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Review

Biochemical Characteristics of Laccases and Their Practical Application in the Removal of Xenobiotics from Water

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Abstract: The rapid growth of the human population in recent decades has resulted in the intensive development of various industries, the development of urban agglomerations and increased production of medicines for animals and humans, plant protection products and fertilizers on an unprecedented scale. Intensive agriculture, expanding urban areas and newly established industrial plants release huge amounts of pollutants into the environment, which, in nature, are very slowly degraded or not decomposed, which leads to their accumulation in water and terrestrial ecosystems. Researchers are scouring extremely contaminated environments to identify organisms that have the ability to degrade resistant xenobiotics, such as PAHs, some pharmaceuticals, plasticizers and dyes. These organisms are a potential source of enzymes that could be used in the bioremediation of industrial and municipal wastewater. Great hopes are pinned on oxidoreductases, including laccase, called by some a green biocatalyst because the end product of the oxidation of a wide range of substrates by this enzyme is water and other compounds, most often including dimers, trimers and polymers. Laccase immobilization techniques and their use in systems together with adsorption or separation have found application in the enzymatic bioremediation of wastewater.

Keywords: laccase; xenobiotics; protein engineering

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Citation: Gałązka, A.; Jankiewicz, U.; Szczepkowski, A. Biochemical Characteristics of Laccases and Their Practical Application in the Removal of Xenobiotics from Water. *Appl. Sci.* **2023**, *13*, 4394. https://doi.org/10.3390/app13074394

Academic Editor: Elida Nora Ferri

Received: 7 March 2023
Revised: 20 March 2023
Accepted: 28 March 2023
Published: 30 March 2023

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1. Introduction

Laccases are detected in successive groups of organisms. In addition to fungi (including lichens) and bacteria, these enzymes have been found in sponges, plants and insects [1–5]. Depending on the source of origin, laccases are involved in the processes of synthesis (anabolic pathways) and degradation (catabolic pathways), and these result in their various functions in the metabolic pathways of living organisms [6]. In reaction catalysis by laccases of different origins, there are various products from substrate degradation as a result [7].

The quality of water resources has deteriorated significantly in recent years. This is related to the rapid growth of the population and, thus, dynamic industrial development and the intensification of agricultural activity. In order to meet the nutritional needs of people, the use of chemical plant protection products and pharmaceuticals in animal husbandry is increasing in agriculture. As a result of urbanization and intensive agricultural and industrial activities, many xenobiotics, such as pesticides, steroid hormones, antibiotics and dyes, enter aquatic environments [8,9]. The wide use of dyes is associated with their mass production, which results in the fact that a significant part of them penetrates both water and soil ecosystems. Annually, the textile industry alone generates nearly 200 billion liters of colored wastewater [8,10]. Up to 50% of the amount of industrial wastewater containing dyes is discharged directly into aquatic ecosystems. Azo dyes account for over 70% of global industrial demand (~9 million tonnes) [11]. Xenobiotics were found also in drinking water. Concentrations of PAH, one of the most commonly found xenobiotics in

drinking water, range from trace amounts expressed in ng/L in treated drinking water to as much as about 140 mg/L in untreated drinking water, especially in poor countries with deficiently developed systems of treatment plants and treatment plant water [12].

Another important group of xenobiotics is pharmaceuticals, which include about 10,000 different pharmaceuticals containing about 3000–4000 different active ingredients. Every year, hundreds of tonnes of pharmaceutical compounds are used worldwide [13], which are released into the environment unchanged or after metabolic changes in living organisms [14]. In ecosystems contaminated with pharmaceuticals, such as amoxicillin, azithromycin or erythromycin, populations of microorganisms with antibiotic resistance genes often develop. In addition, especially under the influence of EDCs, which include, e.g., hormones and nonsteroidal anti-inflammatory agents, endocrine, neurological or metabolic disorders occur in both invertebrates and vertebrates [13,15]. The occurrence of pharmaceuticals and their metabolites in surface water, groundwater, coastal seawater, drinking water and sediments has been reported [9].

Biodegradation of xenobiotics is most often a multistage process and consists of the decomposition of organic substances by microorganisms and the enzymes produced by them. The scope and speed of biodegradation changes are conditioned by a number of factors, among which the most important are considered to be the availability of the xenobiotic, metabolic and degradation potential of the microorganism, the oxygenation conditions and the presence of easily assimilable energy and building substrates in the environment [16].

Enzymes are an essential part of the metabolic pathways of all living cells and can be secreted outside cells, as is the case with microorganisms. Bacteria and fungi, depending on the species and even the strain, produce different classes of enzymes in variable amounts. This is closely related to their adaptation to life in various environments with different abiotic conditions (e.g., temperature, pH, pressure and oxygenation) and biotic conditions (including the availability of nutrients and sources of C, N and P). Enzymes enable microorganisms to use organic and inorganic substances, such as carbon and energy sources, by catalyzing the degradation of specific substances [17], which was used in the biodegradation of environmental xenobiotics. Laccases are currently being intensively researched for potential use in the biodegradation of xenobiotic compounds, such as pharmaceuticals, dyes or plasticizers [18]. The costs of the industrial production of enzymes and their sensitivity to unfavorable conditions, such as temperature, pH or the presence of inhibitors in wastewater, are a problem. The optimization of the production of laccases resistant to extreme environmental conditions, immobilization and recombination techniques will, in the future, reduce the costs of bioremediation with enzymes [19].

In this review, the biochemical characteristics of laccases of various origins, their functions in nature and potential applications in industry and water bioremediation will be discussed. The mechanisms of the laccase-assisted removal of xenobiotics from the environment and the possibilities of improving their biochemical properties and productivity using traditional methods and with the use of genetic engineering and protein engineering will also be discussed in general. Some problems encountered in enzymatic bioremediation and their possible solutions are also listed.

2. Characteristics of Laccases

Metal-dependent laccase enzymes of the oxidoreductase class [EC 1.10.3.2] are included in the ligninolytic complex. Together with ascorbate oxidases, ceruloplasmin, bilirubin oxidase, phenoxazinone synthase and metallo-oxidase Fet3p, they belong to the multicopper oxidase (MCOs) family. These enzymes are characterized by their broad substrate specificity and in catalyzed reactions, they use molecular oxygen as an electron acceptor and produce a water molecule as a result of oxygen reduction. Oxidases of the MCO-type oxidize many polyphenolic substrates and monomeric phenolic compounds, as well as diamines and metal ions [20]. The family of multicopper oxidases is related by the common structure of the catalytic center, in which at least four copper atoms are

present. Based on the spectroscopic and magnetic properties of these copper atoms, they are classified as types T1, T2 and binuclear T3. The final product formation occurs through the oxidation of the substrate molecules to oxide radicals with the simultaneous reduction of an oxygen molecule to two water molecules according to the general notation: $4RH + O_2 \rightarrow 4R- + 2H_2O$ [21–23]. Laccases form multimetric complexes that can be mono-, di- or tetrameric glycoproteins. Each monomer has four copper atoms in its catalytic center: a type 1 (T1), type 2 (T2) and type 3 (T3). In the active center of MCOs, T2- and T3-type copper atoms occur close to one another, forming a trinuclear copper cluster (TNC). The T1-type mononuclear copper center occurs at a position approximately 12 Å away from the others [24].

The first of these, type T1, is the initial acceptor of electrons formed during the substrate oxidation reactions catalyzed by laccase, and the redox potential of the enzyme also depends on it. Typically in fungal laccases, this copper atom is bound to a histidine residue and one cysteine residue. Bacterial and plant laccases show a slightly different mechanism, in which the copper ion is coordinated to two histidines, one cysteine and an additional axial bond to one methionine, resulting in a tetrahedral geometry. In addition, T1 gives the enzyme its blue color. A charge transfer from the cysteine residue to Cu (II) is responsible for the formation of the intense absorption band at 600 nm, which is associated with the blue color [24,25].

Based on the redox potential (E0) of the T1 copper center, we distinguish between laccases with low, medium and high redox potential. Low potential is characteristic of most laccases synthesized by bacteria and plants. Laccases with medium redox potential are typical of fungi of the genus *Myceliophthora* or *Coprinopsis*. In contrast, fungi of the genus *Trametes*, belonging to the so-called white rot fungi, synthesize laccases with high redox potential [24–28]. Selected representatives of this group are shown in Figure 1.

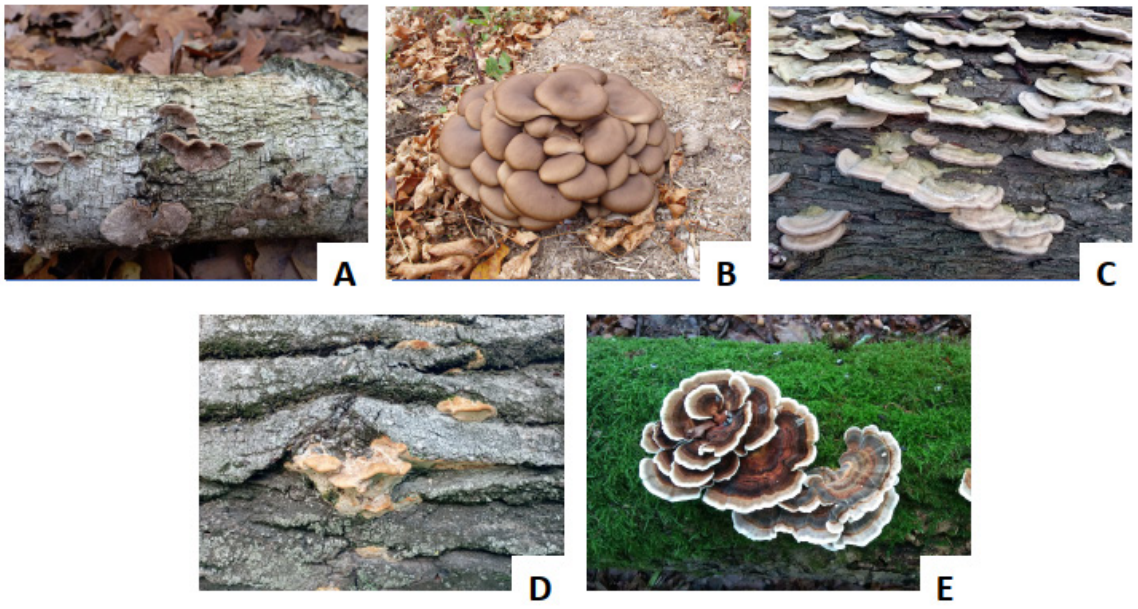

Figure 1. (**A**) Basidiomata of *Cerrena unicolor*, Poland. (**B**) Basidiomata of *Pleurotus ostreatus* and the white rot wood, Poland. (**C**) Basidiomata of *Trametes hirsuta*, Poland. (**D**) Basidiomata of *Trametes trogii*, Poland. (**E**) Basidiomata of *Trametes versicolor*, Poland. Photography by Andrzej Szczepkowski.

One of the essential functions of the T1-type copper center is to oxidize the substrate by taking up electrons and transferring them via the cysteine–histidine pathway to the NTC cluster. This mechanism results in the reduction of oxygen directly to water. The trinuclear cluster consists of binuclear type III copper atoms and mononuclear type II copper atoms. A Cu T2 atom with much lower light absorption is coordinated by two histidine molecules and one water molecule. Type III copper shows strong absorption at 330 nm as a result

of charge transfer from the μ-hydrox bridge (μ-OH) to type III Cu (II). The T3 atom is coordinated by three histidine residues and one water molecule [24,29,30].

3. Occurrence and Function of Laccases

Laccases are commonly synthesized by living organisms, including bacteria, plants, insects and fungi, and are involved in various biological processes that are different depending on the organism producing them [22,27,31].

Producers of prokaryotic laccase can include Gram-positive and Gram-negative bacteria living in different environments, among which are representatives of *Streptomyces*: *S. lavendulae*, *S. cyaneus*, *Ralstonia solanacearum*, *Sinorhizobium meliloti*, *Bacillus subtillis*, *Marinomonas mediterranea* and *Escherichia coli*. Currently, the best characterized is laccase CotA synthesized by *B. subtillis* [32–34]. Intracellular laccases are responsible for neutralizing toxic by-products released in biochemical reactions. Under natural conditions, bacterial laccases are also involved in pigmentation, morphogenesis, toxin oxidation and protection from UV light and the cross-linking of envelope proteins in bacterial spores, among others [18,35–40].

Most of the available literature data on laccase-synthesizing fungi concerns species belonging to the phylum *Basidiomycota* and *Ascomycota* [21,40]. One of the main functions of fungal laccases is the breakdown of lignocellulose, which affects the carbon cycle in the biosphere. Fungal laccases also have more specialized functions, e.g., participation in the synthesis of pigment that protects fungal spores from factors such as high temperatures or UV radiation or the synthesis of antibacterial compounds [41,42]. Phytopathogenic fungi have been shown to produce laccase to inactivate plant defense mechanisms. In the case of *Cryptococcus neoformans*, laccase is considered a virulence factor. Immunocompromised individuals, such as those with AIDS or patients taking high levels of corticosteroids, are particularly vulnerable. The enzyme is thought to convert host catecholamines into melanin, which promotes protection of the pathogen and allows it to cause more damage to the host [43,44].

