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Review

Advanced Biocatalytic Processes for the Conversion of Renewable Feedstocks into High-Value Oleochemicals

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Abstract: Oleochemicals, which are obtained from vegetable and animal fats and oils, have become indispensable in the food, cosmetics, pharmaceutical and biofuel industries. Traditionally, they are synthesized using chemical catalysts, a process that is often associated with high energy requirements and a considerable environmental impact. Biocatalysis, using enzymes such as lipases, has emerged as a transformative alternative that offers high specificity, environmental friendliness and cost-efficiency. This review comprehensively examines the current state of biocatalysis for oleochemical synthesis, highlighting key reactions such as esterification and transesterification and their integration into industrial processes. A bibliometric analysis uncovers global trends and collaborations, while case studies illustrate cost efficiency and scalability. The article outlines recommendations and future research directions to advance biocatalytic processes. This review is intended to be an important resource for researchers and industries transitioning to sustainable oleochemical production.

Keywords: biocatalysis; lipase; oleochemical synthesis; esterification; transesterification; sustainability; cost-effectiveness; biodiesel production

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1. Introduction

Oleochemicals are biodegradable compounds consisting of a diverse group of aliphatic chemicals derived from plant or animal sources, usually derived from vegetable oils or fats. These compounds are versatile raw materials as they can be used in a variety of industries for the production of a wide range of products such as detergents, lubricants, emulsifiers,

polymers, cosmetics, food additives, pharmaceuticals, herbicides, fuels and others [1,2]. The industrial processing of these raw materials leads to chemical reactions that produce various compounds which, depending on the technology used, pose significant hazards and usually require appropriate management to prevent damage to water and soil ecosystems or air pollution [3,4].

As an alternative, the scientific endeavours of recent decades suggest the use of enzymes as biocatalysts for oleochemical production processes. Their use in various processes is associated with several advantages over chemical catalysts, mainly because each enzyme is highly specific with respect to the substrate it catalyses, which eliminates the possibility of unwanted parallel reactions, facilitates process control and produces products of high purity [5]. A classic example is the production of biodiesel from oily sources, where conventional alkaline transesterification requires high-purity feedstocks (moisture < 200 ppm and free fatty acids < 0.5%wt) to prevent saponification of the triglycerides [6,7].

Replacing the chemical catalyst with an enzyme allows the use of feedstocks with a high free fatty acid contents, as lipases can catalyse both the esterification of the free fatty acids and the transesterification of their triglycerides to methyl esters of fatty acids, the main component of biodiesel [8,9]. This approach can significantly reduce process costs. In addition, the optimal reaction conditions commonly used in enzymatic synthesis are mild, which significantly reduces the energy requirements of the process [10,11].

Large-scale enzymatic reactions are increasingly seen as a sustainable alternative to conventional chemical processes. Although biocatalysts were more expensive than chemical catalysts in the past [12,13], recent advances have significantly improved their cost/benefit ratio. The favourable cost/benefit ratio of enzymatic processes makes biocatalysis a promising candidate for scaling up from the laboratory to the industrial level. In addition to their well-known environmental benefits, enzymatic processes are also becoming economically friendly and offer a sustainable solution that maintains profitability.

The optimization of these technologies is expanding their application possibilities so that they can compete with conventional methods and often outperform them in terms of efficiency and environmental impact. In addition, a clear understanding of the economic benefits of biocatalysis is driving innovation that reduces costs and improves process performance. Over the last decade, significant progress has been made in reducing the cost of enzymes and expanding their industrial use through successful pilot and commercial applications [14,15].

This review aims to fill a critical gap in the literature by comprehensively evaluating the cost efficiency of biocatalysis in oleochemical synthesis. The cost components of enzymatic processes, including enzyme production and operating costs, are evaluated in comparison to conventional chemical catalysts. Successful applications of biocatalysis, such as the production of biodiesel and the utilization of by-products such as glycerol, are highlighted through an analysis of case studies. This review also examines the trade-offs between economic feasibility and sustainability and shows how biocatalysis can strike a balance between these factors. Finally, future research priorities and technological innovations are outlined to overcome the current economic barriers and make biocatalysis a practical and scalable solution for the oleochemical industry. By addressing these aspects, this review aims to guide researchers and industry representatives towards the utilization of biocatalysis as a cost-effective and sustainable alternative for oleochemical synthesis.

2. Biocatalysis in Oleochemistry: Current Status and Progress

2.1. Oleochemical Synthesis and Chemical Modification of Fatty Acids: An Overview

Throughout the history of oleochemistry, various methods have been essential for the synthesis and modification of fatty acids and oils and have developed in parallel with

advances in chemical engineering, biotechnology and materials science. According to Behr and Seidensticker [16], oleochemicals can be categorized into basic types, including fatty acids, fatty acid methyl esters or other alkyl groups, fatty alcohols and fatty amines. Industrial oil products also include vegetable and seed oils, which are primarily obtained from animal or vegetable sources by processes such as extraction, refining, conversion and stabilization. Firstly, the oils are extracted or crushed by mechanical pressing and/or solvent extraction. This is followed by the refining process, in which pigments, metals, phospholipids, flavourings and other undesirable substances are removed. At this stage, the oil can be modified by hydrogenation, winterization or crystallization. After refining, the fatty acids are stabilized in order to achieve certain properties, such as greater stability and safety for the final products [17,18].

In industry, fats and oils are often modified by chemical or biocatalytic reactions. Common chemical strategies include hydrolysis in alkaline media and high-pressure steam. Alkaline hydrolysis usually produces fatty acid soaps, which require further treatment, e.g., acidification, to obtain pure free fatty acids (FFAs). In this reaction, fats and oils are hydrolysed with sodium or potassium hydroxide. The search for new methods to produce fatty acid derivatives began in the late 19th century. Twitchell and Colgate-Emery, for example, used an acidic naphthalene stearosulphonic acid catalyst for industrial fatty acid modification [19]. Although this approach was an improvement over previous methods, it was associated with problems such as high energy requirements and corrosiveness, resulting in lower quality products. To overcome these problems, the process was modified and converted from a batch to a continuous process.

The chemical processes in oleochemistry are primarily hydrolysis reactions, which are influenced by factors such as temperature and pressure. In addition, other reagents can be used in the industry instead of water, leading to the formation of various fatty acid derivatives, e.g., methanol in methanolysis or amines in aminolysis. Other reactions such as hydrogenation, esterification, transesterification, oxidation and epoxidation are examples of reactions that can be carried out using chemical methods [20].

Figure 1 gives an overview of common reactions that are used in chemical processes involving fatty acids as a model for oleochemical products.

Biocatalysis for the modification of fatty acids has been researched since the early 1900s, with enzymatic hydrolysis proving to be a promising application for the chemical industry. The advantages of using enzymes, both in soluble (non-immobilized) and immobilized form, as well as whole cells and engineered modified microorganisms are widely recognized. Biocatalysis can work through different mechanisms, such as the chemical modification of fatty acids and oils from renewable resources or the conversion of fatty acids into alkyl esters that can be applied in several industrial contexts [21].

Research in the field of oleochemical biocatalysis focuses on the development of sustainable, cost-effective methods for the synthesis of oleochemicals with multiple applications, taking into account the challenges related to enzyme stability, substrate compatibility and process scalability [5]. These methods offer notable environmental advantages as they produce bioproducts with low toxicity and high biodegradability and operate under milder conditions [22], reducing the formation of by-products compared to conventional chemical processes and offering flexibility in reactor design. Despite these advantages, challenges such as high energy consumption, the cost of the enzymes and problems related to enzyme inactivation and stability remain. However, the ability to reusing biocatalysts can mitigate these concerns, making the overall process economically viable and environmentally sustainable. Recently, enzymatic reactions and whole-cell biotransformations have gained importance due to their high selectivity, mild operating conditions and sustainability. Enzymes such as lipases [22–25], phospholipases [26,27], esterases, yeast

P450-monooxygenases [28–31] and oxidases are used to catalyse various transformations in oleochemistry, including transesterification, hydrolysis and oxidation reactions. As a result, enzymes are increasingly used in the synthesis of many oleochemical products, as objectively illustrated in Figure 1.

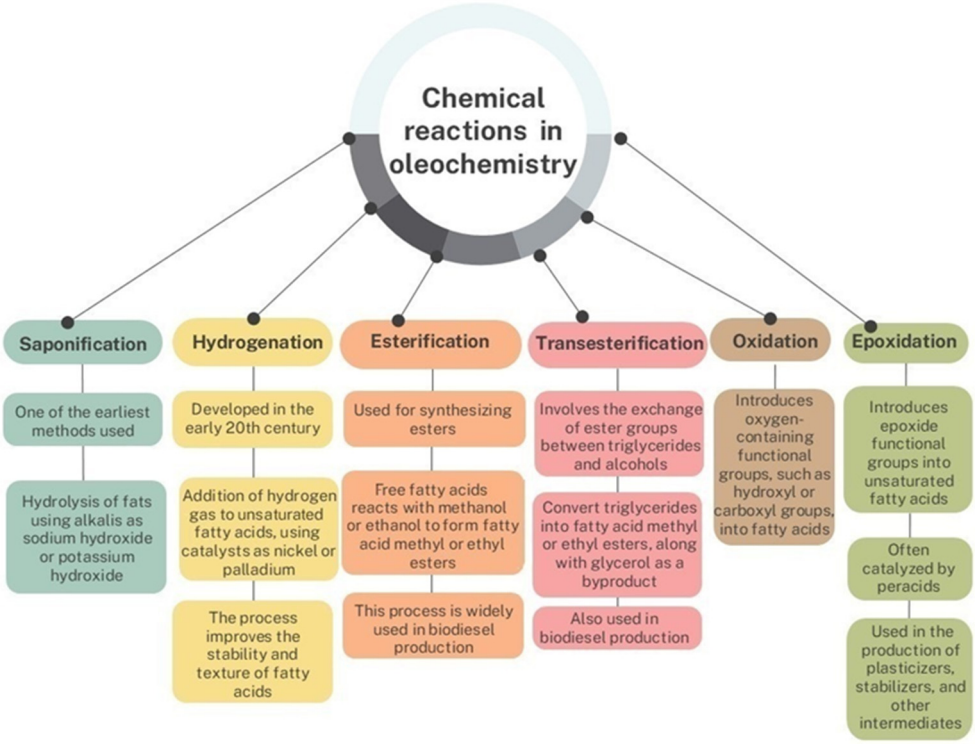

Figure 1. An overview of the common chemical reactions used to produce oleochemical products.

