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Review

Recent Advances in Lipases and Their Applications in the Food and Nutraceutical Industry

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Abstract: Lipases are efficient enzymes with promising applications in the nutraceutical and food industry, as they can offer high yields, pure products under achievable reaction conditions, and are an environmentally friendly option. This review addresses the production of high-value-added compounds such as fatty acid esters, with the potential to be used as flavoring agents or antioxidant and antimicrobial agents, as well as structured lipids that offer specific functional properties that do not exist in nature, with important applications in different food products, and pharmaceuticals. In addition, the most recent successful cases of reactions with lipases to produce modified compounds for food and nutraceuticals are reported.

Keywords: lipases; high-value compounds; antioxidant; flavors; structured lipids; food; nutraceutical industry

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1. Bioactives, Nutraceuticals, and Functional Foods Update

In recent years, consumers have been increasingly interested in so-called functional foods and nutraceuticals. The concept of functional food was first introduced in Japan and is claimed to promote health and well-being beyond its nutritive properties [1]. Similarly, "bioactives" are nutritive substances that have a favorable impact on human health [1,2]. The bioactive compounds that are extracted from the original food and maintain their beneficial properties for health are called nutraceuticals [2]. In the nutraceutical market, lipases represent a great tool, and their economic cost is relevant because with added use in 2020, they were valued at USD 585.56 million. It is expected that by 2028 it will reach USD 961.85 million, at a compound annual growth rate (CAGR) of 6.4% from 2021 to 2028 [3].

The definitions of "functional foods" vary from place to place. In the USA, the Institute of Food Technologists [4] defined functional foods as foods and food components that provide a health benefit beyond basic nutrition for the intended population [5]. In Japan, the term "Food with Health Claims" (FHC) is used instead and refers to foods that comply with the specifications and standards established by the Ministry of Health, Labor, and Welfare and are labeled with certain nutritional or health functions. In Europe, the European Commission Concerted Action on Functional Food Science in Europe (FUFOSE) published a consensus concept that states that a food is "functional" if it is satisfactorily demonstrated to beneficially affect one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health, well-being or reduction of disease risk [6]. Subsequently, the European Food Safety Authority (EFSA) adopted regulations about health claims that state, suggest, or imply that a relationship exists between a food category, a food, or one of its constituents [7].

The current awareness of the population toward the consumption of functional foods and nutraceutical products demands that they provide not only nutrition but also functional properties and benefits to health.

2. Lipases as Biocatalysts in the Food and Nutraceutical Industry

In the search for alternatives to improve the production of food and nutraceutical supplements, including omics, biotechnology has provided tools to achieve and cover the requirements demanded by legislation and consumers [8]. One way to produce and improve such compounds is by using biocatalysts. Lipases are widely used in the food industry [9,10]. Lipases (triacylglycerol hydrolases EC 3.1. 1.3) play a crucial role in numerous industrial food processes [11,12] because they participate in reactions that improve product quality and provide greater stability, solubility, durability, and better organoleptic characteristics [10,13,14].

2.1. Lipase Characteristics

These enzymes can hydrolyze triglycerides to obtain free fatty acids, monoacylglycerols (MAGs), diacylglycerols (DAGs), and glycerol; on the other hand, they can synthesize new products in organic media by esterification, transesterification, and aminolysis mechanisms (Figure 1) [15,16]. Lipases have a highly conserved catalytic triad comprising serine as a nucleophile, an aspartate/glutamate as an acidic residue, and histidine. In their active conformation, lipases present in their active center a group of hydrophobic residues arranged around the catalytic serine that constitute an electrophilic region known as an oxyanion cavity. Lipases are also characterized by the presence of disulfide bridges that give them stability and are critical for their catalytic activity [16]. Some lipases also have a structural feature covering the active site, called the "lid," that opens at hydrophobic/hydrophilic interphases. Ancient classifications denoted esterases as lipolytic enzymes lacking a lid. However, because some lipases, such as *Candida antarctica* lipase B (CALB), lack the lid, an alternative classification has been proposed [17].

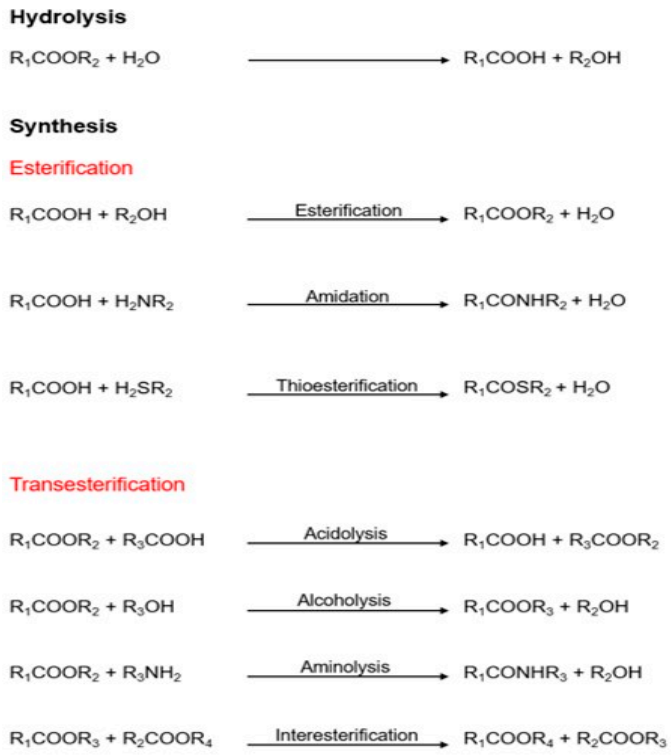

Figure 1. Different reactions are catalyzed by lipases [15].

Lipases are characterized by maintaining their activity and high production in non-aqueous media [18], high production, and stability at pH ranges and do not require cofactors. According to their substrate specificity, lipases can be chemoselective, regioselective, or stereoselective. The first lipase type can selectively catalyze a reaction. The second type catalyzes a reaction specifically with one of the triglyceride positions (*sn*-1,3 regioselective, *sn*-2 regioselective, or nonregioselective). Additionally, the third type catalyzes reactions selecting only one of the stereoisomers from a mixture of enantiomers [10,16].

2.2. Sources and Tools to Improve Lipase-Catalyzed Reactions

Lipases are ubiquitous enzymes produced by various organisms, including microorganisms, plants, and animals [12,19–24]. Because of the increased commercial interest in these proteins in the food and nutraceutical industry, the use of recombinant production technology is critical.

The productivity of lipase production bioprocesses has been increasing, reducing the cost of enzymes by using cell factories for the heterologous production of lipases. Between them, *Komogataella phaffi* (*P. pastoris*) is one of the most common cell factories used [25].

Lipases have been improved using natural evolution techniques, protein engineering, bioinformatics design, directed evolution, saturation mutagenesis, site-directed mutagenesis, and DNA shuffling [26]. However, in the food industry, the native form is often preferred (Figure 2).