All plant laccases have one common function, which is to participate in a multienzymatic system involved in the synthesis of lignin in wood cells responsible for maintaining the structure and rigidity of the cell wall. It is found in the xylem, where it is involved in the initial phase of lignin biosynthesis by oxidizing monolignols [45,46]. This enzyme is also involved in the repair mechanism of damaged plant tissues. Above this, its participation can also be seen in plant defense processes, iron accumulation and the polymerization of phenolic compounds [21,47]. In the plant family *Anacardiaceae*, it is found in resin ducts, indicating a defensive function of the enzyme against herbivores, predators and microorganisms. In the common radish (*Arabidopthis thaliana*), on the other hand, the aforementioned enzyme is involved in the polymerization of flavonoids needed for seed coating and in the production of brown polymers with a putative protective function. In green algae present in both aquatic and terrestrial environments, the main role is the detoxification of phenolic compounds and participation in the synthesis of cell walls and UV-absorbing compounds, as well as in nutrient acquisition [21,48].

Insects are the best-known laccase producers in the animal world. The presence of this enzyme has been found in insects of the order *Hymenoptera*, *Diptera*, *Lepidoptera* and *Coleoptera* [2,49–51]. The main role of laccase produced by insects is its involvement in epidermal synthesis, wound healing, morphogenesis and immune system development [2,21,52,53]. In insects, laccase, located in the intestinal cells, plays a defensive role against toxic lignin derivatives entering the host organism as a result of its consumption of plant products. In these organisms, the aforementioned enzyme is also involved in epidermal hardening in larval forms, pupae and adults, as in *Drosophilia virilis* [3]. In insects, there are two main forms of laccase: laccase-1, which is present in the salivary glands, midgut, Malpighian tubules and epidermis, such as in *Manduca sexta*, playing a protective role by oxidizing toxic compounds ingested by the insect, and laccase-2 involved

in the hardening of its epidermis. Furthermore, in the gut, laccase is involved in the production of melanin, an immune system response to the presence of parasites [21,54,55].

4. Biochemical Properties of Laccase

The suitability of enzyme proteins for biotechnological applications is determined by their biochemical properties, especially their stability in temperature and pH. Laccases are enzymes with diverse biochemical properties, depending on the type of organism synthesizing the enzyme. Bacterial laccase enzymes are mostly monomers with molecular masses in the range of 30 to 80 kDa. There are also a few subunit laccases in this group [21,56]. The laccases mainly act intracellularly, although there are also extracellular laccases in this group of enzymes [57–59]. These enzymes are highly variable in their pH and temperature optima and often exhibit thermostability. Temperature optima, depending on the bacterial species, range from 25 to 85 °C. A similar trend is observed for pH optimum values. Bacterial laccases have been known to be active in acidic environments as well as in neutral and alkaline environments [18,21]. For example, *A. lipoferum* laccase shows the highest activity for syringaldazine at 70 at pH 6.0 [56], while *B. subtilis* $\leq$ pH 3.0 at pH 7.0 for ABTS [60]. Under laboratory conditions, bacterial laccase shows activity against many substrates, including 2,4 dimethoxy phenol (*B. licheniformis* LS04), azinobis(3-ethylbenzthiazoline-6-sulfonic acid, ABTS) (*Pseudomonas aeruginosa*), guiacol (*B. subtilis*), syringaldazine (*Stenotrophomonas maltophilia*) and hydroquinone (*P. desmolyticum*) [18,58,61,62].

Fungal laccases are among the best characterized. The stability of fungal laccases varies widely, depending on the source of origin. Typically, however, fungal laccases have lower thermal stability than bacterial laccases. It is likely that the stability has to do with the interaction of copper with the salt bridges, as well as hydrogen bonds that are part of the internal protein structures and the presence of certain amino acids [43,57,63]. These are overwhelmingly glycosylated enzymes that act extracellularly. The molecular weight of these enzymes typically ranges between 50 and 140 kDa. Most laccases purified from fungal cultures are monomeric proteins, but subunit enzymes have also been described [21,40,64]. The majority of fungal laccases are enzymes that operate in an acidic environment, with the optimum usually falling in the range of pH values 3–6, depending on the substrate. The temperature optimum for the activity of typical fungal laccases is between 50 and 70 °C [21,64,65]. In the case of fungal laccases, a frequently used substrate is ABTS or syringaldazine, which is often referred to as a specific substrate for laccases [66,67].

Laccases of plant and animal origin are less well described in the scientific literature. Plant laccases are glycoproteins secreted into the apoplast. Usually the molecular weight is between 60 and 150 kDa. The pH optimum is between 5 and 7. Plant laccase utilize typical laccase substrates, including ABTS, hydroquinone, catechol and 4-methylcatecholals [21,40,43,68].

Laccases are localized intracellularly in most insects, and their molecular weight ranges from 70 to 100 kDa. These enzymes show activity against ABTS, 4-methylcatechol, and dopamine and its derivatives as substrates [54,67,69,70].

Table 1 summarizes the biochemical properties for certain laccases of different origins.

Table 1. Sources and biochemical characterization of laccases.

Type of Source Organism	Source/Organism	MW, Subunit Structure	Optimum pH and Temperature	Substrate (Most Efficient)	Regulation of Activity/Synthesis	References
Plant	*Tetracystis aeria* SAG 89.80	220 kDa, heterooligomer: two polypeptides highly N-glycosylated: 110 and 71 kDa	pH 2.5	ABTS	Not mentioned	[71]
	Leucaena leucocephala	~220 kDa, heterodimer: two subunits of 100 and 120 kDa	pH 7.0, 80 °C	Catechol	Mn^{2+}, Cd^{2+}, Fe^{2+}, Cu^{2+}, Ca^{2+} and Na^{+} activation laccase; Co^{2+}, Hg^{2+}, DTT, SDS and EDTA inhibition laccase	[72]
	Pistacia atlantica Desf.	60 kDa	pH 7.5, 45 °C	DMP	Cu^{2+} activation laccase; Zn^{2+} and Mg^{2+} have a stabilizing effect; Hg^{2+} Fe^{2+} inhibition laccase	[73]
Bacteria	*Bacillus amyloliquefaciens* B10	30.9 kDa	pH 6.0–8.0, 40 °C	Aflatoxin B1 (AFB1)	Significant reduction in activity in the presence of metal ions: Cu^{2+}, Co^{2+}, Fe^{3+}, Mn^{2+}, and Zn^{2+}; Slight reduction in activity in the presence Na+ and K+	[74]
	Enterococcus faecium A2	50.11 kDa.	pH 6.0, 80 °C	ABTS	Cr^{2+}, Cu^{2+}, Fe and Ag^{+} activation laccase	[75]
	Bacillus sp.	63–75 kDa	pH 7 40 °C	ABTS	Not mentioned	[76]
Fungi	*Trichoderma harzianum* S7113	Two isoenzymes: 63 kDa (LacA) and 48 kDa (LacB)	pH 3.0, 50 °C (LacA) pH 2.5, 50 °C (LacB)	ABTS	Mg^{2+}, Zn^{2+}, K^{+}, and Ni^{2+} activation laccase; Hg^{2+} and Pb^{2+}, β-mercaptoethanol, EDTA and SDS, sodium azide inhibition laccase	[77]
	Ganoderma leucocontextum	65.0 kDa/monomer	pH 3.0, 70 °C	Guaiacol	Ca^{2+}, Cu^{2+} and Zn^{2+} activation laccase	[78]
	Agrocybe pediades	55–60 kDa/monomer	pH 5.0 45 °C	2,6-DMP	Not mentioned	[79]
Insect	*Plutella xylostella*	66.09 kDa	pH 3.0, 35 °C	ABTS	Cu^{2+} increased laccase activity	[80]
Crabs	*Chiromantes haematocheir*	67.708 kDa (deduced)/monomer		2,6-DMP	Presence of $CuSO_4$ in culture medium was essential for laccase activity	[81]

5. Applications of Laccases

According to Business Communication Company (BCC) Research, the market for enzymes for industrial applications is expected to grow from USD 5.5 billion in 2018 to USD 7.0 billion in 2023 [82].

Laccase was first used industrially in the 1990s, and several laccases are now commercially available. Commercially available laccases come from *Trametes versicolor*, *Agaricus bisporus*, *Pleurotus ostreatus* and *Rhus vernicifera* [40,83]. Due to the simplicity of production and purification, the amount of enzyme produced in relation to the costs incurred (the possibility of culturing on agricultural and food industry waste in the presence of readily available and cheap inducers), almost all commercially available laccases come from fungi [6]. Although these organisms have a fairly slow growth rate and the enzymes they produce are unstable under conditions of high temperatures, alkaline stress and high salt contents, they are used in most industrial processes. The reason for this is that fungal laccases have a much higher redox potential than bacterial laccases. New laccases of bacterial origin are currently being sought as they show better stability in a wide range of pH, less susceptibility to inhibitory factors, such as salinity or the presence of metal ions, and are resistant to hot temperatures. In addition, bacterial laccases, compared to fungal laccases, are quite easily subjected to all genetic and protein engineering treatments [84].

White rot fungi (WRF) are a significant source of laccases. Laccase, along with lignin peroxidase and manganese peroxidase, is the main enzyme associated with the ability of WRF to degrade lignin [85,86]. Lignocellulose is the most common source of carbon on earth and accounts for more than 60% of total plant biomass [82]. This includes but is not limited to sawdust and paper mill waste, waste paper, agricultural residues (straw, peelings, cobs, stems, nutshells, nonfood seeds and bagasse), household waste (including sewage), residues from the food industry and solid municipal waste. Lignocellulosic feedstocks are renewable resources that can potentially be used to synthesize fine chemicals, such as biofuels, cellulose and paper, enzymes, composites and animal feed [87]. Unfortunately, lignocellulose is a polymer material with high resistance to degradation, thanks to lignin, a polymer composed of aromatic alcohol monomers [88]. Enzymatic delignification with laccases depolymerizes the lignin, which increases the bioavailability of the resulting biomass for cellulolytic enzymes at a later stage. The advantages of the enzymatic pre-treatment of lignin compared to other methods include the production of fewer by-products, including those toxic to the environment, low energy input, significant biomass conversion and mild operating conditions [87,89,90]. The laccases of the halophilic bacteria *Aquisalibacillus elongatus* and *Chromohalobacter salexigens* showed the ability to delignify beet pulp and almond shell biowaste, respectively. The enzymes were highly stable extracellular laccases, resistant to the presence of organic solvents, salts, metals, inhibitors and surfactants in the reaction environment and showed high catalytic efficiency in a wide range of phenolic and nonphenolic substrates differentiated in terms of structure and redox potential. Laccases can be an alternative to chemical methods of lignocellulosic fiber processing, the extraction of lignocellulosic biowaste or the delignification of lignin and lignin-derived industrial waste [91,92].

The processing of plant biomass and delignification of agro-industrial materials leads to the simultaneous production of glucose, which can be further used to produce bioethanol [87,90]. During the production of bioethanol from lignocellulose, in addition to a mixture of sugars, phenolic compounds are also formed that inhibit yeast fermentation and, thus, the production of alcohol. To increase fuel ethanol production from renewable feedstocks, *T. versicolor* laccase was expressed under the control of the PGK1 promoter in *S. cerevisiae* to eliminate phenolic compounds from lignocellulosic hydrolysates [32,93,94].

The potential of laccase applications in the field of biotechnology and the bioremediation of contaminated environments and industries is huge. Laccase oxidizes a wide range of compounds directly or indirectly in the presence of mediators, with the simultaneous reduction of molecular oxygen to water, which is the purest co-product of the reaction [95]. During the oxidation of substrates, apart from water, free radicals are formed, which further

react either with each other or other substances present in the reaction mixture, which is the reason for the production of various products by laccases [93], with a wide field of practical applications.

Figure 2 shows the sources of laccases and their potential applications.

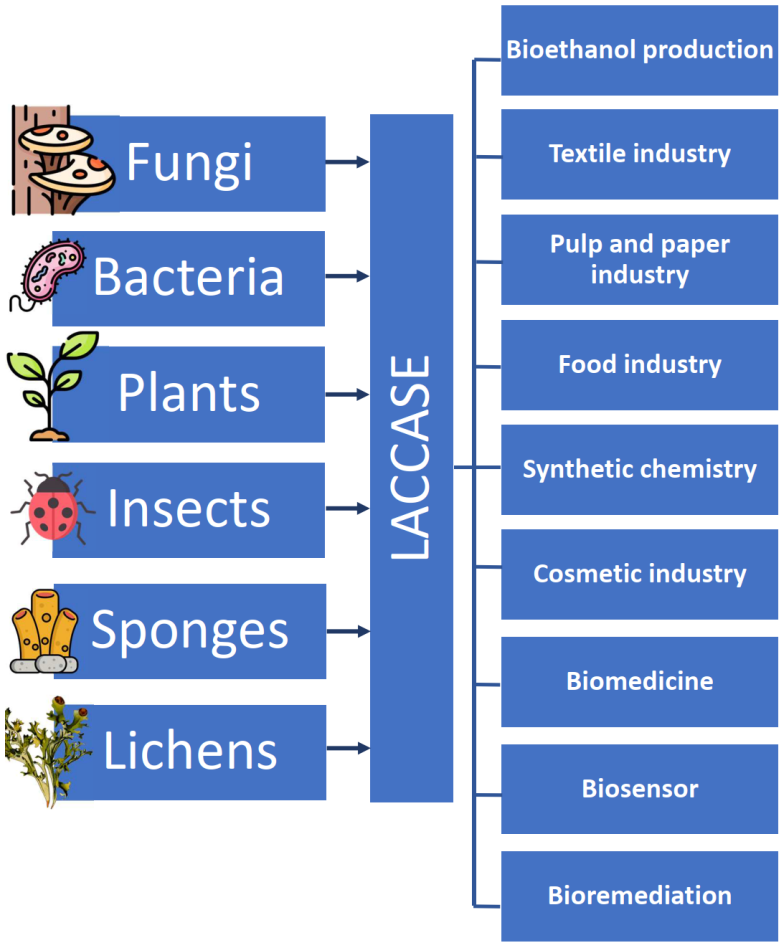

Figure 2. Sources of laccases and their potential applications.