Enzymes such as lipases can also be combined with other chemical reactions. For example, enzymes do not directly catalyse hydrogenation reactions, which involve the addition of hydrogen atoms to unsaturated compounds, typically carbon–carbon double bonds, to produce saturated compounds. However, enzymes can indirectly influence hydrogenation processes through their role in metabolic pathways. For instance, certain enzymes involved in lipid metabolism can catalyse the synthesis or degradation of unsaturated fatty acids, which are substrates for industrial hydrogenation reactions. This relationship allows the production of modified fats tailored to specific properties.

Lipases (EC 3.1.1.3, triacylglycerol hydrolases) are most frequently used enzymes in biocatalytic processes for the conversion of oleochemical compounds [32]. This preference is mainly due to the fact that fats and oils serve as natural substrates that do not require cofactors and that lipases are chemo- and regioselective and exhibit high activity and stability [33–36]. Numerous lipases have been documented to be used in various oleochemical applications, including those from *Rhizomucor miehei*, *Thermomyces lanuginosus*, *Burkholderia cepacia*, *Candida rugosa* and *Rhizopus oryzae* [37,38].

In oleochemistry, lipases are frequently used for the synthesis of fatty acid methyl esters (e.g., biodiesel) and the modification of lipids [39]. A typical example is the use of ricinoleic acid as a substrate for lipase catalysis. This compound, which is also known as cis-12-hydroxy-9-octadecenoic acid or 12-hydroxyoleic acid, is contained in large quantities in castor oil. This unsaturated fatty acid can be used as a starting material for the production of various compounds with specific industrial applications, such as lubricants, polyesters and other oleochemical products [40–45].

Further applications can be found in the production of chemical products for the cosmetics industry, in particular through esterification reactions catalysed by biocatalysts. In addition, these processes are used in the food industry to convert conventional oils into structured lipids with functional properties that benefit human metabolism; this is performed by modifying the fatty acids at specific positions of the triglycerides through interesterification. Various emollient esters such as myristyl myristate, decyl cocoate, acetyl ricinoleate and isocetyl palmitate can be obtained from natural sources such as coconut oil or kernel oil [46].

Other enzymes such as thioesterases, phospholipases and lipoxygenases have also been extensively studied in biocatalysis and oleochemistry [47]. Lipoxygenases, for example, play a crucial role in the production of hydroperoxides, important intermediates in the synthesis of oleochemicals. However, despite their potential, the industrial application of these enzymes remains difficult due to problems such as low stability, limited catalytic activity and the lack of efficient overexpression systems capable of producing sufficient enzyme quantities [48]. Conversely, phospholipases can be used to upgrade waste cooking oils to oleochemical feedstocks [49].

Upgrading processes such as degumming, neutralization, bleaching and deodorization are essential steps in the production of high-quality vegetable oils for various oleochemical applications. These steps improve the quality, stability and nutritional properties of vegetable oils and thus support their use in oleochemistry.

2.2. Recent Innovations and Chemical Mechanisms of Biocatalysis in Oleochemistry

In recent years, innovative strategies have been developed to make oleochemical processes more profitable and scalable, including the increasing use of microorganisms as bioreagents for the production of intermediates or high-value products. This is made possible by genetic manipulation to increase the yield and scalability and the use of low-cost matrices [50,51]. Metabolic engineering serves as a key tool in the search for energy-rich oleochemicals, liquid fuels for transport and high-value chemicals, especially from renewable resources, by optimizing genetic and regulatory processes to increase cellular production while minimizing energy input [52]. The most common strategies include blocking competing metabolic pathways, redirecting metabolism to oil synthesis pathways and the overexpression of specific enzymes, which are often accompanied by manipulation of tolerant cells to intermediates to reduce stress. The integration of biocatalysis into oleochemical processes aims to develop more sustainable and efficient methods, such as the production of biopolymers, enzymatic biodiesel and the valorisation of glycerol to high-value compounds such as 1,3-propanediol, acrolein and epichlorohydrin using green solvents and ionic liquids to improve efficiency and environmental sustainability [15].

On the chemical side, enzymatic oleochemistry involves key reactions such as hydrolysis, acidolysis, esterification, transesterification, enzymatic oxidation and enzymatic epoxidation, which are summarized in Equations (1)–(6).

$$\text{Triglyceride} + 3H_2O \xrightarrow{Lipase} \text{Glycerol} + 3\text{Free fatty acids} \quad (1)$$

$$\text{Ester \#1} + \text{Fatty acid \#2} \xrightarrow{Lipase} \text{Ester \#2} + \text{Fatty acids \#1} \quad (2)$$

$$\text{Fatty acid} + \text{Alcohol} \xrightarrow{Lipase} \text{Ester} + H_2O \quad (3)$$

$$\text{Triglyceride} + \text{Alcohol} \xrightarrow{Lipase} 3\text{Acyl esters} + \text{Glycerol} \quad (4)$$

$$\text{Unsaturated fatty acid} + O_2 \xrightarrow{Oxidase} \text{Hydroperoxide} \quad (5)$$

$$\text{Unsaturated fatty acid} + H_2O_2 \xrightarrow{Peroxidase} \text{Epoxidized fatty acid} + H_2O \quad (6)$$

Looking at the reaction mechanism of these reactions, enzymatic catalysis begins with the recognition and activation of the substrate by the biocatalyst, a critical step to ensure the specificity and efficiency of the process. For lipases, this involves the formation of an enzyme–substrate complex facilitated by interfacial activation, in which hydrophobic interfaces lead to a conformational change that exposes the active site of the enzyme. Once the substrate is positioned at the catalytic site, it is oriented to favour the cleavage or formation of bonds, such as ester or amide bonds.

Lipases operate via a conserved catalytic triad of serine, histidine and an acid residue (aspartic acid or glutamic acid). In this mechanism, serine acts as a nucleophile and attacks the electrophilic carbonyl carbon of the substrate, while histidine removes a proton from serine, which increases its reactivity. The acid residue stabilizes the histidine through electrostatic interactions and thus promotes proton transfer.

This process leads to the formation of a covalent "acyl-enzyme" intermediate, a key step in hydrolysis, esterification and transesterification processes. Enzymes also have complementary domains that confer high selectivity for acyl chain length and nucleophilic groups (such as alcohol, amine and water) and enable reactions with high regio- and enantioselectivity. After the formation of the acyl-enzyme intermediate, the enzyme transfers the acyl group to a second nucleophile, e.g., an alcohol, an amine or water, which completes the reaction. This transfer step is essential for the conversion of the substrate into the desired oleochemical products and is strictly regulated by the microenvironment of the active site, which stabilizes the transition state through hydrogen bonding, steric effects and specific hydrophobic interactions that increase both the selectivity and efficiency of catalysis. Following product release, the enzyme is regenerated in its active form, allowing several reaction cycles that increase productivity and reduce enzyme consumption. Lipases also exhibit regiospecificity, recognizing and selectively reacting with functional groups at particular positions, and enantioselectivity, distinguishing between enantiomers of chiral compounds.

This specificity results from the highly organized architecture of their active sites, which impose spatial and electronic constraints to precisely control the positioning and orientation of functional groups during modification. Such selectivity enables the production of optically pure compounds with a high enantiomeric excess compared to conventional chemical methods, which is essential for applications in the fields of pharmaceuticals, fragrances, surfactants and polymers. This section provides an overview of various classes of enzymes involved in fatty acid modification, highlighting their structures, mechanisms and industrial applications.

2.2.1. Hydratases

Fatty acid hydratases, classified under enzyme EC 4.2.1.53, are specialised catalysts that enable the stereo- and regioselective addition of water molecules to carbon–carbon double bonds in fatty acids. This enzymatic activity leads to the formation of chiral hydroxy fatty acids, which are of great biological and industrial importance. These enzymes contain flavin adenine dinucleotide (FAD) as a prosthetic group and mainly target the cis-9 and cis-12 double bonds in monounsaturated fatty acids and polyunsaturated fatty acids (PUFAs) with chain lengths of C14 to C22.

The most common reaction mediated by fatty acid hydratases is the addition of water to the cis-9 double bond in oleic acid to form (S)-10-hydroxystearic acid (denoted as (S)-10-HSA, Figure 2) [53,54].

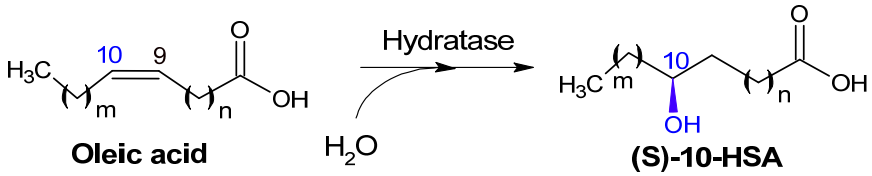

Figure 2. Synthesis pathway to produce (S)-10-hydroxystearic acid from oleic acid catalysed by hydratase.

