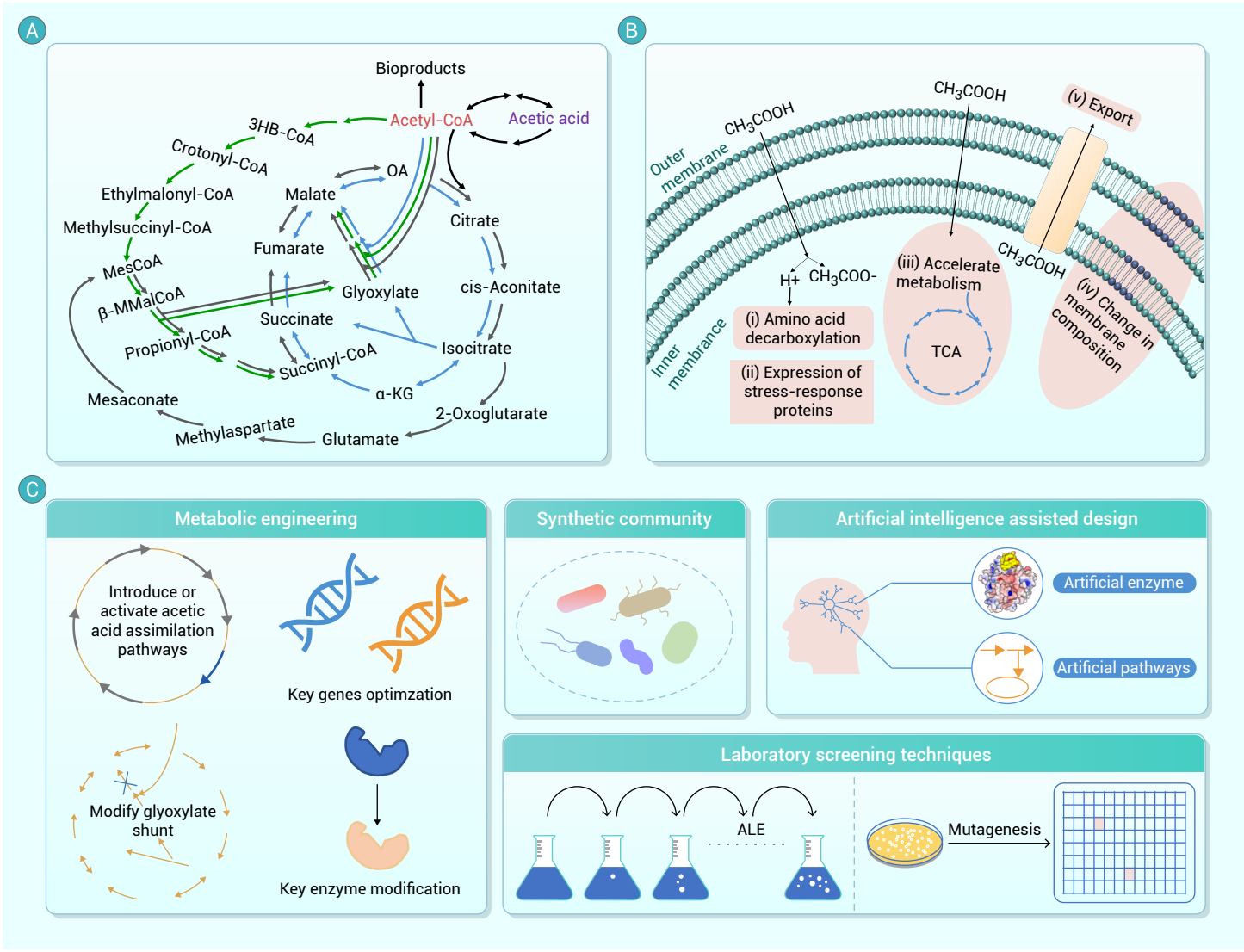

Figure 5. Microbial acetic acid utilization (A) The metabolic pathways of acetic acid in microorganisms. 3HB-CoA: 3-hydroxybutyryl-CoA; β-MMalCoA: β-Methylmalyl-CoA; OA: Oxaloacetate; MesCoA: mesaconyl-CoA; α-KG: α-Ketoglutarate. (B) Toxicity mechanism of acetic acid. (C) The strategies to develop microorganisms for valorizing acetic acid. ALE: Adaptive laboratory evolution.

the primary concerns is the presence of inhibitors or toxic compounds in crude glycerol can negatively impact microbial growth and product yield.[122] Nevertheless, purifying the waste glycerol is difficult and energy intensive. It would be preferable to find a productive use for waste glycerol requiring little to no refining. Moreover, studies demonstrate the feasibility of strain and fermentation technology optimization for glycerol bioconversion, but improvements in the conversion rate and yield via further strain engineering will truly realize the industrial potential of microbial glycerol utilization (Figure 6C).

FATTY ACID

Overview of fatty acid

Fatty acids, also called nature's 'petroleum', can serve as a critical feedstock for fermentation processes.[123] These long-chain hydrocarbons can be derived from various renewable sources, including plant oils (such as palm, soybean, and canola oils), animal fats, and microbial oils, all of which are rich in fatty acids.[124,125] Additionally, waste streams from agricultural processes—including spent cooking oils and byproducts from the food industry—provide an economically viable and ecological approach to sourcing fatty acids. For instance, long-chain fatty acids like palmitic, stearic, oleic, and linoleic acids, which are abundant in widely consumed vegetable oils, have been explored as carbon sources for the production of polyhydroxyalkanoates (PHAs) by *Cupriavidus necator* H16.[126] Utilizing these feedstocks not only mitigates waste but also reduces reliance on fossil fuels, thereby contributing to a circular economy.

