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Review

Catalytic Routes to Produce Polyphenolic Esters (PEs) from Biomass Feedstocks

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Abstract: Polyphenolic esters (PEs) are valuable chemical compounds that display a wide spectrum of activities (e.g., anti-oxidative effects). As a result, their production through catalytic routes is an attractive field of research. The present review aims to discuss recent studies from the literature regarding the catalytic production of PEs from biomass feedstocks, namely, naturally occurred polyphenolic compounds. Several synthetic approaches are reported in the literature, mainly bio-catalysis and to a lesser extent acid catalysis. Immobilized lipases (e.g., Novozym 435) are the preferred enzymes thanks to their high reactivity, selectivity and reusability. Acid catalysis is principally investigated for the esterification of polyphenolic acids with fatty alcohols and/or glycerol, using both homogeneous (*p*-toluensulfonic acid, sulfonic acid and ionic liquids) and heterogeneous (strongly acidic cation exchange resins) catalysts. Based on the reviewed publications, we propose some suggestions to improve the synthesis of PEs with the aim of increasing the greenness of the overall production process. In fact, much more attention should be paid to the use of new and efficient acid catalysts and their reuse for multiple reaction cycles.

Keywords: polyphenolic esters; bio-catalysis; acid catalysis; homogeneous catalyst; heterogeneous catalyst; biomass

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1. Introduction: Properties and Potential Applications of Polyphenolic Esters

Over the past few years, the search for valuable bio-based chemicals is gaining increasing attention from the scientific community [1–6]. Several synthetic strategies were recently proposed for the production of value-added compounds with the aim of meeting the twelve principles of Green Chemistry [7], e.g., the reduction of waste, the use of catalysts and of renewable feedstocks [8–15].

In this context, the production of polyphenolic esters (PEs) from biomass feedstocks is an attractive task for research. In fact, among natural compounds, polyphenols are one of the most plentiful, showing several properties including anti-oxidative, anti-inflammatory, antibacterial, antiviral and anticancer effects [16–19]. A polyphenol refers to a compound with more than one phenolic hydroxyl group attached to one or more aromatic rings. Generally, these chemicals are classified based on their structure into phenolic acids, flavonoids, stilbenes and lignans [20]. Epidemiological studies indicate that many polyphenols have roles in the regulation of metabolism, chronic diseases, weight, and cell proliferation, showing beneficial effects on noncommunicable disorders such as cardiovascular and neurodegenerative diseases, cancer, and obesity [21].

However, due to their high polarity, the majority of naturally occurred polyphenols have low miscibility with lipophilic matrices, which limits their applications [20]. In fact, lipophilic phenolic compounds are interesting lipid antioxidants, but their presence in nature is not widespread [22]. To overcome this problem, lipophilization of phenolic compounds, which makes them more compatible with lipophilic matrixes, can be performed. The structure of polyphenols can be altered by incorporating a hydrophobic group while

retaining their original bioactivity. Both chemical and enzymatic methods are employed to modify the hydrophilic structure of natural phenolic compounds, and consequently improve their solubility and compatibility with lipophilic matrices [20,22–26].

Several reaction pathways have been investigated and can be broadly classified into conjugation with proteins/amino acids, esterification, and polymerization [20]. Among these strategies, the esterification of polyphenolic compounds can be achieved through: (1) reaction of acid moieties with short or long alkyl chain alcohols; (2) reaction of hydroxyl functions with short or long alkyl chain acids (Figure 1).

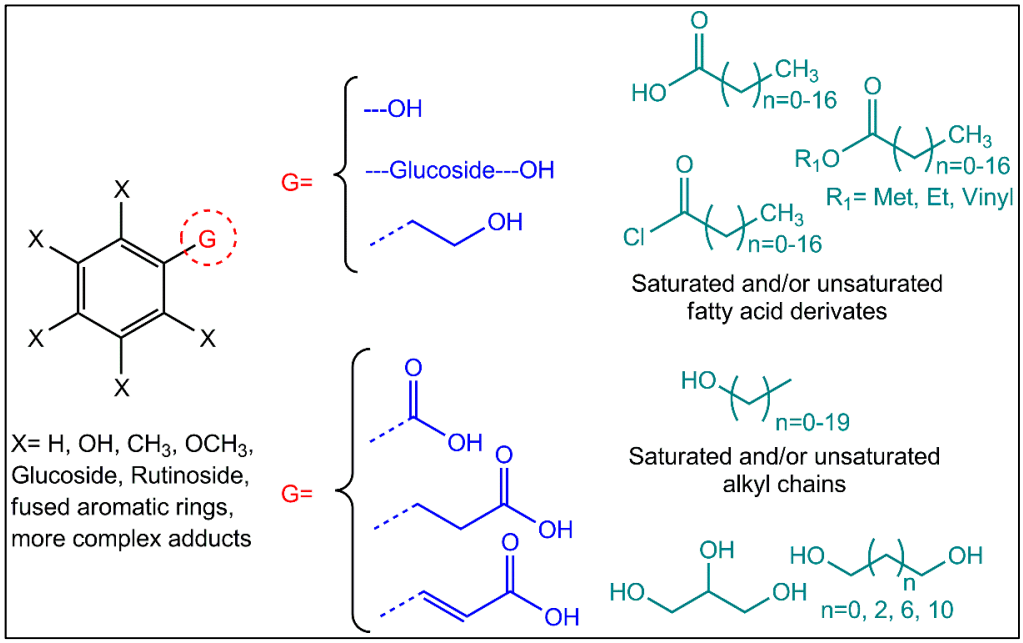


Figure 1. Schematic representation of the polyphenolic functionalities that can be esterified with the main reactants employed in the literature. G represents the functional group of the polyphenolic moiety that is involved in the reaction.

Moreover, it is necessary to evaluate the antioxidant activity of lipophilized compounds regarding their effective use as antioxidant compounds in different materials [27]. Several authors have investigated the antioxidant activity of synthesized PEs, and in some cases the PE retained almost the same antioxidant activity as that of the polyphenol used as starting material [22,23,28–30]. For example, it was shown that the radical scavenging and antioxidant capacity of a PE of hydroxytyrosol, with an acyl chain bonded at the primary alcohol group, is similar to that of hydroxytyrosol itself, but the PE is more akin to lipophilic matrices [31]. In addition, recent studies showed that hydrophilic PEs (with other interesting usages) could be obtained through the reaction of polyphenolic acids with glycerol [32].

Taking into account all the above-discussed features of PEs, their synthesis through catalytic routes is an interesting research field that must be improved.

2. Methodology

In this review, the authors attempt to discuss the different catalytic routes reported in literature for the synthesis of polyphenolic esters with the aim of guiding future research toward improved overall production process in term of greenness. The keywords "polyphenolic esters", "bio-catalysis", "acid catalysis", "homogeneous catalyst", "heterogeneous catalyst", and "biomass" were selected individually or jointly to search for relevant information on Google Scholar, Scopus and Web of Science. Key literature published between 1997 and 2022 (up to February) was assimilated and analyzed. We considered only studies in

which all reaction parameters (temperature, ratio of reactants, amount and type of catalyst, reaction times, and yields) were clearly stated.

3. Synthesis of Polyphenolic Esters through Bio-Catalysis

Enzymatic catalysis is the most-investigated catalytic route for the lipophilization of polyphenols [22–24,33,34]. Enzymes are biological catalysts, so they are very sensitive to medium and reaction parameter changes. Enzyme-catalyzed reactions are carried out in mild conditions with no toxic solvents, generating a low amount of by-products, so they are considered environmentally friendly processes [29]. However, some characteristics of enzymes tend to be far from industrial requirements. In fact, they can be unstable, water-soluble or inhibited by reaction components [35]. To overcome these practical problems, enzymes can be immobilized on an inert support and reused for many catalytic cycles. Nowadays, enzyme immobilization is established as a powerful tool for improving enzyme features. Immobilized enzymes are those "which are physically confined in a certain defined region or attached to an inert, or insoluble support matrix, to hold or retention of their catalytic activities" [36]. Immobilization can increase enzymes' performance in terms of their activity, specificity, selectivity, and stability [37,38].