These hydroxy derivatives are valuable starting materials for the synthesis of γ-lactones, compounds that are frequently used as flavouring agents in the food industry [55,56]. Microbial hydration of oleic acid was first observed in 1962, when Wallen et al. [57] documented that *Pseudomonas* species converted it into 10-hydroxystearic acid. Since then, numerous other bacteria and fungi from different genera have catalysed similar reactions, expanding our understanding of microbial fatty acid hydration.

The first cloning and detailed characterization of a fatty acid hydratase was performed by Bevers et al. in 2009 [58]. This was followed by research by Volkov and colleagues, who successfully identified and reclassified enzymes from *Streptococcus pyogenes*, *Bifidobacterium breve* and *Lactobacillus species* as specific (cis)-9-hydratases [59–61]. The structural elucidation of a (cis)-9-hydratase from Lactobacillus acidophilus was an important milestone, as the enzyme was crystallized in both ligand-bound and unbound states (PDB codes: 4IA6 and 4IA5). This enzyme functions as a homodimer that has an extended substrate binding channel and an N-terminal lid domain in each protomer, which facilitate fatty acid recognition and catalysis. Further progress was made in 2015 with the structural resolution of the oleate hydratase from *Elizabethkingia meningoseptica* (PDB code: 4UIR), which was studied together with mutagenesis experiments to elucidate the reaction mechanism [62].

These studies revealed that although FAD is not directly involved in the addition of water, it plays a crucial role in maintaining the proper organization of the active site and stabilizing charge formation during the transition state. These findings led to attempts to recombinantly express other (cis)-9-hydratases, including those from *Lysinibacillus fusiformis*, *Stenotrophomonas maltophilia* and *Macrococcus caseolyticus* [63–65].

Interestingly, many of these hydratases show high specificity for (cis)-9 double bonds, while their activity is generally limited for (cis)-12 double bonds, such as those in linoleic acid. However, there are some exceptions; for example, a (cis)-12 hydratase from *Lactobacillus acidophilus* has been identified that predominantly catalyses the formation of the 13-hydroxy derivative of linoleic acid [66,67]. In addition, Hirata and colleagues demonstrated that certain (cis)-12-hydratases from *Lactobacillus* species can also act on longer-chain PUFAs such as arachidonic acid (C20) and docosahexaenoic acid (DHA, C22) and convert them into the corresponding 15- and 14-hydroxy fatty acids [68]. These enzymes are remarkably efficient. For example, recombinant (cis)-9-hydratases expressed in Escherichia coli have been shown to tolerate high concentrations of oleic acid up to 1 M, allowing for scalable biotransformation [69]. In practical applications, whole-cell biotransformations with *E. coli* harbouring (cis)-9-hydratases from *Stenotrophomonas maltophilia* have shown remarkable efficiency, achieving a yield of 91% relative to the starting oleic acid and a final concentration of 46 g/L 10-hydroxystearic acid in the culture medium [65].

In summary, fatty acid hydratases are versatile and potent enzymes with significant potential for industrial biocatalysis that enable the regio- and stereoselective modification of fatty acids to produce valuable hydroxy derivatives. Ongoing structural and functional studies deepen our understanding and open new opportunities for the development of these enzymes for tailored applications in the fields of flavours, pharmaceuticals and bio-based materials.

2.2.2. Hydroxylases

Hydroxylases play a crucial role in lipid biochemistry, especially in the specific modification of fatty acids. Among them, the 12-hydroxylases (enzyme class EC 1.14.13.26) are the best-researched enzymes of this group. These enzymes catalyse the hydroxylation of oleic acid at the 12th carbon position and convert it into ricinoleic acid, an important precursor for the production of various oleochemical derivatives, including lubricants, polyesters and other valuable bio-based products (Figure 3).

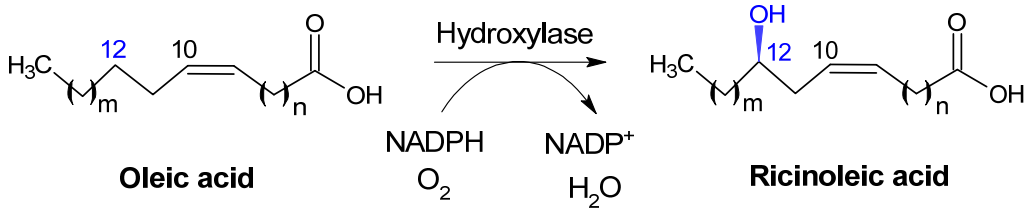

Figure 3. Synthesis of ricinoleic acid from oleic acid catalysed by hydroxylase.

The presence of 12-hydroxylases has been demonstrated in plants such as Ricinus communis, commonly known as castor bean, which is known for its high content of ricinoleic acid. Structurally, these enzymes have a di-iron centre that favours their catalytic activity. They utilize molecular oxygen and NADPH to carry out the hydroxylation process, which is highly regio- and stereoselective and ensures precise modification of the fatty acid substrate. Interestingly, 12-hydroxylases are evolutionarily related to 12-desaturases, enzymes that typically introduce a double bond into fatty acids, particularly in the conversion of oleic acid to linoleic acid. This close relationship suggests a common evolutionary origin and a similar structural framework. In fact, scientists have shown that by exchanging only four amino acids in a 12-desaturase for the corresponding amino acids in a fatty acid hydroxylase, desaturase can be converted into an efficient 12-hydroxylase. This remarkable switch highlights the subtle structural differences that determine the specificity and activity of the enzyme [44,70]. Overall, hydroxylases like 12-hydroxylases are important tools in biocatalysis and metabolic engineering, opening up avenues for the production of customized fatty acids for industrial applications. Their ability to catalyse highly specific reactions underlines their importance both for natural lipid metabolism and for biotechnological innovations.

2.2.3. Hydroperoxidases

In addition to hydroxylation processes, hydroperoxidation at specific activated sites in fatty acids, in particular at the α-carbon (α-C-H bonds) and at allyl positions, was also investigated in detail. In particular, α-dioxygenases (α-DOx) are a key class of enzymes involved in these transformations (Figure 4) [71].

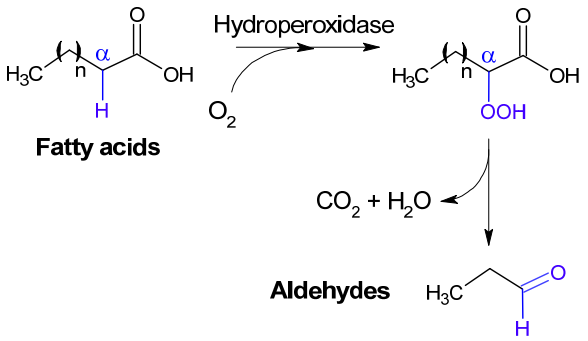

Figure 4. Synthesis of aldehydes from fatty acids catalysed by hydroperoxidase.

The main products of α-DOx activity are α-hydroperoxyacids, which are spontaneously decarboxylated to aldehydes. Given the high reactivity and versatility of aldehydes as starting materials, they serve as valuable intermediates for a variety of chemical syntheses, suggesting that interest in α-DOx enzymes is likely to increase in future research. Despite their potential, the application of α-DOx in synthetic chemistry is still relatively limited, and there are only a handful of studies investigating their utility [72,73]. In contrast, lipoxygenases (LOXs) are better-researched enzymes. They catalyse the hydroperoxidation of the cis,cis-1,4-pentadiene system found in polyunsaturated fatty acids. These enzymes usually facilitate the subsequent cleavage of the hydroperoxide intermediate by hydroperoxide lyases, which leads to the formation of volatile compounds.

This enzymatic system of combining lipoxygenase and hydroperoxide lyase is well established in the flavour and fragrance industries to produce C6 aldehyde odours known as "green leaf volatiles" [74]. Recently, interest in the utilization of these enzymatic transformations to produce bifunctional polymer precursors from unsaturated fatty acids has increased, expanding their potential applications in materials science [75,76]. Another interesting class are the diol synthases. These enzymes catalyse allylic hydroperoxidation reactions similar to lipoxygenases: the generated hydroperoxide intermediates are directly used as oxygen donors in intramolecular hydroxylation reactions. Diol synthases exhibit regioselectivity, e.g., 1,2-, 1,3- or 1,4-positions relative to the hydroperoxidation site [77–79] (see Figure 5). Despite their promising catalytic capabilities, these enzymes have not yet attracted much attention in the biocatalysis community. In summary, the unique potential of α-dioxygenases and diol synthases needs to be further explored, even though lipoxygenases and their associated metabolic pathways are better established and widely utilized. Their ability to selectively modify fatty acids though hydroperoxidation opens up avenues for innovative applications in synthesis, materials science and flavour chemistry and promises exciting developments in the future.

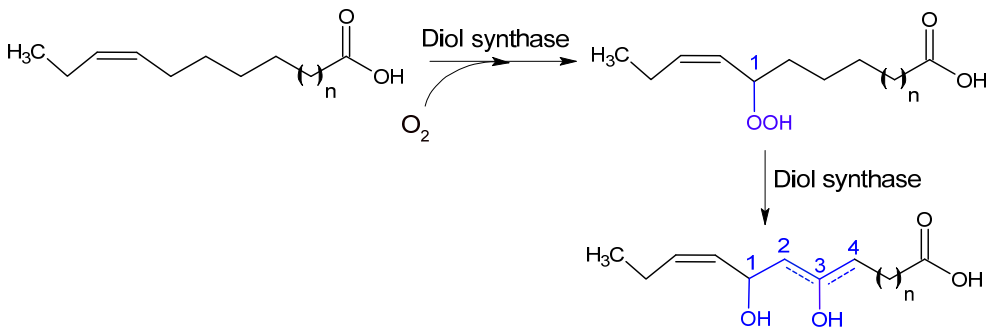

Figure 5. Mechanism of diol synthetase for the synthesis of 1,2-, 1,3-, 1,4- diols.

