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Research review paper

Biosynthesis of alkanes/alkenes from fatty acids or derivatives (triacylglycerols or fatty aldehydes)

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ABSTRACT

This review summarizes the most relevant advances in the biological transformation of fatty acids (or derivatives) into hydrocarbons to be used as biofuels (biogasoline, green diesel and jet biofuel). Among the used enzymes, the fatty acid decarboxylase from *Jeotgalicoccus* sp. ATCC 8456 ($OleT_{JE}$) stands out as a promising enzyme. $OleT_{JE}$ may be coupled in cascade reactions with metalloenzymes or reductases from the Old Yellow Enzymes (OYE) family to perform the hydrogenation of α-olefins into paraffins. The photodecarboxylase from *Chlorella variabilis* NC64A (CvFAP) is an example of coupling biocatalysis and photocatalysis to produce alkanes. Besides the (photo)decarboxylation of free fatty acids and/or triacyclglycerols to produce alkanes/alkenes, by enzymes has also been employed. The cyanobacterial aldehyde decarbonylase (cAD) from *Nostoc punctiforme* is an outstanding example of this kind of enzymes used to produce alkanes. Overall, these kinds of enzymes open up new possibilities to the production of biofuels from renewable sources, even if they have many limitations on the current situation. The possibilities of improving enzymes features via immobilization or coimmobilization, as well as the utilization of whole cells haves been also reviewed.

1. Renewable hydrocarbon biofuels: biocatalysis as an alternative

The current scenario on fuels consumption derived from petroleum has two major problems. First, the anthropogenic CO_2 emissions caused by the petroleum-derived fuels is causing global warming, which may be tackled by capturing the produced CO_2 or by using fuels whose net CO_2 balance is nearer to zero (Jackson et al., 2018; Al-Ghussain, 2019; Gizer et al., 2022; Krūmiņš et al., 2022; Raju et al., 2022). Second, petroleum is a non-renewable and a strongly contaminant source of energy, which makes the search for alternative renewable fuel sources recommendable (Ragauskas et al., 2006; Naik et al., 2010; Abbasi et al., 2021; Khan et al., 2022). In this context, the development of processes to produce biofuels to be used in internal combustion engines (Agarwal, 2007; Nigam and Singh, 2011; Carneiro et al., 2017; Mobin Siddique et al., 2021) is attracting great interest (Chew and Bhatia, 2008; Ong and Bhatia, 2010; Choi et al., 2015). However, currently fossil fuel sources (oil, coal and natural gas) still account for about 85% of the global energy demand (Lund, 2007; Østergaard et al., 2020). Although the advanced liquid biofuels industry has been sluggish due to early stage technological development, high production costs, immature supply chains, dependence on government support and, therefore, uncertainties about around its market size, the liquid biofuels use grew by 19% annually from 2000 to 2010 (IRENA, 2019); and, the global demand for biofuels is projected to grow by 41 litters, or 28%, over 2021–2026 (IEA, 2021).

The most common biofuel is biodiesel, which is produced by the transesterification of acylglycerols or by the esterification of free fatty acids with short-chain alcohols (ethanol or methanol) (Hoekman et al., 2012; Maheshwari et al., 2022). The high oxygen content of biodiesel promotes its immiscibility with fossil fuels (restricting its use in blends), increases its viscosity (worsening its cold flow properties), and makes it

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very reactive and unstable (increasing the tendency to produce gum and sludge formation by polymerization and decreasing thermal and storage stabilities) (Mohammad et al., 2013). As a consequence, there have been efforts to produce renewable liquid hydrocarbons (biogasoline (Hassan et al., 2015; Oi et al., 2019), green diesel (Douvartzides et al., 2019; Koul et al., 2021) and biojet fuel (Gutiérrez-Antonio et al., 2017; Wei et al., 2019)) from lipids or derivatives. Their chemical composition is similar (or even identical) to petroleum-based fossil fuels (Sousa et al., 2018a; Scaldaferri and Pasa, 2019a, 2019b; Moreira et al., 2020), thereby solving the problems of using biodiesel.

Lipid-based renewable hydrocarbon biofuels are usually produced by the hydroprocessing of esters and fatty acids (HEFA) under high H_2 pressures and temperatures (Pattanaik and Misra, 2017; Khan et al., 2019; Monteiro et al., 2022). Usually, these reactions are catalyzed by supported noble or transition metals (Ooi et al., 2019; Lee et al., 2020). The intensive use of expensive and rare noble metals (Pd and Pt, for example) and high H_2 consumption (Popov and Kumar, 2013) are the main problems against the implementation of renewable hydrocarbon biofuels. High H_2 consumption is a specially relevant problem, since hydrogen is mainly produced from non-renewable resources (Acar and Dincer, 2014; Martinez-Burgos et al., 2021).

In this context, the biological production of renewable hydrocarbon biofuels has been proposed as an alternative to chemical production of gaseous and liquid renewable hydrocarbon biofuels (McInerney et al., 2010; Rahman et al., 2018; Amer et al., 2020). In this review, the production of potential hydrocarbon-based biofuels by the modification of free fatty acids and/or triacylglycerols from natural oils and fats by biological catalysts (enzymes and microbial platforms) will be reviewed. Herein, the focus will be on the biological decarboxylation, decarbonylation and hydrogenation of fatty acids and derivatives to produce renewable hydrocarbon biofuels.

The use of biological catalysts may reduce the previously stated problems. Although the reactions that we intend to perform are complicated (see later in this review), the availability of many different alternatives to solve the problems causes us to be optimistic on the future. The next sections include a critical evaluation of the potential of biocatalysis as an alternative to conventional catalysis and the tools available to improve the prospects to implement them. Biocatalysis aims to avoid the environmental problems generated by the conventional chemical production methods and to cover the demand for more sustainable production of goods and chemicals (Sheldon and Brady, 2021; Domínguez de María, 2021; Nazor et al., 2021; Guajardo and Domínguez de María, 2021; Santi et al., 2021; Wu et al., 2021; Alcántara et al., 2022).

Enzymes are normally very active in aqueous medium under mild conditions of temperature and pressure, and very selective and specific, thereby becoming an ideal solution for the development of greener processes (Sheldon and Brady, 2021; Domínguez de María, 2021; Nazor et al., 2021; Guajardo and Domínguez de María, 2021; Santi et al., 2021; Wu et al., 2021; Alcántara et al., 2022). However, enzymes have been designed by natural evolution to fulfil their physiological role, so that several enzyme features do not fit well the requirements of the chemical industry. Enzymes are homogeneous catalysts, with low/moderate stability, and with good activity, selectivity and specificity normally occurring towards their physiological substrates under physiological environment. This discrepancy between enzyme features and industrial requirements has delayed their implementation (Schoemaker et al., 2003). Nowadays, huge advances have been made in different tools at all the levels of biocatalyst and bioprocess development that enable to obtain enzymes with proper features for the industrial requirements or to improve them if they do not reach the required performance targets. First, it is possible to design a better starting enzyme. Biodiversity may be fully utilized (at least in theory) by employing metagenomics tools, which enable to obtain any enzyme, even from no longer existing or non cultivable organisms (Lorenz et al., 2002; Schoemaker et al., 2003; Steele et al., 2009; Fernández-Arrojo et al., 2010). The enzyme features may be enhanced by using enzyme modeling/site directed mutagenesis (Bordes et al., 2009; Mohandesi et al., 2017) or by mimicking natural evolution using directed evolution (Markel et al., 2020; Qu et al., 2020; Bunzel et al., 2021; Stucki et al., 2021; Gargiulo and Soumillion, 2021). The enzymes may be further improved by chemical modifications (Boutureira and Bernardes, 2015; Giri et al., 2021; Naowarojna et al., 2021; Taylor, 2022), with increasing precision and control (Spicer and Davis, 2014), often coupling site directed mutagenesis to chemical modification (Davis et al., 1998; Wu et al., 2009; Chalker et al., 2009; Gunnoo and Madder, 2016). This raises the necessity of performing the enzyme modification every time, thus bringing additional costs of chemical compounds, their storage, transport, and the residues disposal, if compared to the single genetic modification treated above, which requires only initial development costs.

Enzyme immobilization may be also an opportunity to further improve some enzyme features. Immobilization was originally launched to solve the problem of enzyme recovering and reuse, and also allowed a better control of the reaction and increased the diversity of bioreactors that may be utilized (DiCosimo et al., 2013; Liese and Hilterhaus, 2013). However, nowadays, a proper enzyme immobilization protocol should solve other enzyme limitations. Enzyme stabilization is one of the main goals of immobilization (Fig. 1); this may be achieved for different reasons (prevention of proteolysis, aggregation or interaction with external interfaces, enzyme rigidification, prevention of enzyme subunits dissociation (Fig. 2), generation of favorable enzyme environment, etc.) (Rodrigues et al., 2021). A more stable and immobilized enzyme may enlarge the window of operation where the reaction may be performed to more extreme conditions, making it feasible to find adequate conditions for process yields/productivity and enzyme activity/stability (Rodrigues et al., 2021). All these advantages add some costs to the biocatalyst, such as the support (including the price of the support itself, but also the transport, storage, and disposal after use), the immobilization process itself (facilities, reagents and personnel), and the possible losses of enzyme activity caused by the immobilization (Bolivar et al., 2022).