Concerning the esterification/transesterification of polyphenolic compounds, the most used class of enzymes is that of lipases (triacylglycerol acylhydrolase, EC 3.1.1.3 according to the Enzyme Commission number), which specifically catalyze the hydrolysis of glycerides and the synthesis of esters [39]. Lipases are mostly obtained from microorganisms. Microbial lipases find many applications, including organic synthesis and bioconversions in several industries (e.g., food, detergents, cosmetics, medicine and waste treatment) [40]. Many commercially lipases are produced by *C. antarctica, Candida rugosa*, *Rhizomucor miehei*, *Rhizopus arrhizus* and *Aspergillus niger* [41].

The most used enzymes are Novozym 435 (lipase obtained from *Candida antarctica*, CALB, expressed by *Aspergillus orizae* fixed on microporous acrylic resin) [42] and Lipozyme (lipase from *R. miehei*, immobilized onto a macroporous anion exchange resin).

3.1. Enzymatic Synthesis of Polyphenolic Esters from Flavonoids

Enzymatic acylation of flavonoids has been investigated in order to increase the solubility and stability in lipophilic systems of glycosylated flavonoids (most flavonoids from natural sources occur in this form) and improve their applications as antioxidants in the pharmaceutical, cosmetic, and food industries. Generally, the hydroxyl function of flavonoids is converted into esters through an acylation reaction with aliphatic or aromatic acids/esters. Lipase-catalyzed syntheses of flavonoid esters, and the impact of the acylation reaction on their biological activities, were recently reviewed [22,24]. Consequently, in the present review few considerations regarding the synthesis of PEs from flavonoids are reported.

Several factors such as the nature and chain length of the acyl donor, the acyl donor/flavonoid molar ratio, temperature and water content affect the regioselectivity and conversion of the enzymatic acylation of flavonoids. Often an organic solvent is necessary to ensure simultaneous solubilization of both the nonpolar acyl donor and the polar glycosylated flavonoid, leading to high conversion rates. Furthermore, molecular sieves were often added to the reaction medium for the removal of the formed water, thus increasing the reaction yield by minimizing hydrolysis reactions.

Among lipases, Novozym is the most used, followed by Lipozyme. For example, the esterification of naringin, a flavonoid found in citrus fruits, with oleic acid [43–45], lauric acid [46] and palmitic acid [47] (fatty acid/naringin molar ratio from 20/1 to 4/1), was performed using both Novozym 435 and Lipozime TL IM as catalysts. The authors evaluated the performance of these enzymes at different temperatures in the range 40–60 °C, and in the presence of a solvent (acetone, acetonitrile or tert-amyl alcohol). After 48–96 h of reaction, naringin conversions in the range 36–96% were obtained, depending on reaction parameters (solvent type, reaction temperature, type of fatty acid and fatty acid/narginin

molar ratio). The choice of appropriate reaction conditions is crucial to achieve the best yields. In fact, the conversion of naringin via Lipozyme-catalyzed esterification with oleic acid increased from 24%, when an oleic acid/naringin molar ratio of 5/1 was used, to 54% for a higher molar ratio (20/1), after 48 h of reaction at 50 °C in the presence of tert-amyl alcohol as solvent [43]. When using acetonitrile instead of tert-amyl alcohol at 40 °C, the conversion increased to 93% thanks to the solvent's higher dielectric constant. However, if DMSO was used as solvent, naringin conversion decreased sharply to 18%, probably because of the inactivation of enzymes in DMSO.

Recently, ionic liquids were proposed as greener alternatives to classic organic solvents for this type of reactions. They can easily be separated from products and/or catalysts and recycled for reuse [48]. Lipophilization of anthocyanin monoglucosides with octanoic acid, catalyzed by Novozym 435, was investigated in the presence of ionic liquids and microwave irradiation [49]. In the presence of 2-methyl-2-butanol as solvent, a reduction of reaction time of approximately 10-fold (from 14 to 1.5 h) was achieved when microwave irradiation was used, compared to the conventional method (heating at 60 °C). Among ionic liquids tested, 1-Butyl-3-methylimidazolium trifluoromethanesulfonate is the only one that allowed for obtaining of the reaction product. Moreover, in this case, microwave irradiation could be performed using lower energy consumption (20 W compared to 150 W when 2-methyl-2-butanol was used). However, lower reaction rates in the enzymatic esterification of glycosides are sometimes observed when ionic liquids are used as solvents compared to those recorded with the optimal organic solvents, probably due mass transfer limitations that cause lower activity of the enzyme in these liquids [50]. To overcome this issue, a binary ionic liquid solvent system could be employed, which would allow for enhancement of lipase performance compared to that achieved with ionic liquid alone [51].

Interestingly, lipase-catalyzed esterification of different flavonoids, i.e., esculin, naringin, and phloridzin, was also investigated using vegetable oils (coconut, linseed, and sunflower oils) as acylating agents. The use of Novozym 435 as catalyst, an acyl donor/flavonoid molar ratio of 1/6 and acetonitrile as solvent allowed for conversions in the ranges of 78–91%, 75–85%, and 65–67% for phloridzin, naringin and esculin, respectively, after 92 h of reaction at 70 °C [52].

Since the use of a solvent is beneficial for these reactions, the environmental impact must be taken into account, with preference given to solvents with lower toxicity. However, the most employed solvents for PE via flavonoid synthesis are acetone, acetonitrile and 2-methyl-2-butanol, while recently ionic liquids have been tested as more sustainable alternatives. Concerning lipase catalytic performances, reaction temperatures in the range 50–70 °C are preferred in order to obtain high activity without altering enzyme stability. A higher acyl donor/flavonoid molar ratio allows the achievement of greater PE yields in a lower reaction time, while with increases in the length of the alkyl chain of the acylating agent (beyond approximately 10 carbon atoms) lower reaction efficiencies are observed.

Based on the peculiarities of these reactions, we suggest investigating in more detail some aspects of catalysis. In order to achieve a truly sustainable process, the recovery and reuse not only of the catalyst but also of the solvents used (especially in the case of expensive ionic liquids), and of the acyl donors used in large excess, should always be evaluated.

3.2. Enzymatic Synthesis of Polyphenolic Esters from Polyphenolic Acids and Alcohols

Several authors investigated the lipase-catalyzed synthesis of PE from polyphenolic acids (PAs) and alcohols (Table 1). In fact, PAs are heat-sensitive and susceptible to oxidation under certain pH conditions [53], and the use of lipases for the synthesis of PEs from PAs could face this issue. Many studies reported the enzymatic synthesis of PE from hydroxytyrosol and tyrosol, in which the alkylating agent was a fatty acid or a fatty acid ester, while other examples concerned the enzymatic esterification of PAs with alcohols.

Table 1. Enzymatic synthesis of lipophilic PEs *.