2.2.4. Lipoxygenases

Lipoxygenases (LOXs) are a family of oxidative enzymes characterized by their non-haem iron or manganese cofactors. The formation of conjugated hydroperoxy derivatives known as hydroperoxydienoic acids is the primary function of these enzymes when they catalyse the dioxygenation of polyunsaturated fatty acids containing a cis-1,4-pentadiene structure. Their primary function involves catalysing the dioxygenation of polyunsaturated fatty acids (PUFAs) that contain a cis-1,4-pentadiene structure, leading to the formation of a conjugated hydroperoxy derivative known as 15-Hydroxyeicosatetraenoic acid (denoted as (S)-15-HETE, Figure 6) [80].

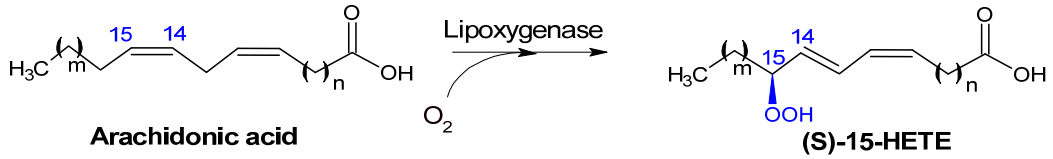

Figure 6. Synthesis of (S)-15-HETE from arachidonic acid by using lipoxygenase.

The ability of LOXs to produce hydroperoxides has opened the door to numerous industrial applications. In the food sector, for instance, LOXs are used to bleach coloured components by oxidizing carotenoids, resulting in a clearer appearance for products like flour. LOX-mediated oxidation also helps with bleaching processes in the paper and textile industries. In addition, LOXs are also used to modify lipids from various raw materials and to produce valuable oleochemicals and aromatic compounds, such as (Z)-3-hexenal, which contributes to fresh, green fragrances.

Despite their promising potential, the widespread industrial utilization of LOXs faces significant challenges. The main obstacles include the low stability of the enzymes under operating conditions, the relatively low catalytic activity and the lack of efficient expression systems that can produce large amounts of active enzymes. These limitations hinder the scalability and economic viability of LOX-based processes, as noted by Heshof et al. (2016) [48]. One notable commercial application of LOXs is in the bleaching of wheat flour. Here, soybean flour enriched with LOX enzymes is used to oxidize carotenoid pigments, thereby enhancing the flour's whiteness [81].

To improve their functional properties, scientists have turned to protein engineering techniques to modify LOXs. In recent years, efforts have focused on modifying their regio- and stereospecificity, understanding structure–function relationships [82], optimizing metal ion selectivity and improving enzyme stability [83]. Such modifications have identified critical amino acids in the active site of the enzyme, providing insight into how these enzymes can be tailored for specific tasks. A remarkable aspect of LOX biochemistry is its stereoselectivity, which appears to depend on a single conserved amino acid residue in the active site. In LOXs that produce (S)-stereoisomers, this residue is typically an alanine, whereas in (R)-stereoisomers, it is a glycine. Mutational studies have shown that replacing glycine with an alanine can partially change the stereospecificity of the enzyme, effectively converting an (S)-LOX into an (R)-LOX, or vice versa [84,85].

Laboratory-scale studies on OX-mediated hydroperoxide production have yielded promising results. For example, 13-hydroperoxy-(9Z,11E)-octadecadienoic acid was successfully synthetized from linoleic acid using LOXs derived from *Gaeumannomyces graminis* and *Pseudomonas aeruginosa*. Both biotransformations showed high yields (88% and 75%) with respect to the starting linoleic acid and good selectivity (74% and 61%). It is noteworthy that the reaction with *Pseudomonas aeruginosa* LOX required a much lower substrate concentration (10 g/L) and longer incubation times (48 hours) compared to the *G. graminis* enzyme [84,85].

Scale-up experiments with *G. graminis* LOX at industrially relevant linoleic acid concentrations (100–300 g/L) showed a decrease in yield; however, a volumetric productivity of about 3.6 g per litre per hour was still achieved [86]. The combination of LOXs with hydroperoxide lyases (HPLs) represents an interesting route to produce green fragrances, which are highly valued in the fragrance and flavour industries. In initial experiments, crude homogenates from soybean (as LOX source) and guava (as HPL source) were used to produce C6 compounds like (Z)-3-hexenal and (Z)-3-hexenol, which contribute significantly to the characteristic green aroma. HPLs are classified as CYP74 enzymes and carry out the homolytic isomerization of fatty acid hydroperoxides to unstable hemi-acetals, which are then broken down into C6-aldehydes and C12-oxo acids (see Figure 7).

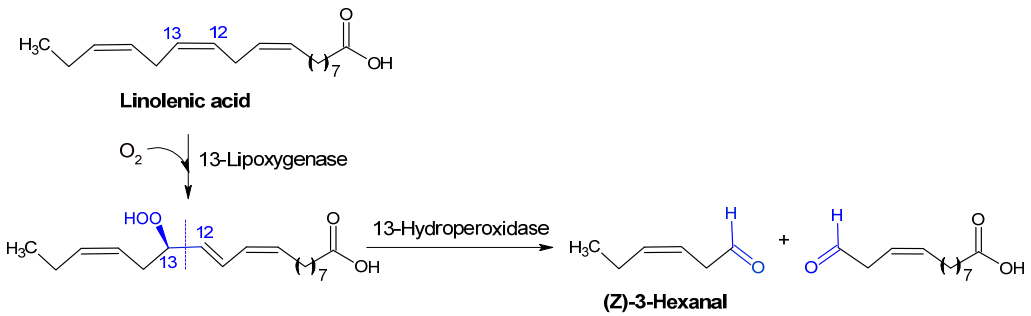

Figure 7. Combined use of 13-Lipoxygenase and 13-hydroperoxidase for the synthesis of (Z)-3-hexanal starting from linolenic acid.

The C6-aldehyde can be reduced to its corresponding alcohol, although isomerization to (Z)-2-aldehyde and (Z)-2-alcohol has also been observed. The functional expression of the guava HPL gene in *Escherichia coli* has led to significant progress in this field. Subsequently, directed evolution techniques, including DNA shuffling and random mutagenesis, were applied to improve the performance of the enzyme. The result of these efforts was a variant with fifteen times higher productivity, primarily due to improved expression and increased thermostability of the enzyme [87]. More recently, an enzyme cascade process was developed in which the engineered 13-HPL enzyme, used as a crude cell lysate, was combined with a commercial ketoreductase. Using this approach, (Z)-3-hexenol was successfully produced with an isomeric purity of 99% and a high concentration of approximately 8 g/L, demonstrating the potential for the scalability of the process [88]. In summary, LOXs are versatile enzymes with significant industrial potential, especially when combined with other biocatalysts. Ongoing research into enzyme engineering, process optimization and scale-up strategies continues to push the boundaries of their applications from food processing to fragrance manufacturing despite existing challenges related to stability and expression efficiency.

2.2.5. Decarboxylases

The oxidative decarboxylation of fatty acids to produce terminal alkenes has emerged as a fascinating area of enzymatic bioconversion that primarily involves a series of haem-dependent monooxygenases. This conversion was initially documented with a P450 monooxygenase derived from *Jeotgalicoccus* species, known as OleTJe (Figure 8) [89].

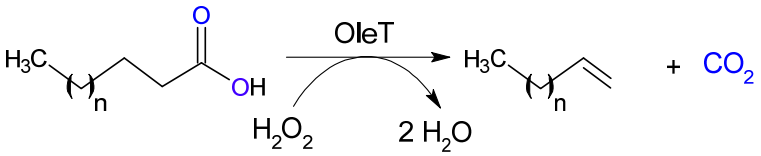

Figure 8. Oxidative decarboxylation of carboxylic acids using OleT.

Since then, similar activity has been observed as a secondary or side reaction in several P450 enzymes, including P450Bsβ [90] and a range of additional P450 monooxygenases [91–93]. In addition to haem-based systems, non-haem iron-containing decarboxylases, like UndB from *Pseudomonas* species, have also been identified that can catalyse decarboxylation processes [94–97]. An innovative approach to synthetize terminal alkenes is to combine OleT with an alditol oxidase enzyme, as shown in Figure 9 [98,99]. This strategy aims to create a comprehensive biocatalytic pathway that valorises natural triglycerides and converts them directly into valuable alkenes. Such holistic approaches are promising for sustainable chemical production utilizing biomass components.

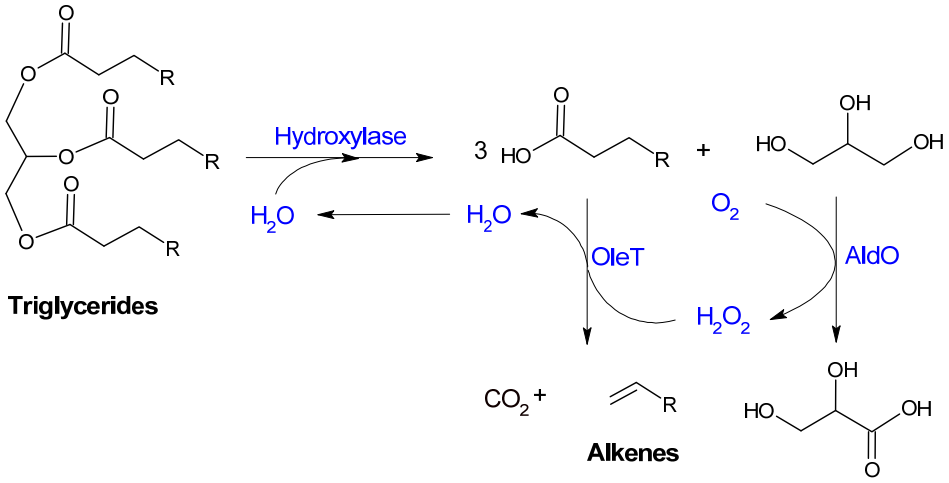

Figure 9. Use of triglycerides for the synthesis of terminal alkenes. The triglyceride is first hydrolysed to glycerol and fatty acids. The fatty acids are then converted to terminal alkenes by OleT with the partial use of H_2O_2, which is formed during the oxidation of glycerol to glyceric acid (catalysed by alditol oxidase, AldO).

