npj | materials sustainability

Review article

https://doi.org/10.1038/s44296-024-00008-w

Microbial conversion of carbon dioxide into premium medium-chain fatty acids: the progress, challenges, and prospects

Kai-Kai Wu[1,2], Pian-Pian Xu[1], Lei Zhao[1] ✉, Nan-Qi Ren[1,3] & Yi-Feng Zhang[2] ✉

The conversion of carbon dioxide to medium-chain fatty acids (CO_2-to-MCFAs) through microbial processes represents a valuable technology for sequestering and exploiting CO_2, generating superior biochemicals from the primary contributor to the greenhouse effect. However, a comprehensive overview and generalization of microbial CO_2-to-MCFAs are presently deficient. Based on this, the present review systematically summarizes the research progress, explicates the process mechanisms, analyses the key challenges and possible solutions, and anticipates forthcoming research perspectives and priorities for the first time. We proposed two original strategies, namely the synchronous strategy and integrated strategy, from current research into microbial CO_2-to-MCFAs. The synchronous strategy concurrently achieves hydrogen (H_2) and CO_2 assimilation, as well as MCFAs production, by employing a reactor that co-cultivates predominant H_2/CO_2-utilizing microorganisms and chain elongation microorganisms. The integrated approaches involve CO_2-to-precursors (i.e., acetate and ethanol) and subsequent precursors-to-MCFAs, achieved through the use of two bioreactors for separately cultivating H_2/CO_2-utilizing microorganisms and chain elongation microorganisms. Mechanistic insights reveal that microbial CO_2-to-MCFAs predominantly encompasses two processes: H_2 and CO_2 assimilation into precursor and subsequent precursors chain elongation into MCFAs, through a Wood-Ljungdahl pathway and a two-round elongation, respectively. The analyses of key challenges and possible solutions for microbial CO_2-to-MCFAs underscore the imperative to enhance efficiency and economy and to shed light on metabolic mechanisms. Furthermore, in order to improve the strategy application potential of microbial CO_2-to-MCFAs, future research perspectives and priorities, e.g. exploitation of functional pure bacteria, screening of functional pure bacteria, multi-omics analysis, genetic modification and enhancement, enhancement of bioreactor stability, specific MCFA production, development of coupled purification technology for MCFAs, and economic benefits and ecological environmental risks, are proposed and prospected. This work is expected to offer a thorough understanding of the microbial CO_2-to-MCFAs, guide and inspire researchers to address critical challenges in-depth and propel the development of CO_2-to-MCFAs.

With the development of human society, the global energy demand is growing rapidly, with more than 80% of the need being met by fossil fuels, e.g., coal, petroleum, natural gas, etc. However, the global carbon dioxide (CO_2) released from fossil fuel combustion is now approximately 36.8 billion tons yearly[1]. If the current uptrend continues, the CO_2 fossil-fuel-related emissions load is likely to double by mid-century, which will cause global warming of about 2 °C[2,3]. This trajectory of climate change entails an array of potential risks associated with climate destabilization, encompassing adverse natural phenomena, glacier melt, and intensified occurrences of extreme weather patterns. Confronted with the dual challenges of

[1]School of Environment, State Key Laboratory of Urban Water Resource and Environment, Harbin Institute of Technology, Harbin 150090, China. [2]Department of Environmental & Resource Engineering, Technical University of Denmark, DK-2800 Lyngby, Denmark. [3]School of Civil and Environmental Engineering, Harbin Institute of Technology (Shenzhen), Shenzhen 518055, China. ✉e-mail: lzhao@hit.edu.cn; yifz@dtu.dk

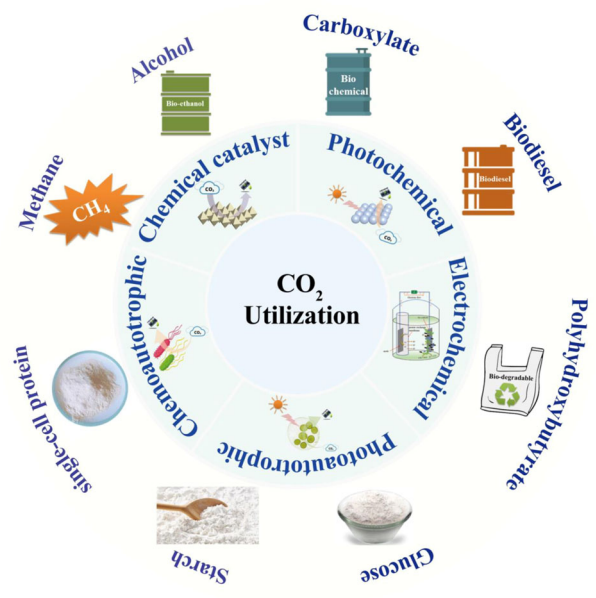

Fig. 1 | Recycling and utilization of CO_2. CO_2 can undergo conversion through various means such as light, electricity, chemical reactions, biological processes, and other methodologies, yielding a diverse array of chemicals and fuels.

escalating energy demand and the exacerbation of greenhouse climate effect, CO_2 capture, utilization, and storage (CCUS) has garnered considerable attention in recent years due to its pivotal role in mitigating the impact of global warming[4–6].

In comparison to CO_2 storage, the conversion and utilization of CO_2 represent a noteworthy renewable energy approach, holding the potential to alleviate CO_2 emissions and diminish reliance on fossil fuels, thereby contributing significantly to combating global warming. Presently, a growing number of CO_2 utilization technologies, including chemical catalysts[7,8], photochemical[9,10], electrochemical[11,12], as well as biogenic source such as photoautotrophic microalgae[13,14] and chemoautotrophic CO_2-utilizing bacterium[15,16], are undergoing development and practical implementation. These technologies facilitate the conversion of CO_2 into a range of renewable energy sources, spanning bio-fuels, bio-chemicals, high-molecular compounds, and degradable plastics. As illustrated in Fig. 1, the bio-products based-CO_2 involve in methane (CH_4)[17], alcohols[18], carboxylates[19,20], biodiesel[21], glucose[22], polyhydroxybutyrate[23], and starch[24], single-cell protein[25], and analogous substances.