Microbial fatty acid utilization

Microorganisms such as bacteria, yeasts, and filamentous fungi possess unique pathways facilitating the assimilation and catabolism of fatty acids. The primary pathway for this utilization is β-oxidation, which is the main route for fatty acid degradation in organisms like *S. cerevisiae*, predominantly occurring within peroxisomes.[127] This pathway is highly regulated and involves a series of enzymatic reactions that release acetyl-CoA molecules from the carboxyl terminus of fatty acids (Figure 7A). Fatty acyl-CoA synthetase is the initial enzyme that activates fatty acids by converting them into fatty acyl-CoA, which is then subjected to β-oxidation. Other pivotal enzymes include fatty acyl-CoA oxidase, which dehydrogenates fatty acyl-CoA to form trans-2-enoyl-CoA, and the multifunctional enzyme Fox2, which further processes trans-2-enoyl-CoA to form 3-ketoacyl-CoA. The final step is catalyzed by 3-ketoacyl-CoA thiolase, which removes an acetyl-CoA molecule, allowing the cycle to continue. These enzymes, along with cofactors such as CoA, NADPH, NADH, and ATP, are essential for the β-oxidation process. Specific microbial strains, including *P. putida*, *Corynebacterium glutamicum*, and various oleaginous yeasts like *Y. lipolytica*, have demonstrated remarkable capabilities in fatty acid bioconversion, resulting in products ranging from biodiesel and biofuels to bioplastics and high-value chemicals.[123] The integration of synthetic biology approaches into these microbial systems has further enhanced productivity and substrate specificity, paving the way for industrial applications that align with the principles of a circular economy and sustainable resource management.

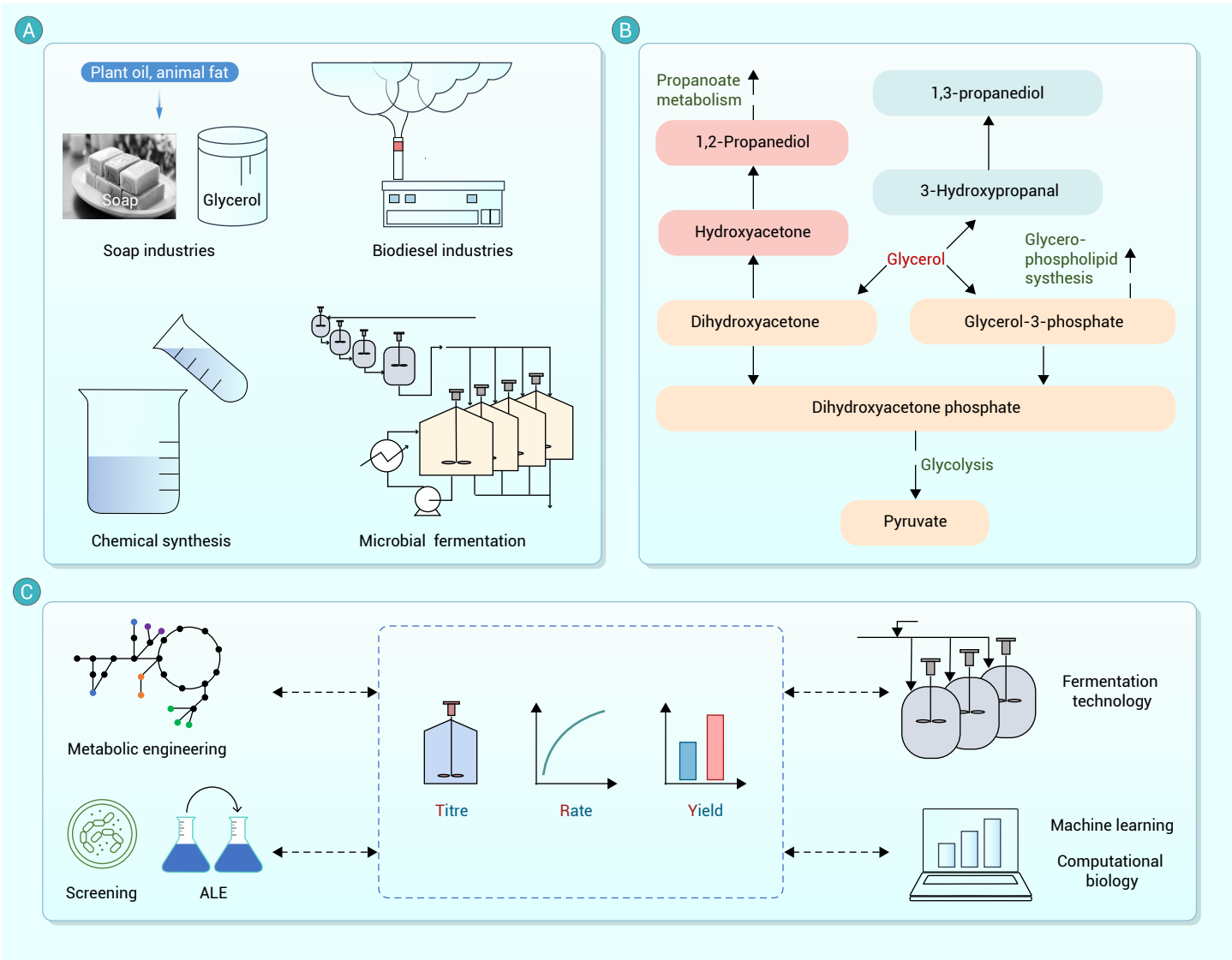

Figure 6. Microbial glycerol utilization (A) Representative sources of glycerol. (B) The metabolic pathways of glycerol in microorganisms. (C) The strategies for valorizing glycerol.