In the paper industry, laccase is mainly used for pulp delignification and paper deinking, as well as for improving the properties of pulp fibers and the tensile strength of paper sheets [96]. The use of laccases in the bleaching of kraft pulp may result in higher yields of pulp and energy savings in addition to a significant reduction in environmental contamination with chemicals [32].

Laccases play an important role in textile processing, such as the biobleaching of fibers (cotton and wool), denim washing, wool washing, dye synthesis and wastewater treatment. [97–103]. Laccase is an effective alternative to the most common whitening agent, hydrogen peroxide [10,96,104]. In the late 1990s, the first Deni-Lite laccase product from Novozymes was launched on the market for use in the textile industry for the bleaching and finishing of denim. This commercial use of a product containing laccase initiated the further development of research and the search for new laccases that could be widely used in textile industry plants [103].

In the food industry, laccase has been used, among others, for stabilizing wine, clarifying fruit juices and baking or producing pectin from sugar beets [31,32,44,96,105–108]. Laccase used in the clarification of fruit juices oxidizes most of the phenols in the juice, minimizing turbidity and increasing its stability [109–112]. As the use of laccase as a food additive is still not allowed, this enzyme is used in the food industry in an immobilized form [32,113,114].

Lacasse participates in the formation of new bonds in homo- and heteromolecular reactions of easily oxidized substrates. The formation of new C-C, C=C, C-O and C-N or C=N and C-S bonds results in the appearance of new hybrid molecules in the reaction mixture [95,115–118], without the need to consume large amounts of energy and without highly polluting chemical compounds. These new homo- and heteromolecular molecules can be therapeutic compounds. such as antibiotics (new derivatives of β-lactams, sulfonamides or aminoglycosides) or cytostatics (including naphthoquinone and benzofuran derivatives) [82]. In general, the formation of new compounds with the laccase department consists largely of the cross-linking of radicals generated by the enzyme with another molecule in which reactive intermediates are trapped [119].

In recent years, laccase has aroused great interest as a potential anticancer and antiviral therapeutic ingredient. The antiviral effect of laccases acquired from *Agaricus placomyces*, *Pleurotus eryngii* and *P. ostreatus* has been described against HIV-1 and HCV [120–122]. The antiproliferative effect of the enzyme isolated from *Abortiporus biennis*, *T. versicolor*, *Trametes mongolicum* and *Agrocybe cylindracea* against HepG2 hepatoma cells and MCF7 breast cancer cells was observed [123–127].

Recently, there has been an increase in the number of publications describing the action of laccases as biosensors for the determination of xenobiotics present in samples of various origins from the food industry to wastewater. Very often, the mechanism of the operation of biosensors is based on the ability of laccases to degrade undesirable compounds in the analyzed matrices [128–130,130–132]. This property of laccases is also exploited in enzyme-based bioremediation to remove xenobiotics present in urban, agricultural and industrial wastewater. The great interest of researchers in the field of potential applications of laccases in the bioremediation of newly emerging pollutants in the aquatic environment results from their beneficial biochemical properties and excellent diversity [93]. Laccase was used to remove emerging pollutants, such as nonylphenol, triclosan, BPA, ethinylestradiol, diclofenac, 2,4-dichlorophenol and others [90,133–160]. In the next chapter, we will summarize the current knowledge on the processes of removing pollutants of various origins from water with the use of laccase.

Laccases show promising potential in a variety of environmental and industrial applications, which will be listed in Table 2.

Table 2. Laccase applications.

Application	Source Organism	Activity	References
Pulp and paper industry	*T. versicolor*	Demethylated and delignified the sulphate pulp	[161]
	Bacillus sp.	Decolorization of old newsprint and the biological bleaching of eucalyptus kraft pulp	[162]
	Fusarium equiseti VKF2	Biological bleaching of newspaper waste	[163]
	T. versicolor	Immobilized laccase on copper ferrite magnetic nanoparticles (CuMNPs) improve the delignification	[164]
Textile industry	*Myceliophthora thermophila*	Altered the shape of wool yarn by laccase-assisted tyrosine grafting	[165]
	Cerrena unicolor	Biocatalyst to transform 8-anilino-1-naphthalenesulfonic acid into a water-soluble green dye with antibacterial and antiallergic properties and high dyeing efficiency of wool fibers	[95]
	Brevibacillus agri	Bleaching denim and decolorizing water-soluble azo dyes	[166]
	Achromobacter xylosoxidans HWN16 *Citrobacter freundii* LLJ16	Biocleaned and discolored jeans discolored the wastewater after washing the fabrics	[167]

Table 2. *Cont.*

Application	Source Organism	Activity	References
Food industry	*Bacillus atrophaeus*	Recombinant laccase covalently immobilized on magnetic iron nanoparticles and then used them to remove phenols and clarify plant juice samples	[105]
	T. versicolor	Improving the stability of emulsifying beet pectin	[168]
	Recombinant laccase from *Pleurotus pulmonarius* expressed in *Pichia pastoris* X33	Degrade mycotoxins zearalenone and aflatoxin B1	[169]
Synthetic chemistry	Laccase *P. ostreatus* immobilized on the $CuFe_2O_4$ nanocomposite	Synthesize arylsulfonylbenzenediols through oxygen oxidative coupling between benzenediols and sodium benzenesulfinates	[170]
	P. ostreatus	Synthesize new organic orange textile dye (N15) by transforming 2-amino-3-methoxybenzoic acid	[115]
Cosmetic industry	*T. versicolor*	Bleaching agents in whitening cream that degraded up to 87% eumelanin	[171]
	C. unicolor	Green compound, a result of the 8-anilino-1-naphthalenesulfonic acid (ANS) oxidation reaction, with antibacterial activity against the growth of bacterial strains *Staphylococcus aureus* ATCC®25923™ and *Staphylococcus epidermidis* ATCC®14990™ commonly found on the skin; antioxidant properties and low cytotoxicity (cosmetic additive)	[95]
	Brevibacillus agri	Hair dyeing	[172]
Biomedicine	*T. versicolor*	Producing laccase cross-linked hydrogels based on silk fibroin and hyaluronic acid modified with tyramine	[84]
	C. unicolor	Antiviral effect against human herpes virus type 1 (HHV-1) and encephalomyocarditis virus (EMCV) anticancer effect against cell lines derived from primary cervical cancer (SiHa) and its metastases to the small intestine (CaSki)	[173]
	Bacillus sp. MSK-01	Antiproliferative activity against a lung cancer cell line A549	[174]
Biosensor	*Bacillus subtilis*	Detection of glyphosate; CotA laccase effectively catalyze the luminol-H_2O_2 reaction, creating a chemiluminescent (CL) signal	[175]
	T. versicolor	The chemiluminescent (CL) immunoassay for the detection of Escherichia coli O157:H7 in synthetic samples (spring water, apple juice, skimmed milk)	[176]
	Laccase *T. versicolor* immobilized on an electrospun zein fiber (ceZL)	Producing smart packaging systems can provide food quality information and the time and temperature index, TTI	[177]
Bioremediation	Recombinant *Bacillus amyloliquefaciens* TCCC 111018 laccase expressed in *E. coli*	Decolorize synthetic azodyes (azofloxine, congo red and adisole black B), anthraquinones (reactive blue 19, reactive blue 5 and remazol brilliant blue R) and triphenylmethane (crystal violet, indigo carmine and malachite green)	[178]
	Trematophoma sp. UTMC5003	Pyrene, anthracene and phenanthrene degrading	[179]
	Sphingobacterium ksn-11	Transformation of diclofenac	[149]

6. Types and Mechanisms of Removing Xenobiotics from Water

Based on the NORMAN network, in aquatic environments in Europe, at least 700 substances have been identified. Substances that enter aquatic ecosystems as a result of human activities, even in small amounts, can bioaccumulate and potentially threaten the life and health of humans and animals [9].

The development of analytical techniques has made it possible to notice the presence of many new compounds in drinking, ground and surface water [180]. New groups of contaminants include compounds such as human and veterinary antibiotics (e.g., erythromycin,

amoxicillin and chloramphenicol), anti-inflammatory drugs (e.g., ibuprofen, diclofenac and acetaminophen), psychiatric drugs (e.g., diazepam and carbamazepine), β-blockers, lipid regulators, X-ray contrast agents, body care products (e.g., phthalates and benzophenone), endocrine-disrupting compounds (EDCs) (e.g., 4-octylphenol and synthetic and natural hormones, such as estrone, 17β-estradiol, estriol, 17α-ethinylestradiol, progesterone, 4-nonylphenol, bisphenol A (BPA), perfluorinated compounds (PFCs), surfactants and surfactant metabolites (e.g., alkylphenol ethoxylates, 4-nonylphnol and 4-octylphenol), flame retardants (e.g., polybrominated diphenyl ethers), plasticizers, industrial additives and agents (e.g., chelating agents (EDTA) and aromatic sulfonates), antiseptics triclosan, chlorophene, parabens and others. In general, pharmaceuticals and EDCs are the largest groups of contaminants [9,180–182]. The main xenobiotics found in aquatic ecosystems are shown in Figure 3.

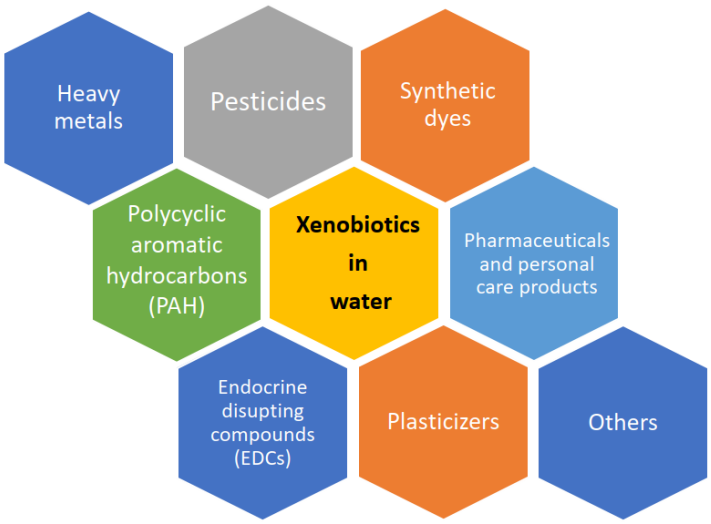

Figure 3. The main xenobiotics found in aquatic ecosystems.

Laccases (EC 1.10.3.2), using the redox capacity of copper, oxidize a whole range of organic and inorganic substrates. The range of substrates amenable to catalyzed reactions can be extended by mediators [82,183–186]. The range of oxidized substrates varies from laccase to laccase [6,187,188].

The key advantages of laccases in bioremediation are (i) action on a wide range of substrates; (ii) the reduction of the molecular oxygen to water while oxidizing the reducing substrate; and (iii) no production of hydrogen peroxide, which could degrade other enzymes added in subsequent steps of bioremediation [6,32]. The redox potential of laccase plays a major role in their reactivity. Wide differences between the redox potential values of different laccases were observed. Redox potential values lie between 0.43 and 0.79 V. Trees and other plants are the sources of laccases with a low redox potential of the T1 site in the active site of the enzyme, while fungal laccases (e.g., *Trametes* (formerly *Coriolus*, *Polyporus*) *hirsuta* (*hirsutus*), *T. versicolor* and *T. villosa*) have the highest known redox potentials [189,190]. Therefore, the search for new sources of laccases and their biochemical characterization is necessary for the further development of biological methods of wastewater treatment of various origins.

6.1. Types of Laccase- Assisted Removing Xenobiotics from Water

6.1.1. Synthetic Dyes

There are about 10,000 different textile dyes, with a global production of more than 700,000 tonnes per year [8]. Dyes are present in many areas of human life. They have many applications, from the textile, tanning, cosmetic and food industries to medicine. The sources of synthetic organic dyes in aquatic environments are industry (including 20% of

the pollution that comes from the textile industry) and households (food dyes, improperly disposed of unused medicines, hair dyes, cosmetics, household chemicals, e.g., shampoos, soaps and washing powders) [8,191,192]. The textile industry uses large amounts of drinking water to produce fibers and, thus, releases huge amounts of wastewater [192].

In 1865, while trying to produce quinine, William Henry Perkin unexpectedly synthesized purple, the first commercialized synthetic organic dye, which marked the beginning of the production of synthetic organic dyes on a global scale [10]. Currently, this market includes around 100,000 substances [8].

Dyes can be divided into natural and synthetic dyes. Synthetic dyes are easy and cheap to produce, come in a variety of colors and are durable, which makes them more widely used than natural dyes [192]. Synthetic organic dyes are divided into groups depending on their chemical structure (acridine, anthraquinone, azo, azine, diphenylmethane, indigoid, methine, nitro, nitroso, oxazine, phthalocyanine, thiazine, triphenylmethane and xanthene) and depending on their use (acidic, basic, direct, dispersive, fibrous, reactive, vat and pickle) [193]. An important feature of synthetic dyes used by the industry is their high resistance to external physical and chemical factors, such as solar radiation, large temperature changes or the presence of detergents and disinfectants in washing agents. This is also related to their poor biodegradability in the environment [106,192,194].