Moreover, only a proper and controlled immobilization protocol will lead to an improvement of the enzyme features, being also possible that the immobilized enzyme may have a poorer performance than the free enzyme, and may even also be released to the medium preventing its reuse (Bolivar et al., 2022). In these instances, the understanding of the enzyme-support interactions plays a critical role, and they are determined by the enzyme orientation and the enzyme and support surfaces nature. We can remark some interesting researches trying to develop proper tools to analyze and understand the effects of these interactions and enzyme orientation (Li et al., 2015; Ogorzalek et al., 2015; Zou et al., 2018; Badieyan et al., 2017; Jasensky et al., 2018; Li et al., 2018; Guo et al., 2021; Li et al., 2015). Even identically oriented enzyme molecules and presenting the same number of enzyme-support covalent linkages have different structures (therefore, different catalytic features) and inactivation pathways determined by the enzyme support interactions (Souza et al., 2021). Furthermore, the possibility of passive enzyme migration of reversibly immobilized enzymes on the support surface (Diamanti et al., 2022a) can produce some unexpected results (Benítez-Mateos et al., 2020; Diamanti et al., 2021). Several of these strategies to improve enzyme features may be utilized together. For example, enzyme immobilization may be benefited from genetic or chemical modifications of the enzyme to improve the immobilization process (Rodrigues et al., 2011, 2014; Rueda et al., 2016; Bernal et al., 2018). One of the outstanding developments integrating diverse strategies to design an optimal biocatalyst may be the recently launched so-called plurizymes, in which the researchers introduced via enzyme modeling and site-directed mutagenesis, in a metagenomics esterase, a second biological active center designed by enzyme modeling (Santiago et al., 2018). Later, the plurizyme activity was improved via site-directed genetic modifications (Alonso et al., 2020), and an irreversible inhibitor attached to an organometallic catalyst was designed and

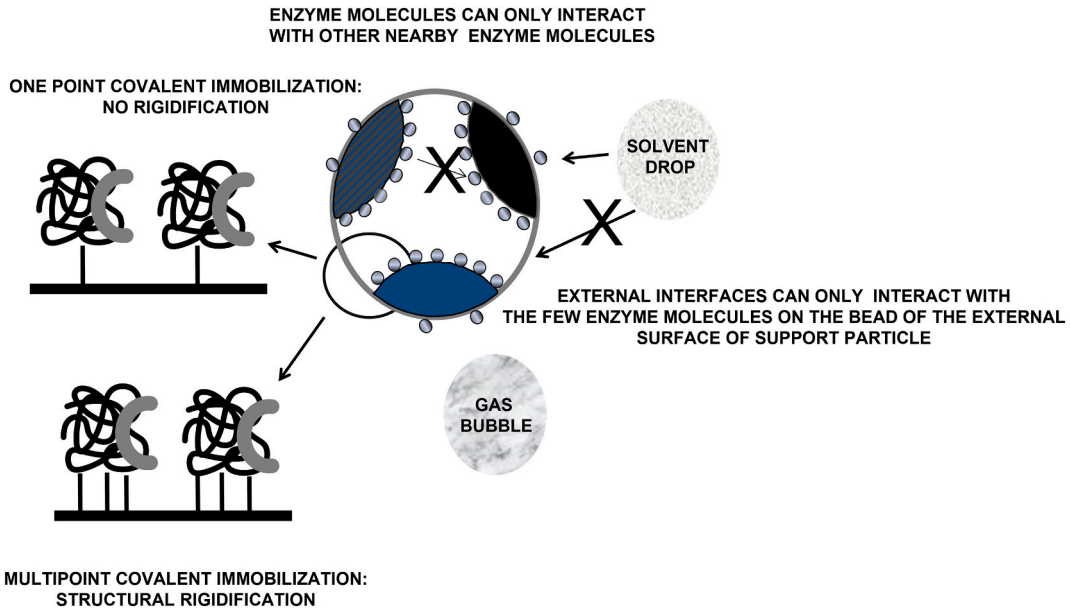

Fig. 1. Enzyme stabilization by covalent immobilization.

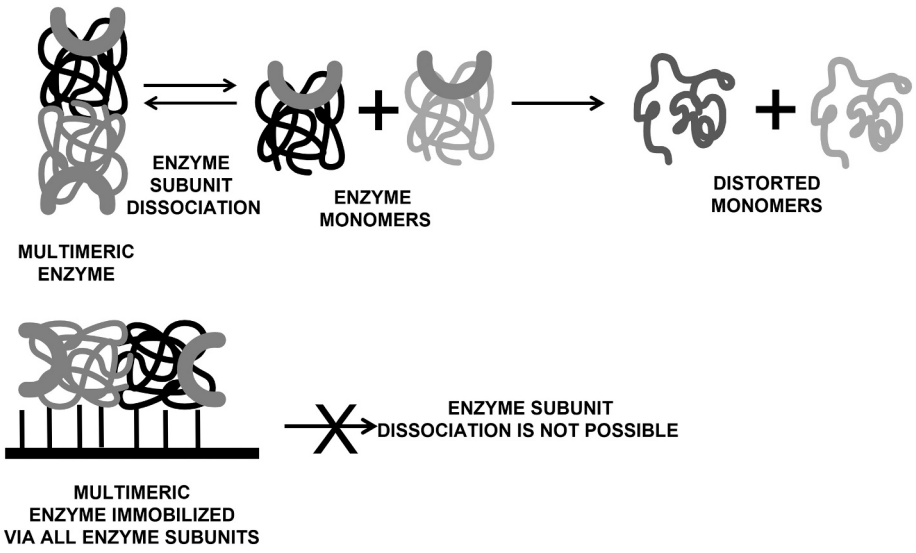

Fig. 2. Multimeric enzyme subunit dissociation prevention by immobilization.

specifically attached to one of the active centers (Alonso et al., 2020) (Fig. 3).

This allowed the generation of a modified plurizyme bearing two different catalytic activities, which was finally employed in cascade reactions (Alonso et al., 2020). The possibility of coupling a biological active center and an organometallic catalyst, able to catalyze reactions not performed by any available enzymes but with its activity tuned by the biological environment, opens new opportunities to the modification of complex substrates, as the ones that are the main topic of this review. This research was later continued generating a plurizyme that presented two biological active centers with different catalytic activity (a transaminase and a hydrolase) (Roda et al., 2022). In fact, there is a great effort to develop enzymes bearing several active centers (Carballares et al., 2022a), and some of these examples can be found in the production of biofuels, as will be presented later in this review. This is because the processes involving several reaction steps, the so-called cascade reactions, have a growing interest, as they allow, like in metabolic chains, to perform very complex reactions in a single pot, shifting equilibria and reducing inhibitions (Lopez-Gallego and Schmidt-Dannert, 2010; Ricca et al., 2011; Guterl et al., 2012; Sperl and Sieber, 2018; Velasco-Lozano and López-Gallego, 2018).

When using several enzymes to develop cascade reactions, the use of these enzymes immobilized in the same porous particle (co-immobilized) may have special interest, as they have some kinetic advantages (Arana-Peña et al., 2021). Some authors attribute these effects to the "proximity" of the enzymes, thereby increasing the flux of reactants through the enzymes active center and hence improving speed and efficiency, but there are some evidences that imply that this enzyme proximity may not be really related to the observed effects (Zhang et al., 2016). Using co-immobilized enzymes, if the immobilization is performed on porous supports, the confined space inside the particle enables that all enzymes in the chain are exposed from the beginning of the reaction to high concentrations of their respective substrates (perhaps saturating ones), as they will be in-situ produced by enzyme located in early stages of the reaction chain (Lopez-Gallego and Schmidt-Dannert, 2010; Rocha-Martín et al., 2012; Schmidt-Dannert and Lopez-Gallego,

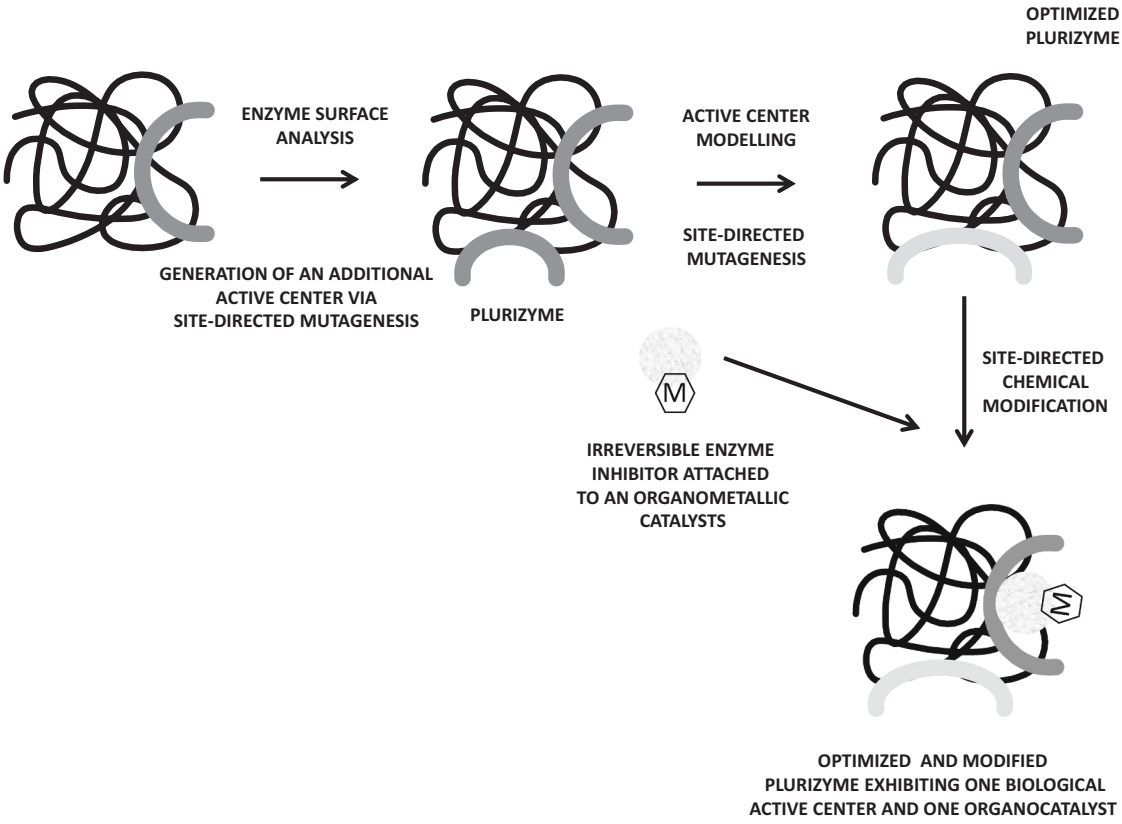

Fig. 3. Plurizyme development by site-directed modifications.