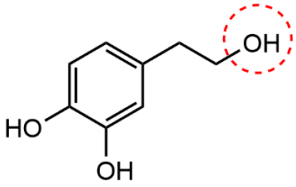
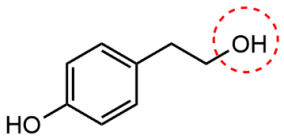
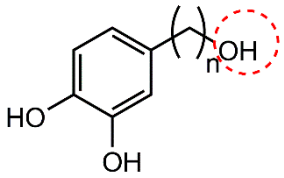
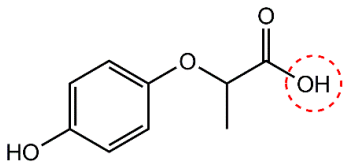
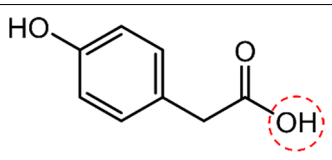
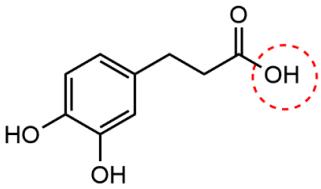
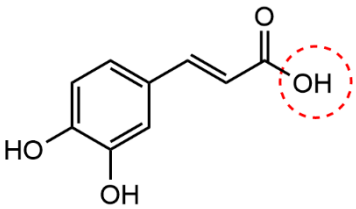
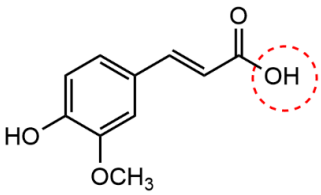
Polyphenol	Reagent/Catalyst	Reaction Condition	Reference
 **Hydroxytyrosol**	Fatty acids (1/1 as mol of fatty acid/mol of polyphenol): octanoic acid Novozym 435 (40 mg)	50 °C, 20 h, n-hexane Yield: 85–90%	[54]
	Ethyl fatty acid esters (30/1 as mol of ester/mol of polyphenol): octanoate, cis-5,8,11,14,17-eicosapentanoate, cis-4,7,10,13,16,19-docosahexanoate Novozym 435 (40 mg)	37 °C, 4–16 h, vacuum Yield: 34–93%	[55]
	Ethyl acetate (316/1 as mol of ester/mol of polyphenol) Novozym 435 (10 g/L)	45 °C, 7 h, Yield: 98%	[56]
	Ethyl octanoate (154/1 as mol of ester/mol of polyphenol) Novozym 435 (10 g/L)	45 °C, 7 h, molecular sieves Yield: 78%	[56]
	Ethyl octanoate (2/1 as mol of ester/mol of polyphenol) Novozym 435 (10 g/L)	45 °C, 5 h, 2-methyl 2-butanol Yield: 69%	[56]
	Fatty acids (2/1–5/1 as mol of fatty acid/mol of polyphenol): decanoic acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid and eicosapentaenoic acid Novozym 435 (54% *w*/*w*)	40–50 °C, 1–24 h, 2-methyl-2-butanol, tert-butanol, isooctane, diethyl ether, ethyl acetate Yield: 45.91–85.61%	[57]
 **Tyrosol**	Methyl or ethyl esters (10 mL/1mmol of polyphenol): acetate, butyrate, laurate, palmitate, stearate, oleate and linoleate Novozym 435 (0.04% *w*/*w*)	55 °C, 1.5–42 h, Yield: 60–92%	[58]
	Oleic acid (1 mol/1 mol of polyphenol) Novozym 435 (10% *w*/*w* relative to mixture)	80 °C, 10 mbar, 2 h Yield: 95%	[59]
 **di-*o*-phenolic compounds**	Ethyl fatty acid esters (30/1 as mol of ester/mol of polyphenol): palmitate, butyrate, stearate, octanoate and eicosapentaenoate Novozym 435 (40 mg)	37 °C, 4–16 h, 5–10 mmHg Yield = 29–98%	[55]
	Fatty acids (2/1 as mol of fatty acid/mol of polyphenol): palmitic acid Novozym 435 (40 mg)	37 °C, 16 h, 5–10 mmHg, acetonitrile Yield = 69–85%	[55]
 **2-(4-Hydroxyphenoxy) propionic acid**	Alcohol: Octanol (large excess) Novozym 435 (37% *w*/*w*)	52.9 °C, 58.2 h Yield = 95.9%	[60]
 **4-Hydroxyphenylacetic acid**	Alcohol (1/1 as mol of alcohol/mol of phenolic acid): octanol CALB (80 mg/mL)	60 °C, 72 h, $[BMIM]PF_6$ Yield = 62.6%	[61]

Table 1. *Cont.*

Polyphenol	Reagent/Catalyst	Reaction Condition	Reference
 **Dihydrocaffeic acid**	Alcohol (8/1 as mol of alcohol/mol of phenolic acid): linoleoyl alcohol Novozym 435 (25 mg)	55 °C, 10 days, vacuum, Hexane/2-butanone (75/25 *v*/*v*) Yield: 99%	[62]
	Alcohols (3/1 as mol of alcohol/mol of phenolic acid): butanol, hexanol, octanol, dodecanol, octadecenol Novozym 435 (100 mg)	60 °C, 3–5 d, Hexane/2-butanone (75/25 *v*/*v*), Molecular sieves Yield: 44–95%	[63]
 **Caffeic acid**	Alcohol (3/1 as mol of alcohol/mol of phenolic acid): hexanol Novozym 435 (100 mg)	60 °C, 5 d, Hexane/2-butanone (75/25 *v*/*v*), Molecular sieves Yield: 20%	[63]
 **Ferulic acid**	Alcohols (3/1 as mol of alcohol/mol of phenolic acid): hexanol Novozym 435 (100 mg)	60 °C, 5 d, Hexane/2-butanone (75/25 *v*/*v*), Molecular sieves Yield: 5%	[63]
	Alcohols (1/1 as mol of alcohol/mol of phenolic acid): hexanol, octanol RML (80 mg/mL)	60 °C, 3 d, $[BMIM]PF_6$ Yield = 38.1%	[61]

* red circles indicate the –OH group involved in the reaction.

Hydroxytyrosol octanoate was synthesized in yields in the range 85–90% through esterification of octanoic acid with hydroxytyrosol at 50 °C and CALB (7–10% *w*/*w*) as catalyst after 20 h of reaction [54]. Using Novozym 435 as catalyst for the enzymatic esterification or transesterification of hydroxytyrosol with several fatty acids or ethyl fatty acid esters, yields of 93, 51 and 34% were reached for hydroxytyrosol oleate, hydroxytyrosol cis-5,8,11,14,17-eicosapentanoate and cis-4,7,10,13,16,19-docosahexanoate, respectively, after 16 h of reaction at 37 °C [55]. At a higher temperature (45 °C) and in the presence of molecular sieves for water absorption, yields of hydroxytyrosyl oleate up 78% were obtained after a lower time (7 h) for the solvent-free reaction of hydroxytyrosol with ethyl oleate (2 eq.). Under optimized reaction conditions, the use of 2-methyl-2-butanol as solvent allowed the reduction of the reaction time to 5 h, achieving a slightly lower yield (69%) [56]. The reaction conditions for the synthesis of several hydroxytyrosyl fatty acid esters and fatty acids (decanoic acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid and eicosapentaenoic acid) using Novozym 435 (54% *w*/*w* respect hydroxytyrosol) as catalyst were optimized in terms of solvents (2-methyl-2-butanol, tert-butanol, isooctane, diethyl ether, ethyl acetate), temperatures (40 and 50 °C), molar ratio of substrates (fatty acid/hydroxytyrosol molar ratios of 1/1, 2/1, 3/1, 5/1) and reaction times (1–24 h) [57]. The best results were obtained with diethyl ether as solvent, 40 °C, molar ratio of 2/1 between fatty acid/hydroxytyrosol and 6 h of reaction time. Results showed that the shorter the fatty acid chain, the higher the conversion rate of hydroxytyrosol. All saturated fatty acids yielded a higher percentage of conversion with respect to unsaturated fatty acids, except for stearic acid. With long-chain unsaturated fatty acids, no relationship between chain length and conversion was seen, as higher conversion was obtained with eicosapentaenoic acid (68%) than with oleic acid (46%). Some studies have shown that the conjugation of longer chain fatty acids with polyphenols results in lower yields [64,65].

The enzymatic synthesis of several tyrosyl-based PEs catalyzed by Novozym 435 through transesterification of methyl or ethyl esters (acetate, butyrate, laurate, palmitate, stearate, oleate and linoleate) with tyrosol reached yields from 60 to 92% after 1.5–42 h at 55 °C [58]. By performing the reaction between tyrosol and oleic acid in vacuum (10 mbar) at 80 °C using Novozym 435 as catalyst, a yield of 95% for tyrosyl oleate was obtained after only 2 h [59].