Among them, the most commonly used dyes are azo dyes, which are resistant to decomposition under the influence of temperature, light or acids and alkalis, which makes their removal from wastewater very difficult [19]. The disposal of approximately 4.5 million tonnes of dyes and their degradation products, a large part of which is highly toxic to living organisms, is a huge environmental problem and entails high costs, e.g., for the construction of the appropriate sewage treatment plant infrastructure [11].

A large amount of water used in industry and the loss of dyes during textile processes generate huge amounts of colored wastewater. The dyes present in wastewater absorb and reflect sunlight. Light penetration is limited, which disturbs the photosynthesis of aquatic flora, and consequently leads to a decrease in the amount of oxygen dissolved in the water. Synthetic organic dyes have a toxic effect not only on the flora but also on the fauna of aquatic ecosystems. In fish, dyes are absorbed through the gills and skin [195]. They are then distributed throughout the body and undergo metabolization. For example, azo dyes are degraded to carcinogenic aromatic amines by azoreductase produced by intestinal microflora [196]. Compared to the parent form, a lot of these metabolites are more lipophilic than the starting material and, therefore, easily accumulate in the fat tissue of fish, for example, and remain in the weight of fish for longer. These mechanisms consequently lead to the bioaccumulation of dyes in the trophic chain [8,11].

Due to their toxicity to living organisms, these dyes should be detoxified or eliminated (usually discolored) prior to discharge into the environment [19,197]. Due to the complex structure of the dyes used and the complex composition of wastewater from various industries [9], physical, chemical and biological methods or a combination of several methods are used to remove dyes [197]. Textile wastewater contains dyes mixed with various impurities in different ranges, such as metals, solvents, salts, surfactants and other chemicals [8,19].

Biological decolorization of this wastewater is an ecological and cost-effective approach that does not generate secondary wastewater [11,19,197]. Laccases have found a particular application in the decolorization of dyes because they are able to oxidize both phenolic and nonphenolic compounds [197].

Myrothecium verrucaria NFCCI 4363, a fungus isolated from soil contaminated with waste from the sugar industry, produces extracellular laccase capable of decolorizing wastewater containing azo, triarylmethane and nitro dyes. The enzyme showed maximum activity at pH 6 and 50 °C and did not significantly change its enzymatic activity in the presence of low concentrations of some metals and solvents (dichloromethane, acetonitrile and methanol). The enzyme without mediators decolorized triarylmethane dyes (bromothymol blue, bromocresol green and bromocresol purple) with an efficiency of about

80%. In the presence of ABTS as a mediator, the laccase discolored acid magenta by about 70% and crystal violet by about 58%. Jawale et al. (2021) suggest that the degree of dye decolorization by laccase depends mainly on the origin of the enzyme and the presence of mediators, metal ions, solvents and other compounds in the reaction mixture [198].

A single laccase with a molecular weight of 41 kDa was produced by the white rot fungus *Oudemansiella canarii* EF72, an edible mushroom from *Agaricales* (mushrooms) commonly found in the Atlantic rainforest, Amazon rainforest and Pantanal [199]. The enzyme showed a broad range of pH stability (from 3.0 to 8.0) for at least 6 h. Laccase decolorized Congo red by 80% in 24 h at 30 °C and pH 5.5. The azo dye Congo red is present in significant amounts in textile and paper industry effluents and has been reported to be carcinogenic to humans and toxic to humans [10]. The analysis of Congo red degradation products revealed that the laccase acts on the chromophore group of the dye and asymmetrically cleaves azo covalent bonds, causing effective fragmentation of the molecule and the formation of products with nitrification of the NH_2 group and loss of the SO_3 group. The nitrified and/or hydroxyl groups of the naphthalene derivatives identified in the reaction mixture were probably derived from the oxidation of the amino groups present in Congo red. In the last stage of degradation, the benzene ring opened, and a fully oxygenated compound with the formula C8H3N2O8 was formed. The native laccase treatment reduced toxicity by 92.5% after 24 h. In conclusion, *O. canarii* laccase can be used in the bioremediation and detoxification of azo dyes.

The laccase of spores of the halotolerant bacterium *Bacillus safensis* S31, isolated from the soil of a chromite mine in Iran, showed the ability to decolorize various classes of dyes. The maximum activity of the enzyme was achieved at 30 °C and pH 5.0. The enzyme tolerated the presence of 10% solutions (*v*/*v*) of solvents, such as methanol, ethanol and acetone and most of the tested metal ions. Unlike many other laccases, NaN_3 at concentrations of 0.1 and 1 mM showed a slight inhibitory effect on enzyme activity (7.5%), which is important due to the fact that NaN_3 is a toxic substance found in textile industry wastewater and dyeing. The enzyme showed the highest decolorization efficiency in relation to malachite green (87%) in the presence of ABTS and in relation to reactive black 5 (75%) in the absence of ABTS. In conclusion, the research by Siroosi et al. (2018) proved that B. safensis S31 spore laccase can be used for the bioremediation of textile wastewater containing a number of dyes due to its high tolerance to metals, salts, solvents and sodium azide [19].

6.1.2. PAHs (Polycyclic Aromatic Hydrocarbons)

Polycyclic aromatic hydrocarbons (PAHs) are aromatic hydrocarbons with two or more fused benzene rings in different structural configurations that do not contain heteroatoms or substituents. The benzene ring systems in PAHs are responsible for their wide range of physical, chemical and toxicological properties [200]. Chemically, we can distinguish low molecular weight (LMW) and high molecular weight (HMW) PAHs. Both low molecular weight (LMW) and high molecular weight (HMW) PAHs can be microbially degraded [201]. LMW PAHs are more susceptible to degradation due to the rather higher volatility and solubility of the compounds [12]. Due to the stability, hydrophobicity and lipophilicity of PAH molecules, they are harmful, persistent, organic pollutants that are very difficult to biodegrade [12,200].

PAHs include a huge number of compounds. The PAH group contains substances such as anthracene, acenaphthene, acenaphthylene, benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, chrysene, fluoranthene, fluorine, naphthalene, phenanthrene, pyrene and many others [200,202]. These compounds are widely used in various industries, e.g., for the production of dyes, pharmaceuticals, plastics, fungicides and insecticides [12].

PAHs are widely distributed in various ecosystems. In aquatic environments, PAH concentrations range from trace amounts expressed in ng/L in the water of the Sea of Japan to values significantly exceeding the standards, as in the case of household wastewater

treatment plants in South Africa, where a record PAH concentration of over 8 mg/L was reported. Chryzene, due to its poor solubility in water and low vapor pressure, is one of the most persistent PAHs in the water column [203]. Moreover, PAHs can bioaccumulate in fish. More than 4 µg/g have been found in *Saurida undosquamis* in Egypt. Such a PAH is benz[a]anthracene (BaA), which tends to accumulate in lipid-rich tissues [12].

Aquatic ecosystems are exposed to PAHs mainly as a result of accidental oil spills, with huge health consequences for the fish, birds and mammals living in these ecosystems. The effects of PAH exposure in fish include immunotoxicity, gill deformity, increased mortality, reproductive disruption, liver tumors, uncontrolled cell growth, reduced growth, embryo malformations, osmoregulatory imbalance and endocrine disruption [201]. In birds, deformities and the death of embryos, low fecundity, slowed growth and metabolic disturbances have been reported [204].

More and more studies report that PAHs are organic compounds with a high degree of toxicity, carcinogenicity and teratogenicity [200]. Of the more than 100 known PAHs, 16 have been classified as priority environmental pollutants by the United States Environmental Protection Agency (US EPA). This group includes acenaphthene, acenaphthylene, anthracene, benzo[ghi]perylene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, fluoranthene, fluorene, indene[1,2,3-cd]pyrene, naphthalene, phenanthrene and pyrene [201]. Among the various PAHs, benzo[a]pyrene (BaP) has the greatest carcinogenic potential.

PAHs from the aquatic environment can be removed by physical, biological and chemical processes [200]. Physical and chemical methods for PAH removal are often inefficient, labor-intensive and expensive [205]; in addition, through the incomplete transformation of PAHs, they can lead to the formation of other stable intermediates that are more toxic than the starting compounds [12,201].

For the reasons mentioned above, interest in the development of biotechnology for the detoxification of PAH pollutants has increased [179]. Bioremediation is an effective strategy for the treatment of organic pollutants, including PAHs, based on the use of microorganisms to convert pollutants into substances inert to the environment. Bioremediation, due to the relatively low cost and greater efficiency for compounds with a high degree of structural complexity, is one of the widely used technologies in the removal of pollutants [200].

The most promising class of enzymes for PAH detoxification are oxidoreductases [206–210]. Oxidoreductases include laccases, which catalyze reactions with a wide range of aromatic impurities, such as phenols and PAHs as substrates [201].

The fungus *Trematophoma* sp. UTMC5003 isolated from soil in Iran could, in the future, be used in the bioremediation of oil-contaminated soils and water. The isolate obtained by Moghimi et al. (2017) is capable of producing biosurfactant and laccase. The fungus degraded 70% of crude oil and 90% of aliphatic compounds and down to 56, 87 and 90% of pyren, anthracen, phenanthrene respectively, within 15 days. *Trematophoma* sp. UTMC 5003 produced 4U/L of laccases in the appearance of petroleum as a carbon source [179].

The laccases produced by *Leucoagaricus gongylophorus* FF-2006, from *Atta sexdens rubropilosa*, were tested for their ability to degrade several PAHs, which are important in aquatic degradation. Degradation reactions were carried out in an aqueous buffer solution at pH 6.0 in the presence of Tween-20 and 50 U/L laccase preparation at 30 °C, with constant magnetic stirring without mediators. Over 70% of the anthracene, 40% of the fluorene and 25% of the phenanthrene were biodegraded within 24 h. The enzyme degraded anthracene to anthrone and anthraquinone. It should be noted that anthraquinones have significant biological activity, such as laxative, anti-inflammatory and anticancer, as well as antimalarial, antiviral and antifungal properties. No metabolites degrading other PAHs were observed, probably due to their water solubility and low concentration [211].

Using *P. ostreatus* laccase, it was possible to completely remove naphthalene and more than 90% of anthracene and 1,10-phenanthroline from the reaction mixture during 5, 11 and 14 days of incubation, respectively. Naphthalene was selected as a model compound for the analysis of the metabolic pathway of PAH degradation. Based on the obtained metabolites,

the researchers proposed the course of naphthalene degradation using *P. ostratus* and its enzymes, naphthalene dioxygenase and laccases. The final product of the reaction was benzoic acid [212], the simplest aromatic carboxylic acid with low toxicity and antibacterial and antifungal activity, most often used in the food industry and cosmetics. In addition, a higher level of the degradation of naphthalene was observed compared to anthracene and 1,10-phenanthroline, further supporting the idea that low molecular weight PAHs are more easily degraded due to their higher solubility and greater bioavailability. It should also be noted that macromolecular organic compounds, such as PAHs, are degraded not by single enzymes but by the cooperation of two or more enzymes. This is confirmed in studies by Pozdnyakova et al. (2018) in which the authors suggest that laccase can catalyze the initial attack on the PAH molecule, which leads to the formation of quinones, and their further oxidation is provided by the peroxidase, which ultimately leads to PAH mineralization [213].

Torres-Farrada et al. (2017) investigated the potential of extracellular crude enzyme extracts of *Ganoderma* sp., a white rot fungus (WRF), from urban ecosystems in Havana, Cuba, to degrade PAHs and noted that *Ganoderma* strains degraded three PAHs (naphthalene, phenanthrene and fluorene) with different efficiency. The presence of HBT, a synthetic mediator, significantly increased the degradation of the studied PAHs. Nevertheless, one strain, *Ganoderma* sp. UH-M, was able to degrade PAHs with the same efficiency with and without a redox mediator, which is advantageous in practical applications [214]. In contrast to the degradation pathway proposed by Elhusseiny et al. (2019) led by *P. ostreatus* laccase, the presence of as many as four compounds, the derivatives of benzoic acid, catechol, phthalic acid and protocatechuic acid, was observed here, and they can be mineralized by fungal enzymes. Laccase from *Ganoderma* sp. UH-M is a favorable enzyme for the bioremediation systems of PAH-polluted ecosystems [214].

Lasiodiplodia theobromae fungus, isolated from a PAH-contaminated soil sample at the Beijing Coking Plant in Beijing, China, was able to degrade benzo[a]pyrene (BaP). *L. theobromae* belongs to the group of botryosphaeriaceous fungi and is the causative agent of storage rot in many fruits and tubers and a serious pathogen of many agricultural and horticultural crops [215]. It turned out that this fungus has the potential to use BaP as a sole carbon source. Within 10 days, up to 53% of BaP was degraded. During the biodegradation of BaP, the activity of lignin peroxidase and laccase was detected, and it should be noted that the activity of laccase was four times higher than that of lignin peroxidase. The addition of Tween 80 (TW-80), glucose and salicylic acid slightly increased the biodegradation of BaP.

It has been reported in the literature that white rot fungi, which produce lignolytic enzymes, can oxidize PAHs by generating hydroxyl radicals by donating one electron, which oxidizes the PAH ring and leads to the formation of quinones and acids, which are finally decomposed to CO_2 and H_2O by hydrogenation, dehydration and so on. *L. theobromae* LAC can catalyze the one-electron oxidation of PAHs, such as anthracene (ANT) and BaP. The effectiveness of LAC increases in the presence of mediators, such as 1-hydroxybenzotriabol (HBT) or 2,2′-azinobis-3-ethylbenzthiazoline-6-sulfonic acid (ABTS) [215].