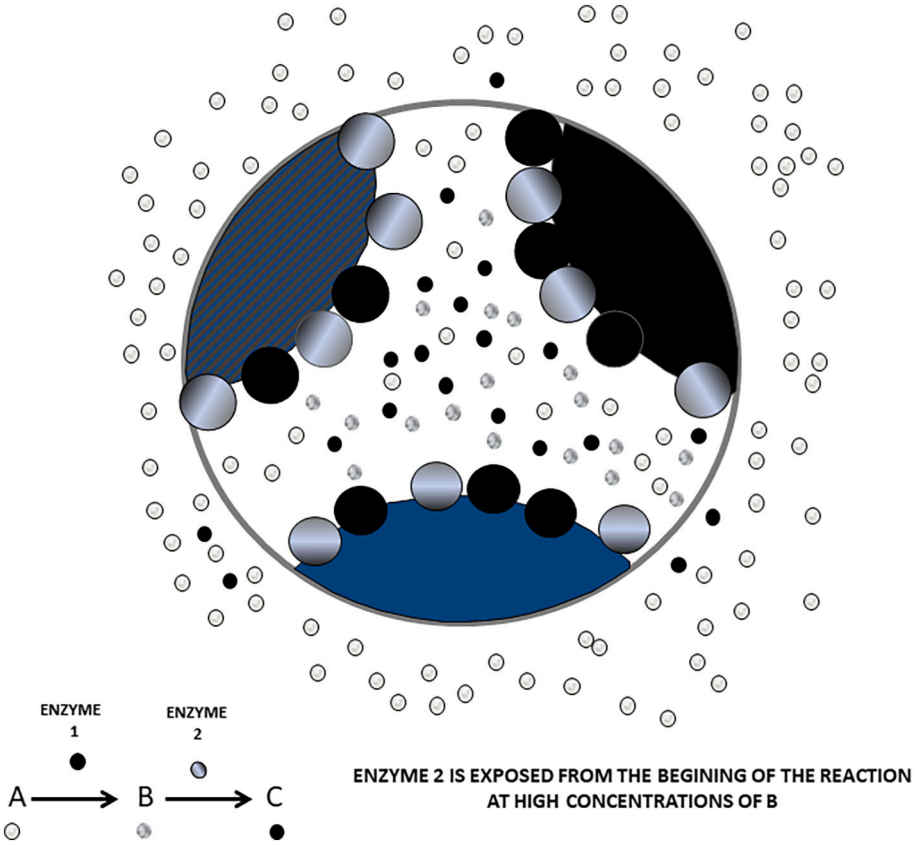

Fig. 4. Kinetic benefit of co-immobilization of enzymes in porous support.

2016; Kornecki et al., 2020) (Fig. 4).

This "intermediate compound" concentration effect has been recently determined in an empiric way, the researchers showed that the main effect of the colocalization of enzymes in coimmobilized biocatalysts was the increase in the local concentration of the respective substrates (Xiong et al., 2022). This intermedium compound concentration effect will be only significant in case substrate diffusion is the rate limiting step (Idan and Hess, 2012, 2013a, 2013b). This scarcely occurs using free enzymes, but it is more frequent using immobilized enzymes, where substrate diffusion limitations may affect the concentration of substrate that is available for the enzyme immobilized in the core of the particle, the in-situ production using co-immobilized enzymes solve this situation (Arana-Peña et al., 2020a,b). (Fig. 5).

This kinetic advantage may save the induction time that will be found using independently immobilized enzymes or even free enzymes. That way, co-immobilization may greatly affect the initial production rate of the target product. However, coimmobilization may not be so relevant if considering the time to end the whole reaction cycle, as the accumulation of the different intermedium substrates in the reaction medium will permit that all enzymes may be exposed to saturation concentrations after some reaction time. Nevertheless, in certain instances, the time to perform the modification of the intermedium product may be critical in the reaction, for example when some of the intermedium products are unstable and can be transformed to undesired products (Arana-Peña et al., 2021). In any case, some problems inherent to this kind of combi-biocatalysts should also be considered (Arana-Peña et al., 2021). For example, all enzymes should be immobilized on the same support surface, which only by chance will be the optimal one for all of them so that the researcher may not take full advantage of the immobilization step to improve the enzyme features (Garcia-Galan et al., 2011). Moreover, the half live of the combi-biocatalysts will be marked by the stability of the least stable component (Arana-Peña et al., 2021). There are some recent strategies to solve these problems (Peirce et al., 2016; Zaak et al., 2017; Arana-Peña et al., 2019, 2020b; Morellon-Sterling et al., 2021; Carballares et al., 2022b, 2022c, 2022d; Arana-Peña et al., 2022), but in any case, they produce a complication in the biocatalyst design That way, before deciding to use co-immobilized enzymes, *pros* and *cons* should be properly evaluated.

Finally, the possibility of applications of enzyme-immobilized catalysts can be increased by reaction and reactor engineering. The development of advanced reaction systems has opened new operation windows such as facilitated implementation of cascade reactions, intensification of mass transfer limited reactions and use of non-conventional reaction conditions (Sheelu et al., 2008; Cabana et al., 2009; Bolivar et al., 2011; Bolivar and Nidetzky, 2013; Detofol et al., 2015; Paula et al., 2015; Bolivar et al., 2019; Bolivar and López-Gallego, 2020; Lorente-Arevalo et al., 2021; Alvarez-Gonzalez et al., 2022).

In some instances, the catalytically active group of the enzyme is not derived from one amino acid. That is the case of the metalloenzymes, whose active center is a metal usually strongly bound to the enzyme in a pocket that confers selectivity, specificity and an extra-reactivity to the metal (Christianson and Cox, 1999; Costas and Company, 2022; Ebensperger and Jessen-Trefzer, 2022; Karlin, 1993). In other instances, the enzyme requires a cofactor that is an organic molecule, of biological origin, transformed during the reaction (Hollmann et al., 2006; Wang et al., 2013). In some instances, like the FAD, the most common cofactor in oxidases (Cohen et al., 2021; Dym and Eisenberg, 2001; Westphal et al., 2021), the cofactor is spontaneously regenerated, thus generating a by-product (hydrogen peroxide). This may become a problem as hydrogen peroxide can damage the enzyme or the reactants (Hernandez et al., 2012). In other cases, the cofactor is not attached to the enzyme (e.g., NAD(*P*)H), and it is added to the reaction mixture in soluble form, it must be regenerated by a second enzyme to make the process economically viable, and this is usually achieved consuming a secondary product using a secondary enzyme (Kragl et al., 2000; Zhao and van der Donk, 2003; Liu and Wang, 2007), making the process design more complex, although there are some other alternative strategies for this cofactor regeneration (Berenguer-Murcia and Fernandez-Lafuente, 2010) (Fig. 6).

In this sense, it has been shown that enzymes and several of these external cofactors may be co-immobilized on anion exchangers, while enabling some cofactor mobility (this is not rare considering the mobility of reversibly immobilized enzymes) (Diamanti et al., 2022b), allowing the use of these co-immobilized systems even in a continuous

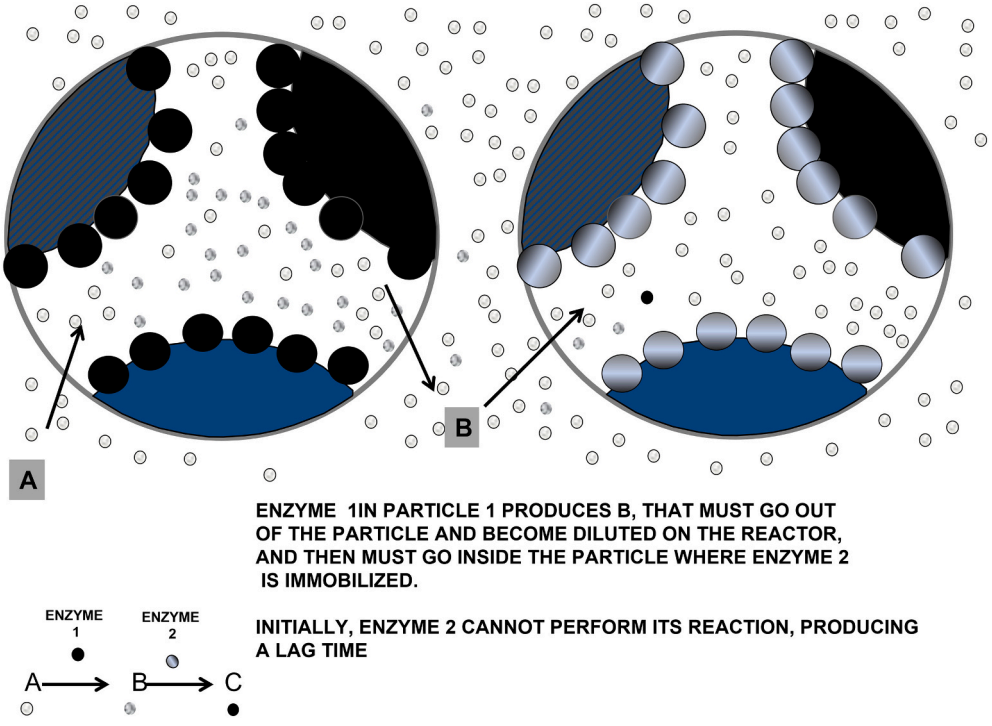

Fig. 5. Reaction rate limitations caused by substrate diffusion in a non-co-immobilized enzymatic system.