Among these bio-products derived from CO_2, carboxylates, consisting of short-chain fatty acids (SCFAs, with 1-5 carbon chain, e.g., acetate and propionate) and medium-chain fatty acids (MCFAs, with 6-12 carbon chain, e.g., caproate and heptylate), are an extremely versatile biochemicals. Notably, MCFAs, serving as high value-added platform compounds, can be directly used as feed additives, plant growth promoters, and antimicrobials or serve as precursors for a broad spectrum of commodities, such as aviation fuel, lubricants, fragrances, paint additives, and pharmaceuticals[26,27]. Furthermore, MCFAs exhibit diminished dissolution properties (caproate of 93.1 mmol L^{-1}, heptylate of 18.5 mmol L^{-1}, caprylate of 4.9 mmol L^{-1}, pelargonate of 1.1 mmol L^{-1}, caprate, undecanoate and dodecanoate are almost insoluble in water, at 25 °C and 1.01 × 10^5 Pa), allowing MCFAs much more straightforward to separate from liquid effluent. This inherent property of lower solubility gives MCFAs a significant advantage in lowering separation costs.

This review aims to present a comprehensive overview of chemoautotrophic CO_2-utilizing bacterium for CO_2 conversion into MCFAs. Our focus is on summarizing the progress of microbial CO_2-to-MCFAs and elucidating the underlying strategies and mechanisms involved. Additionally, the challenges and possible solutions in this process are addressed, and future perspectives and priorities in this field are discussed.

Progress of microbial CO_2-to-MCFAs

Current research into microbial CO_2-to-MCFAs predominantly employs hydrogen (H_2) or H_2 proton (H^+) as an electron donor to assist CO_2 conversion. Additionally, a subset of studies explores the conversion of CO_2 into MCFAs by using co-electron donors and acceptors including short-chain alcohols (e.g., methanol and ethanol), carboxylate (e.g., acetate, propionate, butyrate), and lactate. As delineated in Tables 1–3, these studies on microbial CO_2-to-MCFAs can be systematically categorized into two principal strategies: the synchronous strategy and the integrated strategy.

Function microbial

The research into CO_2-to-MCFAs primarily encompasses two categories of functional microorganisms: H_2/CO_2-utilizing microorganism (also known as Homoacetogen) and chain elongation microorganisms. The both microorganisms togetherly facilitate the efficient conversion of H_2 and CO_2 into MCFAs. In the mixed-culture bioreactors, H_2/CO_2-utilizing microorganism and chain elongation microorganisms play a dominant role in the microbial community. Meanwhile, numerous high-effective Homoacetogens, e.g., *Acetobacterium woodii*[28], *Clostridium ljungdahlii*[29], *Clostridium ragsdalei P11*[30], *Clostridium autoethanogenum*[31], *Clostridium carboxidivorans*[32], etc, along with a select number of chain elongation microorganisms, e.g., *Clostridium kluyveri*[33], have been isolated and screened for their efficacy in converting CO_2 to ethanol and acetate, as well as facilitating the chain elongation process for MCFAs production in the pure-culture bioreactors.

H_2 roles and sources

It is widely believed that H_2 acts as electrons to drive the conversion of CO_2 into acetate and ethanol within H_2/CO_2-utilizing microorganisms. The sources of pure H_2 and H^+ are derived from electrolytic water and anode of microbial electrolysis cells (MEC). The electric power is generated by surplus windmills or solar panels. In addition, the H_2 utilized for driving CO_2 conversion sources from syngas (a mixture of H_2, CO_2, CO), which has a huge capacity emanating from biomass gasification, steelmaking industry, and coke-oven plant[34,35]. Among these H_2 supply means, MEC stands out as a low-input technology capable of overcoming the challenges associated with low-efficiency -H_2 gas-liquid mass transfer. The conversion of syngas into chemicals or fuel represents a noteworthy advancement in waste gas recycling technology.

CO_2 sources

The present investigation into microbial CO_2-to-MCFAs showed that a predominant proportion of the CO_2 utilized for MCFAs production emanates from simulated captured CO_2 gas (Tables 1 and 2). The potential of CO_2 for MCFAs production is very large and abundant. Currently, there exist approximately 40 commercial capture facilities globally, with a total annual capture capacity exceeding 45 million tons of CO_2 (International Energy Agency, 2023). The capture of CO_2 predominantly originates from large point sources, including power generation or industrial facilities that use either fossil fuels or biomass for fuel. Alternatively, the CO_2 can be captured directly from the atmosphere. Some studies also use syngas to provide CO_2 for MCFAs production (Tables 1 and 2). Besides, biogas comprises 35–45% CO_2, attains an annual production exceeding 70 billion cubic meters (bcm) and a global potential of up to 200 bcm per year[36]. Biogas, therefore, can also afford a mass of CO_2 for MCFAs production[37]. In fact, there are many more sources of CO_2 that can be used to produce MCFAs.