Advantages and challenges of fatty acid utilization

One of the primary advantages is the ability of microbes to convert fatty acids derived from various organic waste sources, including agricultural by-products, food waste, and biomass, into valuable biochemicals, biofuels, and biomaterials.[124] The other advantages of fatty acids as a carbon source for microbial fermentation include that they possess high energy density, enhanced solubility, and improved metabolic versatility compared to traditional carbohydrates such as glucose, which enhances their applicability in different industrial contexts.[128] Furthermore, the catabolism of fatty acids often results in fewer byproducts, minimizing downstream processing difficulties and enhancing the overall efficiency of the fermentation process. However, this metabolic versatility comes with challenges that the variability in substrate composition can lead to inconsistent fermentation yields and productivities, complicating process optimization. Additionally, the inhibition of microbial growth and activity by certain fatty acids, particularly long-chain and branched fatty acids, necessitates the development of tailored strains or bioprocess conditions to enhance tolerance and degradation pathways. Moreover, scaling up the production process from laboratory to industrial levels also presents technological and economic hurdles, often leading to platform infeasibility without significant improvements in metabolic engineering and fermentation technologies. Thus, understanding the intricate regulatory mechanisms governing fatty acid metabolism in microbes is essential for engineering robust microbial platforms that can efficiently convert fatty acids into desired products.

METHANOL (CH_3OH)

Overview of methanol

Methanol often regarded as a promising feedstock for fermentation processes in microbial biomanufacturing, has garnered significant attention due to its potential for sustainability and efficiency in the production of high-value biochemicals and biofuels.[69] It is a simple one-carbon compound that can be derived from various renewable and non-renewable sources.[129] Renewable methanol is primarily produced through biomass gasification. This process transforms organic materials into syngas, which is a mixture of CO, hydrogen (H_2), and CO_2, before being catalytically converted into methanol.[130] Additionally, methanol can be synthesized via the catalytic hydrogenation of CO_2, thus enabling the utilization of captured carbon emissions from industrial processes.[131-133] Non-renewable methanol is typically derived from fossil fuels, particularly natural gas, through steam reforming processes that generate syngas followed by methanol synthesis, which is the major production method of global methanol, making methanol a cost-effective feedstock for various chemical and fuel applications.[134] However, the sustainability of this pathway depends on the environmental impact of natural gas extraction and the overall carbon footprint of the conversion process.[132] The adaptability of various feedstock sources positions methanol as a versatile substrate that can be strategically integrated into microbial fermentation processes, setting the stage for innovative biomanufacturing applications aimed at carbon neutrality and circular economy principles.