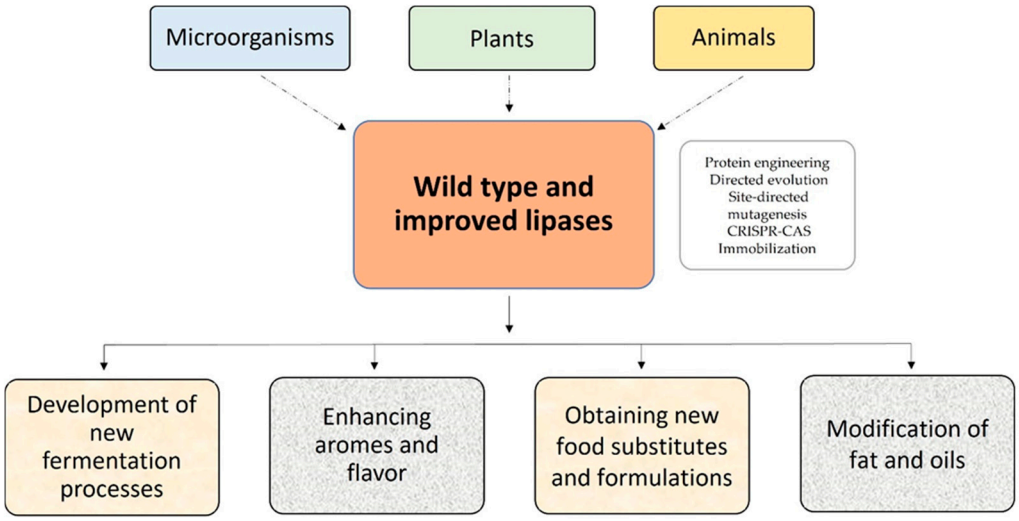

Figure 2. Sources and use of lipases in the food industry.

Table 1 shows some microbial lipases that are commercially available and immobilized on different supports to enhance their efficiency and reuse [27–30]. Most commercially important lipase-producing yeasts belong to the class of ascomycetes, such as *Candida* sp. and *Rhizopus* sp. Novozymes® (Bagsværd, Denmark), DuPont® (Wilmington, DE, USA), Roche® (Basel, Switzerland), and Amano (Yokohama, Japan) are the main companies that produce and commercialize lipases [31].

Other important bottlenecks of the free enzymes in general and lipases are the low operational stability in synthesis reactions using solvents and substrates such as alcohols and organic acids, the high cost of the enzymes, and the need to reuse the biocatalyst minimizing product separation.

Table 1. Sources of lipases with applications in food and nutraceutical industry.

Source/Commercial Name	Type	Application/Products	Reference
Candida antarctica lipase B (CALB)/Novozym 435/Lipozyme 435	Recombinant	Flavor esters	[32]
Candida rugosa	Wild type	Glycerides, production flavor compounds	[33,34]
Termomyces lanuginosus/Lipozyme TL IM	Engineered	Food formulation, Interesterification of fats and oils	[35,36]
Aspergillus sp.	Wild type	Flavor and fragance	[37]
Aspergillus oryzae	Wild type	Interesterification of fats and oils	[36]
Geotrichum candidum	Wild type	Oil with increased unsaturation	[36]
Rhizomucor miehei/Lipozyme RM IM	Recombinant	Enhancing fruit fragrance	[38]
		Modification of the amount and composition of volatile components in bovine milk	[39]
		Ras Cheese Flavor Concentrate (RCFC)	[40]
Rhizopus oryzae	Wild type	Human Milk Fat Substitutes	[41]
Lactococcus chungangensis	Wild type	Flavoring in milk, cream cheese, yogurt and butter.	[42]
Lactobacillus plantarum	Wild type	Fermented food and cheese	[43,44]
Staphylococcus epidermidis	Wild type	Flavor-compound production	[45]
Ophiostoma piceae	Wild type	Flavor-compound production	[46]
Meyerozyma guilliermondii	Wild type	Feed industry	[47]

Different approaches are being applied (Figure 2) to solve these drawbacks. The use of enzyme immobilization methods normally increases biocatalyst stability, specificity and selectivity, allows the reutilization of the enzyme, and minimizes downstream processes, and has been reflected in the number of articles and patents published in this field [48].

Advances in the study of lipases seek to develop more efficient processes and, for this purpose, their stability under certain temperatures, solvents, and pH conditions, among others. The development of a specific reaction medium to increase the activity, stability, and productivity of biocatalysts has been a recurring topic of research over the last three decades. The remarkable properties and useful applications of enzymes, particularly lipases, have inspired various strategies to improve their performance in near-anhydrous media. Therefore, medium engineering can be used to modulate the activity and selectivity of lipase-catalyzed reactions [49].

Ionic liquids (ILs) are molten salts that originate from the association of organic cations and organic/inorganic anions. The use of ILs as solvents in biocatalysis processes has recently received increased attention, and substantial progress has been made, particularly in lipase-catalyzed reactions. ILs have the advantages of low volatility, low inflammability, and a low melting point [50]. Deep eutectic solvents [51] are eutectic mixtures of salts and hydrogen bond donors with sufficiently low melting points to act as solvents. DESs were demonstrated to be a viable alternative to traditional organic solvents and ILs in many biocatalytic processes, particularly for lipases. DESs have additional advantages over ILs in simple preparation and lower costs because of their renewable and readily available raw materials [52].

3. Established Applications of Lipases in the Food and Nutraceutical Industry

Lipases in the food industry and nutraceutical production can be used in aqueous extracts and purified, immobilized, or whole cells to exploit the available raw material and increase their economic and nutritional value. These enzymes can be used to modify fats and oils and synthesize structured lipids or antioxidants with increased antioxidant power or modified lipophilicity, flavors, and aromas [53,54].

3.1. Fats and Oils

Patent searches suggest that lipase has an impressive number of applications in the modification of fats and oils and enhancement of flavor in food products—e.g., cheese, butter, milk, and chocolate [55]. Some applications of lipases in dairy products and the synthesis of structured lipids are described in the following sections.

3.1.1. Dairy Products

In the dairy sector, lipases are used to provide desirable aromatic characteristics to cheddar, provolone, and Romano cheeses conferred by these free short-chain fatty acids generated in the hydrolysis of fats [40,56]. Recent advances have allowed the biosynthesis of short-chain ethyl esters with fruity notes in whole milk by coupling ethanolic fermentation with transesterification using the commercial lipase Palatase. For fermentation, the following microorganisms were used: *Kluyveromyces marxianus*, *Lactobacillus fermentum*, and *L. Paracasei*. Many esters were obtained in ethanolic fermentation using *K. marxianus* yeast and lipase. This method of milk fermentation and lipase addition represents a new alternative for flavoring milk [57].

3.1.2. Structured Lipids

In recent years, structured lipids have become a topic of great importance in the food and nutraceutical industry because technological advances allow a generation of products of better quality and that better meet consumer demands. Within this innovation in food processes, structured lipids (SLs) have been generated [58,59].

Structured lipids are fats and oils whose fatty acid composition has been modified for nutritional purposes to achieve greater bioavailability because they are not naturally occurring. In several cases, lipids have certain limitations of use in their original state because of the specific composition of their fatty acids [60].