Two strategies for CO_2-to-MCFAs

The review introduces two innovative strategies in the current exploration of microbial CO_2-to-MCFAs, as depicted in the schematic diagram presented in Fig. 2. The synchronous strategy employed a reactor primarily housing two collaborating microbes, namely CO_2-utilizing microorganisms and

Table 1 | Current research to synchronous strategy for microbial H_2/CO_2-to-MCFAs

Synchronous strategy for H_2/CO_2-to-MCFAs							
Microbes	**Bioreactors**	**CO_2 source**	**H_2 source**	**Other ED addition**	**Other EA addition**	**MCFAs yield**	**References**
Mixed-culture	MEC	Pure CO_2	MEC (H^+)	/	/	Caproate 3.6 mmol L^{-1}	57
Mixed-culture	MEC	Pure CO_2	MEC (H^+)	/	/	Caproate 0.9 g $L^{-1}d^{-1}$	58
Mixed-culture	MEC	Syngas (CO, CO_2)	MEC (H^+)	/	/	Caproate 15.4%	59
Mixed-culture	MEC	Pure CO_2	MEC (H^+)	Ethanol	Formate	Trace levels	60
Mixed-culture	MEC	Dissolved CO_2	MEC (H^+)	/	/	Trace levels	61
Mixed-culture	MEC	Dissolved CO_2	MEC (H^+)	Ethanol and lactate	/	Caproate 1.6 g L^{-1}	38
Mixed-culture	MEC	Pure CO_2	MEC (H^+)	Ethanol	/	Caproate 4.4 g L^{-1}	62
Mixed-culture	MEC	Pure CO_2	MEC (H^+)	Ethanol	/	Caproate 11.9 g L^{-1}	63
Mixed-culture	MEC	Pure CO_2	MEC (H^+)	Ethanol and lactate	/	Caproate 8.0 g L^{-1}	39
Mixed-culture	MEC	Pure CO_2	MEC (H^+)	/	/	Caproate 7.5 g L^{-1}	20
Co-culture of *A. woodii* and *C. drakei*	MEC	Pure CO_2	MEC (H^+)	/	/	Caproate 1.6 g L^{-1}	64
Co-culture of *C. autoethanogenum* and *C. kluyveri*	Anaerobic bottle	Syngas (CO, H_2, CO_2)	Syngas (CO, H_2, CO_2)	/	/	Caproate 2.5 mmol $L^{-1}d^{-1}$	65
Mixed-culture	Minifors reactors	Syngas (CO, H_2, CO_2)	Syngas (CO, H_2, CO_2)	Lactate	/	Caproate	66
Mixed-culture	MBfR	Syngas (H_2, CO_2)	Syngas (H_2, CO_2)	/	/	Trace levels	67
Mixed-culture	MBfR	Syngas (H_2, CO_2)	Syngas (H_2, CO_2)	/	/	Caproate 5.7 g L^{-1}	34
Mixed-culture	MBfR	Syngas (H_2, CO_2)	Syngas (H_2, CO_2)	/	/	Caproate 0.9 g L^{-1}	68
Mixed-culture	dMBfR	Biogas (CO_2, CH_4)	H_2	Ethanol	/	MCFAs 28 mmol $L^{-1}d^{-1}$	54

H_2 hydrogen, *CO_2* carbon dioxide, *CO_2* carbon monoxide, *CH_4* methane, *MCFAs* medium-chain fatty acids, *MEC* microbial electrolysis cells, *ED* electron donor, *EA* electron acceptor, *MBfR* Membrane biofilm reactor, *dMBfR* dual-Membrane biofilm reactor.

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Table 2 | Current research to synchronous strategy for microbial CO_2-to-MCFAs without H_2 assistance

Synchronous strategy for CO_2-to-MCFAs without H_2 assistance						
Microbes	**Bioreactors**	**CO_2 source**	**Other ED addition**	**Other EA addition**	**MCFAs yield**	**References**
B. methylotrophicum	Anaerobic bottle	Pure CO_2	Methanol	/	Trace levels	69
Mixed-culture	Anaerobic bottle	Pure CO_2	Ethanol	Acetate	Heptanoate 118 mg L^{-1}	40
Mixed-culture	Anaerobic bottle	Pure CO_2	Ethanol	Propionate	Caproate 10.8 g·$L^{-1}$$d^{-1}$	70
Mixed-culture	Up-flow reactor	Pure CO_2	Ethanol	Acetate	57.4 g MCFA $L^{-1}$$d^{-1}$	56
Mixed-culture	Anaerobic reactor	Pure CO_2	Ethanol	Acetate	Caproate 1.9 g COD·$L^{-1}$$d^{-1}$	71
Mixed-culture	Anaerobic bottle	Pure CO_2	Ethanol	Acetate	Caproate 17.6 g COD·L^{-1}	72
Mixed-culture	Anaerobic bottle	Pure CO_2	Ethanol	Acetate	Caproate 21.5 g COD·L^{-1}	73
Co-culture of *C. carboxidivorans* and *C. kluyveri*	Stirred-tank bioreactor	Syngas (CO, CO_2)	Ethanol	Acetate	Hexanoate 0.3 g L^{-1}	31

H_2 hydrogen, *CO_2* carbon dioxide, *CO_2* carbon monoxide, *MCFAs* medium-chain fatty acids, *ED* electron donor, *EA* electron acceptor, *COD* Chemical Oxygen Demand.

Table 3 | Current research to integrated strategy for microbial CO_2-to-MCFAs

CO_2-to-precursors			**Precursors-to-MCFAs**			**References**
Microbes	**CO_2 and H_2 sources**	**To-precursors**	**Microbes**	**Precursors-to**	**MCFAs yield**	
Mixed cultures	Pure CO_2 and MEC	Ethanol and acetate	Mixed cultures	Ethanol and acetate	Caproate 144 mmol carbon	74
Mixed cultures	Syngas (H_2, CO_2)	Ethanol and SCFAs	Mixed cultures	Ethanol and SCFAs	Caproate 6,157 mg L^{-1}	52
Mixed cultures	Syngas (CO, H_2, CO_2)	Ethanol and acetate	Mixed cultures	Ethanol and acetate	Caprylate 68.3 mmol $L^{-1}$$d^{-1}$	75
Mixed cultures	Syngas (CO, H_2, CO_2)	Ethanol and acetate	Mixed cultures	Ethanol and acetate	Caproate and caprylate	46
C. ljungdahlii	Syngas (CO, H_2, CO_2)	Ethanol and acetate	Mixed cultures	Ethanol and acetate	Caproate 1.0 g L^{-1}	53
Mixed cultures	Syngas (CO, H_2, CO_2)	Ethanol and acetate	*C. kluyveri*	Ethanol and acetate	Caproate 40 mmol $L^{-1}$$d^{-1}$	76
Mixed cultures	Syngas (CO, H_2, CO_2)	Ethanol and acetate	*C. kluyveri*	Ethanol and acetate	Caproate 121.9 mmol L^{-1}	77

H_2 hydrogen, *CO_2* carbon monoxide, *MCFAs* medium-chain fatty acids, *SCFAs* short-chain fatty acids, *MEC* microbial electrolysis cells.

