



Review



Structural insights, biocatalytic characteristics, and application prospects of lignin-modifying enzymes for sustainable biotechnology

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ABSTRACT

Lignin modifying enzymes (LMEs) have gained widespread recognition in depolymerization of lignin polymers by oxidative cleavage. LMEs are a robust class of biocatalysts that include lignin peroxidase (LiP), manganese peroxidase (MnP), versatile peroxidase (VP), laccase (LAC), and dye-decolorizing peroxidase (DyP). Members of the LMEs family act on phenolic, non-phenolic substrates and have been widely researched for valorization of lignin, oxidative cleavage of xenobiotics and phenolics. LMEs implementation in the biotechnological and industrial sectors has sparked significant attention, although its potential future applications remain underexplored. To understand the mechanism of LMEs in sustainable pollution mitigation, several studies have been undertaken to assess the feasibility of LMEs in correlating to diverse pollutants for binding and intermolecular interactions at the molecular level. However, further investigation is required to fully comprehend the underlying mechanism. In this review we presented the key structural and functional features of LMEs, including the computational aspects, as well as the advanced applications in biotechnology and industrial research. Furthermore, concluding remarks and a look ahead, the use of LMEs coupled with computational framework, built upon artificial intelligence (AI) and machine learning (ML), has been emphasized as a recent milestone in environmental research.

1. Introduction

Lignin modifying enzymes (LMEs) have long been considered crucial enzymes that act on lignin polymers in a variety of ways, including catalytic cleavage of C-C, C-O-C bond, depolymerization, and valorization [1–7]. Taking advantage of their role in lignin degradation, LMEs have been used in a variety of biotechnological processes and applications including; pulp bleaching for paper manufacturing, food, textile, dye, cosmetics industries, and further sustainable generation of

renewable chemicals for organic synthesis, bio-materials, fuels, and bioremediation of hazardous pollutants [8–12]. The use of LMEs has significantly increased over the last two decades with the awareness of the importance of employing “green approaches” in the industry which are based on sustainable, environmentally friendly, economically viable, and potentially high-yielding processes without producing pollutants during reaction process [13–15]. Fig. 1 portrays a concise summary of LMEs and their respective functionalities in biotechnological and industrial sector. LMEs comprises a set of five different enzymes, which

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similarly perform as an oxidoreductase in catalytic action: lignin peroxidase (LiP; EC 1.11.1.14), manganese peroxidase (MnP; EC 1.11.1.13), laccase (LAC; EC 1.10.3.2), versatile peroxidase (VP; EC 1.11.1.16), and dye decolorizing peroxidase (DyP; EC 1.11.1.19) [16–18]. LMEs member LAC contains multi copper in its protein structure hence called multi-copper oxidase (MCO) [19–21]. It acts on the phenolic substrate in presence of molecular oxygen (O_2) [19]. However, LiP and DyP are heme proteins with Fe (III), while MnP possess Mn (II) centers, respectively [22–24]. Reaction mechanism of these oxidoreductase members except LAC are H_2O_2 -dependent that act on a wide variety of phenolic and non-phenolic substrates in a similar fashion of LiP's catalytic cycle involving H_2O_2 dependent, initiates a two-electron oxidation of a native LiP to first produce an oxoferryl iron radical cation intermediate, Compound I, along with the reduction of H_2O_2 to water, and complete reaction in subsequent cycles [25,26]. Those lignin-degrading peroxidases are likely to be a member of the plant peroxidase superfamily (Class II) [27,28]. Among aforesaid, DyP has been recently identified class of heme-containing peroxidases and given the name DyP because it has an effective, lignin degradation, and dye decolorizing capability on a variety of industrial dyes [3,29–31]. Fungal species are well documented for secretion or production of LMEs in nature, including; *Phanerochaete chrysosporium*, *Phlebia floridensis*, *Trametes versicolor*, *Phlebia fascicularia*, *Dichomitus squalens*, *Daedalea flavida*, *Phlebia radiata*, *Cerrena unicolor*, *Trametes trogii* and many others [32–34]. Fungal LMEs work at weak acid to neutral pH (4–7) and diverse temperature range (30–55 °C) for the activity of the degradation and decolorization processes [35–37]. However, no single fungal species are known to produce all members of LMEs. The white-rot fungi (WRF) has largely been focused on acting as potential lignin degraders, including lignin, xenobiotic, and recalcitrant compounds via the extracellular H_2O_2 -dependent oxidoreductase enzyme mechanism [34,38–42]. Several White-Rot Basidiomycete (WRB) have been examined in recent years to identify viable LMEs producers, while a few fungal species have exhibited promising LAC and lignin-modifying peroxidase synthesis [8,43–47]. *P. chrysosporium* is one of the most investigated species among a range of pollutants degrading fungi by its extracellular enzymes

including; LiP, MnP, and LAC production processes [6,8,48–50]. Although other WRBs from other taxonomic groups have been assessed, additional research is required to identify potential species and its associated nutritional and culture conditions for effective productivity and increased yield of LMEs. In contrast to fungi, bacterial machinery is comparatively less developed for production of degrading enzymes and proper folding protein which could be able to work in an optimum environment [28]. The catalytic activities of LMEs have been employed to oxidize a wide range of phenolic and non-phenolic pollutants, including; endocrine-disrupting chemicals (EDCs), polycyclic aromatic hydrocarbons (PAHs), polychlorinated dibenzodioxins (PCDDs), polychlorinated biphenyls (PCBs), dibenzofurans, and pharmaceuticals and personal care products (PPCPs), and non-steroidal anti-inflammatory drugs (NSAIDs) [11,51–57]. As concerning their extended application, LMEs can act sufficiently on lignin polymer, which is produced enormously from pulp & paper industry. Conversely, enzymatic biotransformation of kraft lignin has been documented extensively in the last two decades, enumerating the transformed low molecular weight (LMW) compounds after treatment either through enzyme or LME-producing species under controlled conditions [8,58–64]. As a byproduct, an enormous quantity of technical lignin serves as a rich source of aromatic compounds that may be further valorized in the synthesis of value-added compound [65–69]. Much effort has been made to develop novel techniques for extracting and converting lignin into value-added compounds, including lipids, polyhydroxyalkanoates (PHAs), vanillin, and other aromatic monomers with the goal of lowering the total costs of the biorefinery process [10,70–72]. Interestingly, the strong oxidizing capabilities of LMEs have been examined in computer-aided research to better comprehend enzyme-pollutant interaction behavior, which could possibly be incorporated into real-time assay to accelerate biodegradation [73–75]. The aforementioned computer-aided framework for virtual screening of LMEs assisted pollutant catalysis often relies on docking and MD-simulation to estimate binding affinity, chemical bonding, and associated crucial amino acid residues, which is believed to be a recent breakthrough in environmental research [74–80]. Despite the fact that the protein constituents of LMEs are not identical with

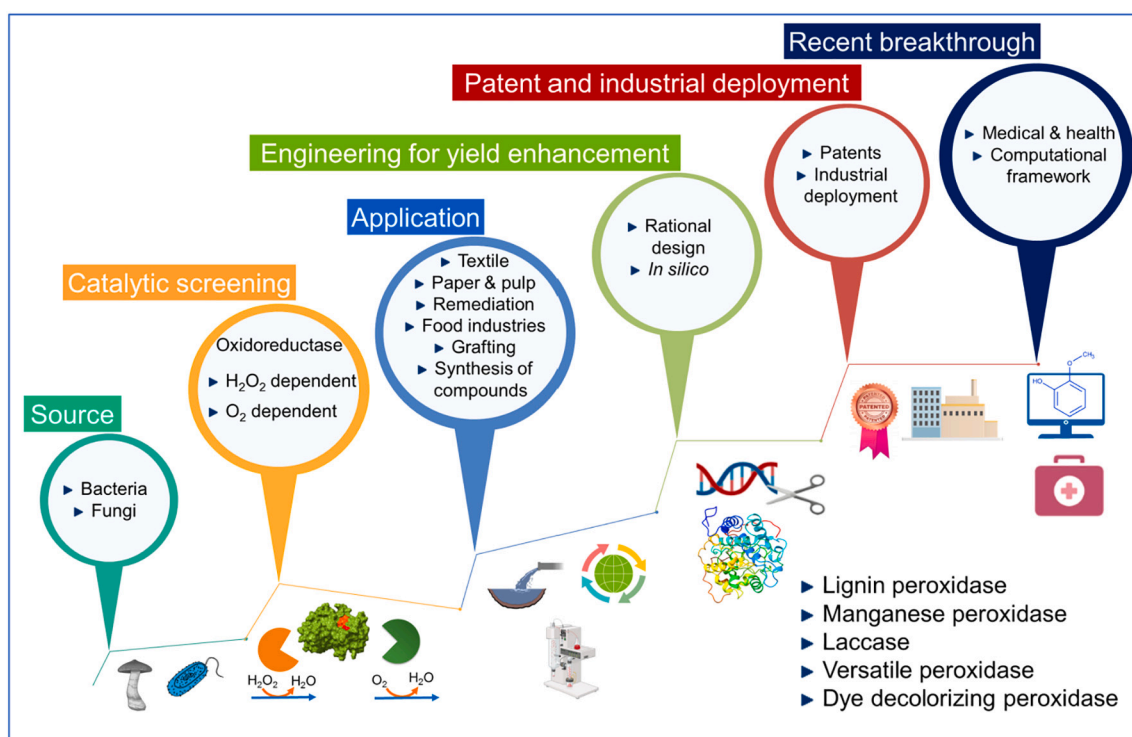


Fig. 1. Highlights of successful milestones in lignin modifying enzymes (LMEs) applications.

respect to helix, sheet, and loop components, therefore pollutant binding mechanism and catalytic activity varies across LMEs members [74,79,80]. Nevertheless, computational finding must be validated utilizing real-time degradation assay to completely understand the biotransformation of parental pollutants, to completely comprehend post degradation toxicity, and fate. In the presented state-of-art, we reviewed the more recent applications of LMEs in biotechnological and industrial research through illustration sketches. Computational aspects and crucial protein features of LMEs have been highlighted. Special emphasis has been furnished on the computational framework, which appears a breakthrough in the last decade as a smart green remediation approach. Furthermore, considerably more significant applications of LMEs in biotechnology, industry, environmental, grafting on materials deployment, computational research, and medical have been outlined with concluding remarks.