In other cases, even when they are available as raw materials, they cannot always meet nutritional demand, e.g., restrictions on the daily intake of saturated fatty acids and trans fatty acids have been increased because they are related to cardiovascular diseases [61,62]. Another clear example would be access to cocoa butter; its availability may be limited by external factors such as climate change, fluctuating prices, and availability [63,64]. Therefore, the search for alternatives to address these major issues is justified.

In principle, deciding which type of fatty acids to use and in which position of the molecule to restructure is possible by obtaining structured lipids [58]. For this procedure, the use of stereospecific enzymes allows new lipids with a stable structure to be obtained. Lipases can hydrolyze a triglyceride in an aqueous medium, but they also catalyze the binding of a fatty acid to a glycerol molecule in an anhydrous reaction medium [65]. Recently, the use of immobilized biocatalysts has minimized the production costs of structured lipids through reusing them in successive batches [58].

With all the knowledge generated on the subject, we can generate these products for nutritional, pharmacological, or industrial use, such as breast milk substitutes, cocoa butter, and low-calorie or enriched triacylglycerols [41,58,66,67].

In the case of low-calorie triacylglycerols, the energy equivalents are reduced. Typically, these compounds are used to control poor fatty acid absorption and other metabolic problems. They are characterized based on triglycerides (TAGs) of this nature containing short or medium-chain fatty acids in the *sn*-1,3 positions; in the *sn*-2 position, they have a long-chain fatty acid esterified; therefore, the absorption of external fatty acids is released and metabolized more rapidly [68]. They can be synthesized by acidolysis of a TAG or oil containing long-chain fatty acids with one of the medium-chain fatty acids or by interesterification of a TAG or oil with methyl or ethyl esters. In the lipase-catalyzed synthesis of SL, ethyl esters are preferred as acyl donors because they avoid the presence of high amounts of free fatty acids (FFAs) in the reaction medium; in food production, methanol poses toxicity risks [69,70]. In this context, the production of low-calorie triacylglycerols was achieved using as raw material cheap oils extracted from agro-food residues, such as spent coffee

grounds and olive pomace, and as catalysts, the regioselective lipase *sn*-1,3 from *R. oryzae*, which was immobilized on magnetic nanoparticles. This enzyme was shown to be a highly promising biocatalyst to produce structured lipids for both oils, presenting even higher activity than the commercial immobilized *T. lanuginosus* lipase (Lipozyme TL IM). For the two oils evaluated, a preference for acidolysis was observed, in addition to high stability when reused in acidolysis and interesterification of olive pomace oil [67].

However, SLs are an option to generate products that partially or totally substitute human milk in certain cases because, in terms of the fatty acid composition and distribution, they are manufactured to improve fat and mineral absorption, promote softer stools, and reduce constipation in infants [58,71,72].

Human milk fat substitute (HMFS) is synthesized by enzymatic interesterification of vegetable oils, animal fats, or oil mixtures, commonly using an immobilized regioselective lipase in either solvent or solvent-free media [70,73].

A recently reported lipase/acyltransferase from *C. parapsilosis* was used as a biocatalyst to synthesize HMFS by interesterification of ethyl oleate with tripalmitin in solvent-free media representing a new alternative to commercial immobilized lipases [70]. Because human milk is one of the most complex mixtures of natural lipids, studies using this approach will continue to advance steadily.

3.2. Vitamin Esters

Food contains components known as bioactive compounds that, when consumed, provide energy to the body, promote good health and minimize the risk of disease. The bioactive compounds that are extracted from the original food and maintain their beneficial properties for health are called nutraceuticals [2]. For consumption and consumer acceptance, the functionality of bioactive compounds, safety, and nontoxicity must be guaranteed beforehand [74]. Highlighting a representative example, antioxidants play a crucial role in the food industry because, during food processing, the matrices used mostly incorporate lipids as emulsifiers or additives, making lipid oxidation a challenge to consider [75–78]. Lipid oxidation involves the attack of molecular oxygen on unsaturated fat molecules, which can generate undesirable volatile flavoring compounds that contribute to rancidity [79]. Even when quality controls are followed during food product preparation and packaging, the rate of lipid oxidation is influenced by several endogenous and exogenous parameters, including oxygen, light metals, and polyunsaturated lipids, primarily because the latter are prone to oxidation [80,81]. Antioxidants are used to mitigate this effect, meaning molecules that reduce, neutralize, or deplete molecular oxygen, remove pro-oxidative metal ions, and scavenge reactive oxygen species (ROS), hydrogen peroxide or superoxide anion radicals [82–85].

Antioxidants occur naturally, and the best known are ascorbic acid (vitamin C), tocopherols (vitamin E), carotenoids, and thiols [86]. During their absorption in the body, they complement the defense action as they help to slow down the use of endogenous antioxidants and improve the body's ability to avoid oxidative stress [82,87–90]. The lack of action of endogenous antioxidants, either by diminution or stress, is related to the modification of lipid membrane components [91], resulting in neurodegenerative, cardiovascular, inflammatory diseases, diabetes, male infertility, and cancers of the breast, lung, liver, colon, prostate, ovary and brain [87,92–97]. The excessive presence of reactive oxygen species promotes the expression of oncogenic genes [93]. Antioxidants, as nutraceuticals, play a key role in the nutritional base because of their close relationship with biological processes; thus, skin benefits are also attributed to them for delaying aging [98–100]. Although the concept of nutraceuticals is not new, the trend to use antioxidants with biochemical properties of high stability and biocompatibility as a complementary ingredient has become interesting [84,101,102].

In this context, the synthesis of vitamin derivatives obtained with biocatalysts is a tool that seems to minimize the technical problems of chemical synthesis or extraction from natural sources and is an ecological and environmentally friendly alternative [74,103–105].

3.2.1. Retinol (Vitamin A) Esters

Retinol is a vitamin A derivative found in foods (fish, dairy products, and meats). This molecule has attracted increased attention in the food and cosmetic industry for all the benefits of its consumption because it controls mitochondrial energy homeostasis by functioning as an electron carrier, maintains visual health, minimizes skin aging, promotes bone growth, and strengthens the immune system; thus, vitamin A plays a crucial role in the health of the organism [106,107]. This process involves a series of several steps, which generate various byproducts; thus, achieving good quality of the final product may require extensive time, derive waste pollutants to the environment and make the disposal of chemical catalysts difficult [108]. This process involves a series of several steps, which generate various byproducts; thus, achieving good quality of the final product may require too much time, deposit too many waste pollutants in the environment, and create difficult disposal of the chemical catalysts [109,110]. Recently, immobilized lipase (Novozym 435) was successfully employed as a biocatalyst to generate a retinol derivative (retinol laurate). The process was previously optimized using biochemical process modeling and prediction tools (artificial neural network, ANN) and ultrasonic systems. The reaction, compared with the traditional method, takes less time, and the final product shows higher stability to oxidation; thus, it could be used as an additive in human food supplements [110].