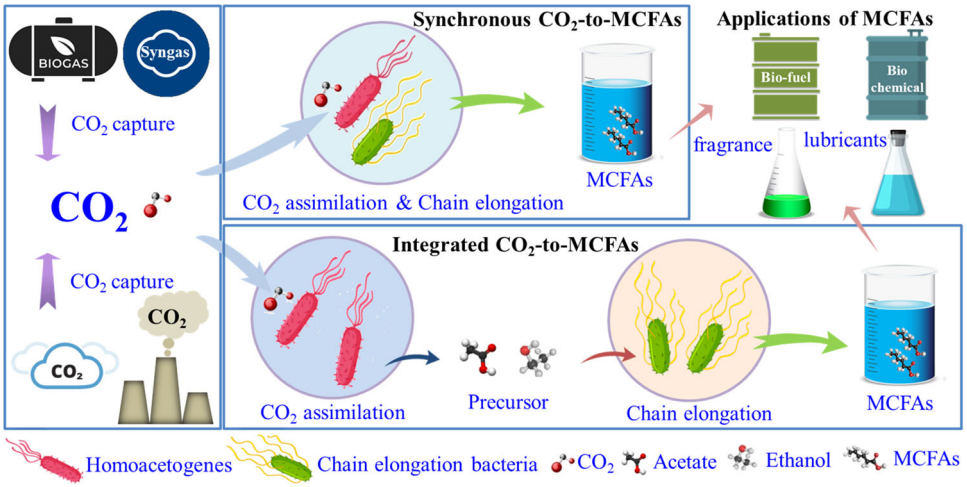

Fig. 2 | The schematic diagram of synchronous strategy and integrated strategy for microbial CO_2-to-MCFAs. The synchronous strategy involved a reactor designed to host two symbiotic microbial populations, namely carbon CO_2-utilizing microorganisms and chain elongation microorganisms, with the aim of enabling concurrent processes of CO_2 assimilation and chain elongation. The integrated strategy employs two distinct bioreactors. In the initial reactor, H_2 and CO_2 are assimilated into precursors (acetate and ethanol) by microorganisms specialized in H_2 and CO_2 utilization. In the secondary bioreactor, dominant chain elongation microorganisms facilitate the elongation of acetate and ethanol into MCFAs.

chain elongation microorganisms, to facilitate simultaneous CO_2 assimilation and chain elongation. In the presence of H_2, H_2/CO_2-utilizing microorganisms and chain elongation microorganisms dominate the microbiome of a mixed-culture bioreactor, allowing for the concurrent assimilation of H_2 and CO_2 into acetate and ethanol and chain elongation of endogenous acetate and ethanol into MCFAs. Moreover, an accompanying strategy for H_2/CO_2-to-MCFAs involves the co-cultivate of pure Homoacetogen and chain elongation microorganisms (e.g., co-culture of *Clostridium autoethanogenum* and *Clostridium kluyveri*) to achieve synchronous H_2/CO_2 assimilation and chain elongation (Table 1). Furthermore, in the synchronous strategy for H_2/CO_2-to-MCFAs, external addition of electron donors (e.g., ethanol) and acceptors (e.g., acetate and propionate) are often implemented to facilitate chain elongation[38,39].

In addition, in the synchronous strategy for CO_2-to-MCFAs, certain studies have showed the feasibility of elongating CO_2 into MCFAs without H_2 assistance. In such cases, electron donors (e.g., methanol and ethanol) and acceptors (e.g., acetate and propionate) play a crucial role in the elongation process, as indicated in Table 2. Additionally, research reported that CO_2 can promote the elongation of acetate and ethanol into MCFAs[40]. However, the underlying mechanism of converting CO_2 and elongating electron donors (e.g., methanol and ethanol) and acceptors (e.g., acetate and propionate) into MCFAs remains unclear. In short, the synchronous strategy synchronously enables concurrent CO_2 conversion and MCFAs production under with H_2 assistance or without H_2 assistance. The primary advantage of the synchronous strategy lies in its cost-effectiveness due to lower equipment investment. However, the synchronous implementation of both processes in a single reactor may lead to mutual inhibition, potentially causing reduced efficiency.

The integrated strategy for CO_2-to-MCFAs involves two separate bioreactors (Fig. 2). In the first reactor, the assimilation of H_2 and CO_2 into precursors (acetate and ethanol) occurs within the H_2/CO_2-to-precursors bioreactor. The microbiome of this bioreactor is primarily composed of H_2 and CO_2 -utilizing microorganisms (e.g., *Clostridium ljungdahlii*, *Clostridium autoethanogenum*). Subsequently, the H_2 and CO_2 fermentation effluent, containing the precursors (acetate and ethanol), is fed into the chain elongation bioreactor. In this second bioreactor, dominant chain elongation microorganisms, such as *Clostridium kluyveri*, facilitate the elongation of acetate and ethanol into MCFAs. In the integrated strategy, the sources of H_2 and CO_2 primarily originate from syngas, MEC, and simulated captured CO_2 gas (Table 3). The coupling approach effectively achieved the sequential objectives of CO_2-to-precursors and subsequent precursors-to-MCFAs. Its primary advantage lies in separating CO_2 assimilation and MCFAs production processes into distinct reaction units, ensuring system stability and enhancing overall performance.