More recently, a new class of enzymes, the so-called fatty acid photodecarboxylases (FAPs), has attracted considerable attention. Sorigué et al. [100,101] characterized FAPs, which represent a breakthrough in light-driven decarboxylation. The enzyme from *Chlorella variabilis* (CvFAP) has become the focus of research, especially considering its potential for biofuel production. Its unique mechanism is based on the photoactivation of a flavin prosthetic group, which enables the direct conversion of fatty acids into alkanes when exposed to light. This process offers several advantages over the conventional biodiesel process based on fatty acid methyl esters (FAMEs), including the reaction being simple and irreversible and the fact that products with higher caloric content are produced.

However, despite the promising prospects of FAPs in the production of next-generation biofuels, their practical application faces significant obstacles. Chief among these is the poor photostability of the enzyme, which limits the operational longevity and, consequently, the economic viability of large-scale processes [102]. A deeper understanding of the mechanisms underlying FAP inactivation and advances in enzyme engineering to improve stability are required to achieve sustained enzyme activity over extended periods of time. To overcome these challenges, several innovative strategies have been pursued to integrate FAPs into synthetic pathways aimed at producing higher-value compounds. Researchers have engineered CvFAP variants to improve selectivity towards different substrates, especially focusing on light-driven kinetic resolution reactions. Li and colleagues [103] have successfully modified CvFAP to achieve better discrimination between α-substituted carboxylic acids and to distinguish between cis- and trans-unsaturated fatty acids.

Such modifications open up exciting opportunities to tailor enzyme activity to specific bioconversion targets and extend the potential applications of FAPs beyond biofuel production to speciality chemicals and fine intermediates. Further research on their stability, specificity and mechanism will be crucial to fully realise their industrial potential.

2.2.6. P450 Monooxygenases

Cytochrome P450 enzymes, commonly known as CYPs, constitute a large family characterized by their prosthetic haem group. These enzymes are capable of catalysing specific oxidation reactions, both regio- and stereoselectively, across a broad spectrum of substrates. A characteristic feature of CYPs is their dependence on a redox partner system that facilitates electron transfer from NAD(P)H to the haem centre of the enzyme, enabling catalytic

activity. These enzymes are essential for the metabolism of xenobiotics, foreign compounds such as drugs and environmental chemicals; they are also involved in the biosynthesis of several natural products, including steroids, fatty acids and secondary metabolites [104,105]. Despite their remarkable versatility and potential for biotechnological applications, the industrial use of CYPs remains limited.

Challenges such as those involving enzyme stability and the need for complex electron transfer systems hinder their widespread use. In addition, many CYPs are either membrane-bound or membrane-associated, which complicates their extraction, purification and utilization as isolated enzymes. Their dependence on NADPH in stoichiometric amounts further complicates their practical application.

A typical reaction mediated by P450 monooxygenases is the hydroxylation of fatty acids, whereby ω-hydroxy fatty acids are formed directly from free fatty acids (Figure 10). These hydroxylated products can subsequently be oxidized to dicarboxylic acids, as has been shown in various whole-cell biotransformations with *Candida* species [106]. Such compounds are multifunctional and have significant industrial value, as they serve as precursors for polymer production and fragrances [107]. Among the different CYPs, the enzyme CYP102A1 from *Bacillus megaterium*, also known as P450-BM3, stands out as the most practical and well-studied example.

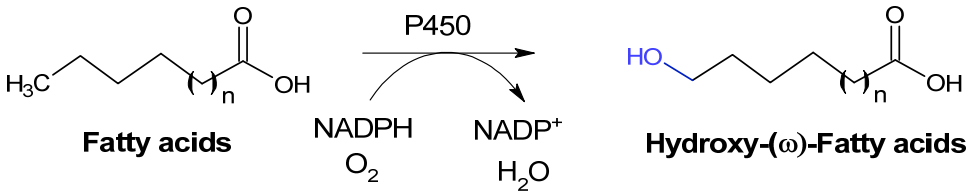

Figure 10. P450 monooxygenase-catalysed hydroxylation of fatty acids to produce hydroxy-(ω)-fatty acids.

This enzyme is a natural fusion protein that integrates both the haem domain and the reductase domain into a single polypeptide chain, giving it exceptional catalytic efficiency. P450-BM3 has the highest turnover frequency among the P450 monooxygenases and is specialised in the subterminal hydroxylation of long-chain fatty acids (from C12 to C22) with high regio- and stereoselectivity [108].

During the development of the protein, extensive efforts were made to modify P450-BM3 to improve its activity, selectivity, stability and substrate range. These modifications include altering its regio-, stereo- and chemoselectivity and reducing its dependence on cofactors. Studies have investigated how specific amino acid substitutions affect the performance of the enzyme, with particular attention paid to residue F87, which has been identified as a key factor for substrate specificity [109,110].

Recent advances include iterative cycles of targeted or random mutagenesis to generate P450-BM3 variants capable of producing terminal hydroxy fatty acids, which are valuable intermediates in chemical synthesis. Some of the most successful variants contained up to 11 amino acid substitutions, three of which, F87, I263 and A328, were close to the substrate binding pocket and had a significant impact on the activity of the enzyme [111].

In addition to P450-BM3, several other self-sufficient CYPs from *Bacillus* and *Streptomyces* species have been characterized and used for biotransformations. For example, P450 monooxygenases from *Sorangium cellulosum* and *Fusarium oxysporum* were overexpressed in microbial hosts such as *Saccharomyces cerevisiae* and *Escherichia coli* and enabled the biosynthesis of medium-chain ω-hydroxy acids, highlighting the versatility and potential of these enzymes for sustainable biocatalysis [112,113].

3. Environmental Benefits of Biocatalysts in Oleochemistry Compared to Chemical Catalysts

In the synthesis of oleochemical products, catalysts play an essential and multifaceted role, significantly influencing the overall efficiency, selectivity and environmental footprint of the process. Traditionally, both homogeneous and heterogeneous chemical catalysts are used to facilitate these reactions.

Homogeneous catalysts, which are soluble in the reaction medium, offer notable advantages such as fast reaction rates, simple operating procedures and easy mixing, resulting in efficient process kinetics. Common examples of homogeneous catalysts are inorganic bases such as sodium hydroxide (NaOH), potassium hydroxide (KOH), calcium hydroxide ($Ca(OH)_2$), potassium carbonate (K_2CO_3) and sodium carbonate (Na_2CO_3), as well as inorganic acids such as hydrochloric acid (HCl), sulphuric acid (H_2SO_4), phosphoric acid (H_3PO_4) and p-toluenesulphonic acid [114–117].

Alkaline homogeneous catalysts are particularly valued for their high reaction speed, low reagent consumption and corrosion resistance, which can increase process efficiency. Acid catalysts, on the other hand, often allow reactions under milder temperature and pressure conditions, which can reduce energy requirements and potentially improve product selectivity. Despite these advantages, homogeneous catalysts have notable limitations. They are difficult to recover and dispose of, resulting in additional purification steps to recover the final products and environmental problems due to the release of toxic waste that needs to be disposed of [118,119]. Some catalysts are corrosive, which can damage equipment, and side reactions can produce unwanted by-products.

Heterogeneous alkaline catalysts such as calcium oxide (CaO) or oxides of alkali and alkaline earth metals require the use of refined oils, as they are sensitive to the presence of free fatty acids, which can lead to the formation of soaps, resulting in their deactivation [120]. The use of heterogeneous acid catalysts has been extensively studied, as they can be easily separated at the end of the process. Examples of effective catalysts are strong acid exchange resins (Amberlyst 15, 20BD, 35, Lewatit K2621, K2620, Tulsion T-42, Dowex M 31) [121–123], magnetically separable iron oxide on a sulphonated graphene oxide [124], zeolites [125] and metal oxides [126–129]. Although heterogeneous catalysts are easier to recover, they can be deactivated by fouling or poisoning, especially when processing raw materials with high FFA contents. In addition, these reactions often require high temperatures and long periods of time, which increases energy consumption and costs.

Lipases have been shown to accelerate and catalyse several chemical reactions that use lipid substrates [130]. Each lipase has an active site consisting of different amino acids so that it can recognize several lipid molecules. For example, the immobilized lipase from *Thermomyces lanuginosus* (Lipozym TL IM) has an active site containing amino acids such as lysine, aspartic acid and glutamic acid [131] and can catalyse a variety of reactions, including the esterification of fatty acids, hydrolysis, alcoholysis, transesterification and the acidolysis of oils and fats. Lipozym TL IM exhibits regioselectivity by catalysing the ethanolysis reaction of trilaurin and trimyristin, leading to the formation of β-monoglycerides, in particular 2-monolaurin [132] and 2-monomyristin [133].

Similarly, the α-monoglyceride compounds, α-glycerol monolaurate (1-monolaurin) and α-glycerol monocaprate (1-monocapryn), were prepared by transesterification of methyl laurate or methyl caprate with 1,2-acetonide glycerol using Lipozym TL IM (Figure 11). These compounds were then deprotected with Amberlyst-15 [134,135].