3.2.2. Fatty Acid Esters of L-Ascorbic Acid (Vitamin C)

Ascorbic acid (vitamin C) is a water-soluble antioxidant not produced by the human body. Among its health benefits, some are derived from its antioxidant properties, such as preventing male infertility and neurodegenerative diseases, in addition to counteracting the effects of solar radiation, smoke, and environmental pollution [111]. The antioxidant property of ascorbic acid is due to its ability to donate individual hydrogen atoms and subsequent formation of monodehydroascorbate (Figure 3), which reacts more rapidly with radicals than with fully reduced or fully oxidized compounds [112]. The drawback of degrading drives the use of strategies such as the addition of fatty acids to improve their stability and physiological and antioxidant activity [113]. These derivatives are formed by the addition of a donor acyl to the primary alcohol to produce the corresponding 6-O-ascorbyl ester without interfering with its antioxidant capacity, catalyzed by lipases, and generating compounds such as ascorbyl palmitate and ascorbyl oleate (Figure 3).

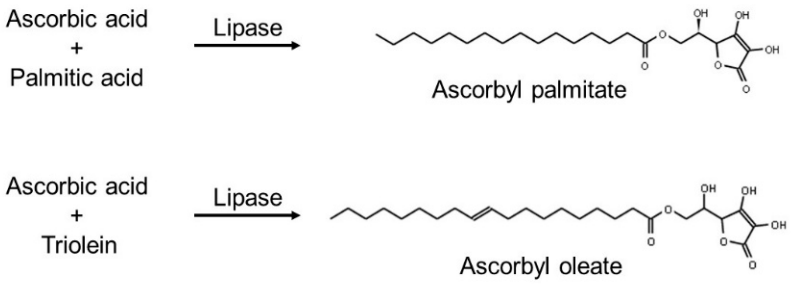

Figure 3. Scheme of monodehydroascorbate, ascorbyl palmitate and oleate palmitate synthesis from vitamin C [114].

Another method to improve the stability and physicochemical properties of vitamin C involve using emulsions and microchannel emulsification, which promote less interaction of the compound with the oxygen present in the medium and provide greater solubility in fats [115,116]. However, ascorbyl esters of unsaturated fatty acids possess equally good properties, such as miscibility in hydrophobic media [117].

Obtaining ascorbic acid derivatives was originally achieved by chemical processes, which have been migrating to the use of lipases because different solvents can be used in regioselective reactions, achieving high yields and easier product isolation. Lipases have been successfully employed to catalyze the synthesis of ascorbyl esters from saturated and unsaturated free fatty acids, alkyl and vinyl esters, TAGs, and oils as acyl donors. The

experimental conditions and yields mentioned in the literature to obtain some ascorbic acid derivatives are shown in Table 2. This type of reaction can also be exploited to synthesize chalcogen-containing vitamin C derivatives and use CALB to obtain esters containing differently substituted selenium, sulfur, and tellurium, which are of interest for their anticancer, antibacterial, and enzyme inhibitory capabilities [118].

Table 2. Summary of enzymatic synthesis of fatty acid esters of vitamin C.

Vitamin Derivative	Acyl Donor	Solvent	Biocatalyst	Reaction Conditions	Conversion (%)	Reference
L-ascorbyl palmitate	Palmitic acid	*tert*-butyl alcohol	Indigenously immobilized lipase PyCal (CALB)	AA:PA molar ratio 1:5; 20 mL tert-butyl alcohol, 0.6 g of biocatalyst, 60 °C (batch)	50	[119]
L-ascorbyl palmitate	Palmitic acid	*tert*-butyl alcohol	Novozym 435	AA:PA molar ratio 1:5; 20 mL tert-butyl alcohol, 0.6 g of biocatalyst, 60 °C (batch)	50	
L-ascorbyl palmitate	Palmitic acid	2-Methyl-2-butanol (2M2B)	Novozym 435	AA:PA molar ratio 1:8; 12 g/L biocatalyst; 55 °C	81	[114]

One of the widely used lipases for the acylation of L-ascorbic acid is *Candida antarctica* lipase B (Novozym 435) because of its good yield and conversion rate (Table 2). However, the price of immobilized has decreased more than chemical reagents because the processes of recombinant enzyme production and subsequent processing increase their prices. During the modification of vitamin C, the most used reaction solvents are tertiary alcohols (e.g., 2-methyl-2-butanol and *tert*-butyl alcohol).

3.2.3. Tocopherols (Vitamin E) Esters

The term vitamin E refers to a group of fat-soluble compounds that includes α, β, γ, and δ-tocopherol and α, β, γ, and δ-tocotrienol (Figure 4), among which α-tocopherol has higher antioxidant activity. In contrast, γ and δ-tocopherols and tocotrienols have higher cancer preventive but lower systemic properties [120]. Additionally, its effects include protecting against reactive oxygen species (ROS), reactive nitrogen species (RNS), and polyunsaturated fatty acid (PUFA) oxidation in the membrane, as well as modulating signal transduction and enhancing the immune response [121]. Furthermore, vitamin E can be combined with vitamin C to enhance the immune system, restore the antioxidant functions of vitamin E, and provide other benefits together [122–124].