Mechanism of CO_2-to-MCFAs

Figure 3 illustrates the mechanisms of microbial CO_2-to-MCFAs. In the context of H_2 and CO_2 as the substrate for MCFAs, H_2/CO_2-to-MCFAs mainly encompasses two key processes: the assimilation of H_2 and CO_2 into precursor (acetate and ethanol) and subsequent chain elongation of these precursors (acetate and ethanol) into MCFAs. In addition, some studies have reported a supplementary process wherein other electron donors (e.g., lactate) and electron acceptor (e.g., propionate) substrates are introduced to facilitate the production of MCFAs.

H_2 and CO_2-to-acetate and ethanol

Whether employing a synchronous strategy or an integration strategy for H_2/CO_2-to-MCFAs, the assimilation of H_2 and CO_2 into precursors (acetate and ethanol) stands as the primary process implemented by H_2 and CO_2-utilizing microorganisms. The majority of H_2 and CO_2 -utilizing microorganisms convert H_2 and CO_2 into acetate and ethanol via a wood-ljungdahl pathway according to the equation $4H_2 + 2CO_2 \rightarrow CH_3COOH + 2H_2O$ $\Delta G = -95 kJ\ mol^{-1}$ and $6H_2 + 2CO_2 \rightarrow C_2H_5OH + 3H_2O$ $\Delta G = -97\ kJ\ mol^{-1}$ [36,41]. These reactions are catalyzed by a series of microbial enzymes. As shown in Fig. 3 (CO_2-to-acetate and ethanol), the assimilation of CO_2 involves two pathways (methyl and carbonyl pathways), in which acetyl-CoA (acetyl-coenzyme A) works as a pivotal intermediate for acetate and ethanol production. In the methyl pathway, CO_2 is first converted into formate with the assistance of H_2, which acts as an electron donor for reducing CO_2. Subsequently, formate undergoes successive transformations into formyl-tetrahydrofolate (formyl-THF), methenyl-THF, methylene-THF, methyl-THF, and further methyl-corrinoid iron-sulfur protein (methyl-CoFeSP). In the carbonyl pathway, CO_2 is first reduced into CO, followed by CO, and along with methyl-CoFeSP, it is transformed into acetyl-CoA. Acetyl-CoA is eventually transformed into acetate and ethanol. In addition to producing the main metabolites of acetate and ethanol, small amounts of $C_{3\text{-}5}$ (with 3-5 carbon chain fatty acids, e.g., propionate, butyrate and valerate) are also generated by Homoacetogens[29,42]. These by-products can also serve as precursors to be elongated into MCFAs.

Acetate and ethanol-to-MCFAs

The process of acetate and ethanol-to-MCFAs consists of two consecutive rounds of elongation implemented by chain elongation bacteria. The corresponding reaction equations are represented:as follows $4H_2 + 2CO_2 \rightarrow CH_3COOH + 2H_2O$ $\Delta G = -95 kJ\ mol^{-1}$ and $5C_2H_5OH + 5C_3H_7COOH \rightarrow C_5H_{11}COOH + 4H_2O + 2H_2$ $\Delta G = -183.5\ kJ\ mol^{-1}$ [43]. Each round elongation is catalyzed by a series of microbial enzymes, and the process results in an increment oftwo carbon chains in each round. As shown in Fig. 3 (ethanol and acetate-to-butyrate and butyrate-to-MCFAs),

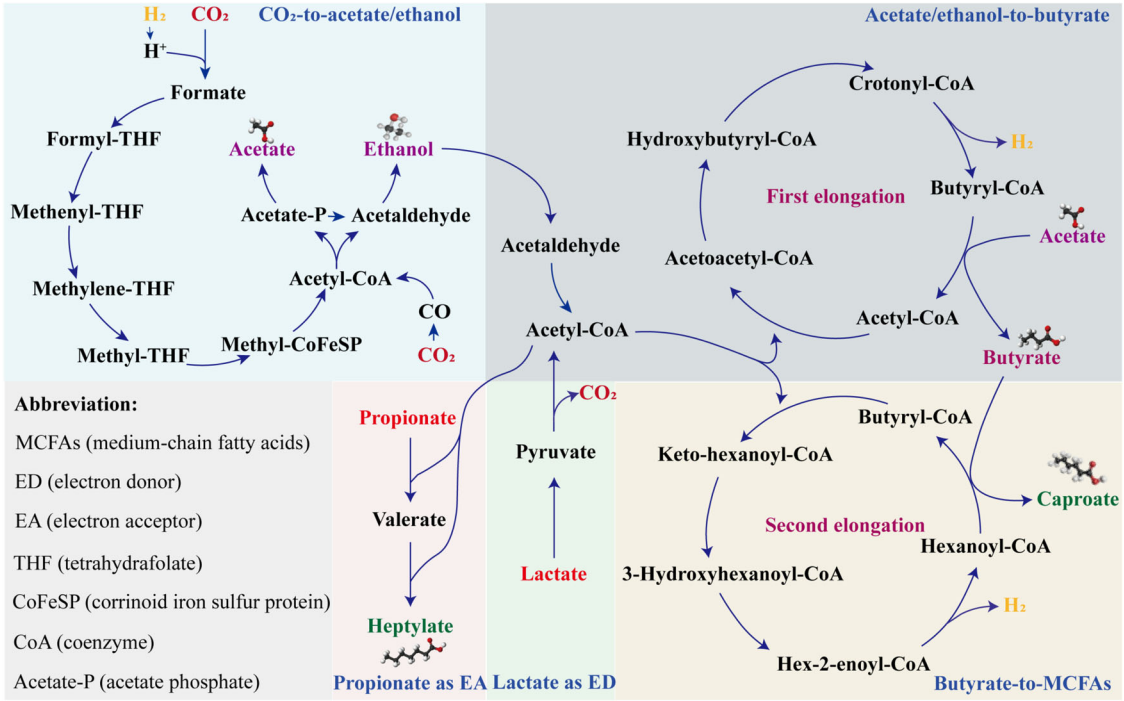

Fig. 3 | The mechanisms of microbial CO_2-to-MCFAs. H_2 and CO_2 are converted first into acetate and ethanol via a wood-ljungdahl pathway. Acetate and ethanol undergo then two consecutive rounds of elongation to form MCFAs. Lactate and propionate can be enzymatically elongated into MCFAs using ethanol as a substrate.