Thus, the affiliation of fungi to different ecophysiological groups and the enzymes they produce, not only laccases, affect the completeness of PAH utilization [216].

6.1.3. Pharmaceutical

The worldwide annual consumption of PhACs is estimated at 100,000 tonnes or more, with the trend increasing due to disease and aging [14].

PhACs are natural or synthetic compounds used in human and animal medicine to diagnose, prevent and act toward many diseases. A wide range of medicines for humans and animals, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, synthetic hormones and others have become essential to the health and well-being of the population, extending life expectancy. PhAC consumption is expected to increase in the coming years

due to the aging of the population and the improvement of health standards [13,15]. Antibiotics, anti-inflammatory drugs, analgesics, antidepressants, antiepileptic drugs, lipid-lowering drugs, β-blockers, antiulcer drugs and antihistamines are the most commonly consumed drugs [15].

Mixtures of pharmaceuticals with their active metabolites are continuously discharged into the environment through wastewater treatment plants, municipal wastewater, wastewater from hospitals, livestock and pharmaceutical industries, the improper disposal of unused or expired pharmaceuticals, the use of manure and sludge as organic fertilizers and leachate from landfill solid waste [15].

The persistence of pharmaceuticals in the environment has become a problem with their ever-increasing production. Potential toxicological effects on nontarget organisms have been observed as a result of the continued presence of these chemicals in the environment at low concentrations (ranging from μg L^{-1} to ng L^{-1}). Some of these compounds have already been placed on the second and third watch lists, as is the case with (i) the antibiotics amoxicillin, ciprofloxacin, erythromycin, clarithromycin, azithromycin, sulfamethoxazole and trimethoprim; (ii) the hormones 17-α-ethinylestradiol (EE2), 17-β-estradiol (E2) and estrone (E1); (iii) the synthetic hormone norethisterone; (iv) the antidepressant venlafaxine and (v) three antifungal drugs, clotrimazole, fluconazole and miconazole [13,217–219].

The overuse of PhACs and unsuccessful wastewater treatment has led to the accumulation of this group of chemicals in aquatic systems, which has been reflected in behavioral and physiological changes in the animals [220]. Pharmaceuticals occurring in the water affect not only fish organ development and function but also their DNA, hormone secretion and others [221]. Hormones, even in low concentrations depending on the type, can cause changes in sex characteristics and sex ratios, the feminization or masculinization of fish or impair the development of their immune system [9]. Silva et al. (2019) further revealed that progesterone and estradiol have an effect on zebrafish (*Danio rerio*) locomotor activity [222].

Ibuprofen and diclofenac are the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs) in the world [223,224]. Diclofenac is a compound of low to moderate toxicity, as indicated by the increased activity of enzyme oxidative stress (glutathione s-transferase (GST) and catalase (CAT)) and lipid peroxidation. Diclofenac is also an endocrine-disruptor compound (EDC).

The source of PhAC in aquatic environments may be insufficiently well-treated sewage from the discharge of a sewage treatment plant or runoff from agricultural areas fertilized with manure from dairy cattle breeding [9]. Currently, such large amounts of pharmaceuticals are released into the environment that ecosystems are unable to mineralize them [15], similar to conventional wastewater treatment [14]. The solution to these inconveniences may be the use of bioremediation, which uses the ability of microorganisms and their extracellular enzymes to decompose various organic pollutants [15]. Among the advantages of PhAC biocatalysis, we can mention low energy consumption, which is mainly associated with ensuring mild reaction conditions and the production of fewer or no toxic by-products. In addition, the substrate specificity of the enzymes allows undesirable side reactions to be minimized by modifying the enzymes through genetic engineering and protein engineering methods [14,225]. Enzymes are an encouraging technique for the selective removal of resistant compounds, such as pharmaceuticals from water and wastewater [40].

Research conducted in recent years has evaluated the effectiveness of PhAC removal by various forms of enzymes, such as whole cell cultures, crude extracts, free and immobilized enzymes, and enzymes obtained by heterologous expression or site-directed mutagenesis [14].

Purified extracellular laccase with a mass of 90 kDa secreted by *Sphingobacterium* ksn-11, isolated from the soil of agricultural fields, was used by Neelkant et al. (2020) after immobilization for the transformation of diclofenac [149]. The enzyme after purification was immobilized in sodium alginate–silicon dioxide–polyvinyl alcohol beads and assessed for diclofenac transformation efficiency. After 4 h incubation at 40 °C and pH 4.5, 75% of diclofenac was transformed without a mediator, and in the presence of ABTS, 81% of

diclofenac was transformed within 90 min. LC-MS analysis confirmed that the immobilized laccase converted the diclofenac to 4,5-dihydroxy diclofenac and 3-hydroxy diclofenac. The presence of the mediator had no effect on the quantity and quality of the products. The authors speculate that the removal of diclofenac occurs in the following steps: (i) hydroxylation, (ii) ring opening reaction and (iii) mineralization. The work clearly indicates the possibility of using *Sphingobacterium* ksn-11 laccase immobilized on a polyvinyl–alginate–silicon dioxide matrix for further research on the degradation of endocrine disruptors and other xenobiotic compounds.

It was recently discovered that the enzyme laccase from the white rot fungus *T. hirsuta* is capable of degrading chloramphenicol (2,2-dichloro-N-[(1R,2R)-1,3-dihydroxy-1-(4-nitrophenyl)propane-2-yl]acetamide) in 7 days without mediators. Chloramphenicol is a broad-spectrum antibiotic pharmaceutical used to treat bacterial infections in humans and animals. It is one of the most durable thermotolerant xenobiotics among hospital waste. The use of the mediator–laccase system allowed for the effective removal of chloramphenicol in higher concentrations (10 mg/L) and shortened the time needed to completely remove the antibiotic from the reaction environment to 48 h. Laccase caused dehalogenation and oxidation of chloramphenicol to chloramphenicol aldehyde, which in MIC tests was nontoxic to the tested microorganisms (*Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*) [226].

Streptomyces mutabilis A17 laccase obtained by solid-state fermentation on agro-waste degraded sulfonamide antibiotics. The maximum enzymatic activity was reached at 50 °C, pH 6.0 and 1 mM HBT for 1 h incubation. The degradation efficiency of sulfadiazine (SDZ) and sulfathiazole (STZ) sulfa antibiotics was approximately above 70 and 90%, respectively. The toxicity of the laccase-treated sulfonamide antibiotics tested in the microbial toxicity test against *B. cereus* LC314797, *S. aureus* KT337489, *S. enterica* MK127926 and *K. pneumoniae* KF771031 was significantly reduced. *S. mutabilis* A17 laccase can be used in the enzymatic degradation and detoxification of sulfonamides from environmental pollutants [227].

Taken together, the results suggest an effective use of laccase and its mediators in the bioremediation of antibiotics and NSAIDs, such as diclofenac, one of the most persistent micropollutants in pharmaceutical waste.

6.1.4. Plasticizers

The consumption of plastics has increased significantly in the last few decades. As a consequence of the huge market demand, the production of plastics increased from 1.7 million tonnes in 1950 to 438 million tonnes in 2017 [228]. Only 10% of plastic waste is recycled; a significant part ends up in landfills or into the environment, which is why it is necessary to develop methods for its effective disposal [228,229].

Materials made of plastics are widely used in everyday life, mainly as food packaging. Primary packaging is typically made of polyethylene. Polymers used in the production of packaging are supplemented with various additives that improve their properties. Such an additive to plastics is BPA (2,2-bis(4-hydroxyphenyl)propane) [230].

BPA is a monomer in the production of polycarbonate plastics and epoxy resins and a plasticizer in the production of plastics. These materials are used in food storage containers or bottles and cans for food and beverages [230]. BPA is also an important ingredient in adhesives, flame retardants, paints, protective coatings, automotive lenses, compact discs, construction materials, thermal paper and dental sealants and composites [213]. The global production of BPA exceeded 4.6 million tonnes in 2012 and will grow at a rate of 4.6% annually from 2013 to 2019 [231,232].

BPA can diffuse into food and beverages. BPA migration from packaging increases during exposure to sunlight and elevated temperatures [230]. People are exposed to the adverse effects of BPA mainly through the consumption of food and beverages stored in plastic containers, bottles and cans. In living organisms, BPA mimics the structure of estrogen and binds to estrogen receptors [233] and, therefore, disrupts the proper functioning of the endocrine system, even at low concentrations.

Excessive exposure of people to BPA can lead to cardiovascular, endocrine and immunological disorders, diabetes and obesity [230]. Research has shown that BPA exhibits genotoxicity, reproductive toxicity, endocrine-disrupting activity, cytotoxicity, neurotoxicity and hepatotoxicity [232]. In women, its presence in the environment has been linked to breast cancer [234], polycystic ovary syndrome, miscarriage, endometrial disorders and premature birth [9,213,230]. In men, BPA has been associated with lower semen quality, fertility, sex hormone levels and sexual dysfunction.

BPA tends to accumulate in aquatic animals, hence its bioaccumulation along the trophic chain. The human consumption of marine fish containing BPA may cause its presence in the human body [230]. Therefore, restrictions on the use of BPA have been introduced. The maximum total daily intake (TDI), according to the US Environmental Protection Agency (US Environmental Protection Agency, 2010), is 0.05 mg/kg body weight/day, and according to EFSA and the European Commission (EC), it is 0.004 mg/kg body weight/day. The EC has also set a specific migration limit for BPA in food at 0.5 mg kg^{-1} (European Food Safety Authority, 2015; European Commission, 2018a; US Environmental Protection Agency, 2010) [233].

BPA enters aquatic ecosystems from a variety of sources, including production plants, wastewater as a result of incomplete treatment, leachate from landfills and leaching from nonrecycled plastics [230]. In the surface and bottom water of the Gulf of Gdańsk, BPA values up to 277.9 ng L^{-1} were recorded [235].

Biodegradation and adsorption are the main BP removal routes in wastewater treatment plants [139,236]. WRFs convert BPA through an enzymatic oxidation reaction into a much less reactive substance. The oxidized form of BPA does not bind to ERα-dependent estrogen receptors. The product of BPA oxidation catalyzed by laccase is 2,2-bis(4-phenylquinone) propane [139,140].

Two isoforms of laccases isolated by Elsayed et al. (2023) from *T. harzianum* S7113 have been used in the biodegradation of BPA [77]. The isoenzymes differed in their tolerance to the presence of Na^+ ions. Na+ decreased LacB activity and stimulated LacA. LacA showed greater catalytic potential toward BPA as a substrate than LacB. LacA degraded BPA at a concentration of 20 mg/L at pH 5.5 over 5 h batch tests at a laccase concentration of 0.75 U/mL, with an efficiency of approx. 70%.

Highly active and stable laccase was isolated from the spore cells of *Bacillus* sp. GZB, a BPA-degrading bacterium. The *Bacillus* sp. GZB strain was obtained from sludge collected from an electronic waste recycling facility in Guiyu, China. Complete degradation of BPA at a concentration of 10 mg/L was achieved after 30 h of incubation. Based on the identified intermediates, the pathway of BPA degradation by bacterial laccase was proposed. Due to the oxidation of BPA by laccase, phenoxy radicals were formed in the first step, and further oxidation or cleavage of the C-C bonds of the radicals resulted in the formation of various organic acids. During degradation, the toxicity of BPA, tested against *Photobacterium phoreum*, gradually decreased. The exceptional laccase resistance of *Bacillus* sp. GZB to changes in temperature and pH is due to the structure of the spore cells, which can serve as a matrix in immobilization. This enables the use of laccase as a natural biocatalyst in wastewater treatment to remove the toxicity caused by BPA [237].

The accumulation of synthetic plastics is a serious problem for the environment and human health. The most commonly used homopolymer in the production of plastics is polyethylene (PE) [228,229].

The rapid increase in plastic production and waste volumes requires the development of effective plastic waste management solutions [228]. Plastic waste in the environment is naturally broken down by photo-, bio- and thermo-oxidative depolymerization as well as friction [229]. Plastic products thrown into the environment terribly pollute water resources and pose a serious threat to aquatic and marine organisms [238,239].

Biodegradation is necessary for water-soluble or water-immiscible polymers because they end up in water streams that cannot be recycled or incinerated [239]. Unfortunately, petroleum-derived (petro)polymers are extremely resistant to natural pathway biodegrada-

tion. Their complete decomposition in the natural environment can take over 50 years [229]. The enzymatic degradation of plastics begins with the adsorption of enzymes on the polymer surface followed by the hydroperoxidation/hydrolysis of the bonds. The sources of enzymes that break down plastics can be found in microorganisms from various environments and in the digestive intestines of some invertebrates [229].

PE is a high molecular weight polymer linked by a C-C single bond [240]. PE is one of the most inert plastics, and its resistant nature is due to its high molecular weight, complex three-dimensional structure and hydrophobic properties that make it difficult for microorganisms to access [239]. Santo indicated that laccase could affect polyethylene molecules by creating carbonyl groups and thus reducing the molecular weight of PE molecules [241]. Another example is the *T. harzianum* laccase and manganese peroxidase from landfill soil in the Shivamogga district which were able to degrade PE to form carboxylic acid groups, aldehydes, aromatic compounds, alcohols, esters, ethers and alkyl halides [239].