In addition, the enzymatic esterification/transesterification of several di-*o*-phenolic compounds with fatty acids/esters catalyzed by Novozym 435 was investigated with the aim of synthesizing new lipid antioxidants based on a catechol structure. The esterification was carried out with palmitic acid at 37 °C, in 16 h with a molar ratio between fatty acid and phenol of 2/1. The maximum yield (85%) was reached for 3–3,4-Dihydroxyphenyl palmitate. Subsequently, the transesterification was carried out with ethyl palmitate, ethyl butyrate, ethyl stearate, ethyl octanoate and ethyl eicosapentaenoate under the following conditions: ethyl fatty acid ester/phenol ratio of 30/1, Novozym 435, no solvent, 37 °C, 6–16 h. The maximum yields were reached for 3,4-dihydrobenzyl palmitate (98%), 3-(3,4-dihydroxyphenyl) butyrate (97%) and 3,4-dihydroxycinnamyl butyrate (96%), 3-(3,4-dihydroxyphenyl) stearate, 3-(3,4-dihydroxyphenyl) octanoate (87%), and 3-(3,4-dihydroxyphenyl) eicosopentanoate (97%). The three-carbon distance of the primary alcohol from the phenolic structure in 3-(3,4-dihydroxyphenyl) propanol probably helped the reaction compete with the hydrolysis reaction of the polyunsaturated ethyl esters [55].

Based on the reviewed literature, to obtain comparable conversions and yields, the enzymatic esterification of PAs with fatty alcohols requires reaction times higher than those for PE synthesis from tyrosol/hydroxytyrosol and fatty acids/esters [61]. For example, Stamantis et al. studied the enzymatic esterification of various cinnamic acid derivatives with aliphatic alcohols in different organic solvents (acetone, octanol, 2-methyl-2-propanol, 2-methyl-2-butanol). Yields of octyl cinnamate of 82% and 59% were obtained with CALB and Lipozyme, respectively, after 12 days of reaction at 50 °C [66]. The esterification of several phenolic acids with butanol, octanol, dodecanol and 9-octadecen-1-ol with Novozym 435 (2.5% w/w) was performed, obtaining yields equal to 98% with octanol within five days of reaction at 60 °C [67]. A total of 58.2 h of reaction was necessary to obtain excellent yield (95.9%) of PEs via the esterification of hydroxyphenylpropionic acid with 1-octanol at 52.9 °C with CALB [60]. Katsoura et al. investigated the use of ionic liquids in the esterification of various cinnamic derivatives with fatty alcohols catalyzed by CALB and Lipozyme. The study showed that was possible to obtain octyl 2-(4-hydroxyphenyl)acetate with a yield of 62.5% after 72 h at 60 °C in 1-Butyl-3-methyl-imidazolium-hexafluorophosphate ([BMIM]PF_6) as solvent and CALB as catalyst [61]. Moreover, they showed that CALB was the best catalyst for this reaction and could be used at least four times without a decrease in reaction yield.

The enzymatic synthesis (Novozym 435 as catalyst) of different PEs from phenolic acids and fatty alcohols (from short to long alkyl chain) was also investigated in binary solvent systems. The esterification of dihydrocaffeic acid with linoleoyl alcohol, catalyzed by Novozym 435, reached a yield of 99% in approximately 10 days when a mixture of hexane/2-butanone (75/25 v/v) was used as binary solvent media at 55 °C [62]. Using the same solvent mixture, dihydrocaffeic acid was esterified with various alcohols (butanol, hexanol, octanol, dodecanol, octadecenol) in the presence of molecular sieves, reaching a maximum conversion of 95% in three days at 60 °C when hexanol was used as alcohol. With increasing length of the carbon chain of the fatty alcohol, the yield drastically decreased to 44% (reached with octadecenol). However, when starting with caffeic and ferulic acid, poor yields (20% and 5%, respectively) were achieved under the same reaction conditions using hexanol as alcohol, probably due to the lower solubility of these polyphenolic acids in the solvent mixture [63]. The yield of the esterification of ferulic acid can be improved (up to 38.1% and 34.9% with hexanol and octanol, respectively) by using the ionic liquid [BMIM]PF_6 as solvent and immobilized lipase from *Rhizomucor miehei* recombinant in *Aspergillus* (RML) as catalyst [61].

Several authors showed that CLB had the best performance compared to other lipases and, in general, that CALB results in better yields and selectivity [61,62,66]. The best solvent system, in some cases, is the binary system hexane/2-butanone (75/25 *v*/*v*) [62,63]. However, for PAs with an unsaturated side chain on the aromatic ring (e.g., ferulic and caffeic acid), CALB showed low catalytic performance, while RML allowed for higher yields in ionic liquids as solvents [61,63]. In general, ionic liquids seem to improve reaction yields for the esterification of these PAs (e.g., caffeic acid) in solvent or solvent-free systems [61]. In terms of reusability, some studies showed that both Novozym 435 and Lypozyme can be reused 5–8 times, but Lypozyme is easier to wash because it adsorbs less oil thanks to its different immobilization support systems (granulated silica for Lipozyme and macroporous acrylic resin for Novozym 435) [68–70].

A common issue and disadvantage within the enzymatic synthesis of PEs from PAs is the very long reaction time required to achieve acceptable yields, mainly due to the mild conditions necessary for enzyme stability. It should be noted that to ensure good solubility of all reagents, the use of a solvent (a single solvent or a binary mixture of classical solvents or ionic liquids) is almost always necessary. These aspects must be considered when evaluating the sustainability of these processes and their industrial feasibility.

3.3. Enzymatic Synthesis of Polyphenolic Esters from Biomass Extracts

Biomass extracts are valuable sources of polyphenols, and their employment in the production of PEs is an appealing and sustainable synthetic approach. Since these extracts consist of mixtures of diverse polyphenols with different functionalities, enzymatic catalysis (with immobilized lipases) is the easiest synthesis route for selective production of the corresponding PEs. As matter of fact, in recent years numerous authors investigated the enzymatic synthesis of PE from biomass extracts in polyphenols (e.g., leaves, seeds, fruits; see Figure 2) [71–77].

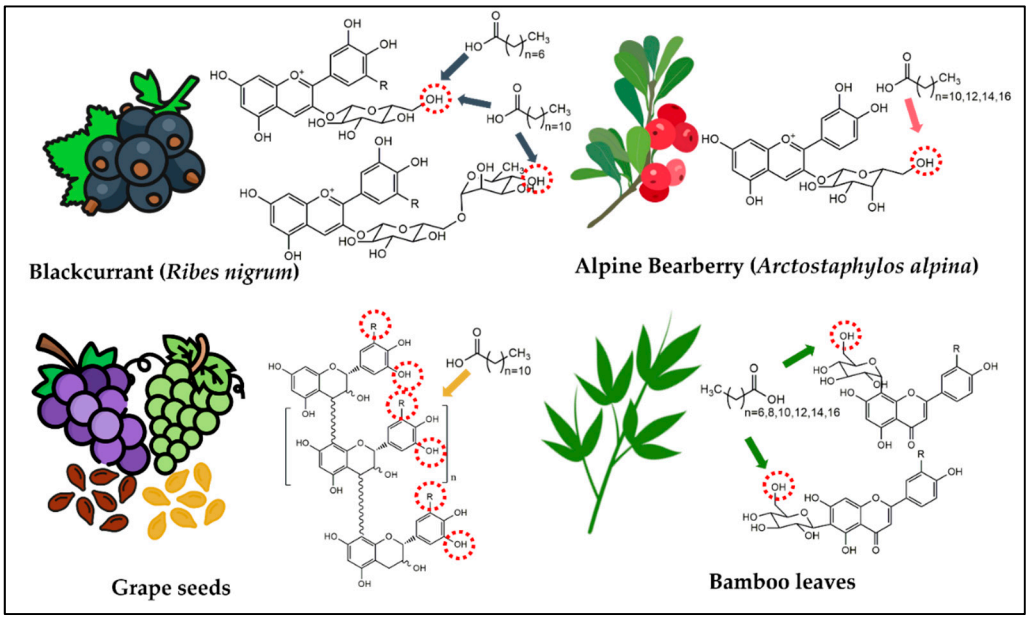


Figure 2. Polyphenols extracted from biomass (blackcurrant skin, alpine bearberry, grape seeds and bamboo leaves) and used as starting material for PE synthesis through reaction with fatty acids. Red circles indicate the –OH moieties involved in the reaction.