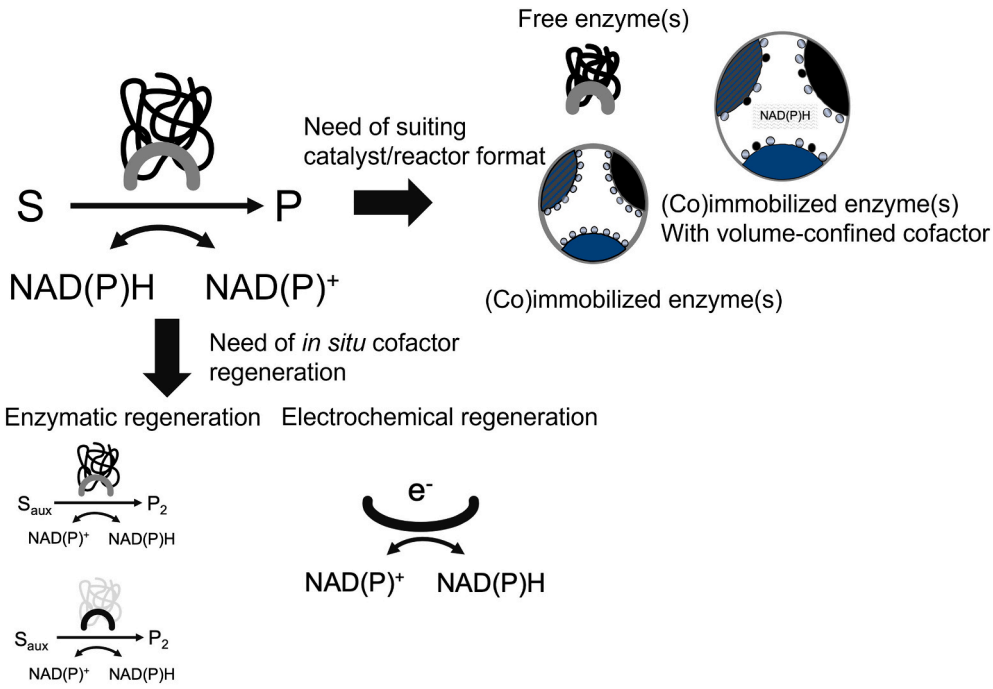

Fig. 6. *In-situ* cofactor regeneration in co-immobilized enzymatic system.

way (López-Gallego et al., 2017; Velasco-Lozano et al., 2017; Schmid-Dannert and López-Gallego, 2019). In these instances, the advantages of enzyme coimmobilization are clear and can make its use advisable. The authors showed how the anionic cofactors may be reversibly retained in the aminated support bead, while maintaining an intraparticle mobility, high enough so as to move from the active center of one enzyme to the active center of the other (López-Gallego et al., 2017; Velasco-Lozano et al., 2017; Schmid-Dannert and López-Gallego, 2019).

This way, enzymes have increased the number of processes where they can be used, and nowadays they are used in production of fine chemicals (Schulze and Wubbolts, 1999; Straathof et al., 2002; Panke et al., 2004; Thompson et al., 2019; Song et al., 2020; Banner et al., 2021) and commodities (Adsul et al., 2011; Akhtar et al., 2013; Straathof, 2014), food industry (Panyam and Kilara, 1996; FitzGerald and O'Cuinn, 2006; Fernandes, 2010; Tacias-Pascacio et al., 2020, 2021; Espejo, 2021), analytical chemistry (Feng et al., 2022; Nemiwal et al., 2022; Prodromidis and Karayannis, 2002; Sassolas et al., 2012) or biomedicine (Li et al., 2021; Tandon et al., 2021; Zhu et al., 2022), where enzyme selectivity and specificity used to be a critical feature. They may also be used in the energy area. Fermentation (that can be considered in a broad sense a biocatalytic process) is currently utilized to produce bioethanol (Devos and Colla, 2022; Kazemi Shariat Panahi et al., 2022; Maity and Mallick, 2022; Melendez et al., 2022; Roukas and Kotzekidou, 2022), while lipases are utilized in the production of biodiesel from oils and fats (Ferreira Mota et al., 2022; Hama et al., 2018; Monteiro et al., 2021; Sankaran et al., 2016; Zhong et al., 2020). In these instances, enzyme selectivity and specificity may become a problem to fully modify the substrates, that really are composed by many different glycerides and fatty acids (Arana-Peña et al., 2020a). Efforts are also directed to the production of bio-hydrogen or bio-methane (Khan et al., 2021a, 2021b; Kumar et al., 2021; Cheng et al., 2022a; Muddasar et al., 2022; Tratzi et al., 2022; Cheng et al., 2022b; Dzulkarnain et al., 2022). Among these possibilities, their use to produce biofuels from fatty acids or derivatives is the main topic of this review.

2. Biological decarboxylation of free fatty acids into hydrocarbons

2.1. Decarboxylating enzymes

Decarboxylases (formally carboxy-lyases, EC 4.1.1) are carbon-carbon lyases capable of catalyzing the decarboxylation of organic compounds (Walsh, 2020). In biological systems, the decarboxylation of organic compounds is one of the most common and important processes (Li et al., 2012); as a consequence, up to a hundred and twenty classes of enzymes capable of decarboxylating different compounds (namely, decarboxylases) are registered in the Braunschweig Enzyme Database (BRENDA, for short) (BRENDA, 2022a). Enzymatic decarboxylation may be performed in the presence of a co-factor (e.g., biotin), a metal prosthetic group, or directly by enzyme amino acids functioning as catalytic active groups (e.g., orotidine monophosphate decarboxylase) (Wu et al., 2002; Li et al., 2012). Remarkably, most decarboxylases use cofactors to delocalize the negative charge of carbanions generated by eliminating CO_2 as a by-product in the decarboxylation of organic compounds; indeed, the decarboxylation of organic compounds may be easier when a nitrogen atom from a co-factor with a partial positive charge is available near the scissile carbon atom (Miller and Wolfenden, 2002).

The use of a fatty acid decarboxylase for the in vitro biological production of hydrocarbons was firstly reported in 1974 (Khan and Kolattukudy, 1974). In that first study, the decarboxylation of long chain fatty acids into hydrocarbons was performed by a decarboxylase from *Pisum sativum* (pea) leaves (Khan and Kolattukudy, 1974). It was suggested that both direct decarboxylation and α-oxidation followed by decarboxylation took place in the production of the hydrocarbons (alkanes, specifically) (Khan and Kolattukudy, 1974). Later on, a similar study was conducted to decarboxylate long chain fatty acids into hydrocarbons; however, the enzymatic decarboxylation was performed by an enzyme from *Zootermopsis angusticollis* (a termite) (Chu and Blomquist, 1980). As previously reported (Khan and Kolattukudy, 1974), it was suggested that both direct decarboxylation and α-oxidation followed by decarboxylation took place in the production of alkanes (Chu and Blomquist, 1980). Furthermore, the addition of ascorbic acid and O_2 was also highlighted to increase the decarboxylase activity of the free

cell enzyme preparations (Chu and Blomquist, 1980; Khan and Kolattukudy, 1974), with ascorbic acid acting as an electron donor and O_2 as an oxidant.

Another family of enzymes of interest for the transformation of fatty acids are the cytochrome P450 enzymes (Hammerer et al., 2018; Munro et al., 2018; Urlacher and Girhard, 2019). The superfamily of enzymes from cytochrome P450 is composed of monooxygenases, peroxidases, and peroxygenases and may be found in archaea, prokaryotes, and eukaryotes (Hrycay and Bandiera, 2012). The cytochrome P450 enzymes are capable of catalyzing a variety of reactions (not only the physiological ones) and thus they are considered among the most versatile biocatalysts in nature (Coon, 2005). Their practical applicability has been traditionally limited by the dependence on complex electron transport chains to mediate reductive oxygen activation by the heme prosthetic group. A recent breakthrough has been the identification of a family of P450s able to utilize H_2O_2 as a shortcut to generate oxyferryl species via the so-called peroxide shunt pathway. These catalysts are named P450 fatty acid peroxygenases and belong to the so-called family CYP152. P450 peroxygenases are thus recognized as both bio-fuel related P450 fatty acid decarboxylases and for fatty acid hydroxylases activity. The same family of catalysts may produce α-hydroxylated or β-hydroxylated but also oxidative decarboxylation reactions that convert the Cn ($n = 4$–22) chain length (FFAs) into Cn − 1 chain length 1-alkenes (i.e., α-olefins) (Hammerer et al., 2018; Munro et al., 2018). Also recently, fungal peroxygenases (EC 1.11.2.4) have been discovered as fatty acid activity modifiers (Carro et al., 2019). A majority of CYP152 peroxygenases catalyze FFAs hydroxylation and decarboxylation reactions simultaneously and the mechanism that controls the product distribution is still not fully understood (Lee et al., 2018). Some studied enzymes are P450SPα (CYP152B1) from *Sphingomonas paucimobilis*, P450BSβ (CYP152A1) from *Bacillus subtilis*, P450CLA (CYP152A2) from *Clostridium acetobutylicum* and OleT (CYP152L1) from *Jeotgalicoccus* sp. Recent results indicate that P450SPα catalyzes exclusively the hydroxylation of fatty acids at the α-position, P450BSβ hydroxylated fatty acids at both the α- and β-positions, with β-hydroxylated fatty acids being the main product. P450SPα accepts C6-C18 as substrates, being myristic acid (C14) the postulated natural substrate. P450CLA hydroxylates fatty acids mainly at the α-position, however with poorer selectivity as SPα. P450CLA (CLA) catalyzes hydroxylation on the α-, and β-position of saturated and unsaturated fatty acids with chain lengths from C12-C16. Shorter fatty acids (C6, C7 and C10) are hydroxylated in α-position (Gandomkar et al., 2018). OleT performs mainly oxidative fatty acid decarboxylation yielding terminal alkenes although β-hydroxylation activity was also observed (Munro et al., 2018).

Probably the most studied novel fatty acid decarboxylase from the P450 cytochrome family is the $OleT_{JE}$. $OleT_{JE}$ was employed for the direct oxidative decarboxylation of saturated free fatty acids (FFAs) into α-olefins. Strictly, $OleT_{JE}$ is an α-olefin-forming fatty acid decarboxylase from *Jeotgalicoccus* sp. ATCC 8456 expressed in *Escherichia coli*; furthermore, $OleT_{JE}$ is a P450 peroxygenase able to convert FFAs into hydrocarbons by a new biosynthetic pathway (Rude et al., 2011), different from the head-to-head condensation of FFAs to long-chain olefins using isolated nucleic acids and isolated polypeptides (Friedman and Costa, 2008; Sukovich et al., 2010a, 2010b; Beller et al., 2010). As a peroxygenase, $OleT_{JE}$ was expected to use H_2O_2 as the sole electron and oxygen donor for removing the carboxyl group of FFAs to obtain α-olefins and CO_2 (Rude et al., 2011) (Fig. 7). Recently, a H_2O_2 independent approach was implemented by coupling the $OleT_{JE}$ with a P450 reductase domain or a flavodoxin/flavodoxin reductase. This allows the large-scale production of low-cost α-olefins biofuels since the need of large amounts of H_2O_2 may be cost-prohibitive, and high concentrations of H_2O_2 in the reaction media may even denature the biocatalysts (Hernandez et al., 2012; Liu et al., 2014). In fact, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), as a redox partner, and O_2 as oxidant, it was possible to efficiently decarboxylate in vitro long chain FFAs into α-olefins by $OleT_{JE}$ (Liu et al., 2014). A range of proteins were reported as efficient heterologous redox partners for the decarboxylation activity of $OleT_{JE}$, especially SeFdx-6 (ferredoxin), from *Synechococcus elongatus* PCC 7942, and CgFdR-2 (ferredoxin reductase), from *Corynebacterium glutamicum* ATCC 13032 (Fang et al., 2017).