In the work of Zhang et al. (2022), recombinant laccase from *Acinetobacter baumannii* Rd-H2 was obtained isolated from a grain and food storage pest [240]. The recombinant AbMCO enzyme led to the occurrence of basic structural changes on the surface of the PE film. The enzyme expressed in *E. coli* showed good stability in the range of 30–45 °C, with an optimum temperature of 45 °C and optimum pH of 4.5. The bacterial treatment breaks the chain of the PE polymer, which reduces the molecular weight and increases the hydrophilicity of the PE polymer.

6.2. Mechanism of Removing Xenobiotics from Water

There are two types of laccase-catalyzed reactions: catabolic and anabolic. The catabolic pathways involve mediators, i.e., small organic substances that facilitate the course of the redox cycle. In contrast with anabolic processes, catabolic processes are mediated by laccases derived from white or brown wood rot fungi [6,242].

Jeon et al. (2013) list two factors that may affect the course of reactions catalyzed by laccase. These are (i) the redox potential of the enzyme and (ii) the stability of the phenoxy radicals formed as a result of oxidation by laccase. Fungal laccases, responsible for catabolic processes and wood decomposition, show a high redox potential compared to laccases involved in anabolic processes [1,9]. As a result of the decomposition of the lignin present in wood, phenols are formed, e.g., syringaldehyde and acetosyringone, which are characterized by high structural stability and a long half-life of the corresponding radicals. The listed properties of the products resulting from the decomposition of wood by laccase shift the course of the reaction toward catabolic processes [6].

The bioremediation and detoxification of xenobiotics present in the environment is an example of the use of laccase's ability to catalyze both catabolic and anabolic reactions (Figure 4) [6,242,243].

Synthetic dyes are high molecular organic compounds with complex structures. For the decolorization of thiazole yellow G, Bankole et al. (2019) used the filamentous fungus *Aspergillus niger* LAG [244]. A significant role in the degradation of this dye was attributed to laccase. The fungus showed significant induction of laccase (71%) and lignin peroxidase (48%) in the presence of xenobiotics. The scheme of the dye decomposition is likely as follows: (i) lignin peroxidase catalyzes asymmetric cleavage of the bond in thiazole yellow G, two sodium 6-methyl-2-phenyl-1,3-benzothiazole-7-sulphate molecules are formed, and (ii) sodium 6-methyl-2-phenyl-1,3-benzothiazole-7-sulphate molecules are desulfonated and demethylated by laccase, resulting in 2-phenyl-4,5-dihydro-1,3-thiazole. These products showed less toxic potential.

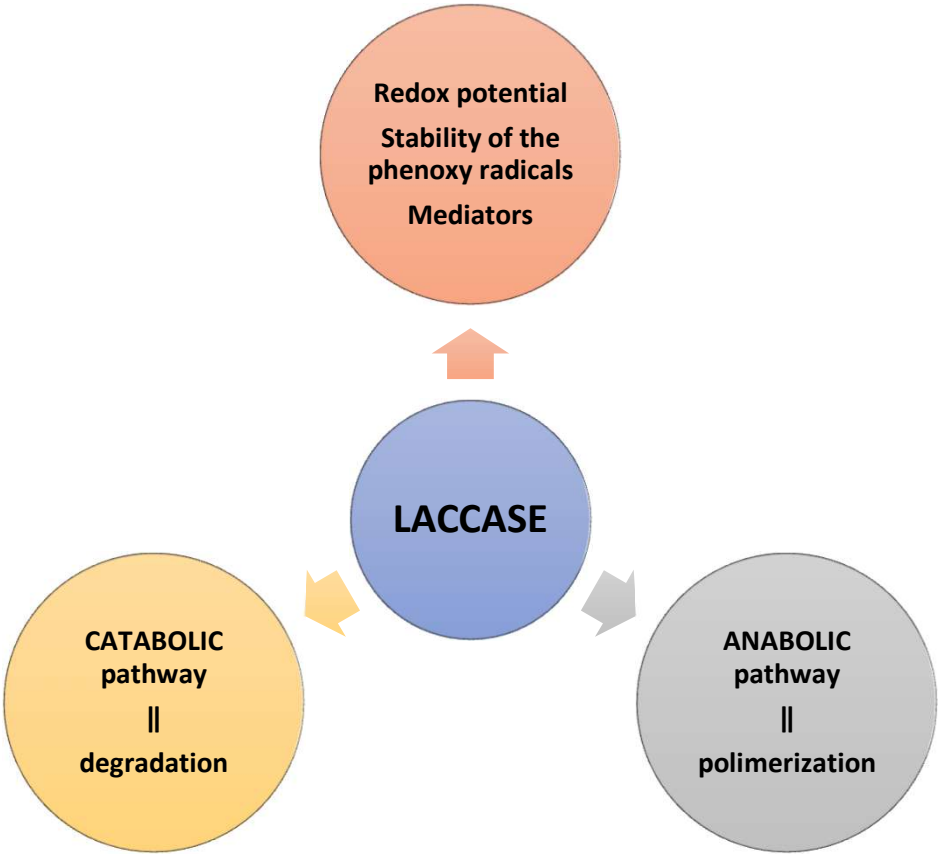

Figure 4. Type of reaction catalyzed by laccase.

As mentioned earlier, polymerization reactions resulting from oxidative coupling are also involved in the removal of organic pollutants. These processes lead to the formation of adducts or copolymer products that are insoluble in aqueous environments. To remove pollutants that polymerize, the wastewater is then filtered or sedimented [243,245].

Sun et al. (2019) proved that the way to remove triclosan, a compound with antibacterial properties, which is resistant to biodegradation [246–248], from water is the enzymatic activity of the *T. versicolor* laccase supported by Cu^{2+} ions [137], in which mainly triclosan dimers, trimers and tetramers are produced. A possible transformation mechanism of the xenobiotic was proposed: (i) laccase catalyzes the oxidation of triclosan to produce intermediate phenoxy radicals, and (ii) phenoxy radicals link together via C-C and C-O-C radical covalent bonds, forming mainly oligomers. The introduction of Cu^{2+} to the reaction environment was probably the reason for the increase in the activity and stability of the enzyme and the intensification of the self-polymerization of triclosan by the formation of more triclosan oligomers.

Acetaminophen is one of the difficult-to-remove types of pharmaceutical contaminants that have been noticed in municipal water. Wang et al. (2018) presented a potential method of removing acetaminophen from water based on the laccase-catalyzed oxidative coupling reaction with the formation of insoluble products that are easily separated from the liquid by filtration [249]. In order to increase the efficiency of xenobiotic removal, a strategy of double pH optimization was used (enzyme solution at pH 7.4 was added to substrate solution at pH 4.2). This strategy enabled the optimal flow of electrons between the substrate and the Cu T1 site of the active laccase center (neutral pH) and between the Cu T1 site and the trinuclear copper center (TNC) (acid pH). In almost 17 min, over 90% of the acetaminophen was converted to biologically inactive oligomers. The route of removing this compound from water with the use of laccase consisted of its oxidation with the formation of unstable free radicals, which then self-polymerized and precipitated in the

reaction mixture. The dual pH optimization strategy, which achieved a higher rate of catalytic oxidation of substrates by laccase, consequently led to a much faster formation of acetaminophen dimers, trimers and tetramers than can naturally precipitate from water.

Das et al. (2018) investigated the pathway of BPA degradation by the laccase of *Bacillus* sp. GZB spores [237]. They noted the presence of BPA degradation intermediates, such as 4-hydroxybenzaldehyde, benzoic acid, 2-hydroxypropanoic acid, 2-methylbutanoic acid and 3-methylbutanoic acid. In other studies where other microorganisms were the source of laccases, the formation of other intermediates was identified. In the reaction of BPA with *T. villosa* laccase, phenol and 4-isopropenylphenol are formed [250]; with the immobilized *Trametes polyzona* laccase on silica nanoparticles, phenol, 4-isopropenylphenol and 4-hydroxyisopropylphenol [251]; with the laccase *T. versicolor*, ethylbenzene, p-xylene, cyclohexanone and 1-methyl-4-isopropenyl-2-cyclohexenylene [252]; with the *Phanerochaete chrysosporium* laccase, 2,2-methylenediphenol, bis(4-hydroxyphenyl)methane and p-(benzyloxy)phenol [142]; and with the *T. versicolor* laccase immobilized on the *Hippospongia communis* spongin scaffolds, phenol, catechol and dimers [253]. In the case of BPA degradation by *Pseudomonas putida* YC-AE1, the intermediates are stilbenol and hydroxyl derivatives of benzaldehyde, acetophenone, phenylacetate and phenacyl alcohol and hydroxyphenyl derivatives of propanol, propanol and propanoate [254]. In general, the biodegradation pathway of xenobiotics and the quantity and quality of the final products depends on the source of the laccase.

The presence of mediators has a significant impact on the course of reactions catalyzed by laccase. Mediators are low molecular weight, water-soluble chemicals with a high redox potential (approx. 900 mV) that can act as one-electron shuttles between the enzyme and the compounds to be oxidized [106,194]. The most effective mediators are N-heterocyclic compounds containing N-OH groups, such as hydroxybenzotriazole (HBT), 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO), N-hydroxyphthaimide (HPI), N-hydroxyacetanilide (NHA) and violuric acid (VLA) [82]. The laccase–mediator system (LMS) has been used in the degradation of a wide range of contaminants as it induces the cleavage of oxidative bonds present in the structure of many types of xenobiotics dissected in this review [186,255–260].

In the studies by Daassi et al. (2016), using the crude laccase enzyme of the fungus *Coriolopsis gallica* (BS54) [KJ412304] led to BPA degradation. The final product of BPA degradation was b-hydroxybutyric acid. Oxidative cleavage of BPA led to the formation of b-hydroxybutyric acid in the absence of HBT and tartaric acid in the presence of HBT. The final products were significantly different from those after treatment with BPA in the laccase/HBT system because the mediator is also oxidized to give other degradation and by-products. Tartaric acid and pyroglutamic acid probably originated from the degradation of HBT. The formation of tartaric acid and β-hydroxybutyric acid could be the result of the oxidation of methyl groups on the propane moiety of the BPA molecule under the action of laccase. Organic acids, such as carboxylic or polycarboxylic acids (tartaric acid and b-hydroxybutyric acid), which are commonly found as intermediates in metabolic pathways, are usually formed by the fusion of aromatic rings [7].

The action of mediators is beneficial because it allows laccases to oxidize large molecules, such as lignin, without the need for direct enzyme–polymer interactions and to increase the range of substrates with compounds with redox potentials exceeding their own. The use of mixtures of mediators enhances their synergistic effect and increases laccase activity [171,261].

6.3. Challenges of Enzymatic Bioremediation

The constantly increasing human population and the resulting rapid development of industry and expansion of urban areas have increased the amount and variety of anthropogenic pollution in the biosphere [262]. These pollutants are common and pose a huge threat to aquatic and terrestrial ecosystems and the organisms living in them due to their toxicity, durability, easy bioaccumulation and resistance to natural biodegradation [263–265].

These toxic pollutants accumulate in the soil, surface water, drinking water and other natural resources as a result of untreated sewage discharged into water bodies [266]. Analyses by Vilela et al. (2022) show that potentially toxic metals (PTMs), hexachlorocyclohexanes (HCHs), polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), organic tins, polycyclic aromatic hydrocarbons (PAHs) and phenols are commonly found at a depth of 200 m and are detected both in organisms as well as in environmental samples. Abiotic conditions such as lack of light, low temperatures and high pressure make it difficult to degrade and remove contaminants in these areas. In general, deep seas can be considered as a potential sink and reservoir of persistent pollutants [262].

Xenobiotics include a wide range of biologically active substances that can be toxic to wildlife and humans at very low concentrations (<1µg/L) [262]. Surface water pollution due to heavy agricultural use of fertilizers, pesticides, herbicides, unmanaged municipal wastewater and unregulated industrial wastewater discharges significantly affects the environment [267,268]. Worldwide, 80% of untreated industrial wastewater goes directly to water reservoirs [266]. Industries, such as paper and pulp, textile, tanning, chemical, pharmaceutical, cosmetics, food processing and petrochemical, and other manufacturing industries, are major sources of industrial wastewater [256,266,269].

The composition of wastewater varies greatly depending on the source of origin [160]. Industrial wastewater is usually characterized by a high content of organic compounds (1–200 g/L), organic solvents, organic acids, natural organic matter (NOM), surfactants, non-neutral pH, temperatures different from those typical for the area, salinity, turbidity and a high content of heavy metals [160,269]. Wastewater from leather manufacturing, food processing and preservation, textile processing and oil refining can have high salt concentrations [269]. For example, paper and pulp industry wastewater is a mixture of the following chemicals in varying proportions: sulfite; bisulfite; sodium sulfide and chlorine dioxide; bleaching agents, such as chlorine, chlorine dioxide, hydrogen peroxide, sodium hydroxide and sodium sulfite; oligophenols; phenolic compounds; lignin derivatives; heavy metals; chlorine derivatives of benzodioxin, biphenyl, catechol, guaiacol, lignin, methane, methylphenol, naphthalenes, phenol, vananiline and vanillin; and many others. In addition, they are characterized by high temperatures (170–180 °C) [270].

Organic and inorganic compounds found in wastewater have a significant impact on the activity of both free and immobilized enzymes [160,271,272]. It should be noted that some substances may have an activating effect, and some have an inhibiting effect on the activity of enzymes. The inhibitory effect of organic solvents and acids strongly depends on their concentration [160]. Importantly, enzymes cannot be used for the detoxification of raw sewage due to the high content of substances that are enzyme inhibitors. These compounds should be removed from the reaction environment before enzymatic purification of hardly degradable compounds takes place [273]. Many factors, e.g., biodegradability, sorption, photodegradation, volatilization and environmental conditions (e.g., temperature and solar radiation), affect the dynamics of xenobiotic transformations in water, which determine the degree of its contamination and the possibility of the bioaccumulation of toxic chemicals in aquatic organisms [262].