Lipids from food waste can be converted into biodiesel using methanol (molar ratio 1:5) and Novozym® 435 as a catalyst. The conversion rate of lipids to biodiesel was 90% at a reaction time of 24 h and 40 °C [136]. Other food waste can be enzymatically hydrolysed to produce hydrosilate, which is subsequently cultured into microalgae biomass.

The transesterification of microalgae lipids with methanol and lipase can also be used to produce biodiesel [137].

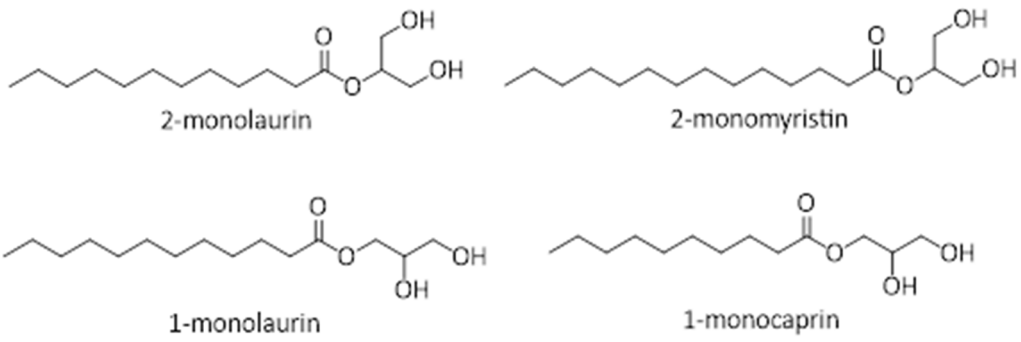

Figure 11. Chemical structure of monoglycerides.

Lipase enzymes offer advantages in terms of green chemistry and sustainability: they are safe and easy to handle, non-toxic, ecologically harmless, energy efficient, renewable and biodegradable [138]. As a result, the amount of waste is reduced to an absolute minimum. Certain types of lipases eliminate the need for toxic solvents and can even occur in aqueous solution [139].

Lipases have found significant strategic and potential application in lipid processes, especially in biogenic and eutectic solvents [140]. It is more productive and environmentally friendly to use lipases in solvent-free systems for lipid conversion processes [141]. These parameters suggest that reaction processes including lipase are more environmentally friendly, less harmful, safer and guarantee long-term viability.

However, it is clear that most oleochemical synthesis processes involving lipases take place in organic solvents, as the lipid substrates are more easily dissolved in them. The solubility of the reagent affects the stability and activity of the enzyme, which in turn controls the reaction rates.

In addition, immobilized lipase is a heterogeneous catalyst that offers several advantages both in terms of industrial production and environmental protection. Easy separation from the target product, reusability and decomposition in the environment upon loss of activity contribute to its favourable properties. The use of immobilized lipase significantly reduces the environmental impact of the catalyst.

Finally, oleochemicals are traditionally synthesized using chemical catalysts. Although these methods are effective, they are often energy-intensive, harmful for the environment and generate large amounts of waste. In contrast, enzymatic catalysis, particularly using lipases, has proven to be a sustainable alternative that is compatible with the principle of green chemistry. This section addresses the environmental benefits of enzymatic processes, with a focus on reducing greenhouse gas emissions, minimizing toxic by-products, energy efficiency and water conservation.

3.1. Reduction of Carbon Dioxide Emissions

One of the most important environmental benefits of enzymatic catalysis is its ability to significantly reduce CO_2 emissions. Conventional chemical catalysis often requires high temperatures (160–220 °C), which leads to significant energy consumption and consequently increased greenhouse gas emissions. In contrast, enzymatic catalysis operates efficiently under milder conditions (35–45 °C), which significantly reduces energy consumption and the associated emissions.

Mustafa and Niikura [142] pointed out that the enzymatic production of isopropyl palmitate leads to a reduction in CO_2 emissions by more than 50% compared to chemical

processes. This reduction results from lower operating temperatures and the absence of CO_2-generating side reactions.

Similarly, Pasha et al. [143] analysed the life cycle emissions of enzymatic versus chemical biodiesel production and found that enzymatic processes can reduce CO_2 emissions from soybean oil and used cooking oil by up to 78.9% and 63.1%, respectively. These results emphasize the potential of biocatalysis to reduce the environmental impact of industrial oleochemical production.

3.2. Minimization of Toxic By-Products

Chemical catalysis often involves the use of hazardous reagents such as strong acids or alkaline compounds, which can lead to the formation of significant quantities of toxic by-products. These substances pose a serious environmental risk, including soil and water contamination, and require extensive post-reaction treatment, further increasing the environmental impact of the process. In contrast, lipase-catalysed reactions are inherently cleaner, highly specific and generate minimal waste.

Hosney and Mustafa [144] demonstrated that the enzymatic production of 2-ethylhexyl esters generated significantly less hazardous waste compared to chemical processes. This fact not only simplifies waste disposal but also reduces the ecological footprint of the process. In addition, enzymatic reactions generally produce more environmentally friendly by-products that are biodegradable or reusable. In the production of biodiesel, for example, the by-product glycerin, obtained by enzymatic processes, is of higher purity and can be more easily converted into value-added products such as 1,3-propanediol or acrolein.

3.3. Improved Biodegradability and Compatibility with Green Solvents

Chemical catalysis usually uses volatile organic compounds as reactants, which contributes to air pollution and pose health risks. However, enzymatic catalysis is highly compatible with environmentally friendly solvents such as ionic liquids, supercritical CO_2 and deep eutectic solvents.

Mustafa and Niikura [142] investigated the use of immobilized *Candida antarctica* lipase in green solvent systems for esterification reactions. The study showed high reaction efficiency and minimal environmental impact, emphasizing the synergy between biocatalysis and using tert-butanol as a solvent. In addition, the enzymatic products are often more biodegradable, which reduces the long-term environmental impact compared to their chemically synthesized counterparts.

4. Market and Economic Considerations

4.1. General Arguments

A direct comparison of the costs of lipase with those of conventional chemical catalysts should be avoided at all costs. Instead, the focus should be on assessing the overall economics of the process. Firstly, enzymatic processes often require less capital investment than chemical technologies due to their simpler processes and lower equipment requirements. Secondly, enzymatic processes usually consume less energy, which makes them economically attractive [145]. Furthermore, the environmental benefits of enzymatic processes should not be overlooked. Given the growing consumer awareness and interest in environmentally friendly products, the clean nature of enzymatically produced goods has become a valuable marketing advantage.

A comprehensive economic evaluation includes several factors that influence the cost of biocatalysts. These include the “lipase production cost” (by submerged or solid-state cultivation), the “lipase reaction cost” (considering the substrate and the final product) and

the "type of support" used in the immobilized lipase process, which directly affects the immobilization method chosen.

Mustafa et al. [146] demonstrated that the manufacturing costs for an enzymatic process for the production of monostearin were 10% higher than those for the chemical counterpart. However, when considering the capital cost of the plant, the process showed a positive return on investment and a net present value, emphasizing its competitiveness with chemical processes. Economic evaluations should focus on the most influential factors, even if not all favourable conditions are present. For example, Andrade et al. [147] identified enzyme reusability—at least 300 cycles—as a critical threshold for economic feasibility.

Alternatively, efforts can focus on reducing the cost for biocatalyst immobilization, as Budžaki et al. [148] found that support materials can account for almost 90% of the total price of a biocatalyst. Optimizing this aspect can significantly increase the overall efficiency of the process. This review highlights the key recommendations to promote investment in enzymatic technologies for oleochemical and biodiesel production. Enzyme suppliers should not only provide biocatalysts but also offer comprehensive solutions to help customers sustain their business. In addition, engineering companies supplying production equipment should work closely with enzyme producers to provide robust and reliable enzymatic technologies for esterification or hydrolysis systems.

Companies introducing enzymatic processes need to ensure that their employees are well-trained to optimize operations and maximize profitability. Ultimately, the affordability and simplicity of enzymatic processes are the main reasons for their growing appeal to manufacturers.

Considering these approaches and the competitive overall costs frequently cited by researchers, the enzymatic process can be a technically and economically viable competitor to conventional chemical processes, which underpins the reasons why the use of these biocatalysts in the synthesis of oleochemicals has been intensively researched over the last two decades, as shown by the bibliometric data in Section 4.2.

4.2. Bibliometric Evaluation

Bibliometric analyses are an interesting way of recognizing trends, mapping knowledge, investigating collaborations and following the scientific development of a particular topic. Accordingly, a bibliometric study of scientific documents dealing with the application of biocatalysts in the field of oleochemistry was carried out on the scientific basis of the Scopus® platform.

In order to select the largest possible number of works, the following string was defined with Boolean operators: (biocatalys* OR bio-catalys* OR enzym*) AND (transesterification OR trans-esterification OR esterification OR hydroesterification OR hydro-esterification OR hydrolysis-esterification OR methanolysis OR ethanolysis OR ethoxylation OR neutralization OR amination OR amidation) AND ("vegetable oil*") OR (fat OR "animal fat*" OR "animal oil*" OR tallow OR suet OR "poultry fat*" OR "abdominal fat*") OR (triglyceride* OR triacylglicerol*) OR ("medium chain triglyceride*" OR "medium chain triacylglycerol*") OR (diglyceride* OR diacylglycerol*) OR (monoglyceride* OR monoacylglycerol*) OR ("fatty acid*" OR lipid*) OR ("fatty alcohol*" OR "fatty acyl alcohol*" OR "aliphatic alcohol*" OR "alkyl alcohol*") OR (biodiesel OR "fatty ester*" OR "fatty acid ester*" OR "fatty acid alkyl ester*" OR FAME* OR "methyl ester*" OR "fatty acid methyl ester*" OR "fatty acid ethyl ester*") OR (glycerol OR glycerin* OR propanetriol* OR triacetin*) OR ("sugar ester*" OR "fatty acid sugar ester*" OR "sugar fatty acid ester*" OR "carbohydrate fatty ester*" OR "carbohydrate fatty acid ester*" OR "glycolipid*") OR ("lubricant ester*" OR biolubricant*) OR ("wax ester*" OR "ester wax*" OR "acyl wax ester*" OR "cosmetic wax*") OR (emulsifier* OR surfactant* OR "emulsion stabilizer*") OR ("2-ethyl

hexyl oleate" OR "2-ethyl hexyl stearate" OR "2-ethyl hexyl ester*") OR ("isopropyl ester*" OR "isopropyl myristate" OR "isopropyl palmitate") OR ("sorbitan ester*" OR "sorbitan stearate" OR "sorbitan oleate") OR ("glyceryl monostearate") OR (soap* OR detergent*).