The simple and direct decarboxylation of FFAs into α-olefins by $OleT_{JE}$ was the motivation for the study of new enzymes with fatty acid

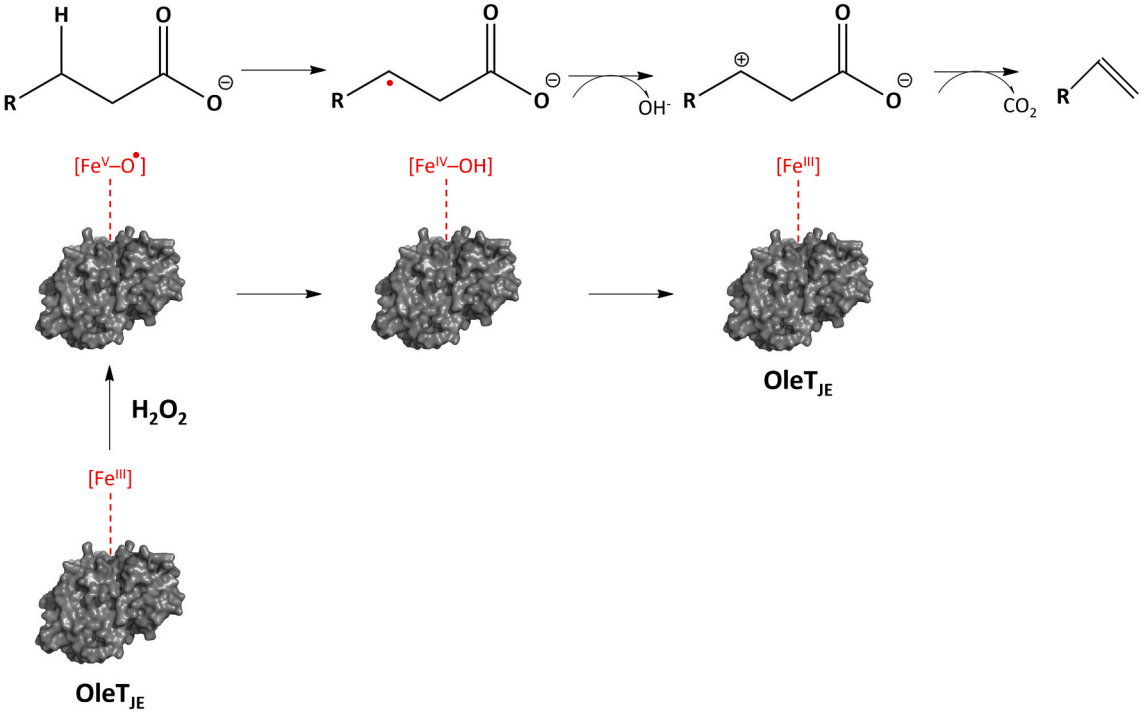

Fig. 7. Decarboxylation of fatty acids catalyzed by the fatty acid decarboxylase from *Jeotgalicoccus sp.* ($OleT_{JE}$) (Rude et al., 2011). PDB code: 4L54 (Belcher et al., 2014; Matthews et al., 2017a). The three-dimensional structure was obtained with the aid of PyMol 2.2.2.

decarboxylation activity. In this way, two peroxygenases from the CYP152 family were expressed, purified and characterized for the first time (Xu et al., 2017), resulting in one efficient $OleT_{JE}$-like fatty acid decarboxylase and one $P450B_{S\beta}$-like fatty acid hydroxylase with marginal decarboxylation chemoselectivity (Xu et al., 2017). The $P450B_{S\beta}$-like fatty acid hydroxylase activity of one of the new peroxygenases is not remarkable, since the $OleT_{JE}$ itself shares significant similarities (structure, substrate scope and mechanism) with the $P450B_{S\beta}$ (Bharadwaj et al., 2018). Nevertheless, $OleT_{JE}$ was reported to bind the carboxyl group in the active site much stronger than $P450B_{S\beta}$ and, thus, the fatty acid decarboxylase may present higher decarboxylation activity than the fatty acid hydroxylase; yet, an increased substrate mobility may enable the rebound mechanism for hydroxylation of $OleT_{JE}$ (Bharadwaj et al., 2018; Amaya et al., 2018). In this sense, the hydroxylation of FFAs might be the secondary reaction performed by $OleT_{JE}$ (Amaya et al., 2018; Bharadwaj et al., 2018; Faponle et al., 2016). In a similar research, three new $OleT_{JE}$-like fatty acid decarboxylases were employed in the decarboxylation of a range of straight-chain saturated fatty acids (C_8–C_{20}), with one of them even presenting decarboxylation activity, kinetic parameters, as well as salt tolerance and stability, similar to $OleT_{JE}$ (Jiang et al., 2019). In addition, due to the halophilic property of their native host microorganisms (*Jeotgalicoccus halophilus*, *Salinicoccus qingdaonensis*, and *Staphylococcus aureus*), the three new peroxygenases were classified as moderate halophilic enzymes (Jiang et al., 2019).

Furthermore, $OleT_{JE}$ was able to efficiently catalyze the decarboxylation of FFAs into α-olefins even in the absence of auxiliary redox partners when it is genetically fused with other enzymes; therefore, $OleT_{JE}$ has been reported to possess a monooxygenase-like mechanism (Hsieh et al., 2017). The production of biofuels would be rationally improved with a more accurate understanding of the factors that control the branch-point between monooxygenation and decarboxylation activities of $OleT_{JE}$ (Hsieh et al., 2017).

Although not always clearly highlighted by the authors, the biosynthesis of α-olefins by $OleT_{JE}$ has been performed under atmospheric pressure and close to ambient temperature, in opposition to the drastic conditions demanded by the standard routes. Therefore, the enzymatic conversion of FFAs into hydrocarbons is less energy demanding than the traditional chemical hydro-treatment pathway, for example, which requires high energy supply, due to high temperatures and pressures involved in the reactions (Arun et al., 2015; Gutiérrez-Antonio et al., 2017). Furthermore, high H_2 pressure is usually required for the chemical conversion of esters and fatty acids into hydrocarbons for the production of biojet fuels, making the process more risky and needing additional safety facilities that are not necessary in the enzymatic routes (Gutiérrez-Antonio et al., 2017). Nonetheless, it may be a major drawback for the large-scale implementation of biojet fuels produced using conventional methods, especially regarding economic and environmental sustainability (Choudhary and Phillips, 2011), since H_2 is mainly produced from non-renewable resources (e.g., natural gas reforming and coal gasification) (Acar and Dincer, 2014). Hence, beyond energy conservation, the enzymatic production of hydrocarbons may avoid the high consumption of H_2 from non-renewable resources, thus reducing the carbon footprint of the production of biofuels.

Unfortunately, $OleT_{JE}$ presents a narrow substrate specificity, thus possessing high specificity for long and linear saturated FFAs to selectively produce long-chain α-olefins (Cantú Reinhard et al., 2020; Dennig et al., 2015; Grant et al., 2015, 2016; Munro et al., 2018; Pickl et al., 2019; Shoji et al., 2007). Consequently, to be used as drop-in hydrocarbon biofuels, $OleT_{JE}$-derived hydrocarbons may need to be cracked into small-chain hydrocarbons in the range of biogasoline (C_5–C_{10}), biojet fuels (C_9–C_{15}) and green diesel (C_{10}–C_{25}) (Sousa et al., 2018b). Even though there have been some efforts to expand the substrate scope of $OleT_{JE}$ (Du et al., 2017; Hsieh and Makris, 2016; Lu et al., 2018), further improvements on enzyme engineering are required to use this enzyme in the production of biofuels with higher selectivity and conversion. Furthermore, to meet the standard specifications for biofuels, α-olefins may need to be saturated into alkanes since they must be the main constituents of biogasoline, biojet fuels and green diesel. Once again, enzyme specificity, an important feature in several enzyme applications, becomes a problem.

Photo-biocatalysis is an emerging technology for the enzymatic conversion of small molecules into value-added products, such as biofuels (Yi et al., 2021). Photo-enzymes drive the conversion of small molecules by mechanisms not otherwise observed in nature by directly using light energy to catalyze reactions (Yi et al., 2021). The photodecarboxylation of FFAs by photodecarboxylases (fatty acid photodecarboxylases, EC. 4.1.1.106) to produce hydrocarbons has been proposed as an alternative approach for the synthesis of biofuels. For instance, taking into account that microalgae are capable of synthesizing hydrocarbons via a light-driven pathway (Sorigué et al., 2016), a photoenzyme in the microalgae *Chlorella variabilis* NC64A (CvFAP, for short) catalyzed the decarboxylation of FFAs into hydrocarbons in response to blue light (Sorigué et al., 2017). It was reported that such fatty acid photodecarboxylase possesses a fatty acid-binding site in a hydrophobic tunnel leading to the light-capturing cofactor (flavin adenine dinucleotide or FAD, for short); furthermore, the mechanism of decarboxylation is initiated through electron abstraction from the fatty acid by the photoexcited cofactor (Sorigué et al., 2017) (Fig. 8). Later on, CvFAP was used for the photodecarboxylation of triacylglycerols and FFAs into alkanes (Huijbers et al., 2018). As reported by the authors, it may be an interesting alternative to the (trans)esterification strategy for the production of biodiesel due to the higher specific heat of combustion of hydrocarbons (alkanes, specifically) and the irreversibility of the process (Huijbers et al., 2018). The long-chain fatty acids specificity and efficient conversion into the corresponding hydrocarbons of CvFAP drove the development of a decoy molecule approach to fill up the vacant substrate access channel of the photodecarboxylase, aiming to broad its applicability as biocatalyst in the production of hydrocarbon biofuels under mild conditions (Zhang et al., 2019).