2. Lignin modifying enzymes (LMEs) producing microbial species

LMEs are extracellular enzymes that are often produced by a few bacterial and fungal species [28,81–84]. Bacterial species including; *Brucella*, *Ochrobactrum*, *Sphingobium*, and *Sphingomonas* genera belonging to the class α -Proteobacteria have been reviewed for producing enzymes that act on lignin [81]. Likewise, another class γ -Proteobacteria including *Pseudomonas fluorescens* (LiP-producing), *Pseudomonas putida* (DyP, MnP-producing), *Enterobacter lignolyticus* (catalase/peroxidase HPI and DyP-producing) and *Escherichia coli* (LAC-producing) have been reviewed by Janusz et al. [81]. Bacterial delignification is both less effective and slower than fungal delignification, and bacterial lignin breakdown is correspondingly limited [84,85]. Bacteria, on the other hand, are increasingly being recognized for their efforts in this process [86,87]. WRF is one of the most studied fungal species which have an efficient lignin-degrading capability in nature [88]. A few potential fungal species have been documented recently for the secretion or production of LMEs in nature, including; *Phlebia floridensis*, *Trametes versicolor*, *Volvariella volvacea*, *Dichomitus squalens*, *Daedalea flavida*, *Phlebia radiata*, *Trametes villosa*, *Trametes pubescens* and many others [89–91]. Extracellular ligninolytic oxidoreductase enzymes such as LAC and peroxidases, as well as other secreted metabolites, facilitate lignin depolymerization by WRF [88,92]. Fungi need more time in contrast to bacteria, often weeks, to develop and generate extracellular enzymes that break down lignin, as outlined in recently reported research [85,93,94]. Additionally, fungal LMEs work at weak acid to neutral pH (4–7) and diverse temperature ranges (30–55 °C) for the activity of the degradation and decolorization processes [35–37]. Several White-Rot Basidiomycete (WRB) has been examined in recent years to identify viable LMEs, while a few fungal species have exhibited promising LAC and lignin-modifying peroxidase synthesis [8,43–47]. Table 1 highlights the few well-studied microbial species that have been identified as LMEs producers.

3. Structural features and catalytic mechanisms of LMEs

LMEs contain unique molecular and chemical functionalities, which can be deployed in a wide variety of diverse applications, in three aspects 1) valorization of lignin, 2) depolymerization of lignin, and 3) oxidative functionalities [1,121–123]. Fig. 2 portrays the schematic oxidative catalytic activity of LMEs on lignin polymer. Molecular and structural aspects are a vital part of LMEs for exploring secondary structure element (SSE), protein topology, and its atomic dynamics against pollutants binding. The protein data bank (<https://www.rcsb.org>) has a repository of the crystal structure information on LMEs, which contains plenty of entries from different origins [124,125]. As described above, the LMEs group encompasses enzymes such as LiP, LAC, VP, MnP, and DyP [28,126]. All members except the LAC are hydrogen peroxidase (H₂O₂)-dependent oxidoreductase, in catalytic

Table 1

Reported microbial species for lignin modifying enzymes production. Species has been explained with its substrate utilization for enzyme production.

LMEs producing microbial species	Produced enzyme	Substrate	Reference
Fungal species			
<i>Bjerkandera adusta</i> TBB-03	LAC	Acetaminophen, bisphenol A, sulfamethoxazole	[95]
<i>Coprinus comatus</i>	LAC	Reactive Dark Blue KR, Reactive orange 1, Reactive Red X-3B, Congo red	[96]
<i>Coriopsis gallica</i>	LAC	Reactive Black 5, Bismark Brown R	[97]
<i>Coriopsis polyzona</i>	LAC	Acid Red 299, Direct Blue 1, Direct Red 28, Disperse Red 1, Disperse Yellow 3, Reactive Black 5, Reactive Red 4, Reactive Yellow 81	[98]
<i>Cyathus bulleri</i>	LAC	Reactive Orange 1	[99]
<i>Daedalea dickinsii</i>	LAC, MnP	Disperse violet-63 Disperse orange-30	[100]
<i>Datronia caperata</i>	LAC	Orange II	[101]
<i>Ganoderma applanatum</i>	LAC, LiP, MnP	Celecoxib, diclofenac and ibuprofen	[57]
<i>Grammothete fuligo</i>	LiP, MnP, LAC	Organosolv, Kraft lignin	[102]
<i>Hexagonia hirta</i>	LAC	Orange II	[101]
<i>Hypholoma fasciculare</i>	LAC	Acid Red 299, Direct Blue 1, Direct Red 28, Disperse Red 1, Disperse Yellow 3, Reactive Black 5, Reactive Red 4, Reactive Yellow 81	[98]
<i>Irpex lacteus</i>	MnP	Remazol Brilliant Violet 5R, Direct Red 5B	[103]
<i>Ischnoderma resinotum</i>	LAC, MnP	Reactive Black 5, Reactive Red 22, Reactive Yellow 15	[104]
<i>Laetiporus sulphureus</i>	LAC, LiP, MnP	Celecoxib, diclofenac and ibuprofen	[57]
<i>Lenzites elegans</i>	LAC	Congo Red	[105]
<i>Oudemansiella canarii</i>	LAC	Congo red	[106]
<i>Peniophora</i> sp. CBMAI 1063	LAC	Syringaldazine (SGD)	[107]
<i>Trametes trogii</i>	LiP, MnP	ABTS (2,2'-azinodl-3-ethylbenzothiazoline-6-sulphuric acid)	[108]
<i>Phanerochaete sordida</i>	LAC	Reactive Black 5	[109]
<i>Pleurotus djamor</i>	LAC, MnP, LiP	Naproxen and ketoprofen	[110]
<i>Pleurotus eryngii</i>	VP	Enhanced pH and thermal stability	[111]
<i>Pleurotus ostreatus</i>	MnP, VP	Orange II, Reactive Black 5 (RB5), (DMP), Phenol Red, Orange II, Reactive Black 5 (RB5), (DMP), Phenol Red	[112,113]
<i>Pleurotus sajor-caju</i>	LAC, MnP	Congo Red, Orange G Reactive Black 5 (RB5) decolorization	[114,115]
<i>Polyporus tenuiculus</i>	LAC	Orange II	[101]
<i>Emmia latemarginata</i>	VP, MnP, LiP	Remazol dye, disperse-dye, indigo dye	[116]
<i>Mucor circinelloides</i>	VP, MnP, LiP	Remazol dye, disperse-dye, indigo dye	[116]
<i>Stropharia rugosoannulata</i>	LAC	Acid Red 299, Direct Blue 1, Direct Red 28, Disperse Red 1, Disperse Yellow 3, Reactive Black 5, Reactive Red 4, Reactive Yellow 81	[98]
<i>Trametes versicolor</i>	LAC	Diclofenac, flufenamic-acid, bisphenol A, Acid Red 299, Direct Blue 1, Direct Red 28, Disperse Red 1, Disperse Yellow 3, Reactive Black 5, Reactive Red 4, Reactive Yellow 81	[98,117]
Bacterial species			

(continued on next page)

Table 1 (continued)

LMEs producing microbial species	Produced enzyme	Substrate	Reference
<i>Agrobacterium</i> sp.	DyP	Lignin	[118]
<i>Comamonas testosteroni</i>	DyP	Lignin	[118]
<i>Klebsiella pneumoniae</i> NX-1	LiP, LAC, MnP	Kraft lignin	[119]
<i>Ochrobactrum tritici</i> NX-1	LiP, LAC, MnP	Kraft lignin	[119]
<i>Pseudomonas fluorescens</i>	DyP	Lignin	[118]
<i>Pseudomonas putida</i> NX-1	LiP, LAC, MnP	Kraft lignin	[119]
<i>Streptomyces ipomoeae</i> CECT 3341	LAC	Lignin	[120]

mechanism [127]. The mechanism of LMEs substrate oxidization has been described in the subsequent sections. The three-dimensional protein structure of all LMEs members has shown in Fig. 3; the related SSE (i.e., alpha helices, and beta-sheets, turn, coils) has reported in Table 2. Nevertheless, the composition of amino acids and other elements are relatively variable in all members of LMEs and feasible to act as oxidoreductase on a wide range of substrates [74,75,79,80].

3.1. Lignin peroxidase (LiP)

LiP (EC 1.11.1.14) is a high redox potential (1.4 V) extraordinarily active heme (Fe)-containing enzyme that acts on a wide range of lignin, lignin-based compounds, non-phenolic, and phenolic model compounds of lignin [2,128–130]. The crystal structure of LiP has been deposited concerning fungal sequence (PDBs: 1LGA, 1LLP, 1QPA, 1B80, 1B85, 6ISS, 3Q3U), however, bacterial crystal structure is very limited or lack in compare to fungal species in the PDB database so far [131–134]. For

an example crystal structure of LiP from *Trametes cervina* (PDB: 3Q3U) has 338 amino acids count in a single chain, while heme (Fe) co-factor is the metallic component of this protein which is competent to perform H_2O_2 -dependent oxidative cleavage of numerous bonds in the substrates i.e. lignin [135,136]. The calculated molecular weight of the LiP is roughly 35 kDa [137]. Alpha helix (Hh), extended strand (Ee), beta turn (Tt), and random coil (Cc) make up 35.80 %, 7.69 %, 4.14 %, and 52.37 %, respectively, of the SSE of LiP 3Q3U (Table 2). A few similar enzymes including LigD from *Sphingobium* sp. SYK-6 bacteria (PDB: 4Y9D) are known for acting on lignin by β -aryl ether (β -ether) cleavage has been reported to functioning those of LiP. Such LigD comprised 305 amino acids count in a single chain, and has a calculated molecular weight of about 32.3 kDa [137,138]. In contrast to fungal LiP, it comprises alpha helix (Hh), extended strand (Ee), beta turn (Tt), and random coil (Cc) making up 49.18 %, 13.77 %, 8.52 %, and 28.52 %, respectively, of the SSE. LiP has been extensively documented for cleaving the C-C and C-O-C (ether bond) linkage present in lignin, and oxidizing benzyl alcohols to aldehydes [22]. Moreover, hydroxylation, quinone formation, and cleaving of the aromatic ring are also reported [139]. A considerable variety of non-phenolic lignin model compounds, particularly β -O-4 linkage type compounds, are readily oxidized by LiP [28,75,84]. The LiP oxidation mechanism involves the formation of radical cations with one-electron oxidation, which leads to the cleavage of the side chain, demethylation, intra-molecular incorporation, and molecular rearrangements on reacting substrate [140]. A detailed LiP chemical catalysis/depolymerization scheme has portrayed in Fig. 4. Bacterial-derived LiP has been reported for efficient KL degradation experimentally but lacks protein crystal structure availability at repository databases [28,59,141,142]. WRF species are substantially more efficient than bacteria on lignin depolymerization, xenobiotic degradation, and decolorization of dyes [4,42,143–146]. Numerous studies have reported recombinant/engineered LiP/DyP, which has demonstrated significantly enhanced catalytic capabilities in an unstable environment [147–150]. A structural representation of LiP and heme (Fe) binding