Blackcurrant (*Ribes nigrum*) skin extract containing four anthocyanins (namely, rutinosides and glucosides of cyanidin and delphinidin) was esterified with octanoic acid [71] and lauric acid [72] using CALB as catalyst. The best results with octanoic acid (100 eq.) were achieved at 60 °C using acetonitrile/DMSO (10/1 *v*/*v*) as solvent, in the presence of molecular sieves (for water removal) [71]. The reaction was highly regioselective, since

acylation occurred only on the primary alcohol, which is the most reactive hydroxyl group of the sugar moiety. In fact, cyanidin and delphinidin glucosides were preferentially esterified, while no acylated rutinosides were detected, due to the absence of a primary hydroxyl group in their saccharide moieties. On the other hand, after 72 h of reaction with lauric acid (10 eq.) at 60 °C using tert-butanol as solvent and molecular sieves for water absorption, conversions were in the range 63–85%, with selective production of monoacylated flavonoids, for both glucosides and rutinosides [72].

Alpine Bearberry (*Arctostaphylos alpina*) extract has a high content of anthocyanins, and, of these, approximately 95% is cyanidin-3-O-galactoside. The esterification of the extracted anthocyanins with different fatty acids (lauric acid, myristic acid, palmitic acid, and stearic acid) was investigated using Novezym 435 as catalyst and molecular sieves as water absorbents [77]. Conversion decreased with the length of fatty acid alkyl chain and the best results were achieved with lauric acid (lauric acid/flavonoid molar ratio of 10/1) using tert-butanol as solvent at 60 °C, which reached a conversion of 73% after 72 h of reaction.

Grape seed extract is mainly composed of monomeric catechin and epicatechin, gallic acid and polymeric and oligomeric proanthocyanidins. These natural polyphenols from grape seed extract were acylated with lauric acid using different immobilized lipases as the catalysts [76]. Lipozyme TL IM proved to be the most active lipase, reaching the highest conversion (84%) after 12 h, when ethanol as solvent and 1 eq. of lauric acid were used at 45 °C. Strangely, if an excess of lauric acid was employed, the conversion decreased, indicating that high levels of lauric acid may inhibit the catalytic activity of this enzyme.

Water-soluble extracts from bamboo leaves, containing four flavonoids (orientin, isoorientin, vitexin, and isovitexin), were reacted with several fatty acids in the presence of Novozym 435, Lipozyme RM IM or Lipozyme TL IM at 65 °C [74]. A fatty acid/extract molar ratio of 20/1 was used, testing tert-amyl alcohol and acetone as solvents. Upon increasing the length of the alkyl chain of fatty acid from C8 to C18, conversion decreased from 80 to 60%. All lipases tested were regioselective with monoester production on the primary hydroxyl group of the sugar moiety, and Novozym 435 proved to be the most efficient one. Conversely, in the chemical acylation of the same extract performed with 1 eq. of fatty acid acyl chloride, in the presence of sodium bicarbonate as catalyst, no regioselectivity was observed [75].

All the above-discussed examples are very interesting. Based on the reported literature, blackcurrant skin and bamboo leaves are the most used biomass extracts for PEs production. However, an extract enriched in polyphenols (obtained after some purification processes) must be used as reactant to achieve good results in terms of conversion rates and yields of the final products. We suggest that attention be paid to this field of research, which has great potential for industrial application but is currently under-investigated.

3.4. Main Aspects on the Currently Used Reactors for Polyphenolic Esters Production

Large scale production of esters generally takes place in a multipurpose stirred tank reactor (STR) operating in batch mode [25,78,79]. However, this configuration places some limitations on enzymatic synthesis due to the mechanical instability of lipases. In fact, violent shaking of the reaction mixture leads to the breakage and collapse of lipases, and consequently to a reduction in their activity. These issues are generally overcome using packed or fluidized reactors [80]. A fluidized tank reactor (FTR), in which a fluid is passed through the solid catalyst at high speeds to suspend it, can reduce damage to biocatalysts and their immobilization supports. Packed bed reactors (PBRs) involve a packed bed of enzymes, and reagents are continuously cycled through this bed until the formation of products. The continuous reaction mode in PBRs also allows for the minimization of mechanical damage to enzymes [81]. In the presence of high molecular weight and high viscosity reagents, PBRs do not perform well, thus other advanced reactors such as membrane reactors and microreactors are preferred in these cases [82].

As matter of fact, microreactor technology was recently investigated for the efficient production of PEs [83]. Microreactors have a specific surface area much larger than that of conventional reactors and allow for great reductions in the reaction time and easy separation of the products and substrates. For instance, in the lipase-catalyzed synthesis of glyceryl caffeate from methyl caffeate and glycerol, microreactors allowed a reduction in reaction time of 75% (also achieving yields of 96.49%) compared to that necessary using a batch reactor [83]. Consequently, this type of reactor currently attracts extensive attention, being advantageous for the synthesis of esters, including PEs. Nevertheless, few studies on microfluidic bioconversion technology for PE production are reported in the literature, and further efforts should be made in this research field.

4. Chemical Synthesis of Polyphenolic Esters

Several synthetic strategies based on classical organic chemistry reactions are reported in the literature. These mainly concern acylation with acyl chlorides or anhydrides, which are performed under inadequately green reaction conditions. Among the class of polyphenols, the majority of studies regard PAs (cinnamic acids, ferulic acid, caffeic acid, sinapic acid, vanillic acid, p-coumaric acid, gallic acid, p-hydroxybenzoic acid) [84–88], followed by flavonoids (epigallocatechin gallate, quercetin, catechin) [89–93] with only a few examples concerning stilbenes (resveratrol) [94].

Starting with flavonoids, alcoholic or phenolic –OH groups may be involved in the esterification reaction, usually performed with acyl chloride. However, contrary to what occurs with bio-catalysis, a mixture of polyphenolic esters with different degrees of esterification was typically obtained. Epigallocatechin gallate was coupled with different acyl chlorides of long-chain fatty acids (stearic acid, docosapentaenoic acid, eicosapentaenoic acid and docosahexaenoic acid) reaching a final yield in the range 30.7–65.9%, with tetra-esters as the main products [89,90]. Mixtures of quercetin esters were produced from quercetin and acyl chlorides of several fatty acids with different chain lengths and degrees of unsaturation (propionic, butyric, caproic, caprylic, lauric, myristic, palmitic, stearic, oleic, linolenic, linoleic, eicosapentaenoic and docosahexaenoic acids) [85,86]. By increasing the acyl chloride/quercetin molar ratio, quercetin esters with a higher degree of esterification were obtained [91,92]. To achieve esterification in only one position, multi-step approaches involving protection and deprotection steps are needed. For example, catechin esters were synthesized in good to excellent yields (65 to 96%) by the use of three subsequent reaction steps, including protection of the phenolic –OH group with a benzyl group (Bn), then acylation of the alcoholic –OH group with different long chain acyl chlorides (from hexanoyl chloride to stearoyl chloride) and finally removal of the Bn protecting groups [93].

Regarding stilbenes, the only one example concerns resveratrol, which was coupled with capryloyl chloride in the presence of triethylamine and ethyl acetate (solvent) at room temperature for 12 h, yielding a mixture of mono-, di-, and tri-esters [94].