Currently, wastewater treatment methods mainly include physical, chemical and biological methods. Physicochemical methods, such as chemical oxidation, photocatalytic oxidation, flotation, coagulation, flocculation, distillation, membrane-based separation and adsorption techniques have been used for wastewater treatment [263,264].

Wastewater treatment plants play a key role in removing organic and inorganic pollutants. Due to the huge amounts of newly formed chemicals delivered to the environment, traditional wastewater treatment is insufficient to completely remove many toxic pollutants that consequently pollute the biosphere. Moreover, climate change, the increasing intensity of precipitation and violent storms contribute to water pollution through overland runoff [262]. The disadvantages of traditional pollution treatment methods include high costs, no specificity and the generation of secondary pollutants [265,274,275]. Bio-

logical methods are more environmentally friendly and can remove most pollutants from wastewater [263,264].

The process that uses microorganisms, plants or their enzymes to restore an environment altered by pollution to its original state is named bioremediation [262,263]. Bioremediation can also be described as "a treatment technology that uses biological activity to reduce the concentration or toxicity of a pollutant". The bioremediation process consists of detoxification and mineralization [266], during which waste is converted into the inorganic compounds CO_2, H_2O and CH_4. Impure water areas where there has been an accidental or intentional release of pollutants or chemicals are locations where bioremediation is applied [276]. The bioremediation of contaminated groundwater or soil is currently the cheapest and least harmful method of removing xenobiotics from the environment [277].

Bioremediation processes can be ex situ or in situ. In ex situ bioremediation, wastewater treatment takes place at a different location than where the pollutants occur/are produced, while in situ bioremediation takes place where they occur [278]. The factors influencing the course of bioremediation processes are (i) the physicochemical bioavailability of pollutants (transport, adsorption, dispersion and volatility of pollutant compounds); (ii) microbial growth and development; (iii) the availability of alternative carbon sources; (iv) type and concentration of contaminants, their solubility, biodegradability, toxicity and chemical structure; (v) the environmental conditions, such as temperature, humidity, pH, oxygen availability, nutrient levels, redox potential, electron acceptor availability and nutrient sources; (vi) the chemistry and mechanics, hydrogeology and soil hydrology at the contaminated site; (vii) enzyme induction; and (viii) the occurrence of horizontal gene transfer and/or mutations in the microbial populations present in wastewater or bioremediation sites [264,278–280].

Enzymatic conversion may be crucial for the removal of structurally diverse and physicochemical properties of xenobiotics from the environment [273]. Compared to conventional chemical processes, enzymatic processes have higher reaction kinetics and require less water and energy; additionally, enzymes not used in the reactions can be recycled [263]. In addition, enzymes are selective and can catalyze targeted conversion reactions. Low concentrations of xenobiotics, usually not exceeding a few μg/L, affect enzyme kinetics and conversion [273]. It should be noted that the use of an enzyme is possible if the enzyme reaction product is less toxic than the substrate [279]. For example, many enzymatic transformation products of pesticides are toxic to the environment; therefore, combining many enzymes is a good way to obtain nontoxic reaction products [263]. However, in the case of most reactions carried out by laccases, the main products are dimers, trimers and oligomers formed as a result of the spontaneous reactions of phenoxy free radicals, which can be easily separated from the post-reaction mixture by simple precipitation and centrifugation or filtration [160].

Bioremediation is an easy, fast, environmentally friendly and socially acceptable approach used to bioremediate resistant xenobiotic compounds from the natural environment [263]. The key to the effective use of enzymes to remove micropollutants in aquatic ecosystems is the high efficiency and resistance of enzymatic reaction systems [273]. Unlike microbial bioremediation or phytoremediation, enzymatic bioremediation does not depend on the growth of a specific organism in a polluted environment but on the catalytic activity of the enzyme. The desirable features of enzymes used in bioremediation are their secretion outside the cell and their independence from cofactors [265]. The advantages of enzymatic bioremediation are also flexible operating conditions, easy control, speed of the process and its costs, specificity in relation to the substrate, the simplicity of processing and storage, standardized activity, mobility (small size) and no need to provide nutrients and biodegradability [265,278,280].

The disadvantages of xenobiotic removal by enzymes include the identification and selection of microbiological sources for the production of appropriate amounts of the enzyme, enzyme stability and activity in real process conditions (enzyme denaturation by substances present in wastewater), difficulties with increasing the scale of the process

and maintaining its efficiency in subsequent cycles of bioremediation, high costs, time-consuming production and the purification of enzymes [266,280]. Mixtures or complex combinations of many organic and inorganic substances are present in the polluted site, not individual pollutants. The complexity of the impurity can be associated with possible negative or positive synergistic effects on enzyme performance [279]. It should be noted that enzymes are catalysts with narrow (chemo-, region- and stereoselectivity) or wide specificity, so they can also be used for many different compounds in a mixture.

Laccases produced by various groups of microorganisms are capable of oxidizing ortho- and paradiphenols, aminophenols, polyphenols, polyamines, lignins, aryldiamines and some inorganic ions [65,187,243,256]. In addition to oxidizing phenolic and methoxyphenolic acids, laccases also attack their carboxyl (decarboxylation) and methoxy (demethylation) groups. These enzymes are involved in the depolymerization of lignin, resulting in the formation of various phenols. The substrate specificity and affinity of the laccase can change with changes in pH. Halides (except iodides), azides, cyanides and hydroxides inhibit laccase catalytic activity, with different laccases having different tolerances to inhibition by these compounds [281].

In order to increase the efficiency of the removal of toxic compounds by laccases, various mediators can be used [273]. Different mediators can have different effects on the same reaction, leading to different toxicity of the resulting transformation products [259]. Unpurified enzymes may contain mediators [282] and unused nutrients, resulting in further contamination [259,261,263,283]. In addition, crude enzymes usually show lower activity than their purified counterparts and can be partially inhibited by the components of the extract [261]. The problems with using this method are the costs of mediators, which are related not only to their production but also to high consumption and their toxicity [263,284]. To prevent the release of the mediator into the environment, it is possible to co-immobilize the enzyme and the mediator, as in the case described by Qiu et al. (2021), where laccase and ABTS were immobilized on chitosan magnetic nanoparticles modified with an ionic liquid with amino groups. Coimmobilization of these compounds increased the speed of the process 2-fold and the efficiency of removing indole, anthracene, BPA and 2,4-dichlorophenol [285].

Enzymes are macromolecules with a very complex structural conformation, and any physical and chemical changes result in a loss of enzyme activity [278]. Lower stability, productivity and activity are fundamental problems in the practical application of enzymes in bioremediation [278,279]. Tools that can help solve these problems are techniques of genetic engineering and protein engineering, which can increase the productivity and activity of enzymes through DNA recombination, the heterologous expression of proteins or introducing modifications to the basic amino acid structure of the enzyme [38,286,287]. The large-scale production of enzymes, with increased stability and/or activity and at lower costs, is possible thanks to the use of recombinant DNA technology [279]. It is also possible to design enzymes to increase their stability and efficiency for special conditions or specific substrates. These issues are discussed in more detail in Section 7 of this paper. Omics technologies play a significant role in designing proteins with desired properties [265]. Metagenomic approaches can be useful to find potential gene-encoding enzymes responsible for the degradation and detoxification of a specific pollutant. The availability of whole genome sequences of environmental microorganisms has enabled the construction and screening of metagenomic libraries to identify genes involved in bioremediation [288,289]. Examples include the University of Minnesota Biocatalysis/Biodegradation Database, EAWAG-BBD (biocatalysis/biodegradation database), ONDB (organonitrogen degradation database), Aromadeg (aromatic hydrocarbon degradation database), OxDBase (biodegradation oxygenase database), RHObase (a database of ring-hydroxylating oxygenases) and MetaRouter [288,290]. Advances in synthetic biology techniques and the exploration of expanding nucleotide databases will eventually enable the design of enzyme-based systems for the mineralization of organic compounds [291].

Another approach to improving the performance of enzymes in the detoxification of pollutants is their immobilization on natural and synthetic substrates of various natures and through various immobilization mechanisms [271,292,293]. The immobilization of laccases on a solid support increases their stability, half-life and resistance to proteolytic enzymes [278]. Immobilized enzymes tend to have long-term operational stability, being highly resistant to physical, chemical and biological denaturing agents. In addition, they can be reused and recovered at the end of the process [279,294–296].

Immobilization is a method that limits the rotational movements of enzymes while maintaining their viability and catalytic function. Currently, the following immobilization techniques are known: adsorption, surface binding (electrostatic or covalent), flocculation (natural or artificial), entrapment and encapsulation. The use of a given immobilization method requires the use of carriers with specific properties [277]. The method of immobilization has a large impact on the properties of enzymes; it should not affect the conformation and activity of enzymes [278].

There are physical and chemical methods of immobilization. Chemical immobilization ensures good stability of the enzyme but reduces its activity. The covalent bonds that form between the enzyme and the carrier materials disrupt its native structure. Physical immobilization methods have less effect on the enzyme structure, but enzymes immobilized in this way generally show poor stability [263]. Appropriate immobilization allows for the stabilization of the enzyme and the preservation of high catalytic properties by biomolecules [297].

The beneficial effect of enzyme immobilization on bioremediation consists of (i) increasing the efficiency of pollutant degradation; (ii) increasing the catalytic efficiency; (iii) easy regeneration and multiple uses of biocatalysts; (iv) ensuring a stable microenvironment for the enzymes; (v) ensuring resistance to forces occurring in bioreactors, e.g., pressure; (vi) increasing the resistance of biocatalysts to unfavorable environmental conditions, such as high temperatures, acidic or alkaline reactions, the presence of heavy metals and halides; (vii) increasing the stability of the biocatalyst during storage; and (viii) increasing tolerance to high concentrations of pollutants [159,277]. Immobilization of laccase on a solid support increases the stability and resistance of laccase to proteases [278].

Finding the right immobilization methods and carriers to reduce the loss of enzyme activity and increase the reusability of the enzyme is fundamental [263]. A good carrier used in wastewater treatment processes should be characterized by insolubility in the reaction environment, high mechanical strength and nontoxicity both for the immobilized material and the environment. The carrier should be readily available, inexpensive, stable and easy to regenerate [277]. It should also provide significant affinity to the immobilized enzyme [273]. The modification and functionalization of the carrier surfaces, advanced research and the search for new support materials are ways to find appropriate carriers [263]. Nanotechnology offers tools to increase the stability of enzymes by reducing sensitivity to mechanical stress and maintaining the third structure of enzymes and protection against proteases [265].

Immobilization methods and carriers have a huge impact on the cost of enzymatic bioremediation, enzyme activity and the efficiency of the entire process [263]. Zdarta et al. (2019) emphasize that to achieve high efficiency in the bioremediation of resistant pollutants present in wastewater, solutions based on immobilized oxidoreductases should be used, such as simultaneous adsorption and biodegradation and the use of bioreactors with immobilized enzymes [273]. For the simultaneous immobilization of enzymes and sorption of pollutants, compounds of inorganic origins (e.g., aluminum and iron oxides, silica gel and activated carbon) [298,299], organic origins (e.g., cellulose, chitin, agar, starch, carrageenan, chitosan, pectins, polystyrene and polyvinyl alcohol) [300,301] and hybrid origins (e.g., copper hydroxide nanocages and chitosan–halloysite hybrid porous microspheres) [302,303] and composite origins (e.g., polymers and metal and ceramic composites) [304,305] were used. They are characterized by different morphology, porous structures (pore diameters

and surfaces) or the presence of many different functional groups on the surface of the material [263,273,277,306].

Simultaneous enzymatic biodegradation with adsorption or separation increases the efficiency of pollutant removal, shortens the process time and prevents the accumulation of products in the reaction environment and, thus, its inhibition [273]. Simultaneous adsorption and covalent immobilization have been used to remove toxic compounds from wastewater. This technique reduces the diffusion of substrates and enzymes and provides better exposure of enzyme active sites to the substrates dissolved in solution [89,154,155,273]. Appropriate exposure of the active center for laccases is important due to the fact that their active center requires an appropriate combination of enzyme–substrate and enzyme–carrier. The carrier can act as both an electron donor and an acceptor [273].

Bioreactors with immobilized enzymes enable tight process control. In these devices, parameters such as pH and temperature can be adjusted, the oxygen supply through mixing, the substrate flow rate and volume and the removal of products and by-products [273,307–310]. Mixing is primarily responsible for the heat transfer, substrate and oxygen in the bioremediation process. Higher mixing speeds result in increased biodegradation efficiency due to better oxygen availability in the aerobic processes [280]. Processes carried out in bioreactors are more environmentally friendly, as well as cost- and time-efficient [273].

There are two groups of bioreactors: (i) enzyme bioreactors (EBR) and (ii) enzyme membrane reactors (EMR) [311]. In membrane bioreactors, enzyme molecules can be immobilized in or on the membrane primarily by covalent bonds to prevent elution and loss of the catalytic properties of the enzyme during successive reaction cycles. The enzyme, as well as the structure, physicochemical properties and size of the expected biodegradation products affect the choice of the bioreactor membrane. Therefore, it is important to know the membrane characteristics, such as pore size, material, properties, presence of functional groups, hydrophilicity and surface charge [273,312,313]. A large surface area for enzyme attachment and good porosity and spatial structure are sought-after properties of good membrane support. All these factors facilitate the access of the reaction mixture (polluted sewage) to the active sites of enzymes. The membrane should be made of a material that is inert to the reaction components and mechanically resistant [159]. Based on the pore size of the membrane used, wastewater treatment processes can be divided into microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO). MF, UF and NF membranes are used to remove contaminants of 100–1000, 5–100 and 1–5 nm, respectively [269]. Membrane fouling is a key factor in EMR efficiency, so it is important to use pretreated wastewater without solids and operate the bioreactor in a cross-flow filtration mode [160,261,273].