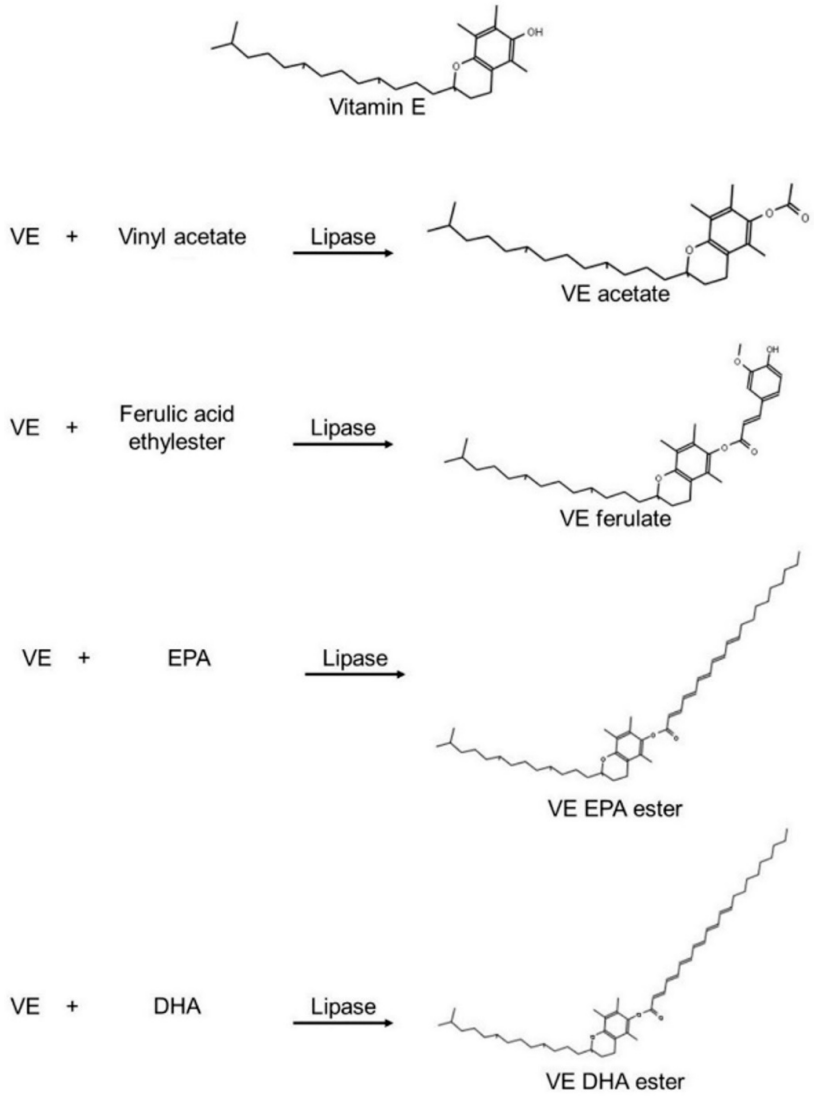

Figure 4. Examples of derivates of vitamin E (α-tocopherol) catalyzed by lipases. VE: Vitamin E; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid [125–127].

Vitamin E is naturally synthesized only by photosynthetic organisms, so it is mainly extracted from plants, nuts, and seeds; therefore, to improve the amount and specific production of α-tocopherol, genetic modifications have been made in crops, such as overexpression of the γ-TMT gene that allows the conversion of γ-tocopherol to α-tocopherol [128]. However, once vitamin E has been extracted from crops, it is enriched using vegetable oil deodorizing distillate processes where lipases such as Lipozyme IM50 (immobilized sn-1,3-specific lipase from *Rhizomucor miehei*) are used, with which enrichments close to 50% are achieved [129]. Vitamin E derivatives are a more stable form than their precursor and can be synthesized chemically [130] or enzymatically, the latter being performed by lipases (see Table 2). Thus, in commercial products, we can find vitamin E esters in the form of vitamin E acetate, vitamin E succinate, vitamin E ferulate, vitamin E eicosapentaenoic acid ester, and vitamin E docosahexaenoic acid ester (Figure 4). The synthesis of these vitamin E derivatives is affected by factors such as the enzyme used, reaction medium, water activity, acyl donors, and acyl acceptors employed [125,126,131].

Among the characteristics of α-tocopherol, it has three stereogenic centers at carbons 2, 4″- and 8″- and the RRR-α-tocopherol form is considered the most bioactive of the eight existing ones (RRR-, RSR-, RRS-, RSS-, SRR-, SSR-, SRS-, and SSS-). However, commercially, it is found as a mixture of all its stereoisomers in the esterified form (all-rac-α-tocopheryl acetate), obtained chemically from soybean byproducts [132,133]. For this reason, when

manufacturing food products with the different stereoisomers of this compound, separation strategies such as the use of chromatographic methods should be included [134,135]. Currently, some foods, such as meat, are supplemented with vitamin E to improve shelf life, quality, and nutritional experience [136,137].

3.3. Bakery Products

New requirements in bakery products make the development of new formulations that conform to what would be green or less harmful labels. In bakery products, lipases have been successfully applied to improve dough processing, strength, volume, structure, and softness, decrease stickiness, and increase the quality and shelf life [138,139].

With a focus on the intermediate product of bread, dough plays an indispensable role in becoming the final product because it is a semisolid foam that is converted into a solid cellular sponge upon baking so that the mixture of the lipid fraction of wheat, eggs, or baker's fat exerts major roles in gas incorporation and its stabilization, which are necessary to achieve a fluffy product [140].

Although wheat flour contains low levels of lipids, they affect the quality of fresh bread because they are related to storage duration. Briefly, the studies are directed toward knowledge of the relationship of the flours or their reformulation by adding lipids from other sources and their effect on quality.

Recently, lipases have been successfully applied to investigate how endogenous or exogenous lipids affect bread making. Lipases hydrolyze galactolipids, and their presence in the dough improves bread volume. The flour was defatted and subsequently reconstituted by adding different fractions of these lipids to determine the relationship of endogenous lipids in wheat flour and their impact on bread volume. The hydrolysis of endogenous lipids and their enzymatically released products are responsible for the positive effects on bread [138,141].

To understand the role of endogenous wheat lipids on the evolution of bread crumb firmness during storage, three lipases—Lipopan F, Lecitase Ultra, and Lipolase—were evaluated, and sodium lactylate stearoyl surfactant (SSL) was used as a surfactant. By forming amylose-lipid (AM-L) inclusion complexes, the surfactants retarded bread crumb firming. Some endogenous wheat lipids have surfactant-like structures, so the use of enzymes in bread making would increase the level of free fatty acids that allow the formation of amylose-lipid complexes. The evaluation of three enzymes showed that lipases and SSL similarly affected the texture of breadcrumbs during storage. However, after seven days of storage, the sample containing Lipolase significantly reduced amylopectin retrogradation, evidencing the importance of the formation of amylose-lipid inclusion complexes. Therefore, lipases have been proposed as alternatives to surfactants because they produce molecules in situ that possess hydrophilic and hydrophobic structures like those of surfactants [141,142].

3.4. Flavors and Fragances

In the world market, a high demand exists for fragrance and flavor esters for different industries, including food, cosmetics, and pharma, as ingredients of many products (food, beverages, candies, jellies, jams, wines, dairy products, perfumes, body lotions, shampoos, and other toiletries) [143,144]. The flavor and fragrance market was valued at $28 billion in 2019 and is expected to expand at a compound annual growth rate (CAGR) of 4.7% to $35 billion from 2021 to 2027 [145]. Another characteristic is that many of these products are chiral [146]. This potential chiral product can be consulted in the database [147].

Many of these products are obtained after extraction from their natural sources (plants, fruits, and flowers). However, the low concentration of these products in their natural sources, climatic dependence of the source, and low yield and high production cost of the extraction and purification phases make it challenging to assume an increased world demand [143].

A wide range of flavors and fragrances can be obtained by chemical synthesis, solving the of raw material producing the same products at a lower cost. However, these products have not been labeled as natural according to European legislation (EC 1334/2008), and obtaining pure chiral compounds is challenging. In this context, the substitution of a chemical using biotechnology (microbial biosynthesis or applied biocatalysis) is being widely explored because the products can be labeled as natural if the employed reactants are labeled as natural. The resolution of chiral compounds is generally higher with no problems in selectivity, reaching higher yields and with an easier downstream due to the absence of undesirable side reactions. However, the operational conditions (P, T) are softer than those of the chemical approach. A marketplace of bioflavors is actually 100–500 $/kg, and more than 100 flavor products are commercialized [148]. In 2019, the global biotech flavor market was close to 0.5 billion US$, approximately 1.5% of the estimated global market in the same year and is expected to grow at a compound annual growth rate (CAGR) of 9.3% from 2020 to 2027. Similarly, biotech vanillin represents ca. 3% of the total vanillin market, and it is speculated to increase at a CAGR exceeding 13% by 2023 [149].