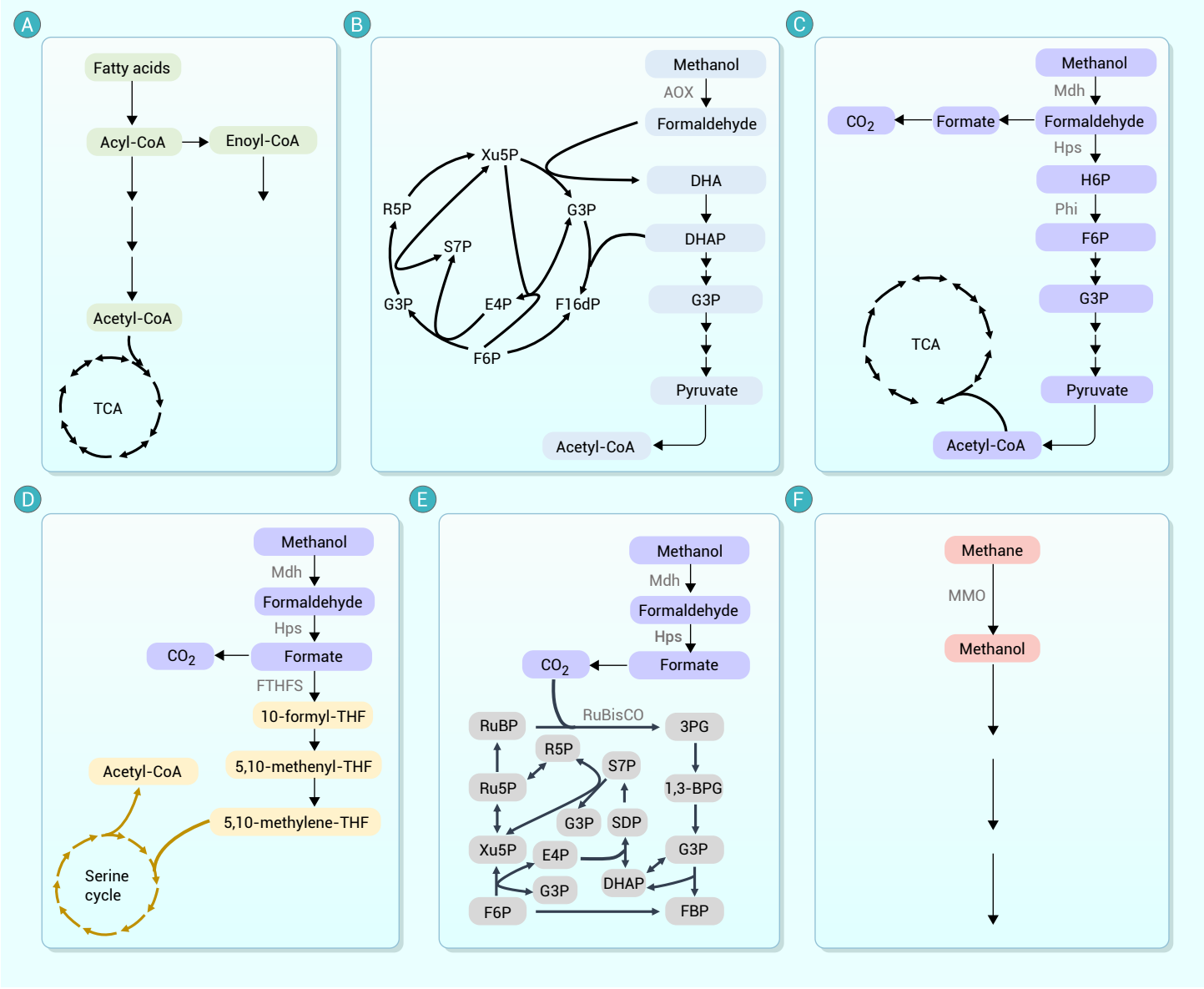

Figure 7. Microbial fatty acids, methanol and methane utilization pathways (A) The metabolic pathways of fatty acids. (B) The metabolic pathways of methanol in native methylotrophic yeasts. AOX: alcohol oxidase; DHA: dihydroxyacetone; DHAP: dihydroxyacetone phosphate; G3P: glyceraldehyde-3-phosphate; R5P: ribose-5-phosphate; S7P: sedoheptulose-7-phosphate; Xu5P: xylulose-5-phosphate; F6P: fructose-6-phosphate; E4P: erythrose-4-phosphate; F16dP: fructose-1,6-bisphosphate. (C) The metabolic pathways of methanol in native methylotrophic bacteria. Mdh, methanol dehydrogenase; Hps: 3-hexulose-6-phoshate synthase; Phi: 6-phospho-3-hexuloisomerase; H6P: hexulose-6-phosphate. (D) The metabolic pathways of methanol by formate assimilate. FTHFS: formyltetrahydrofolate synthetase; 10-formyl-THF: 10-formyl-tetrahydrofolate; 5,10-methenyl-THF: 5,10-methenyltetrahydrofolate; 5,10-methylene-THF: 5,10-methylenetetrahydrofolate. (E) The metabolic pathways of methanol by CO_2 assimilate using Calvin–Benson–Bassham cycle. RuBisCO: ribulose 1,5-bisphosphate carboxylase oxygenase; RuBP: ribulose-1,5-bisphosphate; 3PG, 3-phosphoglycerate; SDP, sedoheptulose-1,7-bisphosphate; R5P, ribose-5-phosphate; S7P, sedoheptulose-7-phosphate; Xu5P, xylulose-5-phosphate; F6P, fructose-6-phosphate; E4P, erythrose-4-phosphate; DHAP, dihydroxyacetone phosphate; G3P, glyceraldehyde-3-phosphate; FBP, fructose-1,6-bisphosphate; Ru5P, ribulose-5-phosphate. (F) The metabolic pathways of methane. MMO: methane monooxygenase.

Microbial methanol utilization

Microbial methanol utilization is a critical process in the bioconversion of one-carbon compounds, offering a sustainable approach to harnessing carbon sources and reducing greenhouse gas emissions. This process involves the metabolic pathways that enable microorganisms to assimilate methanol as their sole biomass and energy source. Key pathways include the ribulose monophosphate pathway (RuMP),[135,136] the modified serine cycle,[137] and reductive glycine pathway (Figures 7B-E).[59] These pathways facilitate the conversion of methanol into useful cellular building blocks. The efficiency of methanol utilization is significantly influenced by key enzymes such as methanol dehydrogenase (Mdh), which catalyzes the oxidation of methanol to formaldehyde, a pivotal step in one-carbon metabolism. And then combined with natural or synthetic formaldehyde assimilate routes, Microbial methanol utilization comes to an efficient direction.[138] The performance of Mdh can be a limiting factor in the overall process, making its optimization a focal point for researchers aiming to enhance methanol utilization.[139,140]

In terms of microbial strains, species such as *Pichia pastoris*, *Ogataea polymorpha Methylorubrum extorquens* and *Bacillus methanolicus* are naturally adept at methanol utilization, with the latter capable of rapid growth with a doubling time of approximately 5 hours at 37°C. Synthetic biology has also enabled the reprogramming of model organisms like *E. coli* to become synthetic methylotrophs, capable of growth on methanol as the sole carbon and energy source.[129] These engineered strains can achieve growth rates comparable to or even exceeding those of natural methylotrophs, demonstrating the potential for industrial application in the production of value-added chemicals from methanol. The products derived from microbial methanol utilization range from simple organic acids like acetate to more complex molecules such as proteins, amino acids, β-farnesene,[141] fatty acids and biopolymers like polyhydroxyalkanoates (PHAs).[142] The versatility of microbial metabolism allows for the redirection of methanol-derived carbon into a variety of biochemical pathways, making it a promising platform for sustainable bioproduction.