Another significant factor in the course of bioremediation in a membrane bioreactor, especially in a batch bioreactor, is the enzyme dose. In general, the efficiency of degradation increases with increasing enzyme concentration until a certain optimum is reached. Degradation efficiency at a specific concentration of the enzyme maintains the appropriate reaction parameters, e.g., contaminant concentrations in the feed material in the batch bioreactor system remain constant [280].

When designing a bioreactor, a thorough study of the biological system used should be carried out, and capital costs, plant construction, maintenance costs, stability and scaling should be considered [159]. In EMR, the membrane should act as both a carrier of enzymes and a separator of products and substrates, which will simplify the process and reduce its costs. The choice of reactor type and operating mode (batch or continuous) is made depending on the process conditions, enzymatic activity, use of a free or immobilized enzyme, the form of the carrier if the enzyme is immobilized and the required purity of the product [273]. Enzyme catalytic activity should be at the highest possible level in terms of enzyme units per gram of support [159].

Currently, bioremediation allows the transformation of a significant part of difficult-to-degrade substances into simpler compounds, but it is not able to completely remove pollutants. Therefore, it is necessary to combine enzymatic degradation with other wastew-

ater treatment techniques, such as photocatalysis, activated sludge or anaerobic digestion to achieve the full removal, detoxification and mineralization of pollutants [154,155,160,263].

7. Methods of Increasing the Productivity and Activity of Laccases

Currently, due to the development of green and white biotechnology, the production of enzymes has significantly increased, including oxidoreductase. Therefore, enzymes with greater activity and stability under extreme conditions of temperature, pH, etc., are also sought. These studies are aimed at improving the economics of the processes compared to those currently available. The main goal is to reduce enzyme production costs and improve their properties [82]. The potential of laccases to degrade xenobiotics can be promoted by improving the catalytic properties of the enzyme using protein and genetic engineering methods [87].

Basidiomycota and *Ascomycota* with high redox potential are used to produce biotechnologically important laccases [106,314]. Laccases of different origins break down pollutants in different ways. Therefore, the result of their enzymatic activity is products that differ in structure and chemical and physical properties, with varying degrees of toxicity. For example, as a result of the degradation of BPA by laccases *Bjerkander adusta* and *T. versicolor*, glycerol is formed, and *C. gallica* forms β-hydroxybutyric acid [7]. Therefore, it is important to search for new sources of laccases and their physiological characteristics in order to optimize the culture conditions, as well as to isolate enzymes and their biochemical characteristics in order to develop rational methods of protein modification and introduce changes favorable for the course of biodegradation processes.

7.1. Improvement of Catalytic Activity of Laccases

In recent years, researchers have used methods such as the optimization of reaction conditions, including the search for reaction mediators or inducers, the use of surfactants, the immobilization of enzymes on matrices with various properties, and modifications of catalytic activity and substrate specificity using molecular biology and engineering techniques to increase enzyme activity [315,316].

In the work of Kupski et al. (2019), it was proposed to optimize the laccase–mediator system (LMS) to reduce pesticide levels in the aquatic environment [183]. Among all the tested mediators, the best degradation efficiency was achieved for the laccase–vanillin system at 30 °C after 5 h incubation. The laccase–mediator system (LMS) can overcome obstacles such as steric hindrance (for macromolecular compounds), very low affinity between the compound and the active site of the enzyme and high redox potential of putative substrates. ABTS is the first synthetic molecule to act as a laccase mediator [106].

To improve the stability of enzymes and increase their activity in a wide range of pH and temperatures, immobilization is being used. This process also allows the enzyme to be used multiple times and facilitates its storage, which reduces the cost of the reaction. Methods such as adsorption, entrapment, encapsulation, covalent bonding, and self-immobilization have been used to immobilize laccase [89,271,292–294,296,317,318]. In the Nair et al. (2013) study, *C. gallica* laccase immobilized on mesoporous silica spheres by adsorption cross-linking has been used to eliminate endocrine-disrupting compounds (EDCs) from wastewater [319]. Compared to the free enzyme, the immobilized enzyme had significantly higher thermostability, with half-lives of 31.5 h and 3.9 h, respectively, compared to 6.1 h and 0.6 h at 55 °C and 75 °C. The improvement in temperature resistance in the biocatalyst was probably due to the reduction of molecular mobility and the improvement in conformational stabilization due to the high degree of multipoint attachment to the substrate. Immobilized laccase used in a continuously stirred membrane reactor eliminated more than 95% of 10 mM BPA and 10 mM EE2 and 70% of 10 mM diclofenac when treated individually and more than 90% when treated as a mixture in a pH 5 aqueous buffer solution for more than a 60 reactor volume. After more than 80 h of real wastewater treatment, over 85% of BPA and EE2 and 30% of diclofenac were degraded.

Much attention is paid to nanomaterials and nanobiocatalysts. The nanomaterial particles form a complex with the enzyme through a covalent bond [320]. Nanomaterials provide a larger immobilization surface, which increases the enzyme load per unit mass of particles and, thus, increases the efficiency of the immobilized enzymes [321,322]. The reuse of immobilized laccases improves the efficiency and durability of the process by reducing the costs associated with the loss of enzymes and materials [159,323]. To improve the decolorization performance of HR dyes, Wehaidy et al. (2019) developed a method of laccase immobilization on a nanoporous Zeolite-X carrier [324] chemically belonging to hydrated aluminosilicates forming a three-dimensional network skeleton with the same size of interconnected pores and channels. Covalent immobilization on the nanomaterial improved enzyme properties such as resistance to pH and temperature changes lowered the activation energy and increased the catalytic efficiency. Complete discoloration of AB 225 occurred after 15 min of incubation and RB 19 after 45 min. In addition, the immobilized formulation retained 100% of its original activity after seven consecutive decolorization cycles. The laccase of *Nigroporus durus* ATCC 26726 immobilized on nanoporous Zeolite-X (ZX) can be successfully used in the textile industry for water treatment.

Genetic engineering and protein engineering techniques are used to modify the thermostability, catalytic activity and substrate specificity of enzymes. Three types of enzyme modification strategies are used in this field, such as rational, semirational and directed evolution methods [87,154]. The site-directed mutagenesis of Xu et al. (2020) obtained mutant S208G/F227A CotA-laccase *Bacillus pumilus* W3, which showed more than five times higher catalytic efficiency than the laccase wild-type CotA and improved the methyl red decolorizing capacity [325].

Based on the method of site-directed mutagenesis, Xu et al. (2019) also investigated the role of N-glycosylation in the specific laccase activity of *Coprinopsis cinerea* Lcc9 expressed in *Pichia pastoris* [326]. It turned out that the glycosylation at N313 affects the affinity of the enzyme for substrates, and the glycosylation at N45 affects the catalytic rate. Notably, N-glycosylation modifications in eukaryotic hosts can significantly improve the thermostability of lignocellulosic enzymes, as the glycan chains act as a protector by attaching to the protein surface via extensive hydrogen bonding [327]. Heterologically expressed fungal laccases exhibit different biochemical properties compared to native fungal laccases. The laccase of *Cyathus bulleri* when expressed in *P. pastoris*, in which the glycosylation pattern was changed, increased thermal stability and salt tolerance, which is likely related to the change in protein structure and function.

Rational engineering increased the substrate specificity of the laccase lccb of *T. versicolor* for the oxidation of large polycyclic aromatic hydrocarbons without a mediator [184]. The authors used structure-based protein engineering to generate rationally modified laccases with an enhanced ability to process large PAHs without a mediator. Computational simulations were used to estimate the effect of mutations in the enzymatic binding pocket on the binding and oxidizing capacity of a selected set of organic compounds. The generated mutants with an enlarged laccase binding pocket showed increased activity without the mediator and functioned over a wider pH range compared to the wild-type enzyme. The enlargement of the binding pocket allowed macromolecular substrates to come into direct contact with the catalytic residues of the laccase, which eliminated the use of mediators for electron transport. The modified laccase degraded ethyl green, a synthetic triphenylmethane dye, by over 90% within 24 h without mediators. The researchers proposed the use of the M1 catalytic site mutant of the F162A/L164A laccase in mediator-free, difficult-to-degrade macromolecular compounds.

Noncatalytic enzyme functional sites are modified according to the primary and tertiary structure of the protein, while catalytic functional sites are designed semirationally and rationally based on molecular docking [328,329]. Using advanced molecular biology tools, i.e., next-generation sequencing, site-directed mutagenesis, fusion proteins, surface display, etc., scientists can now develop enzymes to improve activity, stability and substrate

specificity to meet the stringent conditions of industrial processes and biodegradation of waste from their activities [315].

Currently, work is being undertaken to modify the enzymes, which are then immobilized. When a charged polypeptide tail was added at the C-terminus, the salt resistance of laccase placed in coacervate core micelles (C3M) by encapsulation was enhanced [330]. The use of CotA with a polyglutamic acid tail resulted in more micelles with fewer enzyme molecules per micelle, better stability and increased laccase activity. Enriching the charge of enzymes by genetic engineering appears to be a potential strategy to improve the practical application of C3Ms as enzyme delivery systems in reaction environments.

7.2. Improvement of Laccase Productivity

Laccases are produced by various groups of organisms from bacteria to plants. The production by bacteria and fungi is biotechnologically important. The physiological requirements of microorganisms capable of producing laccases are different. To obtain the maximum amount of enzymes, the influence of many factors, such as the carbon source, concentration and type of nitrogen source, pH, temperature, inducer and other culture conditions on laccase production is studied [106].

The synthesis and secretion of laccase are strictly dependent on the level of nutrients (bioavailability of mainly C and N), culture conditions (temperature, aeration, reaction and light) and the development stage of the cultured microorganism, as well as the addition of inducers to the media (e.g., metal ions). Most of these factors have been shown to operate at the transcriptional level, producing different enzyme isoforms within the same strain and between different fungal species [329]. An inducer of laccase production in fungal cultures, in addition to the high nitrogen content in the medium *Basidiomycete* I-62 (CECT 20197) and *Lentinus sajor-caju*, is the presence of copper and other metal ion or aromatic compounds structurally similar to lignin precursors [106,194].

The cheapest way to overproduce enzymes is to optimize the fermentation conditions, and a spectacular increase in the amount of enzyme produced by a given microorganism can be achieved by changing just a few parameters. A modern method more and more willingly used to optimize the composition of media is the methodology of the response surface (RSM) [316]. With good results, RSM was used to optimize the production of laccase by *A. bisporus* CU13 [331]; *Pseudolagarobasidium acaciicola* AGST3 [332]; and *Penicillium chrysogenum* [225].

Atilano-Camino et al. (2020) optimized laccase production by T. versicolor using RSM in batch-submerged fermenters. Lignocellulosic residues were used in the culture [333]. The optimization of the culture conditions with a temperature of 35 °C and 5 g/L of wheat bran in the medium allowed about 200 U/mL of laccase to be obtained in 11 days in a batch reactor. The postculture fluid was used for the enzymatic degradation of wastewater, with a two-fold increase in the biodegradability index. In conclusion, as noted by the authors, laccase-mediated biodegradation may become a feasible method for the pretreatment of real wastewater.

Wild-type hosts can only produce small amounts of enzymes and are unable to meet industrial demands. Therefore, *P. pastoris*, *Aspergillus flavus*, *A. niger*, *A. nidulans*, *Trichoderma reesei* and *Yarrowia lipolytica* are often used for the heterologous expression of laccases [329].

More recently, Clark et al. (2021) used the insect *Drosophila melanogaster* to functionally express a laccase from the fungus *Trametes trogii* [334]. The short tubulin promoter was used for moderate expression in many tissues of the insect, and native fungal signal peptides were replaced with the signal peptide of the D. melanogaster larval epidermal protein to facilitate extracellular secretion. Lyophilized powder from processed adult flies degraded over 90% of the blue synthetic dye Acid Blue 74 in aqueous solutions. The obtained results showed that transgenic animals can be used for the bioremediation of environmental pollutants in vivo and serve as a new way of producing industrial enzymes.

In summary, the aim of traditional methods of optimizing the production of laccases, as well as methods of genetic engineering in the heterologous expression of enzymes, is to produce as many laccases as possible with appropriate biochemical properties at very low costs [106,329].

8. Conclusions

The increasing population and industrialization result in the generation of large amounts of sewage containing substances dangerous to the health of humans and animals and disrupting the functioning of entire ecosystems. It is necessary to search for environmentally safe methods of removing xenobiotics from water. Enzymatic degradation of pollutants using laccase is a good alternative to traditional wastewater treatment methods, as it does not generate harmful by-products. It is important to search for new sources of laccases, their biochemical characteristics, improvements in their catalytic activity and thermostability and increases in their productivity using modern methods of genetic and protein engineering. This will contribute to the improvement of biodegradation processes involving enzymes and will increase the efficiency of removing xenobiotics from the environment.

Author Contributions: All authors participated equally in the preparation of the text of this work. Conceptualization: A.G. and U.J.; writing—review and editing: all authors. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

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