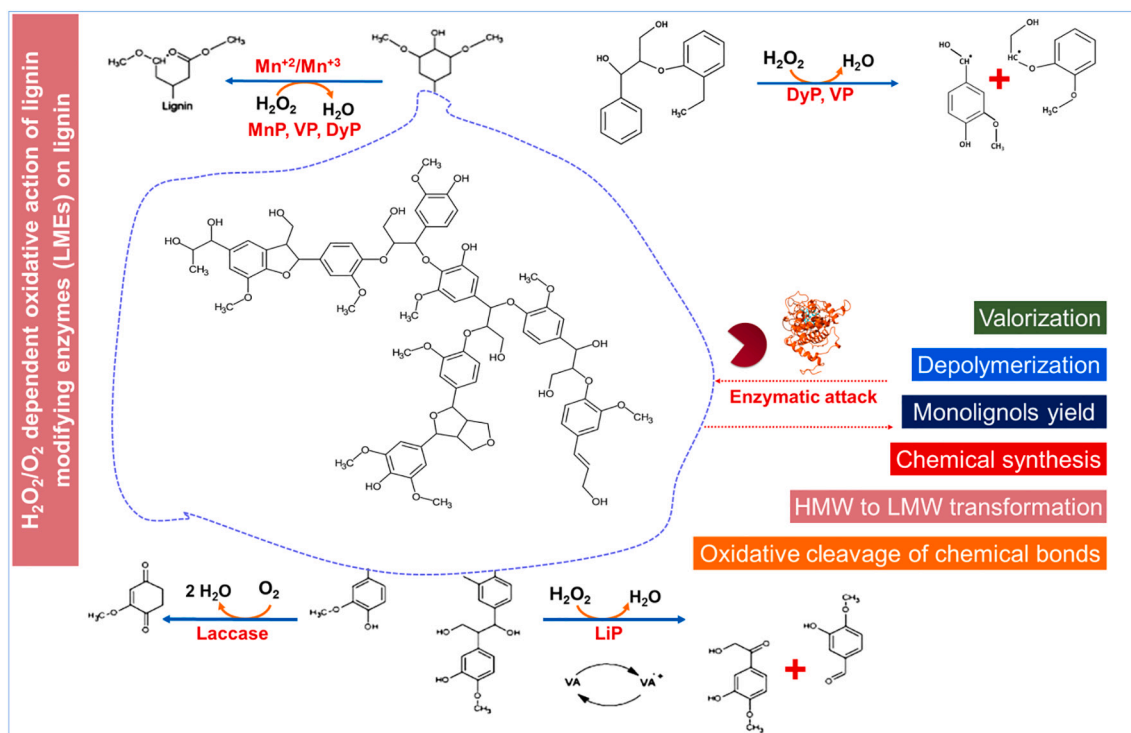


Fig. 2. Chemical catalytic mechanism of lignin modifying enzymes (LMEs). Peroxidases (LiP, MnP, VP, and DyP) share H_2O_2 dependent catalytic mechanism, whilst LAC utilizes molecular O_2 instead of H_2O_2 . The most often used substrate of LMEs is lignin reported in the center, while the right panel highlights the chemical functionalities.

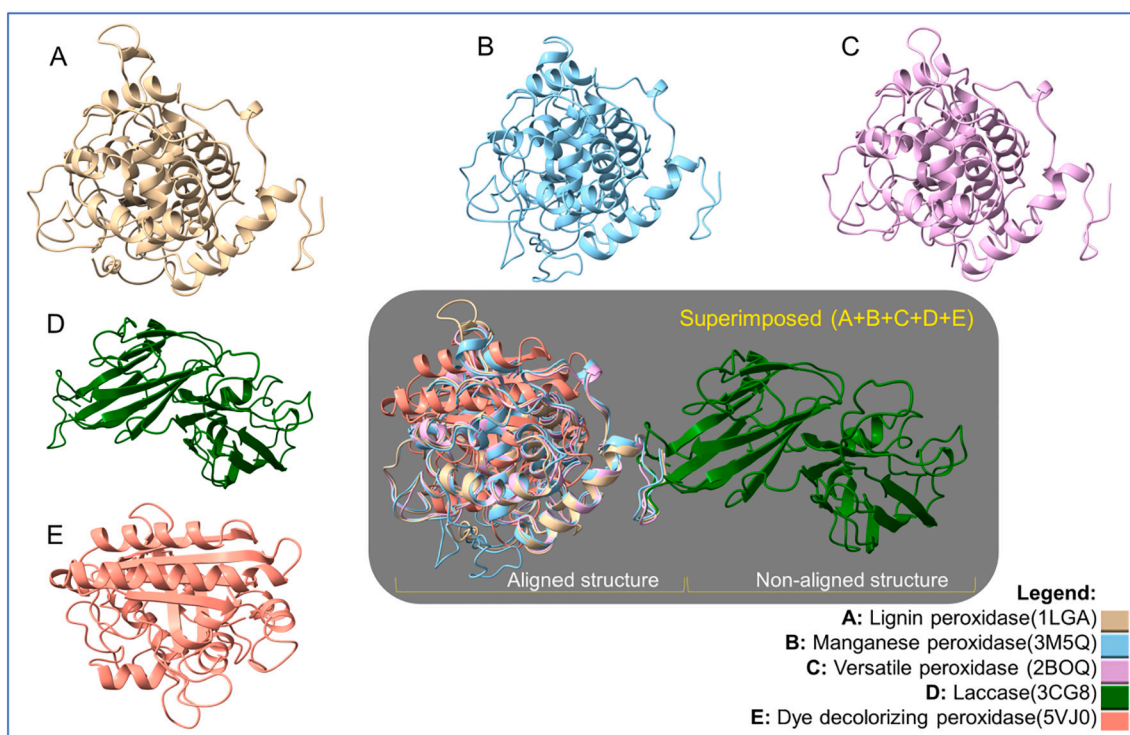


Fig. 3. Three-dimensional rendered structure of lignin modifying enzymes (LMEs). Protein structures have been re-rendered from respective PDB files. A: exhibited cartoon rendered of LiP; B: exhibited cartoon rendered of MnP; C: exhibited cartoon rendered of VP; D: exhibited cartoon rendered of LAC; E: exhibited cartoon rendered of DyP. Middle panel exhibited the superimposed rendered structures, which conclude that LAC has different structural element and exclude from clusters within RMSD of 2 Å.

Table 2

Secondary structural elements (SSE), of LMEs. Each member has listed for different SSE in percentage contribution. LAC can be observed for relatively less helix element, whilst higher in beta component.

PDB ID of enzyme	Origin	Amino acid residues count	Secondary structure elements(SSE)				Reference
			Alpha helix (Hh)	Extended strand (Ee)	Beta turn (Tt)	Random coil (Cc)	
LiP (3Q3U)	Fungal	338	35.80 %	7.69 %	4.14 %	52.37 %	[222,223]
MnP(3M5Q)	Fungal	357	30.81 %	9.52 %	4.48 %	55.18 %	[190,223]
VP (2BOQ)	Fungal	331	35.95 %	6.65 %	4.53 %	52.87 %	[220,223]
LAC (3CG8)	Bacterial	343	14.29 %	25.66 %	7.29 %	52.77 %	[223,224]
DyP(5VJ0)	Bacterial	318	34.91 %	18.55 %	3.77 %	42.77 %	[223,225]

residues, and active site has portrayed in Fig. 5.

3.2. Laccase (LAC)

LACs (EC 1.10.3.2) are multicopper-containing oxidoreductases (MCOs) that oxidize diverse phenolic, non-phenolic, and lignin model compounds utilizing molecular oxygen (O_2) as an electron acceptor, resulting in water generated as a by-product through a chemical reaction (Fig. 2) [151–155]. Unlike other member of LMEs, LAC utilizes O_2 , and highly specialized in phenolic substrate catalysis, with and without mediators [156,157]. Since the discovery of the first laccase in *Rhus vernicifera* from the Japanese lacquer tree *Toxicodendron vernicifluum* in 1883, LACs have been reported in a variety of higher plant species [15]. Besides the plants, it also been identified in bacterial, and insects species [158–162]. Most of these enzymes, however, have been isolated from fungi, which are common LAC producers, and deployed into use for degrading lignin amid the decomposition of wood [15,161,163,164]. Adequate protein crystal structures of LACs from various origin species are available in the Protein Databank (<https://www.rcsb.org>), enabling structural and molecular investigations in research of interest [125]. The structural features of different LAC with different origins including;

plants (*Zea mays*: 6KLG), fungi (*Trametes versicolor*: 1KYA), bacteria (*Streptomyces coelicolor*: 3CG8), and insects (*Drosophila melanogaster*: NP_651441.1) have explained in subsequent figs [134,165–168]. The SSE of LAC (3CG8), consisting of alpha helix (Hh), extended strand (Ee), beta turn (Tt), and random coil (Cc) make up 14.29 %, 25.66 %, 7.29 %, and 52.77 %, respectively [136]. In contrast to LiP, LAC has the lowest helix elements and higher beta component in its protein architect. The crystal structure of *Streptomyces coelicolor* origin LAC (PDB: 3CG8) with a calculated molecular weight of around 36.8 kDa comprises 343 residues in three chains (A, B, and C) [125,137,169,170]. Likewise comparable crystal structure of LAC of fungal origin (*Trametes versicolor*), PDB: 1KYA comprises 499 residues in four chains (A, B, C, and D) [171]. Crystal structure of LAC from plant origin (*Zea mays*), PDB: 6KLG comprises 550 residues in a single chain [172]. The protein structural architecture of LACs from a different source of origin has explained in Fig. 6. Multi copper binding site of LAC has portrayed in Fig. 7. LACs are divided into two categories based on their redox potential: low- (from 0.4 to 0.5 V) and high-redox potential (from 0.5 to 0.8 V) enzymes [159,173,174]. In contrast to the great prevalence of high-redox-potential LAC in fungi, low-redox-potential enzymes are found in bacteria, plants, and insects [159,175]. Gram-positive and gram-negative

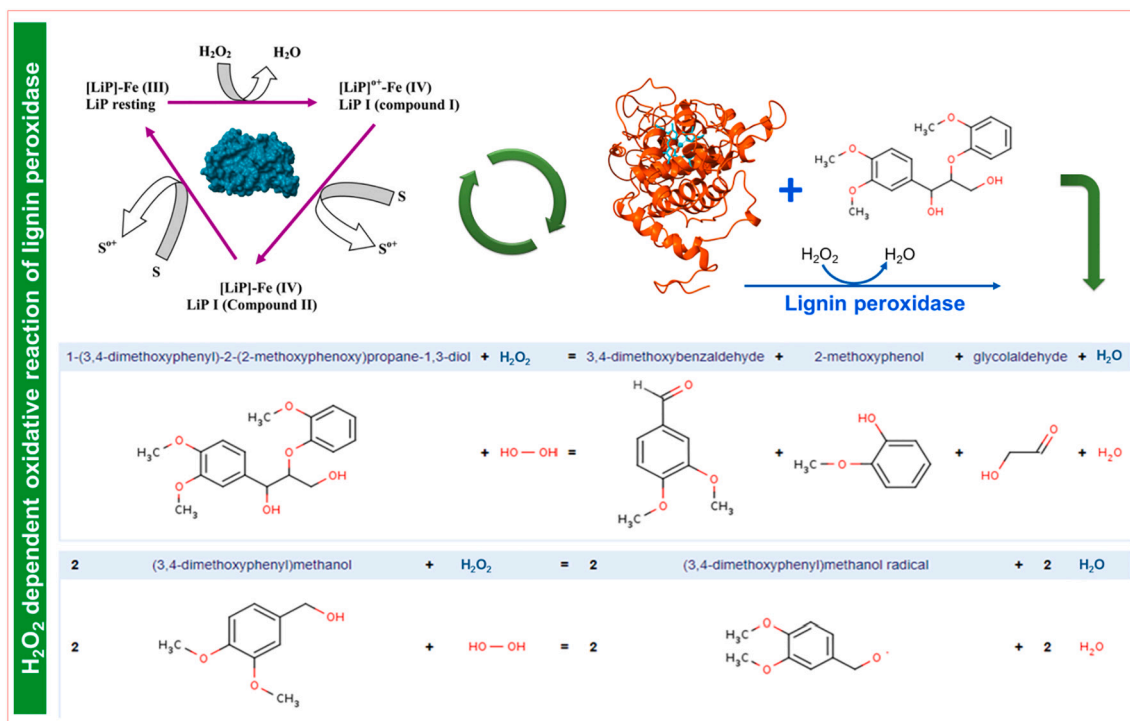


Fig. 4. Catalytic attributes of lignin peroxidase acting on lignin polymer. Left upper panel depicts the basic catalytic scheme, whilst right mechanism of dimer compound catalytic activity by LiP. Bottom panel depicts the detailed illustration of lignin dimer (β -O-4) model compound cleavage.