in the first-round elongation (ethanol and acetate-to-butyrate), ethanol from H_2 and CO_2 assimilation is first oxidized to acetaldehyde and then to acetyl-CoA. coupled to another acetyl-CoA, acetyl-CoA undergoes successive transformations into acetoacetyl-CoA, hydroxybutyryl-CoA, crotonyl-CoA, and further butyryl-CoA, which then is converted into acetyl-CoA and butyrate with acetate formed from H_2 and CO_2 assimilation. The acetyl-CoA continues to participate in the elongation of the first round, while concurrently initiating the second-round elongation by coupling with butytyl-CoA. In the second-round elongation (butyrate-to-MCFAs), acetyl-CoA and butytyl-CoA undergo successive conversions into ketohexanoyl-CoA, 3-hydroxyhexanoyl-CoA, hex-2-enoyl-CoA, and further hexanoyl-CoA. Hexanoyl-CoA is then converted into caproate along with the butyrate generated from the first-round elongation. Notably, H_2 is generated during both rounds of the elongation process. In the integration strategy of CO_2-to-MCFAs, the H_2 release means that some energy will inevitably be lost. However, in the synchronous strategy of CO_2-to-MCFAs, the H_2 is recycled with CO_2 to produce acetate and ethanol, which prevents energy loss.

In addition, except for caproate, a few small quantities of heptylate and caprylate are also produced in the course of two consecutive rounds of elongation, the underlying mechanism of which remains to be conclusively established. In general, the elongation of first-round and second-round work in sync for acetate and ethanol-to-caproate within chain elongation bacteria. Consequently, both butyrate and caproate are produced simultaneously. However, the elongation processes of acetate, ethanol-to-heptylate, and caprylate may unfold successively within chain elongation bacteria. Upon achieving a specific yield of butyrate and caproate, the elongation into heptylate and caprylate is initiated, resulting in the production of heptylate and caprylate. Therefore, heptylate and caprylate are usually produced during the intermediate and later stages of chain elongation process[44].

During the two successive rounds of elongation for acetate and ethanol-to-MCFAs, butyrate acts as an intermediate electron acceptor to produce MCFAs, while butyrate is also a significant by-product with a higher cumulative yield. For example, butyrate, acting as the only electron acceptor, along with ethanol, can also be elongated into MCFAs[45]. Nevertheless, the elongating process of acetate and ethanol-to-MCFAs yields a higher butyrate output. This shows that the more butyrate is elongated into MCFAs, the higher yield of MCFAs is formed. However, a common phenomenon observed in numerous studies involves the substantial accumulation of butyrate without subsequent elongation into MCFAs[33,46]. This butyrate accumulation reduces the yield of MCFAs. Therefore, the efficiency of butyrate-to-MCFAs is a limiting factor to MCFAs production. The aspect warrants meticulous consideration in future research endeavors.

Lactate or propionate-to-MCFAs

Lactate usually acts as an externally introduced electron donor for the production of MCFAs, and it can be oxidized either in conjunction with ethanol as a co-electron donor or as a standalone electron donor[47]. As shown in Fig. 3 (lactate as ED), lactate is initially oxidized to pyruvate, subsequently progressing to further oxidation to form acetyl-CoA. Acetyl-CoA then enter the elongation process of the first and second rounds, ultimately yielding MCFAs. Notably, a portion of CO_2 is released accompanied by oxidization of pyruvate into acetyl-CoA, indicating a part loss of the carbon source when the lactate as an electron donor. In contrast, the synchronous strategy of CO_2-to-MCFAs offers a distinctive advantage, as CO_2 is recycled with H_2 to generate acetate and ethanol, thereby preventing the loss of carbon sources. Conversely, the integration strategy of CO_2-to-MCFAs lacks this particular advantage and is susceptible to carbon source loss.

Propionate typically serves as an externally added electron acceptor for MCFAs production. As shown in Fig. 3 (propionate as EA), the process involves the initial elongation of propionate, which, when coupled with acetyl-CoA, progresses to form valerate. Subsequently, valerate, in conjunction with acetyl-CoA, undergoes further elongation to produce heptylate. Consequently, propionate and valerate can function as either co-electron acceptors or distinct electron acceptors in the production of MCFAs, resulting in the generation of MCFAs with uneven carbon chains.