In the case of phenolic acids, the carboxylic group is converted into a more reactive one, such as acyl chloride and acetyl/vinyl esters, and subsequently is coupled with an alcohol to obtain polyphenolic esters [84–87]. For example, vinyl vanillate, caffeate, sinapate, and ferulate were synthesized through the vinyl interchange reaction of vinyl acetate with the corresponding phenolic acid in the presence of mercury acetate (4% w/w), sulfuric acid (4 eq) and tetrahydrofuran as solvents, and subsequently coupled with sitosterol to obtain phytosteryl esters under enzymatic conditions [84–86]. An alternative strategy is the Verley–Doebner modification of Knoevenagel condensation, performed starting from monomalonates and the corresponding aldehydes of caffeic, ferulic, sinapic and p-coumaric acids in the presence of dry pyridine and β-alanine that allows for the production of polyphenolic esters in good yields (85–100%) [88].

The above-mentioned chemical strategies for the production of polyphenolic esters have several drawbacks that do not allow them to meet the majority of green chemistry principles. As a matter of fact, they provide for the use of organic solvents and unsafe chemicals such as acyl chloride, whereas catalysts are not employed. Although chemical

methods allow the obtaining of high conversions over shorter times than enzymatic synthesis, they typically do not obtain good selectivity and generate numerous by-products. A mixture of products with different degrees of esterification is usually formed. Consequently, several reaction steps and long purification processes are required to obtain the desired PEs at high purity, notably for food applications.

Considering the great potential of PEs, further efforts must be devoted to the search for more sustainable syntheses based on chemical reactions. Undoubtedly, an improvement would be the use of proper chemical catalysts that could allow for overcoming the limitations listed above and obtaining high yields of PEs in a simpler and more sustainable way.

Polyphenolic Esters Synthesis by Acid Catalysis

There are a few examples of chemical catalysis, primarily of the acidic type, on PAs and hydroxytyrosol or tyrosol (see Table 2). To enhance the lipophilicity of polyphenols, PAs were coupled with alcohols at different lengths of alkyl chains, such as methanol, ethanol, propanol, butanol, pentanol, hexanol, octanol, decanol, dodecanol, hexadecanol, octadecanol, eicosanol, myristyl alcohol, cetyl alcohol, and stearyl alcohol. In addition, PEs with enhanced hydrophilicity could be obtained from the esterification reaction of PAs with glycerol (Table 3).

Table 2. Acid-catalyzed synthesis of lipophilic PEs *.

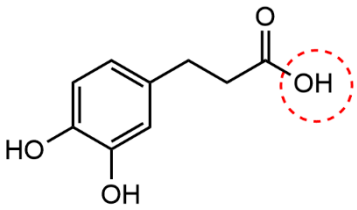
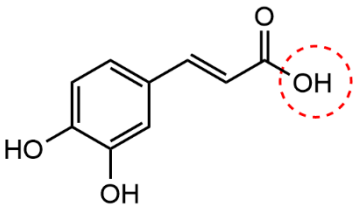
Polyphenol	Reagent/Catalyst	Reaction Condition	References
 **Dihydrocaffeic acid**	Alcohols (30 eq.): propanol and hexanol Homogeneous catalyst (1 mol%): *P*-TSA	80–90 °C, 2 h Yield: 88–99%	[95]
 **Caffeic acid**	Alcohols (30 eq.): propanol Homogeneous catalyst (1 mol%): *P*-TSA	90 °C, 2 h Yield: 85%	[95]
	Alcohols (12 eq.): Octanol Homogeneous catalyst (20 mol%): SA	100 °C, 2 h Yield: 67%	[96]
	Alcohols (8 eq.): Octanol, decanol, myristyl alcohol, cetyl alcohol, stearyl alcohol Heterogeneous catalyst (5% *w*/*w*): A-35	85 °C, 12 h Conversion: 25–45%	[97]
	Alcohol (5–50 eq.): ethylene glycol, 1,4-butanediol, 1,8-octanediol, 1,12-dodecanediol Homogeneous catalysts (3% *w*/*w*): SA	90 °C, 2 h Yield: 30–80%	[98]
Deep eutectic solvent consisting of choline chloride and **Caffeic acid**	Alcohols (8 eq.): Octanol, decanol, myristyl alcohol, cetyl alcohol, stearyl alcohol Heterogeneous catalyst (5% *w*/*w*): A-35	85 °C, 12 h Conversion: 80–90%	[97]

Table 2. *Cont.*

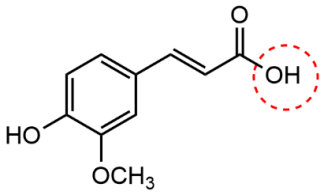
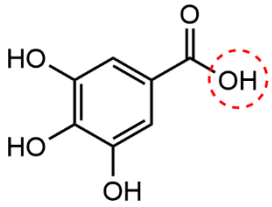
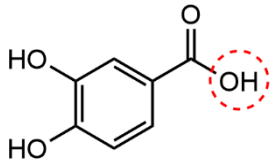
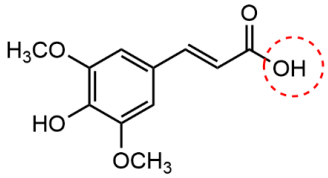
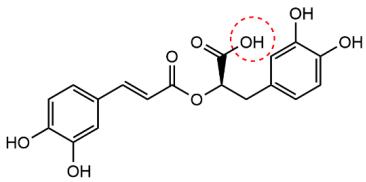
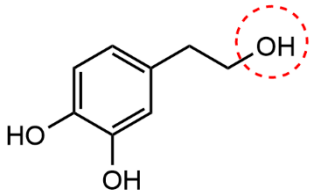
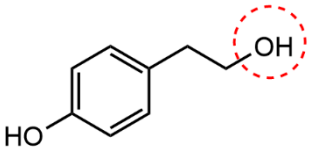
Polyphenol	Reagent/Catalyst	Reaction Condition	References
 **Ferulic acid**	Alcohols (6 eq): methanol, ethanol, propanol, isopropanol, butanol, isobutanol, pentanol, isopentanol Homogeneous catalyst (10 mol%): SA	Reflux, 8–28 h Yield: 46–81%; Microwave irradiation (75–148 °C) 3–5 min Yield: 91–95%	[99]
	Alcohols (12 eq.): Octanol Homogeneous catalyst (20 mol%): SA	100 °C, 3 h Yield: 81%	[96]
 **Gallic acid**	Alcohol (30 eq): propanol Homogeneous catalyst (1 mol%): *P*-TSA	90 °C, 2 h Yield: 88%	[95]
 **Protocatechuic acid**	Alcohols (154–285 eq): methanol, ethanol and propanol Homogeneous catalyst: SA	RT, 5 days Yield: 71–81%	[100]
 **Sinapic acid**	Alcohols (180–400 eq): methanol, ethanol, propanol and butanol Homogeneous catalyst: SA	RT, 5 days Yield: 79–94%	[28]
	Alcohols (12 eq.): Octanol Homogeneous catalyst (20 mol%): SA	100 °C, 3 h Yield: 93%	[96]
	Alcohol (5–50 eq.): ethylene glycol, 1,4-butanediol, 1,8-octanediol, 1,12-dodecanediol Homogeneous catalysts (3 % *w*/*w*) SA	90 °C, 2 h Yield: 35–72%	[98]
 **Rosmarinic acid**	Alcohols (200–2200 eq.): methanol, butanol, octanol, dodecanol, hexadecanol, octadecanol and eicosanol Heterogeneous catalyst (5% *w*/*w*): A-IR-120H	55–70 °C, 4–21 days Yield: 82–99%	[101]
 **Hydroxytyrosol**	Ethyl or methyl esters (1/25 as mL of ester/mg of polyphenol): acetate, butyrate, laurate, palmitate, stearate, oleate and linoleate Homogeneous catalyst (9 mol%): *P*-TSA	RT, 24 h Yield: 65–86%	[102,103]

Table 2. *Cont.*

Polyphenol	Reagent/Catalyst	Reaction Condition	References
 **Tyrosol**	Methyl or ethyl esters (10 mL/1mmol of polyphenol): acetate, butyrate, laurate, palmitate, stearate, oleate and linoleate Homogeneous catalyst (6 mol%): *P*-TSA	70 °C, 2–32 h Yield: 65–98%	[58]

* red circles indicate the –OH or –OR group involved in the reaction.