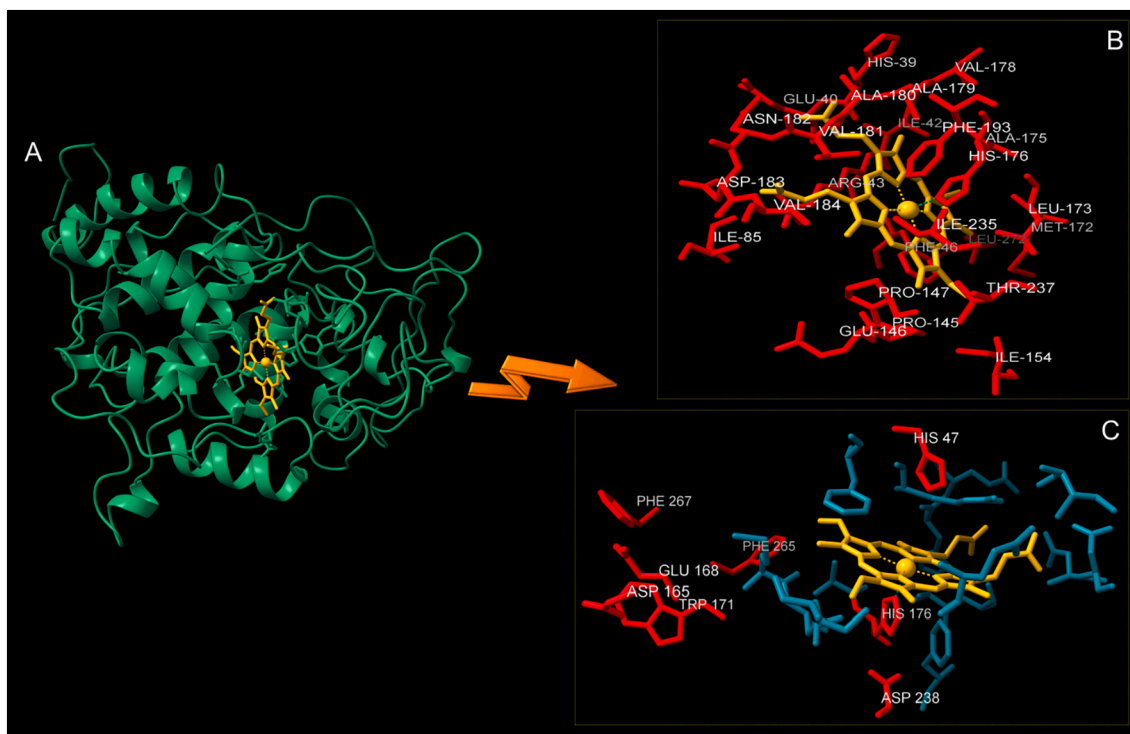


Fig. 5. Structural analysis of lignin peroxidase (PDB ID: 1LGA). A: depicts the rendered image of LiP with heme (Fe) in center. B: predicted interactions of amino acid residues corresponding to heme atom. C: depicts the active site of LiP for substrate binding. However, active site is substrate dependent, might be change with different substrate binding. A, and B has been re-rendered with respective PDB.

bacteria from soil and water that are a part of the phyla α - and γ -proteobacteria, *Firmicutes*, *Cyanobacteria*, *Aquificae*, and *Deinococcus-Thermus*, as well as bacteria from the class Archaea, has been recognized for producing prokaryotic LAC [176]. The redox potential of bacterial and

fungal LACs have changed throughout evolution, this lead to broadening the variety of complex substrates that may be oxidized. It has been noted that LAC from *Ganoderma lucidum* is more stable at low temperatures (30 °C) and an acidic pH of 3.0 than other bacterial LACs [177].

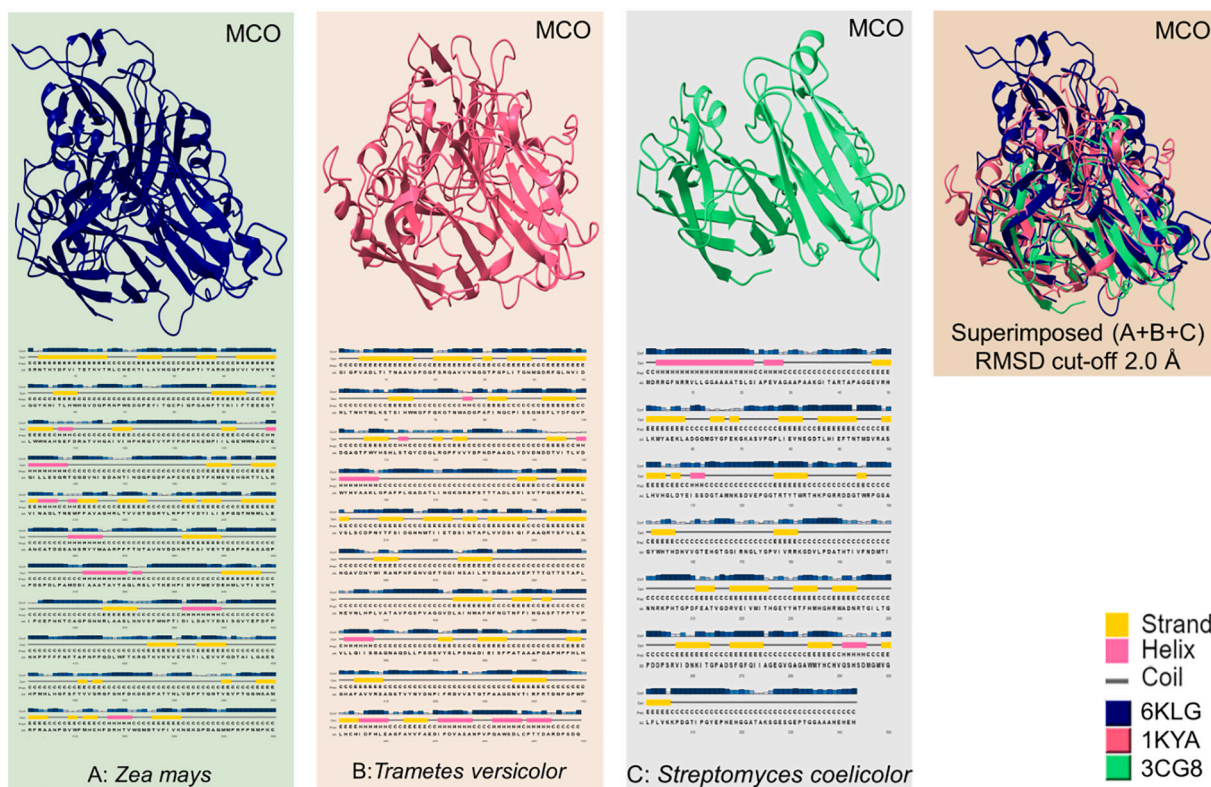


Fig. 6. Protein structure of Laccases-multi-copper-oxidase (MCO). A: highlights the protein structure of LAC from *Zea mays* in the upper panel, whilst protein secondary structure element topology in the bottom panel. B: highlights the protein structure of LAC from *Trametes versicolor* in the upper panel, whilst protein secondary structure element topology in the bottom panel. C: highlights the protein structure of LAC from *Streptomyces coelicolor* in the upper panel, whilst protein secondary structure element topology in the bottom panel. A clear structural differences can be visualized in the structural topology of LAC from different members with a cut-off RMSD in 2.0 Å, which exhibited similar enzymes has different structural architect which are not aligned in superimposed rendered (upper right panel).

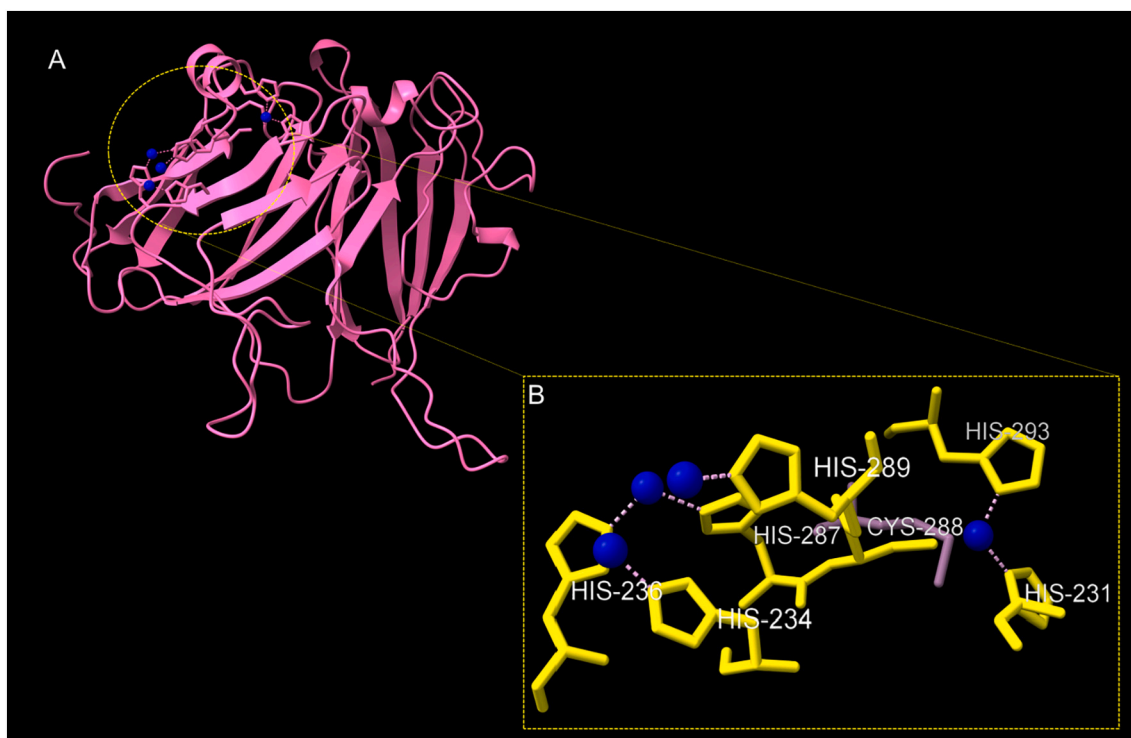


Fig. 7. Protein structure of Laccases-multi-copper-oxidase (MCO). A: Highlights the protein structure of LAC, has been rendered from respective PDB IDs. B: Highlights the predicted copper binding site residues corresponding to copper atoms.