Key challenges and possible solutions for CO_2-to-MCFAs

The key challenges for CO_2-to-MCFAs primarily revolve around the low microbial conversion efficiency, resulting in an insufficient yield of MCFAs. Additionally, the economic viability of the strategy is a matter of contention, and certain aspects of the process mechanisms remain inadequately elucidated (Fig. 4). These formidable challenges have considerably impeded the

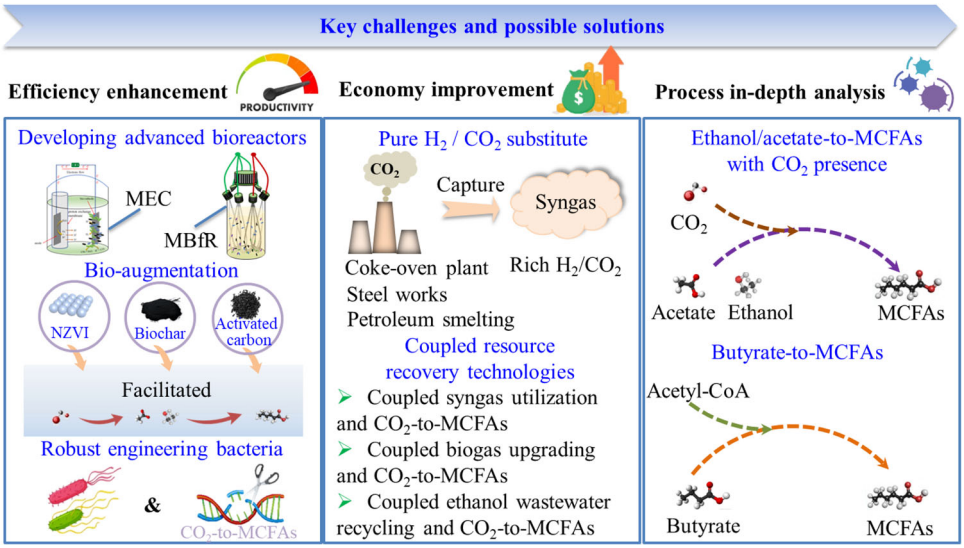

Fig. 4 | The key challenges and possible solutions for CO2-to-MCFAs. The key challenges and possible solutions encompass enhancing the biotransformation efficiency, optimizing the economic viability of real-world engineering implementations, and elucidating the underlying mechanisms governing the biotransformation process.

seamless transition of the strategy from laboratory research to practical application.

Efficiency improvement

As shown in Tables 1–3, whether employing a synchronous or integrated strategy for H_2/CO_2-to-MCFAs, numerous studies supplied H_2 and CO_2 in the form of gases, alongside MEC providing H_2 protons. However, it is essential to note that H_2 and CO_2 gases exhibit a lower dissolution of 0.8 mmol L^{-1} and 33.9 mmol L^{-1} under 25 °C and 1.01 × 10^5 Pa. Moreover, H_2 and CO_2 can be captured and converted by Homoacetogenes before being dissolved into the liquid phase. Therefore, the lower gas-liquid mass transfers of H_2 and CO_2 are a crucial limiting condition to microbial conversion efficiency in H_2 and CO_2-to-acetate and ethanol processes, ultimately resulting in the lower production of MCFAs. As shown in Fig. 4, to address this challenge of suboptimal H_2 and CO_2 gas-liquid mass transfers, all kinds of advanced reactor designs, such as hollow-fiber membrane aerated biofilm reactors and MEC[48], should be developed to enhance H_2 and CO_2 gas-liquid mass transfer. Meanwhile, the advanced bioreactors must be capable of trapping more microbes and facilitating the timely dissociation of MCFAs. The increased retention of microbes within bioreactors is a direct and effective approach to augment the performance of CO_2-to-MCFAs. Concurrently, the prompt dissociation of MCFAs is pivotal in mitigating the toxicity of MCFAs to microorganisms.

In addition, the low efficiency observed in microbial transformation of CO_2-to-MCFAs in current studies is due to the inherently low metabolic activity of microorganisms. Employing bio-augmentations and powerful engineered bacteria may be effective solutions to improve the efficiency of microbial transformation for CO_2-to-MCFAs. Some studies have demonstrated the effectiveness of bio-augmentations, e.g., the addition of zero-valent nano-iron (ZVNI), biochar, and activated carbon, in bolstering microbial transformation efficiency by maintaining the system stability and enhancing microbial metabolic activity[49,50]. Furthermore, using robust pure bacteria or genetically modified engineering bacteria have been proved to be effective means to improve the efficiency of H_2 and CO_2 assimilation and ethanol and acetate chain elongation[29,51].

Economy improvement

While microbial approaches for CO_2-to-MCFA$_S$ are gaining increasing popularity, concerns have been raised regarding their economic viability. As shown in Fig. 4, various coupled resource recovery technologies, e.g., syngas-to-biofuel, biogas upgrading, acetate and ethanol of wastewater recycling, and the like, with microbial approaches of CO_2-to-MCFAs, presents a promising avenue to enhance economic feasibility. Notably, syngas-to-biofuel has been extensively documented. Additionally, the successful coupling techniques involving biogas upgrading and recycling from acetate and ethanol wastewater with CO_2-to-MCFAs have also been demonstrated in previous studies[52,53]. For instance, synchronous biogas upgrading and MCFAs production respectively achieve greater than 96% CH_4 purity and 24 mmol $L^{-1}d^{-1}$ MCFAs production rate[54,55]. Another study reports a feasible approach of concurrently recycling of liquor-making wastewater and yielding the high output of MCFAs[47]. Moreover, the utilization of cheaper mixture gases of H_2 or CO_2 instead of pure H_2 and CO_2 can contribute to reducing costs. In addition, with the rapid development of CO_2 capture technology worldwide and the growing environmental benefits of CO_2 reduction in response to climate change, the associated costs are expected to decrease.

Process in-depth analysis

The lack of elucidation in certain the mechanisms governing CO_2-to-MCFAs represents a significant challenge, impeding its practical application. As mentioned above, the mechanism involved in converting CO_2 and the elongating of electron electrons (e.g., methanol and ethanol) and acceptors (e.g., acetate and propionate) into MCFAs remains unclear. While some studies have posited that the conversion of CO_2-to-MCFAs is caused by the H_2 gas assistance produced by the chain elongation of ethanol and acetate[56], the explicit mechanism lacks definitive confirmation. In addition, a comprehensive analysis of the mechanism governing butyrate-to-MCFAs is warranted to enhance its transformation efficiency. The large accumulation of butyrate and failure to elongate into MCFAs are also important reasons for lower yield of MCFAs.