An excess of alcohol in the presence of homogeneous acid catalysts, e.g., *p*-toluensulfonic acid (*P*-TSA) and sulfuric acid (SA), and to a lesser extent heterogeneous ones (strongly acidic cation exchange resins), is typically employed to obtain PE from PAs such as dihydrocaffeic acid, caffeic acid, gallic acid, ferulic acid, sinapic acid, protocatechuic acid and rosmarinic acid.

Few examples are available regarding the transesterification of different ethyl esters (i.e., acetate, butyrate, laurate, palmitate, stearate, oleate and linoleate) with hydroxytyrosol [102,103] and tyrosol [58] using *P*-TSA as homogeneous catalyst. Depending on the length of the alkyl chains of ethyl esters, PE of hydroxytyrosol could be obtained at yields in the range 65–86% after 24 h of reaction at room temperature with 9 mol% of *P*-TSA [102]. When carrying out the reaction at 70°C and 6 mol% of *P*-TSA [58], excellent yields were obtained for tyrosol acetate (95%) oleate (90%), and butyrate (98%) after 2, 3 and 7 h of reaction, respectively. Longer reaction times (15–32 h) were needed to obtain good yields of tyrosol laurate (92%), palmitate (74%), stearate (65%) and linoleate (76%).

P-TSA was able to catalyze the esterification of PAs such as dihydrocaffeic, caffeic and gallic acids with propanol at catalyst loading of 1 mol% and an excess of alcohol (30 eq.), reaching a yield of 88, 85 and 88%, respectively, after 2 h at 90 °C [95]. Moreover, the reaction of dihydrocaffeic acid with hexanol catalyzed by 1 mol% of *P*-TSA at 80 °C led to a higher yield of the corresponding PE (99%) after 2 h. SA was also employed as a homogeneous catalyst (20 mol%) for the esterification of caffeic, ferulic and sinapic acids with octanol (12 eq.). PE yields of 67, 81 and 93% were obtained, respectively, for octyl caffeate, ferulate and sinapate after 2 h (for caffeic acid) and 3 h (for ferulic and sinapic acids) of reaction at 100 °C [96]. Interestingly, the esterification of ferulic acid with different alcohols (methanol, ethanol, propanol, isopropanol, butanol, isobutanol, pentanol and isopentanol) catalyzed by 10 mol% of SA saw improved performance when microwave irradiation was used instead of reflux conditions (6 eq. of alcohol used as solvent). In fact, excellent yields (91–95%) were obtained after only 3–5 min of reaction under microwave irradiation (temperatures in the range 75–148 °C), compared to yields in the range 46–81% after 8–28 h of reaction when reflux conditions were used [99]. When performing the reaction at room temperature, higher reaction time is necessary to achieve good PE yields. For example, PEs of protocatechuic acid [100] and sinapic acid [28] with methanol, ethanol, propanol and butanol in the presence of SA were synthesized in yields in the ranges 71–81% and 79–94%, respectively, after five days at room temperature.

Concerning heterogeneous catalysis, strongly acidic cation exchange resins such as Amberlite IR-120H (A-IR-120H) and Amberlite 35 (A-15) were tested for the synthesis of PE from rosmarinic and caffeic acid. Upon increasing the length of the alkyl chain of alcohols from methanol to eicosanol, the reaction time needed to achieve excellent yield (82–99%) of alkyl rosmarinate in the presence of A-IR-120H (5% *w*/*w* of total weight of both substrates), at temperatures in the range 55–70 °C increased from 4 to 21 days [101]. It must be noted that the authors used a fixed volume (5 mL) of alcohol for all of the alcohols tested, so the molar ratio between alcohol and rosmarinic acid varied from 2000 (for methanol) to 200 (for eicosanol). Since a lower alcohol/polyphenolic acid molar ratio is typically detrimental to these reactions, this could be an explanation for the much longer reaction time for alcohols with longer alkyl chain. Recently, A-35 (5% *w*/*w*) was used for the esterification of caffeic

acid with 8 eq. of octanol, decanol, myristyl alcohol, cetyl alcohol and stearyl alcohol [97]. Poor conversions of caffeic acid (25–45%) were reached after 12 h of reaction at 85 °C. By contrast, starting from a deep eutectic solvent (DES) consisting of caffeic acid and choline chloride instead of caffeic acid itself, higher conversions (80–90%) and yields (up to 90%) were achieved under the same reaction conditions. The increase in caffeic acid conversion and yield of the corresponding PEs was due to the fact that the deep eutectic solvent, being a liquid, could act as both reactant and solvent, thus reducing the mass transfer resistance.

PEs were also obtained via the reaction of glycols with polyphenolic acids. In particular, caffeic and sinapic acids were esterified with an excess of ethylene glycol, 1,4-butanediol, 1,8-octanediol, and 1,12-dodecanediol using SA as catalyst (3% *w*/*w*) [98]. After 2 h of reaction at 90 °C, the corresponding PEs were produced in yields ranging from 30 to 75%. Moreover, the as-obtained hydroxyalkyl esters were further reacted with the appropriate phenolic acid to produce bis-aryl esters through the Mitsunobu reaction. Bis-aryl esters exhibit a higher antioxidant activity than hydroxyalkyl esters, making them suitable for applications in the field of materials (e.g., as additives in packaging with antioxidant properties).

Recently, the production of hydrophilic PE was also investigated, with the esterification being performed with glycerol (see Table 3). This reaction pathway is very attractive, since glycerol is one of the most important sustainable feedstocks [104–107]. Moreover, these interesting compounds have increased water solubility, which makes them suitable for specific applications. For instance, feruloyl glycerol, obtained from the esterification of ferulic acid with glycerol, is a valuable free radical scavenger and inhibitor of peroxyl lipid oxidation and can be used in the food and cosmetic industries (e.g., sunscreen products) as a natural antioxidant and UV-absorbing ingredient [108].

Table 3. Acid-catalyzed synthesis of hydrophilic PEs *.

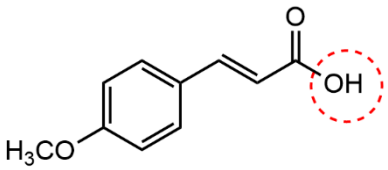
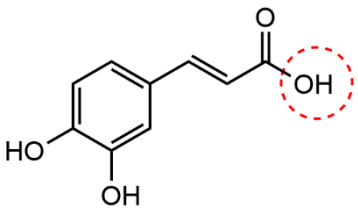
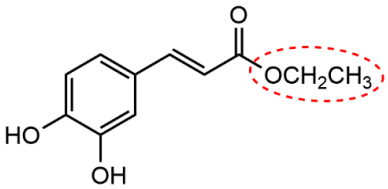
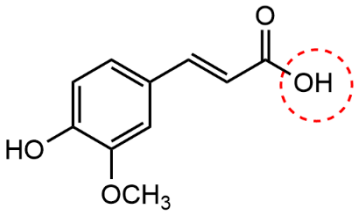
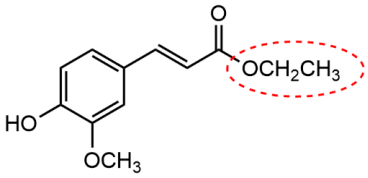
Polyphenol	Reagent/Catalyst	Reaction Condition	Reference
 **4-methoxy cinnamic acid**	Alcohol (1 eq): Glycerol Homogeneous catalysts (6 mol%): *P*-TSA	110 °C, 2 h Yield: 20%	[109]
 **Caffeic acid**	Alcohol (10 eq.): Glycerol Homogeneous catalysts (10% relative to the weight of all substrates): Ionic liquids, H_2SO_4 *P*-TSA	90 °C, 2 h Yield: 10–95%	[110]
	Alcohol (3 eq.): Glyceryl monoleate Heterogeneous catalysts (10% *w*/*w*): Solid acids (A-15, A-35, NKC-9, SO_4^{2-}/ZrO_2 and SO_4^{2-}/Fe_2O_3)	100 °C, 36 h Conversion: 5–38%	[32]
Deep eutectic solvent consisting of choline chloride and **Caffeic acid**	Alcohol (3 eq.): Glyceryl monoleate Heterogeneous catalysts (10% *w*/*w*): Solid acids (A-15, A-35, NKC-9, SO_4^{2-}/ZrO_2 and SO_4^{2-}/Fe_2O_3)	100 °C, 36 h Conversion: 5–87%	[32]