Notwithstanding, only a few bacterial and fungal origin LACs have been widely exploited in biotechnological applications and environmental studies including food industries, biocatalysis, pharma, cosmetics, agrochemicals, bioremediation, sensor, nanobiotechnology and biomedicine [178–180]. In biotechnology, they are characterized as a “Green Tool” or “Green Catalysts” for a wide array of biotechnological applications [181–183]. With the remarkable potential in oxidative catalysis, LAC has gained interest in various biotechnical applications in previous decades [151]. Catalytic reaction triggers the cleavage in a unique way, i.e., C-C cleavage, oxidation, and alkyl-aryl cleavage. LACs have broad substrate specificity; hence can catalyze phenolic and nonphenolic compounds efficiently [163,184]. The detailed catalytic mechanism of LAC has portrayed in Fig. 8.

3.3. Manganese peroxidase (MnP)

MnP (EC 1.11.1.13) is a heme (Fe), and manganese (Mn)-containing extracellular enzyme frequently synthesized by many bacterial and fungal species (WRF) [24,108,185]. Several MnP-producing microorganisms (bacterial, fungal, mainly WRF) have been well documented that acts on lignin, including lignin degradation, lignin valorization, and bioremediation [24,126,186–188]. MnP has also been used in dyes, phenol and pharmaceutical products degradation [24,189]. The crystal structure of MnP (PDB: 3M5Q) from *Phanerothoria chrysosporium* has a single chain with 357 residues and has a calculated molecular weight about of 37.45 kDa [137,190,191]. The SSE of MnP (3M5Q) has reported in Table 2. The substrate action mechanism of MnP is an oxidation-reduction biochemical process that follows the ping-pong mechanism and encompasses second-order kinetics in enzymology. MnP works in the presence of H_2O_2 or biologically produced peroxidase. It employs one cofactor heme (Fe) and Ca^{2+} is essential for carrying out the catalysis. The chemical reaction of MnP involves the one-electron oxidation of Mn (II) to Mn (III), which in turn oxidizes a large number of phenolic substrates. The chemical reaction mechanism has been explained in Fig. 2. More precisely, in the initial step, H_2O_2 enters the active site of MnP, where it binds to Fe (III) ion in the heme cofactor to

form a heme peroxidase complex (Fig. 2). After that, two electrons are transferred from Fe^{3+} to peroxidase, which breaks the oxygen-peroxidase bond to form H_2O and Fe (IV) oxo-porphyrin radical complex [192]. MnP catalyzes Mn (II) to Mn (III) peroxide-dependent oxidation. The Mn (III) is released in complex oxalate from the enzyme such that the oxalate-Mn (III) compound is thus used as a diffused redox mediator that oxidizes lignin [193].

3.4. Dye decolorizing peroxidase (DyP)

DyP (EC 1.11.1.19) is a recently identified family of heme (Fe)-containing peroxidase, which has received significant attention owing to its ability to dye decolorization, degradation of lignin, and other compounds [23,121,194–196]. This enzyme is also hydrogen peroxide (H_2O_2) dependent, as an electron acceptor to catalyze the oxidation of a wide range of substrates, including lignin, dyes, and other organic compounds [197]. DyP has been expressed in bacterial species and a few other eukaryotic organisms (fungal species) [126,198–200]. DyPs have been categorized into different groups depending on their sequence features as A, B, C, and D types [200]. Several DyPs are included in the protein databank (<https://www.rcsb.org>), under the keyword “lignin peroxidase” based on lignin as the active substrate. A considerable number of DyP-producing bacteria have been reported in recent years, even though it is consistent with the investigation that verified DyP genes are commonly prevalent in bacterial genomes [51,194,201]. The crystal structure of DyP from *Enterobacter lignolyticus* (PDB: 5VJ0) has 318 residues dispersed in four chains (A, B, C, and D) with a molecular weight of about 35 kDa [125,137,194]. The SSE of DyP (5VJ0) has reported in Table 2. Few bacterial species, including *Bacillus subtilis* KCTC2023, have been studied for their ability to degrade lignin and a few dyes, including reactive blue 19 and reactive black 5 [202]. DyP enzymes cleave the C-C linkage or bond without the presence of any oxidative mediator [203,204]. DyP enzymes have long been exploited in the decolorization of dyes and the remediation of lignin and phenolic compounds [29,31,147,205]. DyPs-assisted applications in dyes removal from wastewater, lignin content removal, oxidation of lignin

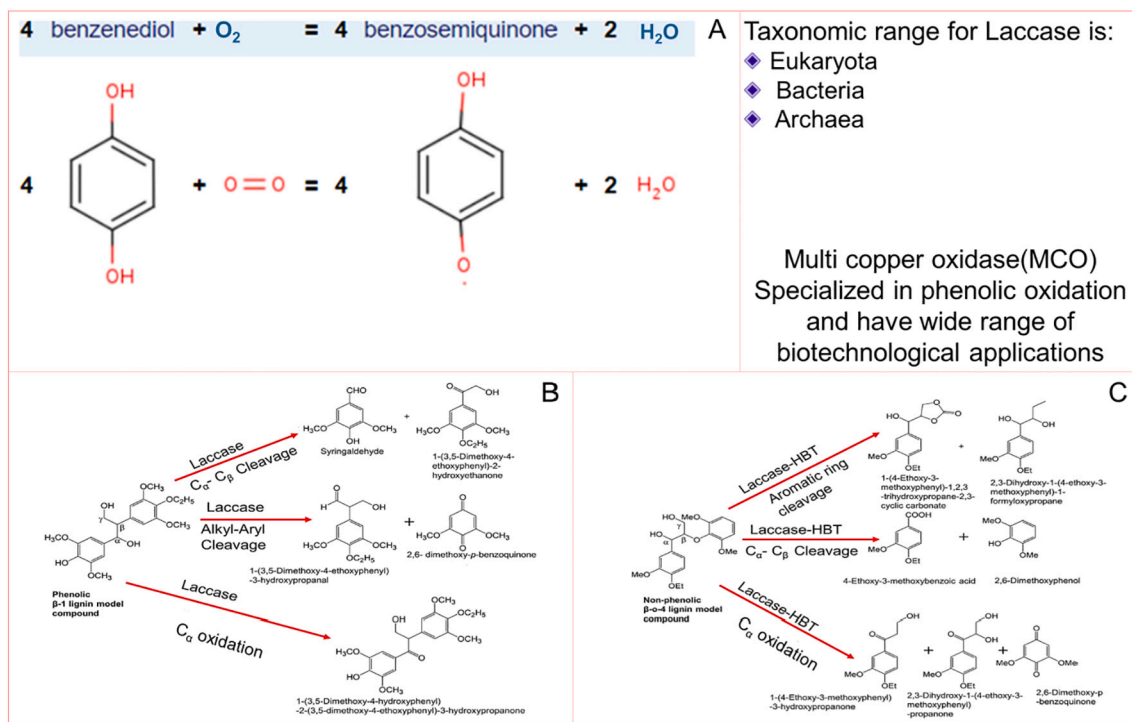


Fig. 8. Laccase (multi-copper-oxidase (MCO)) catalytic mechanism. A: Highlights the basic oxidative mechanism of LAC. B: Illustrative scheme of phenolic lignin model compound (β -1) catalysis. C: Illustrative scheme of non-phenolic lignin model compound (β -O-4) catalysis.

model compounds, phenolic compounds oxidation, and other biotechnological applications have increased in published literature due to their excellent catalytic activity in recent years [122,196,201,206–210]. Many recent investigations have revealed the role of DyP in the catalysis of β -O-4-unit lignin model compounds as well [75,118,147,211]. Fig. 2 represents the catalytic mechanism of DyPs similar to heme peroxidase (LiP).

3.5. Versatile peroxidase (VP)

VP (EC 1.11.1.16) is a heme (Fe)-containing oxidoreductase with a hybrid molecular architecture that combines many oxidation-active regions, allowing high redox catalytic capacity for a wide range of substrates [212–214]. Given its strong redox potential, VP has been a robust biocatalyst for widespread industrial applications [215]. A range of bacteria and fungi have been documented for VP production and their active application in bioremediation of environmental contaminants [42,216–219]. From structural perspective, the crystal structure of VP from *Pleurotus eryngii* (PDB: 2BOQ) consists of 331 residues distributed in a single chain, with a molecular weight of 34.6 kDa [137,220,221]. The SSE of VP (2BOQ) has reported in Table 2. The VP catalysis mechanism is similar to that of oxidoreductase family enzymes (LiP, MnP). At the active sites of VP, H_2O_2 and cofactor initiate catalysis. VP's catalytic versatility is advantageous for low and high-redox-potential aromatic substrates in Mn^{3+} -mediated and Mn-independent reactions. Phenolic compounds, synthetic dyes, and lignin may all be oxidized using H_2O_2 -dependent VP, which employs ferric heme center to catalyze the oxidation of two molecules of reducing substrate with concomitant oxidation of Mn^{2+} to Mn^{3+} [213]. The specific catalytic mechanism of VP has been portrayed in Fig. 2.

4. Industrial and biotechnological applications of LMEs

Despite the remarkable deployment in diverse array of application, LMEs has been commercialized by different vendors and available in

pure form [226–229]. LMEs have been reported in wide range of applications including; bioremediation, biofuel, biobleaching in pulp & paper industries, textile, biosensor, bio-based compound synthesis, cosmetics, pharmaceuticals, wastewaters treatment and so on [180,230,231]. LMEs serve as vital biocatalysts that conduct eco-friendly degradation/catalysis of an array of environmental pollutants (e.g., EDCs, PPCBs, NSAIDs, lignin, phenolics, chlorinated phenol, etc.) from environmental matrices owing to their broad redox potential range [5,232]. Over the last several decades, there has been a surge in research on LAC's potential as biocatalysts to replace traditional chemical processes in the textile, pulp & paper, and pharmaceutical sectors [180]. The cosmetic, paint, and furniture industries are just an application that might benefit from these enzymes [180]. Furthermore, LACs have a role in the lignocellulose-based feedstock used in the manufacturing of bio-ethanol [180]. The investigation of LAC and potential applications in industrial and biotechnology is a rapidly expanding research area [180]. LiP has also been shown to have a possible biotransformation functioning in the industrial-scale synthesis of vanillin from different substrates [233]. Despite the various features like, relatively low production cost, comparably high yield (LAC, MnP), short cultivation, high thermostability, and improved enzymatic activities have rendered LMEs mass deployment in industrial and biotechnology applications. Nevertheless, issues with cost, stability, and recycling/reuse rates of LAC's limit their use in biotechnological applications [234]. A few detailed applications of LMEs have been outlined in subsequent sections. A schematic illustration of LME-mediated deployment in industrial and biotechnological applications has highlighted in Fig. 9.