Future perspectives

The synchronous and integrated strategy for microbial CO_2-to-MCFAs holds a promising potential for CO_2 recycling and MCFAs production. MCFAs, as renewable bioenergy sources, derived from waste CO_2, offer an opportunity to reduce the dependence on fossil fuels and contribute to the mitigation of CO_2 emissions, thereby being conducive to tackling global climate change and energy supply shortage. However, the technology of microbial CO_2-to-MCFAs has yet to transition from laboratory research to practical engineering applications. As the escalation of global CO_2 emissions and the increasing severity of climate change, the technology, although slow to start, is developing rapidly.

Fig. 5 shows future research perspectives and priorities aimed at boosting the application potential of CO_2-to-MCFAs. The exploitation of functional pure bacteria is a the cornerstone for high-efficiency CO_2-to-MCFAs. In particular, screening vital functional pure bacteria serves as a

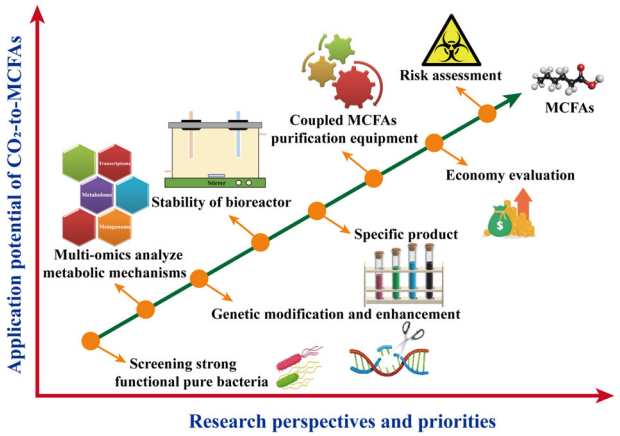

Fig. 5 | The future research perspectives and priorities for boosting application potential of CO_2-to-MCFAs. The forthcoming research outlook and focal points encompass the utilization of functionally pure bacteria, screening of such strains, elucidation of metabolic pathways, genetic modification for enhanced performance, bolstering bioreactor stability, tailored production of specific MCFAs, advancement of coupled purification techniques, and comprehensive assessment of economic viability and ecological ramifications.

catalyst for technological advancement. The application of multi-omics, e.g., metagenome, metabolome, transcriptome, proteome, etc., is crucial for a comprehensive understanding of the metabolic pathways and transformation processes of microbial CO_2-to-MCFAs. This knowledge, in turn, will pave the way for genetic modification and enhancement. With the rapid development of biotechnology, the trend in future research and development is expected to focus on genetically modified and enhanced engineered bacteria. The stability of bioreactor is paramount for practical applications, yet ensuring their prolonged stability and efficient operation remains an urgent challenge. Notably, current studies predominantly yield mixed MCFAs, including caproate, heptylate, and caprylate. However, achieving product separation and generating a specific MCFA suitable for targeted product formation presents a complex challenge. Meanwhile, the promotion of the synchronous CO_2-to-MCFAs and MCFAs purification is advocated. This approach aims to achieve the simultaneous production and purification of MCFAs,, mitigating the toxic effects of MCFAs on microorganisms and stimulating the production of MCFAs. Furthermore, before practical engineering application, a meticulous assessment of economic benefits and ecological environmental risks is imperative.

In addition, future research will center on coupled resource recovery technologies, e.g., coupled syngas utilization and CO_2-to-MCFAs, coupled biogas upgrading and CO_2-to-MCFAs, and coupled acetate and ethanol recycle from wastewater and CO_2-to-MCFAs, among others. These coupled resource recovery technologies offer a dual advantage: enhancing economic viability while simultaneously integrating and synergizing diverse process chains to achieve the production of energy products entirely from waste.

Conclusion

This review first comprehensively summarizes current research progress to microbial CO_2-to-MCFAs, proposing two innovative strategies for microbial CO_2-to-MCFAs, namely, synchronous strategy and integrated strategy. Then, the underlying mechanisms of the two original strategies are interpreted in detail. Moreover, a thorough analysis of the key challenges and possible solutions in microbial CO_2-to-MCFAs is presented. Furthermore, future research perspectives and priorities of microbial CO_2-to-MCFAs are prospected and discussed, aiming to enhance the strategy application potential. In a word, the microbial CO_2-to-MCFAs emerge as a favored technology for high-value CO_2 resource recovery, presenting an opportunity to reduce the dependence on fossil fuels and mitigate CO_2 emissions, thus helping address global climate change and energy unsustainability.

Data availability

No datasets were generated or analysed during the current study.

Received: 10 December 2023; Accepted: 26 January 2024;
Published online: 26 March 2024

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Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. U22A20443, No. 52076063); the Fundamental Research Funds for the Central Universities (No.HIT. OCEF.2023014, No.HIT. OCEF.2021031); the Heilongjiang Provincial Natural Science Foundation of Excellent Young Scholars (Grant No. YQ2023C031); Open Project of Key Laboratory of Environmental Biotechnology, CAS (Grant No kf2020009); Heilongjiang Touyan Innovation Team Program; and the Fundamental Research Funds for the Central Universities (HIT. DZJJ.2023058); State Key Laboratory of Urban Water Resource and Environment (Harbin Institute of Technology) (2023DX04).

Author contributions

Kai-Kai Wu: Investigation, Methodology, Validation, Writing – original draft. Pian-Pian Xu: Resources. Lei Zhao: Supervision, Writing – review & editing. Nan-Qi Ren: Supervision, writing-review & editing. Yi-Feng Zhang: Conceptualization, Supervision, Resources, Funding acquisition, Writing – review & editing.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Lei Zhao or Yi-Feng Zhang.