The search yielded a total of 7160 documents published between January 2004 and March 2024. The data was then exported to VOSviewer® software (version 1.6.20) to enable a textual and geographical analysis of the topic.

Figure 12a,b show the network visualization (periodic and temporal, respectively) derived from the frequency of keywords used by the authors in the documents, considered and characterized by a representation of the co-occurrence of frequently used terms in the dataset.

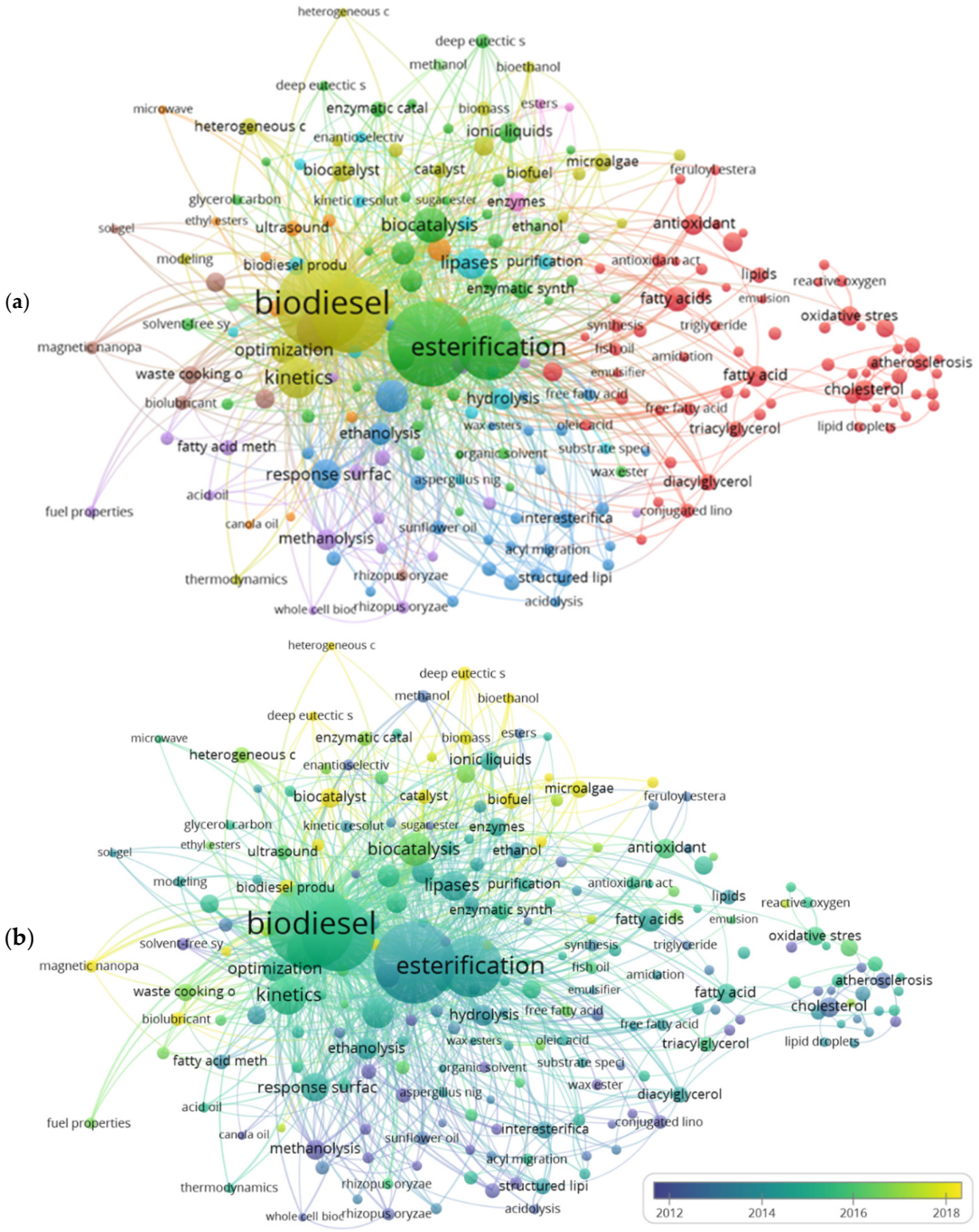

Figure 12. Periodic (**a**) and temporal (**b**) VOSviewer® representation of the co-occurrence of author keywords in scientific articles published between 2004 and March 2024 on the topic "biocatalysis" and "oleochemical synthesis". The data is based on the scientific platform Scopus®.

To improve the understanding and the context of the bibliographic map, the minimum number of occurrences of each keyword was set at 15, i.e., each keyword had to occur at least 15 times within the observation period to be included in the analysis. A total of 223 keywords were considered and presented in 11 clusters, with the largest cluster comprising 159 keywords. The most important keywords were "biodiesel" (1258 occurrences), "lipase" (1133), "transesterification" (904), "esterification" (639), "immobilization" (263), "kinetics" (248), "biocatalysis" (186), "immobilized lipase" (164), "lipases" (155) and "response surface methodology" (145 occurrences).

In addition, a geographical mapping of the VOSViewer® global bibliographic linkage network was created based on the same string/dataset, as shown in Figure 13a,b. The maximum number of countries per document considered in the analysis was 25, with each nation having at least 10 documents, resulting in a total number of 60 countries in five clusters. China (1278 documents and 35,128 citations), the United States (1118 documents and 57,799 citations), India (674 documents and 24,839 citations), Brazil (535 documents and 14,947 citations), Spain (436 documents and 14,265 citations), Germany (363 documents and 13,509 citations), Japan (350 documents and 11,655 citations), Canada (311 documents and 13,338 citations), France (283 documents and 12,615 citations), Malaysia (279 documents and 11,214 citations) and South Korea (257 documents and 7814 citations) are the most important countries conducting research on this topic.

Spatial bibliographic analysis provides information about the performance of a study network, which may include different collaborators around the world (Figure 13). Clusters representing the frequency of the co-occurrence of articles provide a direct indication of the relationships between these groups. The degree of co-occurrence of each country is indicated by coloured groups, where countries with the same colour form a cluster.

The information presented in Figure 13a indicates a strong research alliance in the field of enzymatic synthesis of oleochemicals involving Eastern countries, especially countries known for their scientific development, such as China, India and South Korea. As you can see, there is also a solid partnership between North American countries (United States and Canada) and European countries, particularly Germany, the United Kingdom, Italy and Sweden. Brazil and Japan also stand out and are at the top of the other two influential groups related to the topic under study, with both countries still maintaining close relations with the groups led by China and the United States, respectively.

Scientific collaboration between the researchers from different countries is common in a globalized society, of which many examples can be found. Interestingly, Razzaghi et al [149], in collaboration with authors from Iran, Italy, Canada, India, China and Mexico, investigated the application of nano-biocatalysts in different industrial processes and evaluated the immobilization of enzymes in different nano-compounds with the aim of improving their stability in the reaction system for subsequent reuse. Similarly, Melo et al. [150] discuss, in an article co-authored by Brazilian and Polish scientists, the research progress, trends and updates related to magnetic biocatalysts. Pereira et al. [151], in a partnership between Brazilian and French researchers, comprehensively describe the importance of lipases in the synthesis of phytosterol esters.

Figure 14 shows the evolution of published works on the topics of "biocatalysis" and "oleochemical synthesis" (Scopus® data platform) using the same keywords used to create the bibliographic maps presented previously. Using this data, it is possible to establish a certain consistency in the works published since 2011. However, it is important to emphasize that the vast majority of these works include aspects related to the evaluation of the technical feasibility of the subject. This situation is confirmed by the inclusion of terms relating to economic assessment in the search. By adding the string (econom* OR "economic review*" OR "economic examination*" OR "economic discussion*" OR

"economic assessment*" OR "economic stud*" OR "economic evaluation*" OR "economic appraisal*" OR "economic* consideration*" OR "operational cost*") to the other keywords, only 339 documents were found in the period from 2004 to March 2024, that is less than 5% of the total number of papers. Therefore, this critical debate emphasizes that further efforts need to be made to enable the commercialization of the enzymatic process, focusing on a technoeconomic discussion.