Table 3. *Cont.*

Polyphenol	Reagent/Catalyst	Reaction Condition	Reference
 **Ethyl caffeate**	Alcohol (10 eq.): Glycerol Homogeneous catalysts (10% relative to the weight of all substrates): Ionic liquids, SA *P*-TSA	90 °C, 3 h Yield: 5–85%	[110]
 **Ferulic acid**	Alcohols (15 eq.): Glycerol Heterogeneous catalyst (14% *w*/*w*): A-35	90 °C, 7 h Yield: 98%	[111]
 **Ethyl ferulate**	Alcohol (10 eq): Glycerol Homogeneous catalysts (14% relative to the weight of all substrates): Ionic liquids, SA *P*-TSA	80 °C, 10 mmHg, 14 h Yield: 5.5–98%	[108]

* red circles indicate the –OH or –OR group involved in the reaction.

4-methoxy cinnamic acid was esterified with glycerol (1 eq) using *P*-TSA (6 mol%) as catalyst and toluene as solvent in reflux conditions (110 °C). Since diesters and other by-products were also formed during the reaction, the corresponding PE was obtained at low yield (20%) after 2 h of reaction [109]. Several homogeneous catalysts (*P*-TSA, SA and ionic liquids) were tested for the esterification of caffeic acid and the transesterification of ethyl caffeate [110] and ethyl ferulate [108] with glycerol. *P*-TSA (10% relative to the weight of all substrates) promoted the reaction of caffeic acid with glycerol (10 eq.), achieving a yield of 90% after 2 h of reaction at 90 °C. SA, by comparison, at the same catalyst loading, reached a yield of only 50% after 2 h at 90 °C. Among ionic liquids tested, 1-butylsulfonic-3-methylimidazolium tosylate gave the best results with a conversion of caffeic acid of 95.6% and a PE yield of 93.8% achieved after 2 h at 90 °C (catalyst loading of 10%, glycerol/caffeic acid molar ratio 10/1) [110]. For all tested catalysts, starting from ethyl caffeate, 3 h of reaction were needed under the same reaction conditions (catalyst loading, temperature, and excess of glycerol) to reach yields close to those obtained with caffeic acid. Concerning the transesterification of ethyl ferulate, almost all of the same catalysts were investigated at a catalyst loading of 14% (relative to the total weight of reactants) and a glycerol/ethyl ferulate molar ratio of 10/1 and 10 mmHg of vacuum pressure. After 14 h of reaction at 80 °C, *P*-TSA allowed the total conversion to reach 94.5% and the yield 85.1%, while a conversion of 64.2% and yield of 56.6% were obtained with SA. Under the same reaction conditions, ionic liquids allowed for the achievement of higher conversions and yields; in particular, 1-butylsulfonic-3-methylimidazolium tosylate reached a conversion of 98.0% and yield of 88.7% [108].

Very recently, heterogeneous catalysts such as A-35 (14% *w*/*w*) were employed for the esterification of ferulic acid with glycerol (15 eq.) at 90 °C. A hydrophilic PE was obtained in high yield (98%) using this cheap heterogeneous catalyst after 7 h, a reaction time half that of the homogeneous catalysts previously reported [111]. A screening of heterogeneous catalysts (cation exchange resins and sulphated metal oxides) was performed regarding the synthesis of glycerol caffeates, starting from both caffeic acid and DES consisting of

choline chloride and caffeic acid, the same as in the study previously mentioned on the esterification of caffeic acid with octanol [32]. Both caffeoyl donors were reacted with 3 eq. of glyceryl monoleate at 100 °C for 36 h in the presence of strongly acidic cation exchange resins (A-15, A-35, NKC-9) and sulphated metal oxides (SO_4^{2-}/ZrO_2 and SO_4^{2-}/Fe_2O_3) at a catalyst loading of 10% *w*/*w*. Glyceryl monocaffeate and glyceryl dicaffeate were formed as the main products. In both cases, caffeic acid conversion was much higher with cation exchange resins (up to 87%) than with sulphated metal oxides (up to 13%). The authors asserted that this phenomenon is due to the presence of a large pore diameter in A-35, NKC-9 and A-15, which makes the inner active sites of the catalysts more accessible to the reactants. Starting from the considered DES, the conversion (maximum of 91%) was twice that obtained when caffeic acid itself was employed (44.6%). Among all catalysts, NKC-9 gave the best result in terms of yield of products (considering the sum of glyceryl monocaffeate and glyceryl dicaffeate), which was approximately 55%.

In the esterification reactions of PAs with alcohols, conversion typically decreased with increases in the length of the alkyl chain of the alcohol, and consequently longer reaction times were necessary to achieve good yields. Only strong Brønsted acids such as *P*-TSA and SA were tested as homogeneous catalysts, and at relatively high catalyst loading (from 1 to 20 mol%). For heterogeneous catalysis, strongly acidic cation exchange resins were primarily investigated, at loadings from 5 to 14 % *w*/*w*, giving interesting results. However, the majority of the studies focused on the production of the desired lipid phenolics with the aim of evaluating their antioxidant properties. Only a few examples concern deep investigations of the performances of the considered catalysts under different reaction conditions (varying the catalyst loading, temperature, and PA/alcohol molar ratio). Some important aspects of catalysis, such as the recovery and reuse of the spent catalyst [112], are still missing in the literature and need to be considered in future studies. According to our point of view, further efforts must be devoted to the employment of highly active and selective catalysts such as metal-based ones, both homogeneous and heterogeneous, starting from those currently used in esterification and transesterification reactions [113–115] and moving to other efficient acid catalysts (Brønsted and Lewis acids) [116–118]. These catalysts, together with optimization of the reaction parameters, could allow reactions to achieve good yields with lower reaction times, using smaller amounts of catalyst and generating less by-products, thus increasing the greenness of the overall synthetic process.

5. Conclusions

Polyphenolic esters are valuable bio-based compounds, with increased solubility in lipophilic matrices that makes them useful as antioxidants in different industrial fields. The present review aims to discuss all the catalytic routes reported in the literature for their production, emphasizing research gaps that must be covered. Analysis of the available literature showed that most studies involve the use of enzymatic catalysis, while there are few examples of chemical catalysis. Novozym 435 is the preferred lipase due to its high reactivity and ease of separation from the reaction mixture. This lipase is also able to regioselectively esterify complex structures such as those of flavonoids. However, long reaction times are required, mainly due to the mild conditions required for bio-catalysis. By comparison, chemical catalysis is primarily investigated for the esterification of PAs with both fatty alcohols and glycerol. Brønsted acids such as *P*-TSA and SA are the most tested homogeneous catalysts, although ionic liquids were recently investigated as sustainable alternatives. Interesting results were obtained using strongly acidic cation exchange resins (e.g., different amberlites); nevertheless, no studies verify the possibility of recovery and reuse of these heterogeneous catalysts. Considering the industrial potential of PEs, future research should focus on the search for more efficient catalysts, including metal-based ones, in order to improve the sustainability of the overall synthesis process.

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