Advantages and challenges of methanol utilization

Microbial methanol utilization stands as a pivotal strategy in the quest for sustainable bioprocessing, given its ability to transform methanol—a simple, abundant, and cost-effective carbon source—into a spectrum of high-value products, including biofuels, bioplastics, and industrial chemicals. One of the foremost advantages of utilizing methanol lies in its accessibility and versatility; it can be sourced from various renewable processes such as biomass gasification, capturing CO_2 from the atmosphere, or even as a byproduct of industrial activities, thereby facilitating a circular economy.[69] Meanwhile, its complete miscibility and ease of storage and transport make it a practical choice for industrial applications.[69] Furthermore, the metabolic pathways of microbes can be engineered to optimize yields of desired products from methanol, mitigating the need for extensive chemical processing, which is often associated with higher energy consumption and environmental impacts.[143]

However, despite these advantages, several challenges must be addressed to fully harness the potential of microbial methanol utilization. Although synthetic microbes have been successfully engineered, they still indicate slower growth and lower biomass yield.[14] The optimization of metabolic pathways for specific product formation can be intricate whether for native strains or model organisms, requiring a deep understanding of cellular metabolism and genetic regulation. Additionally, the potential for byproduct formation during methanol conversion poses a risk of yield loss, necessitating careful metabolic engineering and process control. Strain robustness is another critical challenge. Microorganisms must be able to withstand diverse environmental conditions common in industrial settings without significant loss of activity. Moreover, scaling up production from laboratory conditions to industrial bioreactors is complicated by issues such as mass transfer limitations, shear stress, and maintaining microbial consortia stability. To overcome these hurdles, integrated approaches combining synthetic biology, systems biology, and advances in bioprocess engineering will be essential. Collectively, addressing these challenges while leveraging the advantages of microbial methanol utilization could pave the way for innovative, sustainable production systems that align closely with global sustainability goals.

METHANE (CH_4)

Overview of methane

Methane, a potent greenhouse gas and the primary component of natural gas, is increasingly recognized as a valuable feedstock for biomanufacturing processes, particularly in microbial fermentation. The most prominent sources of methane for fermentation include natural gas, biogas from anaerobic digestion processes and landfills sites, industrial waste gases (such as steel manufacture, oil refining, and coal processing), terrestrial ecosystems (such as wetlands and ocean sediments), and ruminant livestock farming.[144-147] Natural gas being the most direct and abundant source, is predominantly obtained from fossil fuel extraction. Methane from these sources is primarily generated by methanogens, especially the methanogenic archaea,[148] a strictly anaerobic group of organisms that can produce methane by coupling the oxidation of a limited number of electron donors with the reduction of CO_2.[149] The methane produced from these sources can be captured and used as a substrate for methanotrophic bacteria, which can convert methane into various value-added compounds through metabolic engineering strategies.[146] This conversion not only mitigates the environmental impact of methane as a greenhouse gas but also provides a sustainable platform for the production of chemicals and fuels. Therefore, understanding and optimizing the microbial fermentation of methane from these representative sources is essential for developing a sustainable biomanufacturing industry that can help reduce greenhouse gas emissions while creating valuable products.

Microbial methane utilization

Microbial methane utilization is a critical bioconversion process in which living organisms convert methane into valuable products while mitigating greenhouse gas emissions.[150] The pathways for microbial methane utilization are diverse and can be broadly classified into aerobic and anaerobic processes. Aerobic methanotrophs, such as *Methylomicrobium alcaliphilum* 20ZR, initiate the conversion of methane through the action of particulate methane monooxygenase (MMO), which is a mixed function oxidase that incorporates one atom of oxygen into methanol and the other into water, requiring two electrons and two protons. The subsequent step involves periplasmic pyrroloquinoline quinone-linked methanol dehydrogenase, which further oxidizes methanol to formaldehyde (Figure 7F). Formaldehyde is then metabolized through multiple pathways, including tetrahydromethanopterin- and tetrahydrofolate-linked pathways, formaldehyde dehydrogenase, and the oxidative ribulose monophosphate cycle.[151] While anaerobic methanotrophs utilize a different set of enzymes. Methyl-coenzyme M reductase homolog (aMCR) is a key enzyme in anaerobic methanotrophs that catalyzes the reverse oxidation of methane and the reduction of CoBS–SCoM heterodisulfide.[144] The efficiency of these microbial pathways has been a focal point of research, with studies indicating that certain methanotrophs can exhibit remarkable methane oxidation rates, with conversion efficiencies exceeding 80% under optimal conditions. The highest methane uptake is 22 mmol/gDCW/h.[152] Furthermore, various methanotrophic strains, such as *Methylosinus trichosporium* and *Methylococcus capsulatus*, have been identified for their ability to convert methane into biochemical products such as PHAs, single-cell protein (SCP), and bioplastics, highlighting the potential in mitigating atmospheric methane levels while creating sustainable bioproducts.