Thus, the significant demand for these esters has boosted the need for greener production routes and food safety aspects for human consumption, making enzymatic synthesis a favorable alternative to chemical catalysts [150,151]. Approximately 4000 enzymes are known, and close to 200 have been mainly commercialized for stereoselective organic synthesis and the biotechnological production of flavor compounds [148]. Between them, lipases are the most applied enzyme family to produce flavor and fragrances. Although their natural biocatalysis is the hydrolysis of lipids to produce free fatty acids, glycerol, or other alcohols, they also work in reactions of esterification and trans- and interesterification and the transfer of acyl groups from esters to other nucleophiles (e.g., amines and thiols) [143,152].

3.4.1. Short-Chain Fatty Acids and Isoamyl Alcohol Esters

Among the critical fragrance compounds produced via the esterification of short-chain alcohols and short-chain fatty acids, isoamyl alcohol esters, such as isoamyl butyrate and acetate, can be found. These esters serve as flavoring agents in numerous industries because of their characteristic fruity banana and intense banana flavor, respectively [153–156]. However, the use of short-chain fatty acids, being more hydrophilic, lowers the pH of the microenvironment and may lead to enzyme inactivation, while the use of short-chain alcohols tends to strip the essential water from the enzyme and serves as a dead-end inhibitor, making the enzymatic synthesis of esters challenging. Additionally, the use of isoamyl alcohol, which has a branched structure, exerts a higher steric hindrance on enzyme activity. Therefore, isoamyl alcohol might serve as an interesting model for understanding esterification with such acids and alcohols [157,158].

Isoamyl acetate (IAAC) has been produced in batch and continuous packed bed columns using porcine pancreatic lipase and *Candida rugose* lipase immobilized on chitosan and Ca-Ag chitosan. Operational conditions were optimized, and the amount of IAAC was close to ten times higher in a batch than in a continuous reactor [159]. IAAC was also obtained from the acylation of isoamyl alcohol with acetic anhydride by *Candida antarctica* B (CALB; Novozym 435) in ionic liquids in a continuously operated miniaturized enzymatic packed bed reactor. Up to a 92% isoamyl alcohol conversion with a volumetric productivity of 61 mmol L^{-1} min^{-1} was obtained. Interestingly, no decrease in productivity was observed 14 days after the operation [160]. Applying the same reaction and immobilized CALB from Sigma-Aldrich, the reaction was also made successfully in a miniaturized intensified reactor, obtaining a concentration of IAAC close to 1.2 mol L^{-1} [161]. In addition to using biocatalysis as an environmentally friendly approach for ester production, the use of byproducts as substrates for flavor ester production has emerged as a relevant way to support circular economy principles and reduce waste generation [162].

During large-scale bioethanol synthesis for fuel or food production, fusel oil is generated, a byproduct obtained in the fermentation and distillation steps, and removed

during alcohol rectification. This byproduct accounts for approximately 0.25% by volume of bioethanol [163]. The quality and amount of generated fusel oil are affected by the processing parameters, such as the mash preparation, fermentation conditions, and distillation process. Higher alcohols (e.g., isoamyl alcohol, isobutanol, and butanol), water, aldehydes, and esters are the main compounds found in fusel oil samples [4,164]. Due to its intense odor, the use of fusel oil as a solvent is limited, although it has been used as a *foam* coating or added into diesel or gasoline to increase the cetane index and octane number. However, because of its high alcohol content (specifically isoamyl alcohol), it is attractive as a low-cost substrate for esterification and the production of various aromatic esters [164,165].

IAAC was produced from fusel oil in supercritical carbon dioxide (SC-CO_2) using immobilized CALB (Lipozyme 435), demonstrating that acetic anhydride was a better acyl donor than ethyl acetate and acetic acid [21] in terms of IAAC conversion and specific productivity [4]. The same authors tested the same strategy using CALB (Novozyme 435) in a continuous packed bed reactor, obtaining the highest conversion at the lowest substrate rate. Additionally, Novozyme 435 maintained its stability and activity during the bioprocess [4].

IAAC was also obtained from the transesterification reaction of isoamyl alcohol and ethyl acetate using *Aspergillus oryzae* lipase obtained by fermentation and immobilized on sodium alginate with in situ ethanol removal. Under optimal conditions, conversion of IAAC of 89.55% and a yield ethanol extraction of 69.60% were obtained [166].

The production of isoamyl butyrate (IABU) from fusel oil and butyric acid in hexane using Lipozyme TL IM was also optimized, obtaining a conversion close to 96% in 24 h, a concentration of IABU of 1.64 mol L^{-1}, and a productivity of 0.19 mmol ester g^{-1} mixture h^{-1} [164].

Another example of the production of IABU from fusel oil and butyric acid using cyclohexane as a solvent was described using a covalently immobilized heterologous *Rhizopus oryzae* lipase. The enzyme showed better performance (1.8 times higher yield) in the synthesis of IABU than IAAC. The results were scaled up to a 150 mL reactor, and no differences were observed in the yield, initial reaction rate, operational stability, and productivity using commercial isoamyl alcohol and fusel oil. Additionally, the structural isomers of isoamyl alcohol were evaluated. In conclusion, isoamyl ester industrial production has been proposed [167].

The esterification of fusel oil alcohols by butyric acid has also been reported with pancreatic lipase and *Candida rugosa* lipase with high yield under the optimized conditions of temperature, time, and acid/alcohol ratio [168].

Lipases are also used in the biocatalytic production of natural Green Leaf Volatiles (GLVs), which are aroma compounds associated with the green note odor. GLVs are widely used as aromas and food additives in the cosmetics and perfumes industry as well as in the food industry [169].

These examples indicate the successful synthesis of IAAC from fusel oil in a two-phase system, demonstrating that it is a viable alternative to pure isoamyl alcohol and an example of a circular economy reducing the waste generated from ethanol production plants.

The use of lipase-displaying microorganism whole-cell biocatalysts is a promising alternative to classical immobilization supports with the advantage of low-cost preparation and, in some cases, high enzymatic activity [170]. CALB-displaying *K. phaffii cells* have been tested in the synthesis of a set of flavors esters, between them IAAC and IABU, and scaled up to a 5 L batch enzymatic bioreactor with conversions higher than 95% after four hours of reaction, with excellent operational stability. After ten batches, only an activity loss of 10% was detected in the presence of solvents [170].

A novel lipase obtained from metagenomics studies [171] is another example of a successful approach using whole cells—in this case, in the cell factory *E. coli*—to produce isoamyl acetate in a fluidized bed reactor with a reutilization of at least five cycles [172].

3.4.2. Other Flavors and Alternative Reaction Systems

Other flavors, such as ethyl butyrate, are the major component of many fruit flavors, such as pineapple, passion fruit, and strawberry [144]. The esterification was successfully implemented using *Rhizopus oryzae* lipase as a biocatalyst immobilized onto different supports. The best results were obtained with an acid:alcohol ratio of 1.45, and the reaction rate increased with increasing butyric acid concentration [173,174]. However, too high concentrations of butyric acid deactivated the enzyme [175].