Enzymatic decarboxylation of FFAs into hydrocarbons has also been combined with other enzymes in cascade reactions to use simpler substrates or to attain a better control of some dangerous products, such as hydrogen peroxide (Hernandez et al., 2012). For example, since the immobilized lipase (triacylglycerol ester hydrolases, EC. 3.1.1.3) from *Rhizopus oryzae* was very stable under the influence of blue light, it was employed for the in-situ hydrolysis of soybean oil and waste cooking oil into FFAs, which were subsequently decarboxylated by CvFAP as a whole cell biocatalyst in a one-pot-one-step cascade reaction, reaching the near-complete hydrolysis/decarboxylation of both substrates (Ma et al., 2020). Due to the irreversibility of the decarboxylation process, it is reported as an interesting alternative for the production of green diesel since the traditional (trans)esterification of the feedstock to produce biodiesel may require a significant molar excess of the alcohol (e.g., ethyl or methyl alcohol) to achieve near-full conversion due to equilibrium issues (Ma et al., 2020; Zhang et al., 2019). This example uses both enzymes individually “immobilized” (one as immobilized cell free enzyme, other as a whole cell biocatalyst).

In another interesting example, lipase from *Candida rugosa* performed the hydrolysis of triacyclglycerols into FFAs and glycerol; then, an alditol oxidase performed the oxidation of the released glycerol to produce in situ two equivalents of H_2O_2; finally, the released H_2O_2 (exogenous glycerol may be added to solve the shortage of one equivalent of H_2O_2) was employed in the $OleT_{JE}$ decarboxylation of the FFAs into α-olefins (68.5% of yield) and CO_2 (Jiang et al., 2020). Accordingly, the endogenous production of H_2O_2 not only mitigated the detrimental effect of H_2O_2 on the stability and activity of the lyophilized enzymes, but also lowered the overall costs on the biosynthetic pathway (Jiang et al., 2020). The oxidation of glycerol to produce H_2O_2 by an alditol oxidase was further evaluated in a fused system with $OleT_{JE}$ (Matthews et al., 2017b). In this different approach, the generation of H_2O_2 was regulated by substrate titration to mitigate the oxidative inactivation of

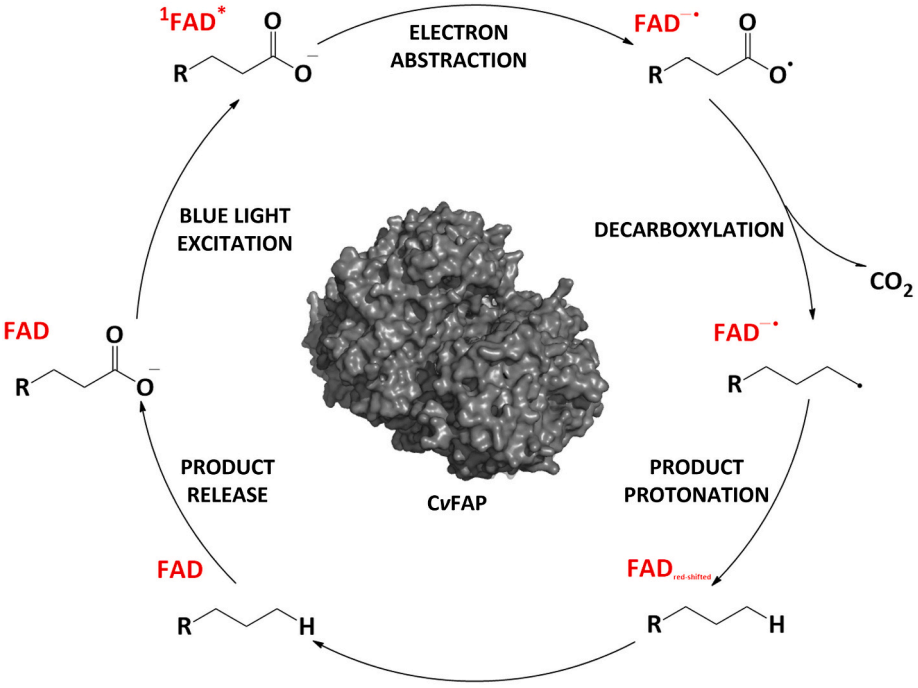

Fig. 8. Photodecarboxylation cycle of fatty acids catalyzed by the fatty acid photodecarboxylase from *Chlorella variabilis* (CvFAP) (Heyes et al., 2020). PDB code: 5NCC (Sorigué et al., 2017). The three-dimensional structure was obtained with the aid of PyMol 2.2.2.

the fatty acid decarboxylase by this oxidant and, thus, enhance its activity and of α-olefins production (Matthews et al., 2017b). In another example, the endogenous production of H_2O_2 was performed by the oxidation of glucose by a glucose oxidase, employing a fatty acid decarboxylase from *Staphylococcus aureus* ($OleT_{SA}$, for short) instead of $OleT_{JE}$ (Zhang et al., 2020). As a result, the efficiency of the process was significantly improved, compared to the systems based on the exogenous addition of H_2O_2, which may decrease the $OleT_{JE}$ activity by the degradation of the heme group (Zhang et al., 2020).

To catalyze these cascade reactions, in some instances the researcher tried to the couple the enzyme activities in a single structure, in some instances in a single molecule of enzyme bearing both activities (e.g., enzymes of fusion) (Carballares et al., 2022a; Elleuche, 2015; Gudiukaite and Gricajeva, 2017), as described herein.

Some cascade reactions were explored using fused enzymes (Bülow et al., 1985; Carballares et al., 2022a). This strategy utilizes the genetic fusion of two genes expressing the target activities, and attached via a polypeptide linker, being this the critical point in the design of these fusion proteins (Carballares et al., 2022a; Lu and Feng, 2008). For example, to engineer a self-sufficient biocatalyst for the scalable production of α-olefins from FFAs, the approach for fusing $OleT_{JE}$ with other enzymes was exploited (Lu et al., 2018). $OleT_{JE}$ was fused with the reductase domain of P450BM3, a cytochrome P450 from *Bacillus megaterium*, to produce linear α-olefins, but using O_2 as the oxidant and NADPH as the electron donor (without the need for auxiliary redox partners) (Lu et al., 2018). The stability and scalability of the fusion enzyme demonstrated its potential for the enzymatic production of linear α-olefins (Lu et al., 2018). This strategy is very elegant and can show some clear advantages, but it also presents some problems (Carballares et al., 2022a). Related to differences on the two fused enzyme stability, the inactivation of just one of the enzymes makes that the other enzyme may be discarded even when the other activity is fully maintained, similar to the problems found in the enzyme co-immobilization (Arana-Peña et al., 2021). Moreover, the use of these proteins has some intrinsic issues, for example the optimization of enzymes activities ratio problems (Carballares et al., 2022a). However, it is an option that must be explored.

2.2. *Co-immobilization*

In the context of cascade reactions used to produce α-olefins, there are some reports showing the use of co-immobilized enzymes to obtain the desired products. Before using co-immobilized enzymes, the problems that co-immobilization may present, already described in the Introduction section, should be considered, although they are usually not taken into account (Arana-Peña et al., 2021).

That way, a lipase and a fatty acid decarboxylase have been used in co-immobilized form. The hydrolysis of acylglycerols into FFAs and glycerol was catalyzed by lipases and the produced FFAs were subsequently decarboxylated to produce α-olefins and CO_2 catalyzed by fatty acid decarboxylases. For example, lipase from *Thermomyces lanuginosus* (TLL) and $OleT_{JE}$ were co-immobilized onto a cellulose carrier by (Li et al., 2019). It was highlighted that the co-immobilized enzymes exhibited more than 9.2-fold enhancement in the initial reaction rate and much higher conversion yields (69%–72%) when compared to the mixture of free enzymes. Thus, the co-immobilized biocatalyst was able to efficiently convert triacylglycerols into fatty alkenes (but this was not compared to the mixture of individually immobilized enzymes) (Li et al., 2019). Here, it could be interesting to compare the individually immobilized enzymes, as the immobilization could produce some enzyme stabilization, being this the possible responsible for improving yields, and not the fact that the enzymes are co-immobilized.

Similarly, a fatty acid decarboxylase ($OleT_{SA}$) was co-immobilized with a glucose oxidase. The *co*-immobilization of the enzymes on polymeric nanoparticles increased the initial activity of the biocatalyst compared to the free enzymes due to the co-localization of the enzymes on the surface of the nanostructures (Zhang et al., 2020). Here, although the authors do not explain this in detail, it is possible to assume that the rapid transformation of the in situ produced hydrogen peroxide may be key to prevent undesired effects of this reagent (Lu et al., 2018). Overall, it was a simple and efficient strategy to biologically convert triacylglycerol-based feedstock to industrially important chemicals, such as biofuels (Zhang et al., 2020).