Advantages and challenges of methane utilization

Microbial methane utilization stands at the forefront of sustainable energy solutions, harnessing the unique metabolic pathways of methanotrophic bacteria to transform methane—a potent greenhouse gas—into useful bioproducts such as biofuels, organic acids, and methane-derived chemicals. The advantages of this biological approach are profound. It not only mitigates methane emissions from various anthropogenic sources, including agricultural practices and landfills, but also provides a renewable method for energy production, thereby contributing to a circular economy.[153] Furthermore, unlike conventional fossil fuels, this process can utilize abundant and widely available methane resources, offering an alternative pathway for carbon capture and utilization.[154]

However, significant challenges persist in the widespread adoption of microbial methane utilization technologies. One of the main challenges in microbial methane utilization is the low efficiency and productivity levels in converting methane to industrially significant products due to the slow kinetics methane monooxygenase (MMO) and the poor solubility of methane in the aqueous phase, which affects mass transfer efficiency.[153] Additionally, the requirement of oxygen as an electron donor for methane oxidation presents safety concerns at an industrial scale due to the risk of explosive gas mixtures.[155] Furthermore, the engineering of methanotrophic strains for enhanced performance presents technical hurdles.[145] Importantly, the economic viability of these bioconversion systems is contingent upon addressing the costs associated with cultivation, harvesting, and downstream processing of microbial biomass.[156]

IMPACTS ON THE ENVIRONMENT OF MICROBIAL CARBON UTILIZATION

In this study, life cycle assessment (LCA) was employed to compare the environmental impact of producing the same chemical (bioethanol) from six carbon sources, following the methodology outlined by Niklas et al.[157] The six carbon sources including CO_2, CO, formic acid, glucose, glycerol, and methanol have been currently reported as carbon sources capable of producing the same product (bioethanol). This assessment effectively mitigates the influence of product differences on carbon emissions, emphasizing the intrinsic characteristics of the carbon sources and adhering to the principle of variable control in scientific research (Figure 8). Moreover, given that microbial bioconversion technologies for some carbon sources (e.g., CO_2 and CO) remain in the laboratory phase, while glucose has already been industrialized, a direct comparison of carbon emissions may overlook the potential for technological optimization concerning energy consumption. Consequently, the LCA operated under three key assumptions. (1) Technological maturity is standardized at the laboratory scale for all carbon sources, despite varying real-world readiness (e.g., glucose utilization is industrialized, whereas CO/CO_2 conversion remains experimental). (2) Bioethanol yield is fixed at 80% of the theoretical maximum, neglecting potential variations in microbial efficiency. (3) Energy consumption during fermentation (electricity/heat) is excluded from the analysis. These assumptions introduce certain uncertainties. Firstly, uniform technology maturity overlooks potential efficiency gains from scaling optimized processes. Second, excluding fermentation energy may underestimate impacts for energy-intensive pathways. Finally, future advancements in strain engineering or bioreactor design could substantially alter the environmental profile, especially for emerging pathways like CO_2

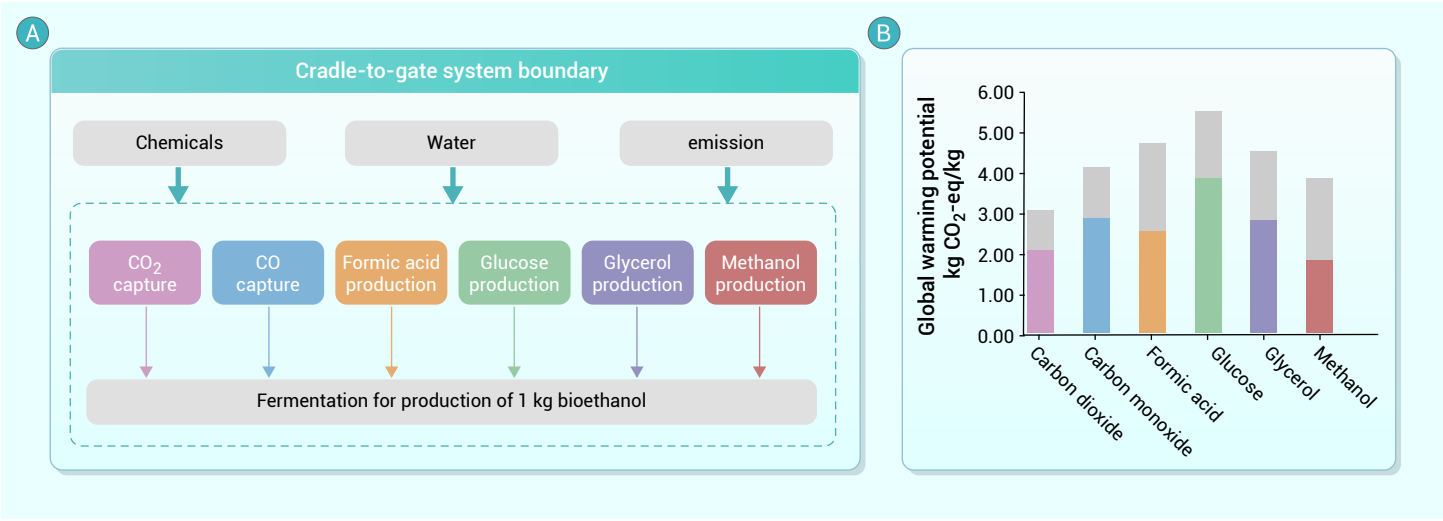

Figure 8. Environmental impacts of six carbon sources for production of 1 kg of bioethanol (A) The system boundary for our study. (B) The result of environmental impacts of six carbon sources for production of 1 kg of bioethanol.

electrosynthesis. Nevertheless, the current life cycle assessment still provides valuable reference for the selection and utilization of carbon sources. Here, the functional unit employed is the production of 1 kg of ethanol, and the system boundary is delineated in Figure 8A, encompassing the production of carbon sources and bioethanol. The details concerning bioethanol production from various carbon sources have been documented in existing literature.[137,158-164] Background process data were sourced from the Ecoinvent V.3.9.1 database. The environmental impact was assessed by using the ReCiPe 2016 Midpoint (H) methodology within OpenLCA v.2.1.1.[165] Global warming potential over a 100-year period (GWP100) was used as indicators for the interpretation.