4.1. Pulp and paper industries: remediation, and bio-bleaching

Lignin causes a barrier in pulp for making paper, therefore its removal is a key step in cellulosic biomass's industrial applications, including the achievement of bioethanol and the manufacture of products such as paper and other products made with cellulose [235]. The growing production rates of paper and pulp industries, including by-

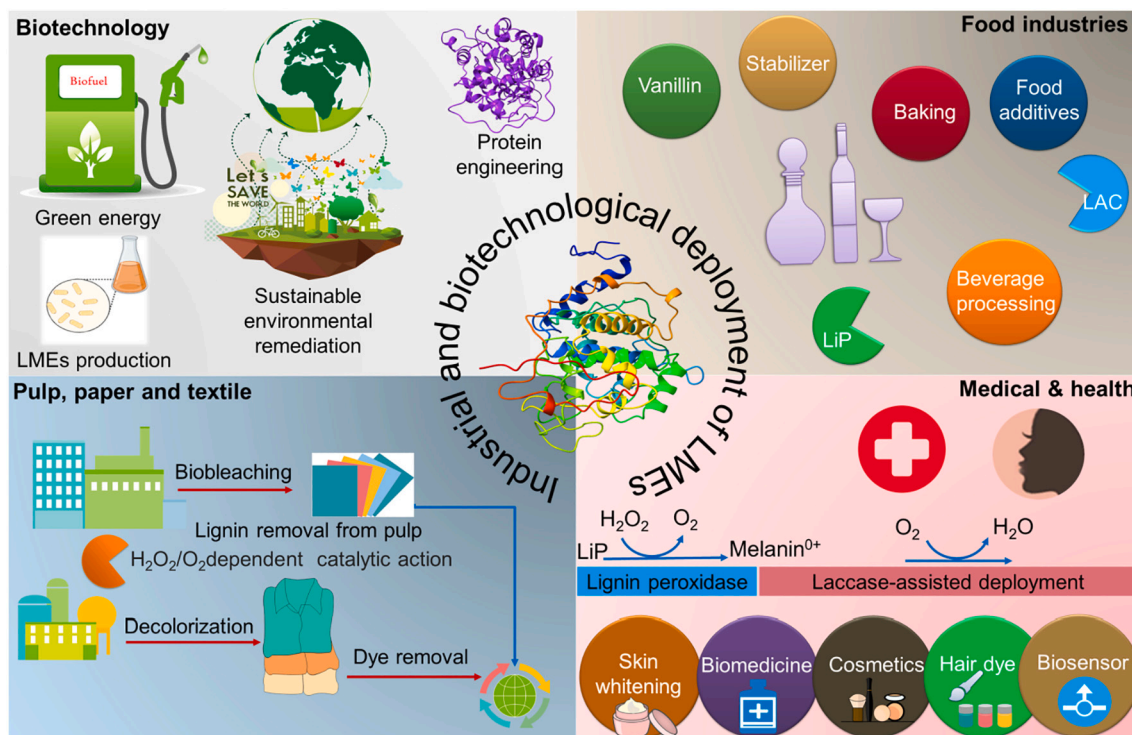


Fig. 9. Schematic illustration representation of industrial and biotechnological deployment of lignin modifying enzymes (LMEs). The different panel depicts the different applications of LMEs in biotechnology, pulp, paper, textile industry, food industry, and medical & health sector.

products (Black Liquor) and wastewater, have caused significant environmental issues, and are accountable for environmental repercussions. However, efforts have been made to mitigate the hazardous effects of effluent from paper industries via laboratory research using a variety of toxicological tests [59,236]. Unfortunately, industry-scale studies have been less performed in this direction. Assays on cytotoxicity, chromosomal aberration, and seed germination suggest a significant toxic impact induced by wastewaters of pulp & paper industries [59,236]. Lignin degradation from wastewaters of pulp & paper industries has been performed by exploiting both bacterial and fungal species. A VP has recently been reported in *Pleurotus* and *Bjerkandera* species, the former genus including species being able to degrade lignin selectively [237,238]. Fungal LMEs have an excellent catalytic ability for a wide range of substrates rather than bacteria. The breaking of C α -C β and C4-ether linkages results in the release of aromatic aldehydes, one of the principal products identified during enzymatic depolymerization of lignin [235]. LACs have no redox potential enough to directly attack on lignin. When redox mediators are present, they may break down such molecules as well as other recalcitrant compounds efficiently [61,235].

LMEs have been used as bio-bleaching agents commercially in the paper industry with quite an impressive efficiency [239–241]. For the white texturing of paper, lignin must be eliminated from the pulp. The current process is based on Kraft (chemical) pulping method, and sodium hydroxide (NaOH) and sodium sulfide (Na₂S) treatment at high temperature and pressure to selectively breakdown lignin while retaining the polysaccharide fibers [1,242–244]. Although poor pulp yield is achieved with the krafting process, even targeted polymer is degraded during treatment [242]. To oppose and cope with such challenges, bio-pulping offers an eco-friendly breakdown of lignin from pulp employing either ligninolytic enzymes or ligninolytic microorganisms [245–248]. Bio-pulping softens the wood while increasing paper quality and lowering energy and chemical consumption [247,248]. Numerous fungal species, including WRF, have been extensively investigated for their potential use in the bio-pulping of wood [248–250]. However, the

yield and cost of enzyme production remain a key challenge in this sector. Orozco Colonia et al. demonstrated significant hemicellulose (26.27 %) and lignin (36.80 %) removal with high pulp yield (74.36 %) using LiP and xylanase synthesized by *Aspergillus* sp. during bio-pulping and biobleaching [148,251]. In comparison to current technologies, the use of LiP may assist in reducing the manufacturing costs of expensive chemicals while also allowing for more eco-friendly treatments of pulp in papermaking steps. However, the biobleaching sector is in a research and development stage along with other uses of enzymes in the pulp and paper industry; the greatest current usage includes sustainable biobleaching for hardwood and soft pulp [252]. A schematic illustration of LMEs in remediation and decolorization of industrial wastewaters, and associated toxicity reduction has explained in Fig. 10.

4.2. Textile effluent treatment and dye decolorization

About 10,000 different dyes and pigments, mostly used in the dye and printing industries, are being manufactured annually worldwide [253]. The chemical contents of synthetic dyes are frequently diversified and classified into distinct groups e.g., azo, triphenylmethane, and heterocyclic/polymeric compounds. Synthetic dyes account for a significant portion of the textile sector and are a major source of global environmental pollution [254,255]. Even though extensive use of various dyes in textile industries meets the need for quality or finished items, the manufacturing process produces a large volume of colorful, toxic wastewater [255]. In fact, during the dyeing processes, 10–15 % of dyes escape into wastewater. Many of these dyes are extremely resistant to light, temperature, and microbial degradation, making these into recalcitrant and toxic chemicals [253]. A variety of successful wastewater treatment solutions (activated carbon, constructed wetland, ion exchange, etc.) have been developed for textile water treatment and reuse [256–260]. Unfortunately, the constructed wetland seems to have weak color reduction efficiency while utilizing a comparatively large, occupied area for implementation. Activated carbon appears to have a

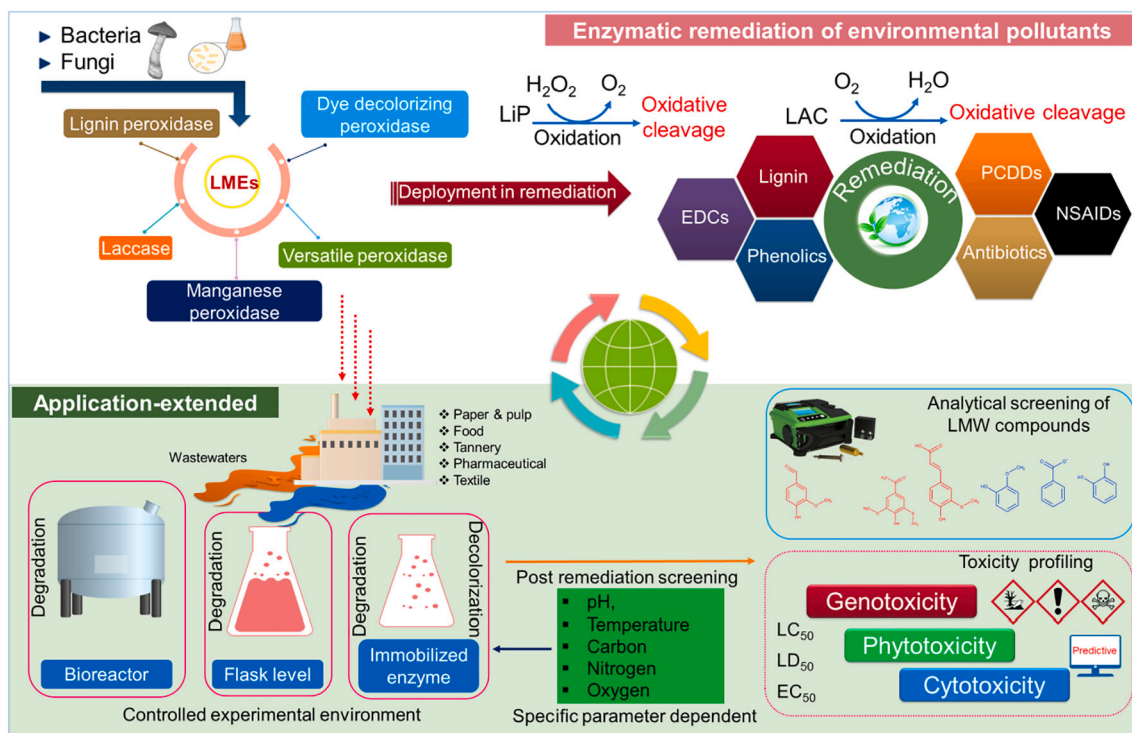


Fig. 10. Application of lignin modifying enzymes (LMEs) in industrial wastewater treatment, decolorization, and toxicity reduction. The upper panel explains the LMEs producers; i.e. fungi, bacteria, and their assisted oxidative deployment in pollutant remediation from water matrices. While the bottom panel describes the extended application exploitation under controlled environment, and post treatment toxicity profile in a variety of choice for assuming the toxic risk assessment.

reasonable removal rate for water-soluble dyes. However, it cannot adsorb suspended solids (SS) or insoluble dyes from wastewaters. These strategies are effective but costly and create a massive amount of sludge that can further lead to secondary pollution problems [261,262]. As a result, microbial or LME-based treatment offers an environmentally friendly alternative for textile water treatment by lowering dye concentration in water matrices and allowing for further water reusability. Recently, a few studies have reported the efficient decolorization of textile effluent employing microbial LMEs [253,263,264]. This has been recognized for years and has proven to be the most robust bioremediation method to decolorize and metabolize dyes components [23,265]. Parshetti et al. reported that purified LiP from *Kocuria rosea* MTCC 1532 was able to decolorize a total of 11 different dyes; azo, triphenylmethane, heterocyclic, polymeric, metallic complexes with a neutral pH (7.0) [266]. Another study reported decolorization and biodegradation of Disperse Red 3B exploiting a consortium made up of the fungus *Aspergillus* sp. XJ-2 and the microalgae *Chlorella sorokiniana* XJK; this system exhibited stronger efficiency in terms of decolorization (98.09 %) and COD removal [267]. The most recent azo dye RB5 biodecolorization has been shown by Fernandes et al. [268]. In their study crude enzyme from *Pleurotus sajor-caju* was employed as the source of LMEs, with the employment of the “artificial neural network” based study in combination with the genetic algorithm and the response surface methodology (RSM) for the prediction of RB5 decolorization [268]. Subsequently, when LMEs producing fungus was grown in pulp wash, the fungi showed higher LAC activity, whereas when immobilized, a higher MnP activity was achieved, but both allowed decolorizing of the dye in about 89.4 % and 75 %, respectively [268].