Another problem concerns the difference in solubility between the substrates. Enzymatic bioreaction is usually performed in an aqueous environment; however, many flavor precursors and flavor products are not well soluble in water. Biphasic and alternative systems (aqueous]/organic, solid/gas, supercritical fluids, and ILs) overcome solubility problems [148].

As an alternative to using an enzymatic approach, the novo synthesis can also produce a mixture of flavors using the whole metabolic pathways of the microorganism. Using genetic engineering techniques, encoding specific genes from other microorganisms in cell factories, such as *E. coli*, has led to increased production of these compounds [148]. Reviews in this field have been recently published [149,176]. These natural metabolic routes have also been implemented in an enzymatic cascade reaction to produce cinnamyl cinnamate via a three-enzyme cascade incorporating the lipase Novozym 435 and in situ cofactor regeneration [177]. Additionally, a three-enzyme system (including lipase) to degrade curcumin to natural vanillin has been proposed [178].

4. Trends in the Use of Lipases in Food and Nutraceuticals

4.1. Phenolic Antioxidants

Phenolic compounds are secondary metabolites mainly extracted from fruits, vegetables, and cereals, to which they impart color, flavor, and fragrance [179–181]. These compounds are mainly classified into flavonoids, phenolic acids, stilbenes, and curcuminoids. They help with the control of diseases such as diabetes, obesity, hypertension, hyperlipidemia, and hyperglycemia, as well as inhibit adipogenesis [182–184].

Despite the benefits of consuming these phenolic compounds, the dose required to obtain their antioxidant power is limited by their low bioavailability and physiological stability, explaining why the synthesis of phenol polymers using enzymes such as glucanotransferases and lipases has been resorted to [185–187].

The antioxidant activity of phenolic compounds present in foods can occur under different mechanisms. In the first case, by transferring a hydrogen atom from part of the phenolic compound to free radicals to be neutralized by a mechanism of transfer of a single electron from the phenolic compound with which it is left with an odd number of electrons distributed in the aromatic ring, the free radical forms an energetically stable spice with an even number of electrons. In the second case, proton transfer occurs from the phenolic compound to form an anion that subsequently donates an electron to transform the free radical into a stable molecule, and finally, a third case occurs by transition metal chelation [188]. However, when phenolic compounds are added to foods, their antioxidant, antimicrobial, anticarcinogenic, anti-inflammatory, antidiabetic, and antiobesity capacities are altered, increasing or decreasing them, because of intermolecular interactions with the macronutrients present. Thus, understanding these changes would allow their exploitation to improve the quality, stability, organoleptic properties, and shelf life of the final products [189,190].

Due to their valuable benefits, the industrial demand for antioxidants in different sectors induces the search for new alternatives that facilitate the availability of these compounds. Thus, the use of new bioinformatics, molecular, proteomic, and biocatalysis tools suggests new antioxidant molecules to enhance their nutraceutical benefits [191,192].

The following section discusses cases of enzymatic modification and the synthesis of antioxidants for their biochemical improvement and benefit using biocatalytic processes to generate new molecules with nutraceutical prospects.

As mentioned previously, using lipases to synthesize food additives is a valuable tool for modifying ester or carboxyl groups. The aim is to improve the organoleptic properties of the ingredients and their miscibility with lipids, for which a hydrophilic element is introduced into the ester molecule. With the intervention of lipases through the acylation process, the structural modification of some flavonoids has been achieved, enhancing their stability and antioxidant activity; however, recent work has focused on the synthesis of lipophilic antioxidants [193]. Thus, a new compound called cyanidin-3-O-(dodecanoyl6) galactoside was obtained, generated after acylating lauric acid with the compound cyanidin-3-O-galactoside extracted from alpine bearberry (*Arctostaphylos alpine* L.) and biocatalyzed by the commercial immobilized enzyme Novozym 435. Modification of this anthocyanin significantly improved its lipophilicity and thermostability while retaining its original antioxidant properties [193].

Another case of success by biocatalysis was performed with a natural phenolic acid, where caffeic acid was esterified by the commercial enzyme Novozym 435 to generate glyceryl-1-caffeate from ethyl caffeate and glycerol. Esterification of this compound with decanoic acid using the immobilized enzyme from *Thermomyces lanuginosus* (TL IM) and Novozym 435 in the presence of propylene carbonate was selective to monoacylated and diacylated products, respectively. This ingenious process is based on the low volatility of the solvent allowing the reaction to be performed under a vacuum and does not require sieves to remove the water produced. Likewise, the glyceryl caffeate ester products had greater stability than α-tocopherol in avoiding the oxidation of bulk tuna oil [194].

The search for new antioxidants with high antibacterial power synthesized from poorly studied precursors generates high expectations in research. For example, the enzymatic acylation of umbelliferone with different vinyl esters catalyzed with the enzyme Novozym 435 has been investigated for the first time. This allowed the generation of umbelliferone esters that presented a minimum inhibitory concentration of 1 mM for strains of clinical interest, such as *Staphylococcus aureus* (resistant to methicillin and oxacillin) and *Klebsiella pneumoniae*; for the *Pseudomonas aeruginosa* strain, its inhibitory capacity was 0.5 mM [195].

Considering that these improved products present greater solubility in lipid substances, the prospect of these compounds as additives, antioxidants, and antimicrobials in different industrial sectors proves to be a real and available alternative.

To improve the bioavailability of a flavonoid, a whole-cell enzyme system, a cell-bound lipase, and an intracellular enzyme were employed, which, by acylation and hydrolysis, respectively, allowed the bioconversion of naringin into two lipophilic derivatives: naringin esters and naringenin. The high antioxidant power of naringin esters was superior to its precursor, in addition to showing markedly enhanced permeability in human intestinal Caco-2 cells. However, naringenin is a product that can reduce bitterness in food products; thus, it has expectations in the industrial sector [54].

Continuing with the acylation mechanism, the antioxidant activity of some phenolipids, such as alkyl ferulate esters generated by biotransformation with lipases, was improved [51]. This new product showed significant antibacterial properties against *Listeria monocytogenes* (0.1 mM inhibitory capacity) and biofilm formation. The possible mechanism of action of the improved compound was related to the permeability and integrity of cell envelopes because it caused leakage of some cellular components in the bacteria under study. The new compound could bind to membrane proteins to disrupt protein activity or inhibit their synthesis, as well as bind to bacterial DNA and form complexes that affect their activity. This new compound has prospects in the nutraceutical industry because it can be employed as an adjuvant to address foodborne infections and biofilms [196]. Modification of polyphenol stilbenes, such as resveratrol, is another success of lipase. An acylation study using lipases from *Alcaligenes* sp. obtained a yield of approximately 70% of a new product that, after being characterized, was identified as 3-*O*-acetyl-resveratrol. The generation of this compound was observed when enzymes from *T. lanuginosus* and *Pseudomonas cepacia* were used. During the kinetic study, formation of the compounds identified as 3,4′-diacetyl-resveratrol and 3,5,4′-triacetylated in which all phenols were substituted was observed.