2.3. Microbial platforms

Microbial platforms have also been employed in the conversion of FFAs to hydrocarbons (Payne et al., 2015). For example, *Pseudomonas*, an abundant and widespread bacteria, was used as microbial platform for the conversion of medium-chain FFAs (C_{10}–C_{14}) into the corresponding α-olefins (Rui et al., 2014). Strictly, UndA was the encoded gene responsible for the oxidative decarboxylation of the medium-chain FFAs into α-olefins, especially lauric acid into 1-undecane (Rui et al., 2014). Furthermore, the biochemical and structural analyses of UndA evidenced an unusual mechanism of β-hydrogen abstraction during the fatty acid decarboxylation (Rui et al., 2014). Similarly, *Pseudomonas aeruginosa* was employed as a novel lipolytic microbial platform for the biological production of hydrocarbons, in which the fatty acid decarboxylases UndA and UndB were cloned and expressed; thus, the microbial platform was able to perform the production of α-olefins in a one-step process (Wang et al., 2018). The yeast *Saccharomyces cerevisiae* is another abundant and widespread microorganism that has been used as platform for the production of FFAs and the decarboxylation of FFAs into hydrocarbons (Tang et al., 2013; Li et al., 2014; Runguphan and Keasling, 2014; Buijs et al., 2015; Feng et al., 2015; Tang et al., 2015; Yu et al., 2017; Foo et al., 2017). In addition, *Saccharomyces cerevisiae* has been considered suitable for industrial applications due its robustness and tolerance towards harsh fermentation conditions (Zhang et al., 2018). For example, the wild-type $OleT_{JE}$, its codon-optimized version and six more homologous enzymes were cloned into a high copy plasmid and transferred into a strain of *Saccharomyces cerevisiae* yeast (Chen et al., 2015). Then, a strain of the yeast was engineered to overproduce fatty acids, with enzyme cofactor accumulation engineered as well (Chen et al., 2015). Finally, by optimizing the combinations of promoters/plasmids and culturing conditions in the bioreactors, the enzyme expression and α-olefins production were enhanced (Chen et al., 2015). The authors highlighted that the combinatorial metabolic engineering of *Saccharomyces cerevisiae* enhanced the production of α-olefins by 67.4-fold (Chen et al., 2015).

In another approach, multi-enzyme systems were surface displayed on *Yarrowia lipolytica* yeast cells (Yang et al., 2018). As a result, through proportional and positional control of cohesion domains, it was possible to optimize the production of hydrocarbons (alkanes and alkenes); indeed, the conversion into hydrocarbons for the cells bearing the multi-enzyme system (71–84%) was much higher than for free enzyme cocktails (8–32%) due to substrate channeling, optimal ratio and positional arrangement of individual enzymes, and the positive effects of the cell surface on the enzyme features (Yang et al., 2018).

Other fatty acid decarboxylases have been engineered for the decarboxylation of FFAs into hydrocarbons using microbial platforms. For instance, a de novo alkene biosynthesis pathway was designed to transform fermentable sugar into alkene in a modified *E. coli*. The route involved a P450 fatty acid decarboxylase from *Macrococcus caseolyticus* ($OleT_{MC}$) and a genetically modified thioesterase (TesA) from *E. coli* with compatible substrate specificities. The alkenes production was improved by overcoming the electron transfer limitations in $OleT_{MC.}$ For this goal, a putidaredoxin reductase (CamA) and a putidaredoxin (CamB) from *Pseudomonas putida* were also cloned in the modified *E.coli* strain. This allowed to increase alkenes production by 2.8 fold (Lee et al., 2018). In a similar study, a fatty acid decarboxylase from *Pseudomonas putida* (UndA) and a thioesterase from *Escherichia coli* were expressed in the bacterium *Acinetobacter baylyi* ADP1 for the production of medium-chain α-olefins from glucose (Luo et al., 2019). In this study, ferulate, a toxic lignin-derived model compound, was employed as sole carbon source for both cell growth and product synthesis; therefore, prior to expression of the enzymes in microbial platform, *Acinetobacter baylyi* ADP1 was engineered to become a highly ferulate-tolerant strain (Luo et al., 2019). The authors pointed out that ferulate alone was capable of supporting both the biomass production and the synthesis of non-native medium-chain α-olefins (Luo et al., 2019). For both studies, the thioesterase from *Escherichia coli* was responsible for the conversion of acyl-ACPs (Acyl Carrier Proteins) into FFAs, thus providing more substrates for the fatty acid decarboxylases ($OleT_{MC}$ and UndA) (Lee et al., 2018; Luo et al., 2019).

Besides the combination with purified and/or immobilized lipases, the fatty acid photodecarboxylase CvFAP was employed to produce hydrocarbons combined with microbial lipolytic platforms as well. The yeast *Yarrowia lipolytica* may produce large amounts of lipids and may therefore be an attractive host for the production of fatty acid-derived biofuels (Bruder et al., 2019). In this sense, CvFAP was expressed in *Yarrowia lipolytica* to produce drop-in biofuels (diesel-like, specifically); ultimately, the production improvement of hydrocarbons was quite dependent on the light intensity, with best results for half-light intensity (Bruder et al., 2019). High light intensity (~450 nm) may lead to the photo-inactivation of the fungi, thereby the fungi cells would be in a nonculturable state (Hoenes et al., 2018); and, especially regarding the blue light, a significant effect on the yeasts respiratory oscillation may be observed (Robertson et al., 2013). Similarly, CvFAP was assembled on the surface of *Bacillus subtilis* spore for the conversion of lipids into hydrocarbons in a one-pot cascade reaction (Karava et al., 2021). In this system, the hydrolysis of the lipids was performed by the commercially immobilized lipase from *Rhizopus oryzae* as well as spores with and without additional heterologous lipase expression (Karava et al., 2021). Overall, it was reported that the produced titers are low compared to those in previous in vitro experiments; however, the authors argued that it was a simple strategy to express and simultaneously immobilize enzymes (Karava et al., 2021).

3. Biological decarbonylation of aldehydes into hydrocarbons

3.1. Decarbonylating enzymes

Aldehyde decarbonylases (also referred as aldehyde-deformylating oxygenases, E.C. 4.1.99.5) are carbon-carbon lyases that catalyze the decarbonylation of aldehydes into alkanes; in fact, the substrate of such enzymes results from the reduction of activated fatty acids to the corresponding fatty aldehydes by acyl-[acyl carrier protein] reductases (BRENDA, 2022b, 2022c; Kudo et al., 2016). The removal of the carbonyl group from aldehydes to form alkanes may be performed by various organisms, such as cyanobacteria, algae, plants and insects (Marsh and Waugh, 2013). The mechanism of decarbonylation of aldehydes decarbonylases is a conundrum since the aldehyde carbons may be converted into CO_2 in insects, formic acid in plants, or CO in plants and algae (Marsh and Waugh, 2013).

The biological decarbonylation of aldehydes for the in-vitro production of hydrocarbons was firstly reported by (Cheesbrough and Kolattukudy, 1984). In that study, the decarbonylation of aldehydes into alkanes was performed by a decarbonylase from *Pisum sativum* leaves, which was severely inhibited by metal ion chelators and presented no requirements for any cofactors (Cheesbrough and Kolattukudy, 1984). Later on, fatty aldehydes were decarbonylated into alkanes by decarbonylases from a microsomal preparation of animal tissue (Cheesbrough and Kolattukudy, 1988) and microalgae (Dennis and Kolattukudy, 1991), which were also inhibited by metal ion chelators and presented no requirement for any cofactors (Cheesbrough and Kolattukudy, 1988; Dennis and Kolattukudy, 1991). Remarkably, even though decarbonylase activity was previously found in particulate preparations from both plants and animals (Cheesbrough and Kolattukudy, 1984, 1988; Dennis and Kolattukudy, 1991), the solubilization of an aldehyde decarbonylase from *Botyrococcus braunu* followed by purification were able to increase the specific activity by 200-fold (Dennis and Kolattukudy, 1992). Furthermore, the aldehyde decarbonylase was reported to have significant amounts of cobalt (Dennis and Kolattukudy, 1992), which may explain its inhibition by metal ion chelators (Cheesbrough and Kolattukudy, 1984, 1988; Dennis and Kolattukudy, 1991). Similarly, a fatty aldehyde decarbonylase from *Pisum sativum* was solubilized

and purified, thereby increasing its specific activity by 1300-fold (Schneider-Belhaddad and Kolattukudy, 2000). Furthermore, such purified enzyme was also inhibited by metal ion chelators, which may indicate the requirement of a metal ion (Cu^{2+} in this instance) for the enzyme activity (Schneider-Belhaddad and Kolattukudy, 2000).

Apart from the decarbonylation of fatty aldehydes into hydrocarbons by particulate preparations from both plants and animals, another pathway has been reported to produce hydrocarbons from the decarbonylation of aldehydes by cyanobacteria. In this pathway, an acyl–acyl carrier protein reductase and an aldehyde decarbonylase converted intermediates of fatty acid metabolism into alkanes and alkenes; even though a decarbonylation reaction is proposed, the C_1-derived coproduct (carbon monoxide) of the decarbonylation reaction was not verified (Schirmer et al., 2010). Indeed, no carbon monoxide was detected in the in-vitro production of hydrocarbons by a cyanobacterial aldehyde decarbonylase (cAD) from *Nostoc punctiforme* (Warui et al., 2011). Instead, formate was detected as the stoichiometric coproduct of the reaction, thereby suggesting a hydrolytic reaction catalyzed by the cAD; therefore, a reducing system was proposed to be more suitable for this novel reaction (Warui et al., 2011). Later on, the conundrum of the cAD from *Nostoc punctiforme* was resolved, thereby showing that the enzyme oxygenates its substrate without oxidizing it; furthermore, a redox-neutral outcome was ensured during the aldehyde cleavage since the reducing system delivers two electrons, besides apart from two additional electrons that return an oxidized form of the cofactor back to its reduced form (Li et al., 2011). In this sense, such enzyme was proposed to be an unusual dimetal oxygenase, due to its mechanism of catalysis and requirement for molecular oxygen (Li et al., 2011). Nevertheless, it was later reported that an aldehyde decarbonylase from *Prochlorococcus marinus* MIT9313, a cyanobacteria, was able to produce alkane and formate; however, even under anaerobic conditions, a reducing system was still required (Das et al., 2011). Therefore, extremely low activity had been observed for the oxygen-dependent cAD, whereas the reaction rate for the oxygen-independent cAD was 100–1000 times higher, thus allowing to decrease the barriers of its use in biofuels production (Das et al., 2011). However, the enzyme activity found in anaerobic conditions was later attributed to the presence of traces of oxygen, being nowadays assumed that the enzymes are oxygen-dependent. Similarly, some studies to elucidate the reaction nature of the aldehyde decarbonylase from *Nostoc punctiforme* (a cyanobacteria) were performed (Eser et al., 2011, 2012). The involvement of the participation of the oxygen as substrate was controversial. While some attempts to perform the reaction under anaerobic conditions were performed (Eser et al., 2011), the involvement of traces of oxygen and microaerobic reactions conditions are revealed (Eser et al., 2012). As mentioned above, for cyanobacterial systems, aldehyde decarbonylases have also been reported as aldehyde-deformylating oxygenases (Das et al., 2011; Hayashi et al., 2015; Pandelia et al., 2013), since they deformylate aldehydes by attacking their the carbonyl C-atom (Krebs et al., 2011).