4.3. Lignin biodegradation, depolymerization, and valorization

Pulp & paper mill effluent has a negative effect on aquatic life because of its chemical make-up and the fact that it is often quite dark or black, probably due to high amounts of lignin [269–274]. Lignin obtained from the kraft pulping process has a complex structure with a prevalence of C-C, and aryl ether linkages, which are recalcitrant and non-hydrolyzable bonds, turn lignin into challenging for chemically and biologically breakdown [2,275,276]. In previous decades massive studies have been performed to *ex-situ* breakdown of kraft lignin, employing ligninolytic producing bacteria and fungi i.e. *P. chrysosporium* and *Serratia liquefaciens* [59,277–285]. Indeed, lignin biodegradation has been studied to evaluate the enzymatic capability and biotransformation of lignin compounds [286–289]. A certain set of motif/linkages are present in lignin polymer (e.g., β -O-4, α -O-4, 5-5, β - β , 4-O-5, β -5, β -1), which are the target points to be act by ligninolytic/LMEs [2,290]. LMEs cleave such motifs using an oxidative mechanism as above discussed to yield the simplest structures and monomers. Lignin catalytic depolymerized into monomers and oligomers from lignin polymer have explained in Table 3. In recent years, a broad array of fungi including WRF, derived enzymes has been described for the transformation of xenobiotic chemicals, lignin, and organic pollutants [6,40,42,291–294]. Enzymatic or LME-producing organisms for lignin depolymerization/valorization have been recognized at a large scale for manufacturing value-added compounds for various applications including second-generation biofuels [12,70,141,281,295–297]. Aromatic monolignols, PHAs, lipids, and bio-oils have been identified as key lignin-depolymerized products [298,299]. Valorization of lignin into value-added compounds by the ligninolytic activity and associated microbial species has explained in Table 4. Even LACs have indeed been documented for biotransformation and bioremediation of water contaminants [161]. A detailed illustration of LMEs in lignin depolymerization and valorization has highlighted in Fig. 11.

4.4. Food industry

The employment of LMEs provides a vast potential for upgrading

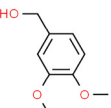
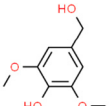
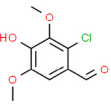
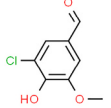
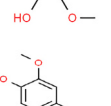
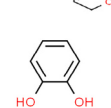
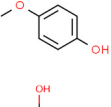
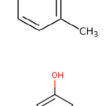
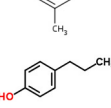
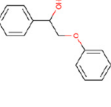
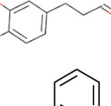
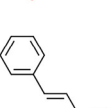

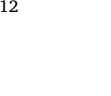
current manufacturing processes and establishing new technologies to obtain high-value products. Enzymes offer cleaner and more efficient production processes and support the sustainable concept. Among LMEs, LACs are exceptionally versatile biocatalysts and have been adopted for 1) removal of phenolic compounds and by-products from food industries, 2) use in food application as enhancers, preservatives, etc. Dedicated applications of LAC and peroxidase in food industries are listed in Table 5. LACs have been employed at an industrial scale in baking, fruit, wine stabilization, etc. [334]. Sugar beet pectin gelation and the stabilization of wine and beer, fruit-juice processing are just a few of the many potential applications of LAC in food industries [335,336]. The phenolic compounds contained in wine are accountable for its color, flavor, and overall taste [180,336]. Therefore, LAC may be used to selectively removal of polyphenols, that retain the wine's organoleptic properties [337]. Beer storage life may be improved by using LAC to remove O₂ at the completion of the brewing process [180]. To prevent the formation of off-flavor precursors, LAC eliminates O₂ that might otherwise react with fatty acids, amino acids, proteins, and alcohols [180]. LAC has also been studied in baking to enhance dough machinability and end-product softness, as well as in teas and oil-containing products for enhancing flavor and color [180]. Furthermore, the gelling effects of LAC in blackcurrant juice, luncheon meat, and milk with added sugar beet pectin have been investigated [180]. A recent research evaluated the influence of LAC and LMS on stirred milk yoghurt in a process that mimicked industrial manufacturing [338]. LAC treatment resulted in protein breakdown at the molecular level, while the inclusion of the natural redox mediator vanillin triggered the formation of higher molecular weight oligomers [180]. LAC convert O₂ to H₂O, and the biosensor then measures the amount of oxygen utilized during analyte oxidation. LAC-based sensors have been extensively utilized in the food sector for determining polyphenols in fruit juices, wine, and teas, as well as to quantify fungal contamination in grape musts [180]. Another LMEs, LiP, has received little attention in the food industry. Vanillin is a remarkable use of LiP in the food industry. Lignin-based artificial vanilla is more often employed as a flavoring agent in foods, drinks, and medicines [339]. Biocatalytic transformations of aromatic substrates such as lignin and guaiacol into vanillin with LiP activity has been reported by exploiting purified LiP and LiP-producing WRF *P. chrysosporium* [148,340,341]. Saikia et al. documented magnetically separable co-immobilized LAC and VP-based framework for transforming lignocellulosic biomass into vanillin [342]. Subsequently depolymerization of lignin by free and immobilized LAC showed a vanillin yield of 24.8 % and 23 %, respectively, at pH 4.0 in 6 h at 30 °C against a vanillin yield of 20 % and 21.7 % by the free and immobilized VP, respectively, at pH 5.0 and 50 °C [342].

5. Emerging contaminants degradation and wastewater treatment

Despite their environmentally friendly nature, LMEs-members have been applied in the treatment of wastewater from a variety of sources, including food industries, tanneries, textiles, pulp & paper, and distilleries [159,178]. Several tons of pharmaceutical chemicals flow through the wastewater treatment system each year [346,347]. Emerging contaminants (EC) are contaminants identified at trace concentrations of worldwide drinking water sources at which human and environmental health hazards are not yet recognized or little known. Pharmaceutical compounds and their accompanying contamination are reported to be EC as they have been identified as a possible source of wastewater treatment plants (WWTPs), which have detrimental effects on surface water when utilized for drinking water if water bodies receive wastewater. NSAIDs are one of the most recalcitrant EC in the aquatic environment [348]. The occurrence of NSAIDs drug products in the environment and wastewater has been regarded as an EC, which is of great concern in the scientific community because of the toxic impact [348]. NSAIDs are one of the principal causes of wastewater pollution;

Table 3

A catalytic depolymerized product of lignin into monomers and oligomers model compounds has listed with chemical and molecular formula.

Lignin derived compound	Type	Structure	Molecular formula	Molecular weight (g/mol)	Reference
Veratryl alcohol	Monomer		C ₉ H ₁₂ O ₃	168.19	[300]
Syringyl alcohol	Monomer		C ₉ H ₁₂ O ₄	184.19	[301]
2-Chlorosyringaldehyde	Monomer		C ₉ H ₉ ClO ₄	216.62	[302,303]
5-Chlorovanillin	Monomer		C ₈ H ₇ ClO ₃	186.59	[304]
Sinapyl alcohol	Monomer		C ₁₁ H ₁₄ O ₄	210.23	[305]
Guaiacol	Monomer		C ₇ H ₈ O ₂	124.14	[306]
Coniferyl alcohol	Monomer		C ₁₀ H ₁₂ O ₃	180.20	[305]
Catechol	Monomer		C ₆ H ₆ O ₂	110.11	[300]
4-Methoxyphenol	Monomer		C ₇ H ₈ O ₂	124.14	[307]
m-Cresol	Monomer		C ₇ H ₈ O	108.14	[306]
p-Cresol	Monomer		C ₇ H ₈ O	108.14	[306]
4-Propylphenol	Monomer		C ₉ H ₁₂ O	136.19	[308]
2-Phenoxy-1-phenylethanol	Dimer		C ₁₄ H ₁₄ O ₂	214.26	[309]
4-Propylguaiacol	Monomer		C ₁₀ H ₁₄ O ₂	166.22	[309]
Anisole	Monomer		C ₇ H ₈ O	108.14	[309]
Cinnamyl alcohol	Monomer		C ₉ H ₁₀ O	134.17	[309]

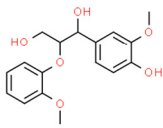
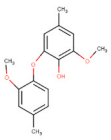
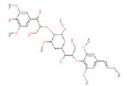
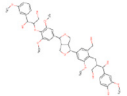





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Table 3 (continued)

Lignin derived compound	Type	Structure	Molecular formula	Molecular weight (g/mol)	Reference
Vanillyl alcohol	Monomer		C ₈ H ₁₀ O ₃	154.16	[309]
Vanillin	Monomer		C ₈ H ₈ O ₃	152.15	[309]
Veratrol	Monomer		C ₈ H ₁₀ O ₂	138.16	[309]
Eugenol	Monomer		C ₁₀ H ₁₂ O ₂	164.20	[309]
Phenol	Monomer		C ₆ H ₅ OH	94.11	[309]
2-Propylphenol	Monomer		C ₉ H ₁₂ O	136.19	[309]
4-Methylanisole	Monomer		C ₈ H ₁₀ O	122.16	[309]
Phenyl-phenyl-ether	Dimer		C ₁₄ H ₁₄ O	198.26	[309]
4-Hydroxybenzoic acid	Monomer		C ₇ H ₆ O ₃	138.12	[310]
Diphenyl ether	Dimer		C ₁₂ H ₁₀ O	170.21	[309]
Benzyl phenyl ether	Dimer		C ₁₃ H ₁₂ O	184.23	[309]
4-Phenoxyphenol	Dimer		C ₁₂ H ₁₀ O ₂	186.21	[309]
Methyl gallate	Monomer		C ₈ H ₈ O ₅	184.15	[311]
Benzoate	Monomer		C ₇ H ₅ O ₂ ⁻	121.11	[312,313]
Ferulate	Monomer		C ₁₀ H ₉ O ₃ [O ⁻]	193.18	[313]
Ferulic acid	Monomer		C ₁₀ H ₁₀ O ₄	194.18	[314,315]
Acetosyringone	Monomer		C ₁₀ H ₁₂ O ₄	196.20	[316]
Vanillyl alcohol	Monomer		C ₈ H ₁₀ O ₃	154.16	[317,318]

(continued on next page)

Table 3 (continued)

Lignin derived compound	Type	Structure	Molecular formula	Molecular weight (g/mol)	Reference
Dimer guaiacylglycerol-beta-guaiacyl ether	Dimer		C ₁₇ H ₂₀ O ₆	320.3	[318,319]
Dimer (guaiacyl 4-O-5 guaiacyl)	Dimer		C ₁₆ H ₁₈ O ₄	274.31	[75,320]
Trimer (syringyl β-O-4 syringyl β-O-4 sinapyl alcohol)	Trimer		C ₃₄ H ₄₄ O ₁₃	660.713	[75,320]
Tetramer(guaiacyl β-O-4 syringyl β- β syringyl β- O-4 guaiacyl)	Tetramer		C ₄₃ H ₅₂ O ₁₄	792.875	[74,320]
Dibenzodioxocin	Dimer		C ₁₄ H ₁₀ O ₂	210.228	[300]
Phenoxyphenol	Dimer		C ₁₂ H ₁₀ O ₂	186.21	[300]
Diphenylmethane	Dimer		C ₁₃ H ₁₂	168.23	[300]
2-Isopropylphenol	Monomer		C ₉ H ₁₂ O	136.19	[300]
Dihydrobenzofuran	Monomer		C ₈ H ₈ O	120.15	[300]