The cradle-to-gate GWP100 of bioethanol production from six carbon sources was quantified and is shown in Figure 8B. The total GWP100 values range from 3.24 kg CO_2-eq/kg bioethanol (CO_2) to 5.70 kg CO_2-eq/kg (glucose), with the production of carbon sources significantly contributing to these impacts. CO_2 caption data from Ecoinvent V.3.9.1 database indicate that the production of CO_2 out of waste gases from different production processes with a value of 2.28 kg CO_2-eq/kg, accounting for 70% of the overall carbon emissions (3.24 kg CO_2-eq/kg). The fermentation processes account for 20~50% of total emissions, with formic acid and methanol utilization showing the highest impact. Glucose utilization exhibits the highest total GWP100 and glucose production from enzymatic hydrolysis of maize starch accounts for over 72% of total emissions, likely linked to agricultural inputs (fertilizers, land-use change).[166] CO_2 and methanol utilization demonstrate the lowest total GWP100 (3.24 and 4.05 kg CO_2-eq/kg, respectively), reflecting advantages in waste valorization or streamlined synthesis pathways. CO_2 and CO utilization show promise due to avoided emissions from waste disposal. However, the microbial conversion efficiencies for these gases remain significant bottlenecks. Formic acid and glycerol utilization show intermediate impacts, with the high emissions from the fermentation of formic acid suggesting opportunities for energy recovery or metabolic engineering to enhance bioconversion efficiency. Conversely, the low GWP100 of CO_2 utilization supports its role in carbon capture and utilization (CCU), aligning with literature that emphasizes industrial waste valorization.[167] Methanol's moderate impact corresponds with recent advancements in renewable methanol synthesis but underscores a dependency on fossil-based hydrogen in conventional production processes. While CO_2 and methanol showcase favorable GWP100 profiles under current metrics, the advancement of bioconversion techniques for methane or biomass-derived sugars could further enhance the sustainability of green biomanufacturing. Hybrid systems that integrate waste-derived carbon sources with renewable energy inputs could bridge the gap between environmental performance and scalability, thereby advancing the goals of a circular bioeconomy.

Beyond the GWP100 metric, a comprehensive multi-category life cycle assessment (Table S2) reveals critical environmental trade-offs among carbon sources. While CO_2 utilization exhibits the lowest GWP100, it shows elevated terrestrial ecotoxicity potential (TETP: 19.12 kg 1,4-DCB-eq) due to energy-intensive capture processes. Conversely, glucose-derived ethanol, despite its high GWP100, demonstrates moderate impacts in categories like fossil fuel depletion (FFP: 1.16 kg oil-eq), yet incurs significant agricultural land occupation (LOP: 7.47 m^2a crop-eq) and freshwater eutrophication (FEP: 0.00175 kg P-eq), reflecting fertilizer-intensive crop cultivation. Methanol utilization balances a relatively lower GWP100 (4.05 kg CO_2-eq/kg) with competitive fossil fuel use (FFP: 2.23 kg oil-eq) but exhibits higher ozone depletion potential (ODP: 8.85E-06 kg CFC-11-eq). Formic acid and glycerol pathways display intermediate GWP100 but face challenges in human toxicity (HTPnc: 3.86 and 13.79 kg 1,4-DCB-eq, respectively) and marine eutrophication (MEP: 0.00258 and 0.02189 kg N-eq). In addition, utilizing organic waste materials as fermentation substrates promotes waste valorization while mitigating the ecological impacts of landfilling. This strategy contributes to resource conservation and reduces emissions related to waste decomposition.[168] Furthermore, the use of renewable feedstocks in biofuel and biochemical production diminishes reliance on fossil fuels and mitigates greenhouse gas emissions.[169-171] These disparities underscore that optimizing carbon sources for sustainability requires holistic evaluation beyond climate metrics, prioritizing synergies between low GWP, minimized resource depletion (e.g., water, land), and reduced ecotoxicity.

ECONOMIC FEASIBILITY OF DIFFERENT CARBON SOURCES

To guide industrial application of microbial biomanufacturing, it is essential to consider not only the biochemical compatibility of carbon sources but also their economic feasibility. Employing low-cost waste materials as substrates can substantially lower production expenses, rendering biomanufactured products competitive with their petrochemical counterparts. Each carbon source presents distinct challenges and opportunities in terms of substrate acquisition cost, availability, and downstream processing requirements (Table S3). Sugar-derived feedstocks such as glucose are widely used due to their high fermentation efficiency and well-established industrial processes. Nonetheless, the associated production costs remain high—driven by crop cultivation, enzymatic hydrolysis, and land use.[172] Waste-derived sugars (e.g., molasses, lignocellulosic hydrolysates) offer lower-cost alternatives but require pretreatment and detoxification to mitigate fermentation inhibitors.[80] While lignocellulose is abundant and inexpensive, its structural recalcitrance increases pretreatment and hydrolysis costs, reducing net economic benefits unless integrated with low-cost waste valorization strategies and high value-added compounds production.[2] Gaseous C1 feedstocks (e.g., CO_2, CO, CH_4) are typically low-cost or even considered waste liabilities, particularly in industrial off-gas contexts. However, their fixation and biological conversion remain technologically limited, often requiring complex reactor systems, gas delivery, or co-substrate support, which increases capital and operational costs.[20,32,173] Liquid C1 sources such as formic acid and methanol are more readily handled and transported. Methanol, particularly from fossil-based sources, is cost-effective but linked to upstream emissions. Renewable methanol and formic acid are emerging as promising,