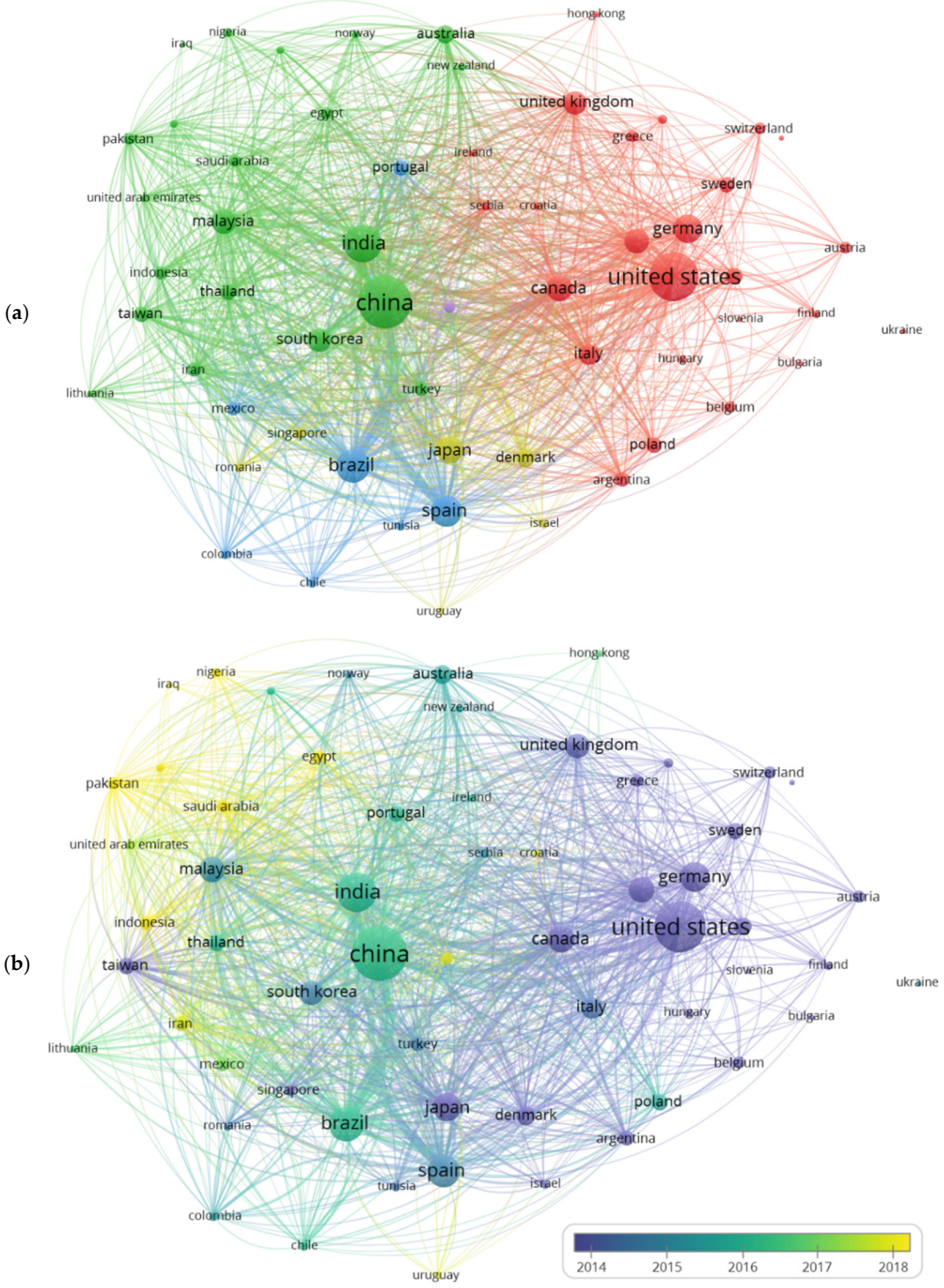

Figure 13. Periodic (**a**) and temporal (**b**) VOSviewer® representation of the bibliographic linkage of nations with at least ten published documents between 2004 and March 2024 on the subject of "biocatalysis" and "oleochemical synthesis". The data is based on the scientific platform Scopus®.

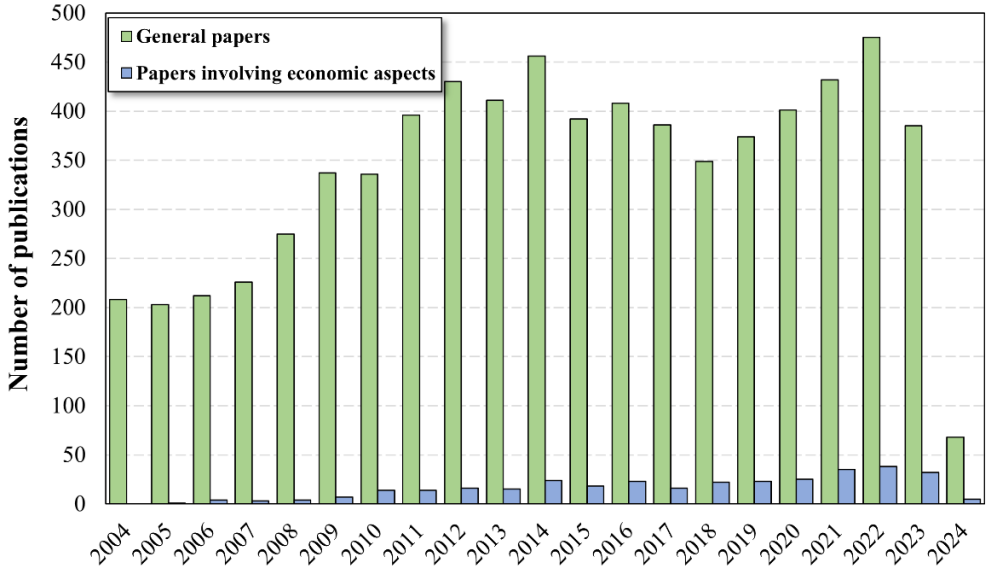

Figure 14. Evolution of the scientific research on the enzymatic synthesis of oleochemicals. The green bars represent studies focusing on the technical aspects of the topic, while the blue bars correspond to papers addressing technical/economic considerations.

5. Limitations, Challenges and Final Considerations

A major limitation in the production of oleochemicals is probably the availability of a wide range of natural plant oil substances, as most bio-based oleochemicals are derived from these natural renewable resources.

Knowledge regarding the morphological and chemical biodiversity of each region, combined with the conversion of these resources, is a competitive advantage for the development of new products and technologies with high added value, especially in the field of oleochemistry. As biodiversity is reflected in the possibilities of oleochemistry, Brazil seems to be a promising region due to its diversity of exotic plants rich in oils, such as "pinhão-bravo" (Jatropha mollissima Pohl Baill), "pinhão-manso" (*Jatropha curcas*), "pequi" (*Caryocar brasiliense*), "oiticica" (*Licania rígida Benth*), "baru" (*Dipteryx alata*) [152,153] and "macaúba" (*Acrocomia aculeata*) [154]. In various biotechnological fields, the use of microorganisms is an alternative approach to conserve natural resources and increase the production of organic products. The main obstacles to the expansion of biocatalytic biodiesel production using enzymes are primarily of an economic and infrastructural nature. Firstly, the high cost of enzymes, especially specialised lipases, has a significant impact on the economic viability of the overall process. The production and purification of these enzymes on an industrial scale is still expensive, which makes them less competitive than conventional chemical processes. Secondly, the established nature of chemical catalysis, based on mature infrastructure and proven cost efficiency, is a significant barrier to adoption. Industry players are often reluctant to switch from established chemical processes to enzymatic processes in the absence of clear, proven economic benefits on a large scale. To overcome these barriers, enzyme costs must be reduced, enzyme stability and reusability improved and the economic viability of enzymatic biodiesel production demonstrated in real industrial settings. It is clear that metabolic engineering optimizes the production of oleochemical derivatives. Microorganisms such as *Escherichia coli*, *Saccharomyces cerevisiae*, *Yarrowia lipolytica*, *Rhodococcus opacus* and *Rhodosporidium toruloides* can produce oleochemical products such as triacylglycerols (TAGs) and FFAs at amounts approaching 100 g L^{-1} with a theoretical yield of more than 90%, as discussed by Yan and Pfleger [3]. Governmental policies on enzymatic biodiesel and oleochemicals focus mainly on promoting the introduction of enzymatic processes for their production with respect to the use of chemical catalysts. The overall objective

is to support the growth of the enzyme sector while achieving environmental and economic targets [155,156]. Accordingly, some key components of this policy should include the following:

i. Incentives and subsidies. To encourage the use of enzymatic processes, governments can provide financial support in the form of tax credits, grants or low-interest loans to producers. These measures can help to offset the higher initial costs associated with enzymatic production [157];

ii. Regulatory framework. Governments should establish standards and regulations to ensure the safety, quality and environmental sustainability of enzymatic biodiesel/oleochemicals. These frameworks often include guidelines for the use of the enzyme, product standards and sustainability practices. Compliance with these regulations is usually a prerequisite for obtaining government incentives or market entry;

iii. Renewable energy requirements. Many countries require that a certain percentage of transport fuels come from renewable sources, especially biodiesel. Producers of enzymatic biodiesel can contribute to meeting these requirements and may be eligible for additional incentives under renewable energy initiatives [158];

iv. Environmental initiatives. Enzymatic biodiesel production is being promoted as a more environmentally friendly alternative as it requires less energy and produces minimal chemical waste. Governments can prioritize the introduction of biodiesel in public transport and official vehicle fleets to reduce greenhouse gas emissions;

v. Education and public relations. Public education campaigns and outreach programs can be funded to raise awareness of the benefits of enzymatic oleochemicals. These efforts will target producers, farmers and the general public to promote broad acceptance of this technology;

vi. Trade and export opportunities. Governments can promote the international trade in enzymatic biodiesel/oleochemicals and related technologies to support economic growth and build global renewable energy partnerships;

vii. Research cooperation. Partnerships between academia, research institutions and industry stakeholders can be supported to drive innovation and accelerate the commercialization of enzymatic biodiesel technologies.

Overall, these policies aim to create a favourable environment for enzymatic oleochemistry and biodiesel production that contributes to greenhouse gas emission reduction, energy security and long-term sustainability. This can be achieved through a combination of financial incentives, regulatory measures, educational initiatives and international cooperation, all aimed at promoting the growth of the enzymatic oleochemical industry.

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