During the development of this study, an increase in temperature from 40 °C to 60 °C had a positive effect on the reaction yield; however, catalyst inactivation also occurred. When evaluating different acyl donors, such as free fatty acids, ethyl esters, and triglycerides, significant effects were only found with saturated and unsaturated vinyl esters. Additionally, the incorporation of long chains such as stearate was analyzed, achieving yields of up to 55% of monoesterified compounds at long reaction times, and the formation of di- and triacetylated compounds was not achieved [197–199].

However, a recent study used lipase from *Candida* sp. immobilized on hydrophobic-modified hollow mesoporous silica spheres (HMSS-C8). The catalytic efficiency of the enzyme was 15 times higher than that of the non-immobilized lipase, and the bioconversion to resveratrol ester was 98.8%, which was achieved in 2 h, the fastest reaction time recorded to date. This new compound presented higher solubility in plant lipids and provided greater stability to oxidation, demonstrating its potential as an oil-soluble antioxidant [200]. The reactions described above can be visualized in Figure 5.

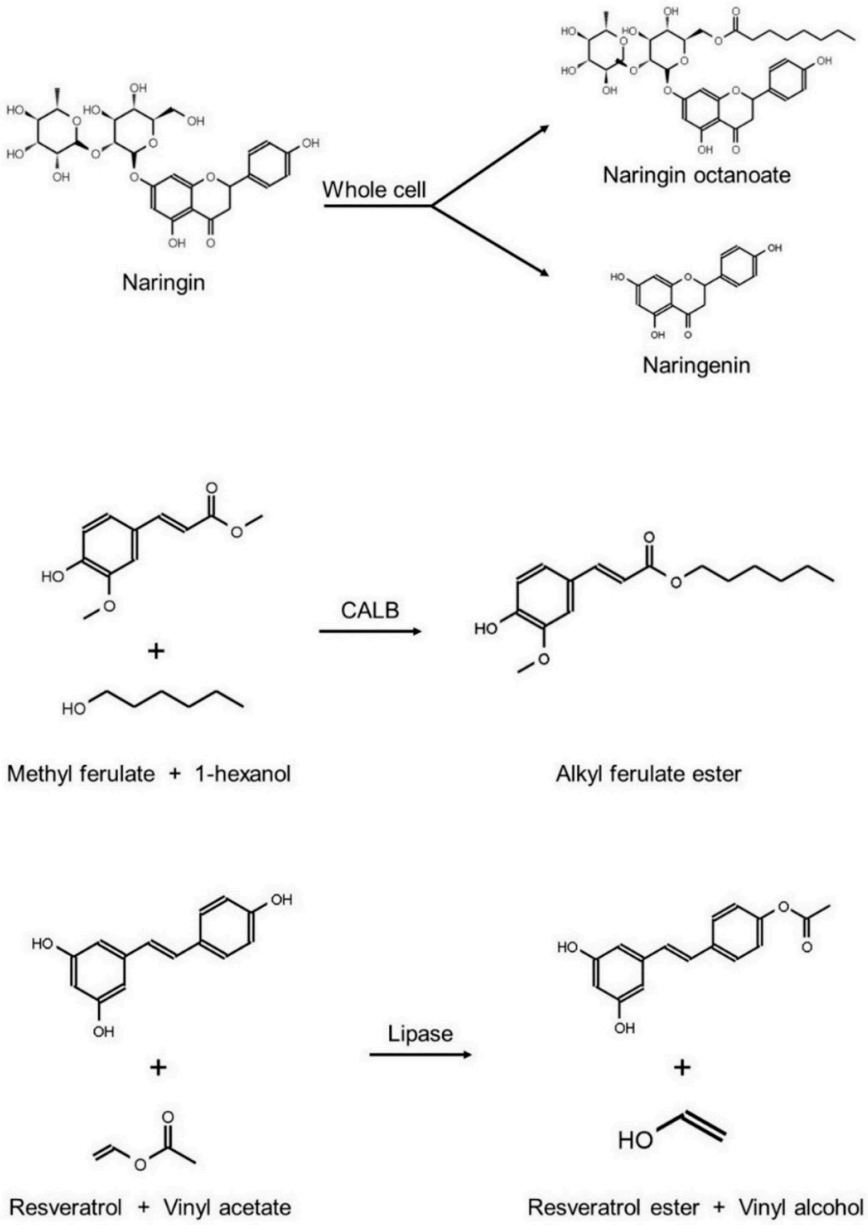

Figure 5. Examples of phenolic antioxidants whose acylation is catalyzed by some lipase [54,201,202].

4.2. Prebiotics and Biosurfactants

Prebiotics are nutrients that are broken down by gut microbiota (probiotics). In recent years, their relationship with human health attracted growing interest [201]. During fermentation, the metabolic activity of microorganisms can change the nutritive and bioactive properties of food matrices, making them beneficial during consumption. Some oligo and polysaccharides act as prebiotic substrates that are fermented by the intestinal microbiota into short-chain fatty acids that are resistant to intestinal digestion. Although more clinical studies demonstrating the full functionality of the new products and strategies to increase yields are lacking, the advances thus far are very promising.

While prebiotic oligosaccharides are water soluble, lipase-catalyzed esterification of oligosaccharides produces functionalized amphoteric molecules with biosurfactant/emulsifying properties and increased prebiotic activity, in addition to other bioactive properties, such as antibacterial, anti-inflammatory, and cytotoxic properties [127,202–204].

The acylation process has also allowed the use of other raw materials, such as sucrose, for value-added purposes, such as sugar fatty acid esters (SFAEs), which are compounds that have a carbohydrate moiety and one or more fatty acids as lipophilic SFAEs are nonionic surfactants that can be synthesized in a single enzymatic reaction step using lipases [205]. These products are employed in the food industry because of their high biodegradability and safety. They are synthesized by chemical and enzymatic methods, the latter being the most recent and studied because the reactions are performed under milder conditions and give greater confidence to the consumer by removing the synthetic chemical label.

In this context, the synthesis of sucrose monolaurate was achieved by transesterification mediated by *T. lanuginosus* lipase immobilized on silica gel (Lipozyme TL IM), which has an antibacterial effect. With this precedent, new uses for biosurfactants alone or as adjuvants to address foodborne infections are sought [202].

Additionally, during the process, several challenges are encountered, such as the selection of the appropriate solvent for the reactions, because some hydrophilic organic solvents can dissolve sugars and fatty acids; at relatively high concentrations, most enzymes are affected. This is where the alternative of ionic liquids seems to minimize these effects, promoting favorable catalysis conditions [206,207].

5. Concluding Remarks

In this work, we observed the fundamental role of lipases in generating new products with high added value in the food and nutraceutical industry. Thus, the demand for these proteins in their different presentations is increasing. Enzymes are an alternative tool to produce new esters. In recent years, the use of lipases at the industrial level has been limited by their availability and costs; however, today, with the presence of new enzymes with properties that confer greater robustness, high yields, and stability to be reused in various reactions, they are positioned as a viable, accessible and compatible tool with the ecosystem that also provides valuable benefits to the food and nutraceutical sector, positively impacting the health of consumers. In the future, new advances in using biocatalysts are expected to continue to reduce the process steps and reaction times required to generate new products.

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