though currently more expensive, substrates. Their future competitiveness depends on improvements in microbial tolerance and synthetic production methods.[69] Organic acids like acetic acid are inexpensive when derived from waste or syngas fermentation but pose toxicity challenges that necessitate strain adaptation or engineering. Similarly, glycerol—a biodiesel byproduct—is cost-attractive; however, crude glycerol often contains impurities (e.g. methanol, salts, free fatty acids such as linoleic acid) that inhibit microbial growth and lower metabolite yields, requiring minimal processing or robust microbial hosts.[174,175] Fatty acids from waste oils or byproducts are cost-efficient and energy-dense but show variability in composition, which affects fermentation consistency and product yield.[176] They also require microbial strains capable of metabolizing long-chain substrates with high efficiency. Additionally, theoretical conversion efficiencies to ethanol, calculated using genome-scale metabolic modeling, are provided in Table S4, further supporting industrial evaluation of substrate selection. In summary, the economic feasibility of microbial carbon sources depends not only on substrate price but also on processing requirements, microbial compatibility, and yield. Waste-derived substrates often show the best promise for reducing costs and enhancing sustainability but may introduce complexity in processing or strain development. A hybrid approach—combining low-cost waste feedstocks with robust microbial chassis—may offer the most feasible path toward scalable, sustainable biomanufacturing.

CONCLUSIONS AND PERSPECTIVES

Microbial carbon utilization is a powerful approach to support global sustainability. By using the natural abilities of microbes, we can turn renewable carbon sources—like farm waste, industrial emissions, and greenhouse gases—into useful products such as biofuels, bioplastics, and chemicals. This helps reduce fossil fuel use and cut greenhouse gas emissions. Recent breakthroughs in biotechnology have made this process more practical. Tools like synthetic biology, microbial community engineering, and machine learning are making microbial systems more efficient and precise. However, some technical challenges still limit progress. Important enzymes, like RuBisCO for CO_2 fixation and MMOs for methane conversion, work slowly. Improving these through techniques like directed evolution could help. Additionally, gases like CH_4, CO, and CO_2 don't dissolve well, making them hard to use in fermentation. New bioreactor designs and ways to improve gas use are needed. Microbes also struggle with toxic carbon sources such as formic acid, acetic acid, and methanol, so boosting their tolerance through genetic and metabolic engineering is important. To scale this field commercially, greater attention must be paid to feedstock availability and upscaling strategies. Over the next 5–10 years, the most practical inputs will be sugars from waste and biomass, glycerol, methanol, and CO_2. These sugars work well with current infrastructure. Methanol, in particular, is promising because it's easy to store and transport, can be made from CO_2 and H_2, and well supports yeast growth. CO_2 use is also advancing through new systems that combine renewable electricity with biology. Moreover, government policy plays a big role in supporting adoption of microbial carbon utilization technologies. For examples, putting a price on CO_2 emission ($50–150 per ton of CO_2) can make CO_2-based products competitive with fossil fuels. Policies rewarding low-GWP feedstocks will favor methanol over glucose. Tax credits for carbon capture and utilization, as well as mandates for bio-based chemicals, can further accelerate progress and stimulate investment in this field.

Future research should concentrate on scaling these biomanufacturing technologies, addressing climatic, economic and operational challenges, and promoting interdisciplinary collaboration to accelerate the transition to a circular bioeconomy. incorporating renewable energy into carbon source production and optimizing production processes could reduce greenhouse gas emissions and enhance the sustainability of microbial carbon utilization. Then, advanced tools like metabolic models can help predict outcomes and guide engineering, but current models still have limits. Making them more accurate by including detailed biological data will make them more useful. Finally, to build a truly circular and sustainable bioeconomy, strategies must match local resources. Processes should be designed to fit regional waste sources, energy supplies, and economic conditions. Strong collaboration across fields—science, engineering, economics, and policy—will be essential to drive this transition forward.

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FUNDING AND ACKNOWLEDGMENTS

The authors acknowledge financial support from Shandong Provincial Natural Science Foundation [ZR2023QC246], National Natural Science Foundation of China [NSF32170084, NSF32401267 and U24A20478], Qingdao New Energy Shandong Laboratory Open Project [QNESL OP202308], Chinese Scholarship Council and Federal Ministry for Economic Affairs and Climate Action of Germany. The author would be thanking Ehsan Salehabadi from Institut für Biochemie, Charité - Universitätsmedizin Berlin for helping analyse FBA data. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

W.F., W.T., W.L., Z.Y., J.X.L., L.W.H., G.Y.Z., X.Z.X., Y.Q., W.B., W.L.J. and L.D.S. wrote and edited the manuscript. Z.H.B. and W.Y.G. supervised and revised the manuscript. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Data availability is not applicable to this article as no new data were created or analyzed in this study.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-life.2025.100159