Yet, because the mechanism of catalysis of cAD was still poorly understood, the mechanism of $C_1 - C_2$ bond cleavage was further investigated using a cyclopropyl group (radical clock); as a result, the inquiry provides evidences for the C − C bond cleavage in the unusual decarbonylation reaction catalyzed by cAD (Paul et al., 2013). Beyond that, iron was reported to be the active group in such cyanobacterial aldehyde decarbonylases; therefore, besides molecular oxygen, such di-iron enzymes may require an external reducing system in the form of ferredoxin, ferredoxin oxidoreductase and NADPH (Das et al., 2011; Eser et al., 2011; Li et al., 2011; Schirmer et al., 2010; Warui et al., 2011) (Fig. 9). In this sense, the very low activity of the cyanobacterial aldehyde decarbonylases was reported to result from inhibition by the ferredoxin reducing system (ferredoxin may form an inhibitory complex with the enzyme, thus preventing product release) and the low solubility of the substrate (Eser et al., 2011). As a matter of fact, aldehyde decarbonylases are capable of converting acyl aldehydes into alkanes;

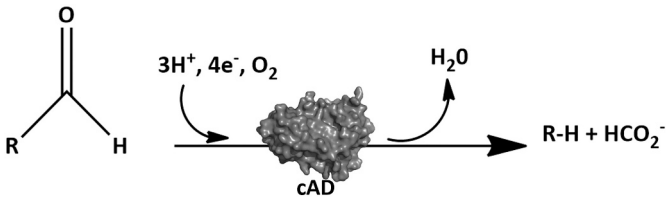

Fig. 9. Decarbonylation mechanisms of fatty aldehydes catalyzed by a cyanobacterial aldehyde decarbonylase (cAD) (Warui et al., 2011). PDB code: 4PGI (Buer et al., 2014). The three-dimensional structure was obtained with the aid of PyMol 2.2.2.

however, the instability and low efficiency of such enzymes may prevent their further applications (Kudo et al., 2019). Recently, it was reported that a C-terminal degradation tag (degron) is common in aldehyde decarbonylases from bacteria; hopefully, eliminating or modifying the degron could stabilize the aldehyde decarbonylase, thus enhancing its efficiency (Liu et al., 2020).

As for studies on immobilization of any of these enzymes, no reports have been found in the open literature, to the best of the authors' knowledge.

3.2. Microbial platforms

Microbial platforms have also been employed to produce hydrocarbons by decarbonylation. In this strategy, a carboxylic acid reductase was employed to convert aliphatic fatty acid into aldehydes and, subsequently, a decarbonylase was employed to convert the aldehydes into hydrocarbons. As an example, *Escherichia coli* strains were employed to host a carboxylic acid reductase from *Mycobacterium marinum* and a cyanobacterial aldehyde decarbonylase to produce fatty alkenes (C_7–C_{15}) (Akhtar et al., 2013). Similarly, a fatty acid reductase from *Photorhabdus luminescens* was combined with an aldehyde decarbonylase from *Nostoc punctiforme* to produce alkanes (Howard et al., 2013). In that study, rather than mimicking the biological production of alkanes found in nature, the authors engineered *Escherichia coli* for the in vivo production of linear and branched-chain alkanes (Howard et al., 2013). To do so, rather than the fatty acid thioesters substrates used by the native cyanobacterial pathway previously reported (Schirmer et al., 2010), exogenous FFAs were used directly by *Escherichia coli* cells (Howard et al., 2013). The authors evaluated such proof of principle as an artificial molecular pathway for the production of renewable and industrially relevant petroleum-replica hydrocarbons (Howard et al., 2013).

Beyond the biological production of fatty alkanes (Choi and Lee, 2013; Kang et al., 2017; Khara et al., 2013; Sheppard et al., 2016; Zargar et al., 2017), short-chain alkanes have been also produced by biological catalysts. For instance, *Escherichia coli* was metabolically engineered to selectively produce short-chain alkanes (propane, butane, pentane, heptane, and nonane) by employing energy efficient reverse-β-oxidation (Sheppard et al., 2016). In this study, specific FFAs were converted into the corresponding aldehydes by a carboxylic acid reductase and, subsequently, cAD converted the aldehydes into short-chain alkanes (Sheppard et al., 2016). As pointed out by the authors, the engineered system tuned the product distribution towards short-chain alkanes (biogasoline, specifically) with desired biofuel properties (Sheppard et al., 2016). Medium-chain alkanes have also been produced by metabolic engineered *Escherichia coli* (Yan et al., 2016). To do so, a combination of enzymes, including an aldehyde decarbonylase from *Nostoc punctiforme*, were engineered into *Escherichia coli* cells; the results pointed out the feasibility and potential of using microorganisms as cell factories for the production of alkanes in the range of biojet fuels (C_8-C_{16}) (Yan et al., 2016). As microorganisms with activity to produce medium-chain alkanes are promising for the production of biojet fuels, a study was conducted for screening microorganisms with that activity

(Ito et al., 2018). As a result, among all strains tested, the genus *Klebsiella* in the *Enterobacteriaceae* family of bacteria was found to have the highest activity to produce medium-chain alkanes from aldehydes via enzymatic decarbonylation (Ito et al., 2018). Noteworthy, *Klebsiella* possesses a gene similar to the aldehyde dehydrogenase from *Escherichia coli* and such gene was found to be a novel alkane-synthesizing enzyme gene (Ito et al., 2019).

4. Challenges

Overall, as recently reviewed, the biological production of renewable hydrocarbons biofuels presents major challenges: the realization of an efficient and robust cell factory and the development of an industrially relevant cell factory (Zhou et al., 2018). Furthermore, as stated above, one of the most promising enzymes employed in the biological production of hydrocarbon, $OleT_{JE}$, as its name suggests, selectively produces long-chain α-olefins. Moreover, depending on the degree of unsaturation of the feedstock, the product may present high olefin content (alkenes and/or alkynes). Differently from paraffins (alkanes), olefins are very unstable due to the double or triple bonds; thus, olefins are more prone to react and form undesirable products under storage and blending conditions. Therefore, unsaturated feedstocks are usually saturated under high H_2 pressure and temperature and in the presence of a chemical catalyst to produce hydrocarbon biofuels (Monteiro et al., 2022).

The hydrogenation of olefins into paraffins may be a challenge for the biological production of hydrocarbon biofuels. The directed hydrogenation of substrates mediated by hydrogen is a synthetic reaction not usually performed by natural enzymes (hydrogenases, for example), since it does not offer any selective advantage for living organisms (Jing et al., 2009). Instead, cofactors (NAD(*P*)H and $FADH_2$, for example) are used to reduce organic substrates during metabolism (Jing et al., 2009). To address the instability, complexity and costs of using cofactors, some efforts have been done to perform the metalloenzymatic hydrogenation of olefins. Metalloenzymatic (bio)catalysts may be produced either by encapsulating the metal inside a protein (Ueno et al., 2004), linking the metal to the protein by a ligand (Skander et al., 2004; Yamaguchi et al., 2006), or by directly linking the metal to the protein surface (Trynda and Pruchnik, 1995; Trynda-Lemiesz and Pruchnik, 1997). Furthermore, the active-site metal of a metalloenzyme may be replaced by another metal. For example, aiming the hydrogenation of olefins, the active-site metal (zinc) was replaced by rhodium(I) on a carbonic anhydrase (CA), which was reported to be the first cofactor-independent reductase to reduce organic substrates mediated by hydrogen (Jing et al., 2009). In a similar approach, a nano-enzyme system of CA was designed and, then, the active-site metal (zinc) was replaced by rhodium (I) and the final metalloenzyme was employed in the hydrogenation of olefins (Yılmaz et al., 2018). The nano-enzyme system was able to enhance the thermal and operational stabilities of the (bio)catalysts (Yılmaz et al., 2018).

In addition, the reduction of olefins has been remarkably performed by reductases from the Old Yellow Enzymes (OYE) family, which are oxidoreductases able to perform the flavin mediated anti-hydrogenation of the olefinic bond (Müller et al., 2007). The discovery, characterization, engineering and applications of ene-reductases as industrial catalysts have been recently reviewed (Toogood and Scrutton, 2018), so the potential of such enzymes to saturate olefins into paraffins is not highlighted herein. Despite their potential, to the best of the authors' knowledge, no reports on the direct hydrogenation of olefins into paraffins have been found in the open literature, in fact, some reports focus on the hydrogenation of activated alkenes. As an example, since these enzymes may exhibit low activity and selectivity towards the substrate, two genes of OYE from a *Bacillus* strain were cloned and overexpressed in *Escherichia coli* BL21(DE3) in an effort to increase the activity and selectivity (Zhang et al., 2014). The recombinant enzymes exhibited activity not only towards α,β-unsaturated aldehydes, ketones, nitroalkenes, and the double activated carboxylic acids, esters, nitriles and cyclic imides but to "borderline" substrates (unsaturated lactones, mono carboxylic esters), thereby increasing the substrate scope of OYE; furthermore, both recombinant enzymes had excellent enantioselectivity (methyl 2-acetamidoacrylate was reduced by >99% conversion and > 99% ee, for example) (Zhang et al., 2014).

5. Conclusions

The chemical hydroprocessing of esters and/or fatty acids to produce renewable hydrocarbons biofuels is usually performed under high H_2 pressure, high temperature and in the presence of a noble metal as catalyst. Enzymes and/or microbial platforms may potentially produce these biofuels under ambient temperature and atmospheric pressure. Beyond genetic modification, multienzymatic cascade reactions may be an efficient strategy to convert triacylglycerol-based feedstocks into renewable hydrocarbons biofuels with desired properties. However, these systems must be further engineered to produce efficient and robust biocatalysts and then, be employed in industrial bio(process) as the production of renewable hydrocarbons biofuels.

Author credit

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