LMEs have been demonstrated efficient capability in the biodegradation of NSAIDs from water matrices [110,349–352]. Cruz-Ornelas et al. demonstrated biodegradation of naproxen (90 %) and ketoprofen (87 %) using WRF *Pleurotus djamor*, during 48 h of incubation [110]. Bankole et al. reported that a combination of three NSAIDs (celecoxib, diclofenac, and ibuprofen) was biodegraded by *Ganoderma applanatum* and *Laetiporus sulphureus* within the incubation period of 72 h [57]. Similarly, Kasonga et al. reported an investigation to eliminate a range of pharmaceutical compounds (carbamazepine (CBZ), diclofenac (DCF) and ibuprofen (IBP)) from wastewater utilizing the ligninolytic fungus *Rhizopus* sp. with LiP, and MnP activity [353]. Apriceno et al. found that NSAID drugs (diclofenac, naproxen, and ketoprofen) were eliminated by employing a laccase-based approach in their recent investigation [348]. García-Morales et al. reported biotransformation of acetaminophen and diclofenac by immobilized laccase adopting titania nanoparticles, which was able to achieve 90 % and 68 %, biotransformation respectively [178]. Although not extensive, an adequate study has shown remarkable ligninolytic efficiency in the elimination of NSAIDs and other pharmaceuticals with an effective breakdown rate [352,354–357]. Potential environmental clean-up applications of LMEs have been listed in Table 6. Since the end of the 1990s, there has been an increase in the number of compounds suspected of interfering with the endocrine system. These compounds like “hormone mimics” impair the endocrine system and trigger unfavorable human, wildlife, and development reproductive and neurological consequences [358–361]. Approximately 800 substances are known or suspected to interfering with hormone receptors. However, only subsets of these compounds have been studied

in experiments capable of detecting overt endocrine effects in intact organisms [362]. Phthalates, PCBs, PAHs, and chemical additives including bisphenol-A, alkylphenol ethoxylates (APEs), pesticides like dichlorodiphenyltrichloroethane (DDT), and other additives are well-reported examples of EDCs [363–366]. Industrial/anthropogenic activities are among the primary sources of EDCs in the environment; as a consequent EDCs reach into the environment and water matrices [367]. EDCs in the environment and water matrices potentially lead to public health risks once exposed to them through various pathways. Therefore, they must be eliminated from the environment for public health safety. Numerous methods exist for removing EDCs; however, oxidoreductase enzyme-mediated removal has received extensive interest for a few decades in eco-friendly mitigation [368–370]. A few fungal species and LME member, including LiP, VP, and LAC has been reviewed for the effective elimination of a wide array of EDCs from water matrices [371–375]. The degradation of various new emerging pollutants by the ligninolytic enzyme-producing WRF has garnered increasing attention [371,376–378]. Several studies have demonstrated the use of LACs for EDCs removal utilizing either independent or subsidiary LAC-aided approaches [368,369,379–386]. Dai et al. demonstrated bisphenol-A elimination by immobilized laccase in electrospun fibrous membranes modified with carbon nanotubes [387]. Zdarta et al. outlined the biodegradation of bisphenol-A and bisphenol-F by *Trametes versicolor* laccase immobilized on *Hippospongia communis* spongin scaffolds [388]. Under optimal conditions, almost 100 % of BPA (pH 5, 30 °C) and BPF (pH 5, 40 °C) was removed from the solution at a concentration of 2 mg/mL [388].

Table 4

Valorization of lignin into value-added compounds by the ligninolytic activity and associated microbial species.

Ligninolytic microbes/enzyme	Utilized substrate	Valorized product	Reference
<i>Cupriavidus basilensis</i>	Kraft lignin	PHA	[321,322]
LAC	Lignin	<i>p</i> -Hydroxybenzaldehyde, vanillin	[323]
LAC, VP	Lignin	Vanillin	[324]
LAC	Lignin	Grafting/lignin-based materials	[325]
<i>Pseudomonas putida</i> KT2440-CJ122	<i>p</i> -Coumaric acid	Pyruvate	[326,327]
<i>Pseudomonas putida</i> KT2440-CJ122	<i>p</i> -Coumaric acid	Lactic acid	[326,327]
<i>Pandora sp.</i> ISTKB	Kraft lignin	PHA	[328]
<i>Paraburkholderia aromaticivorans</i> AR20-38	Lignin monomer	Vanillic acid	[310]
<i>Phanerochaete chrysosporium</i>	Lignin	Succinic acid	[329]
<i>Pseudomonas putida</i> KT2440	Lignin	<i>cis,cis</i> -Muconic acid	[330]
<i>Pseudomonas putida</i> KT2440	Model lignin-derived compound	<i>cis,cis</i> -Muconate	[331]
<i>Rhodococcus opacus</i> PD630	Lignin	Lipid	[332]
<i>Rhodococcus opacus</i> PD630	Kraft lignin	Lipid	[333]
<i>Rhodococcus opacus</i> PD630	Alkaline-pretreated lignin	Gallate	[311]
<i>Streptomyces sp.</i> S6	Kraft lignin	3-Methyl-butanoic acid, guaiacol derivatives, and 4,6-dimethyl-dodecane	[141]

6. Medical applications/pharmaceutical and skin whitening agent

Despite their outstanding oxidoreductase characteristics, only a few members of the LME family (i.e. LAC, LiP) has shown significant potential in few medical applications, including skin whitening agents, development of antibiotics, anticancer drugs, antifungal drugs, and sedative as well [179,396]. LiP has been incorporated into skin whitening agents as one of the most recent breakthroughs for melanin decolorization and as an ingredient for treating pigment impairments in humans [397–399]. Many fungal strains have been identified as a source of LiP for melanin decolorization, and potential use in skin lightening applications [398,400,401]. However, the majority of these applications is still in the development phase and has yet to be commercialized [402,403]. In a recent clinical self-controlled study, 31 persons with melasma on both sides of their faces were given an eight-week full-facial therapy [399]. After that, effective skin whitening was documented at

Table 5

Addition of lignin-modifying enzymes (LMEs) in food processing steps.

Food applications	Value added properties	Reference
Baking	Increase stability, strength, reduction of stickiness improving machinability of the dough	[343–345]
Beer stabilization	Removal of certain polyphenol	[343,344]
Beverage processing	Enhancing the color appearance	[343,344]
Flavor enhancing	Development of flavor, color, and nutritional quality of food	[345]
Food sensory parameters	Reduction of bitterness	[343,344]
Fruit juice processing	Prevention of the hazes by the interactions between polyphenols and proteins	[343,344]
Sugar beet pectin gelation	Crosslinking the beet pectin, by the mechanism of oxidative coupling of the feruloyl groups	[343–345]
Wine stabilization	Removal of oxygen from finished beer	[343,344]

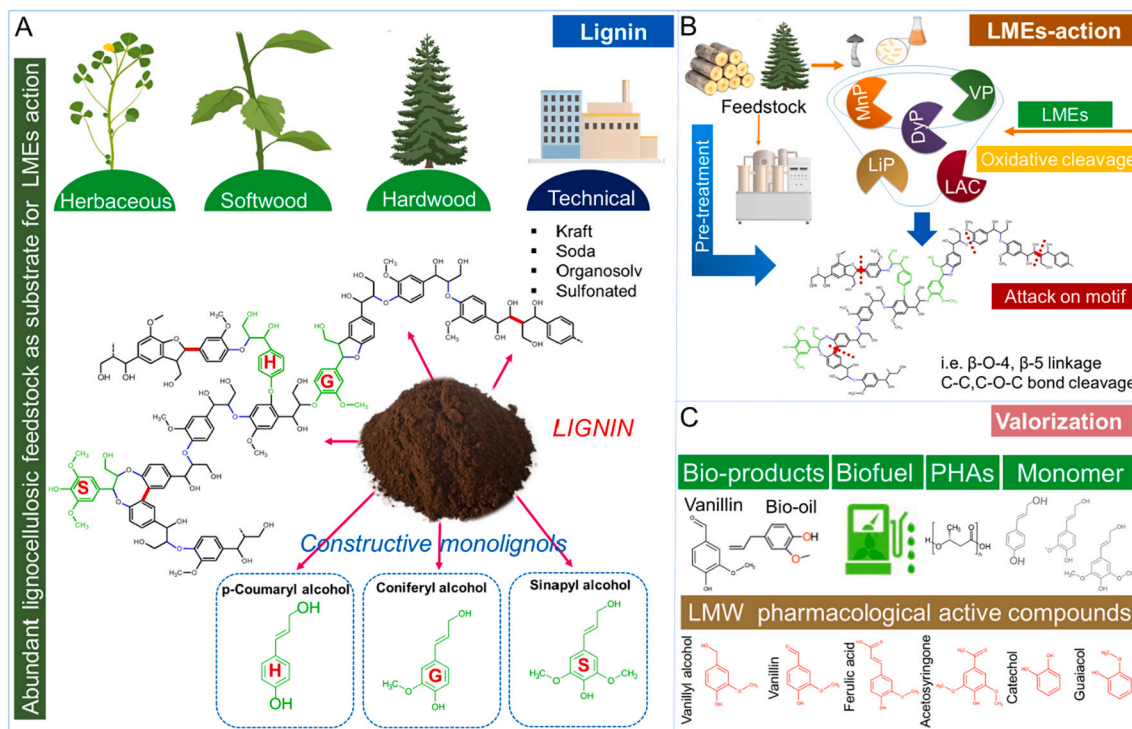


Fig. 11. Catalytic action of lignin modifying enzymes (LMEs) on lignin. A: describes the natural lignin from plants source, and technical lignin along with its types. B: explains the chemical functionalities of LMEs i.e. oxidative cleavage, and attack on lignin motif, to break the chemical bonds and yield lignin derivatives. C: explains the enzymatic-valorization, and value-added compound, fuel, Bio-products, PHAs, and pharmacological monomeric compound yield.

Table 6
Dedicated environmental applications of lignin modifying enzymes in remediation of pharmaceutical compounds (LMEs).

Enzyme	Environmental application	Reference
DyP4 peroxidases	2-Mercaptobenzothiazole (MBT), paracetamol, and furosemide degradation	[26]
LiP	EDCs removal	[375]
VP	Estrone, 17 β -estradiol, and 17 α -ethinylestradiol removal	[389]
LAC	Transformation of anti-inflammatory drugs	[117]
LAC	NSAIDs removal	[348]
LAC	Degradation and detoxification of an array of pesticides	[385]
LAC	Emerging contaminants degradation	[368]
LAC	Removal of endocrine disruptors	[390]
LAC	Degradation of Azo dyes	[391]
LAC	Bioremediation of xenobiotic compounds	[392]
LAC	phenol and bisphenol-A removal	[379]
LAC	Xenobiotic degradation	[393]
LAC and peroxidases	Emerging pollutants biocatalysis	[394]
LAC/oxidoreductases	Biocatalytic degradation of pharmaceutically active compounds	[395]
LiP, MnP, LAC	Pharmaceutical and personal care products (PPCPs)	[366]
LiP, MnP, LAC	Endocrine-disrupting chemicals (EDCs)	[366]

specific therapy intervals (0, 7, 28, and 56 days), with no adverse reaction to the skin/facial color palette [399]. The normal skin luminance (L^*) values were restored after 7 days of administering the LiP whitening lotion [399]. Another LME member LAC's potential to degrade melanin has also been reported for skin-whitening applications [404].

The use of LACs in medicinal chemistry has shown their potential as an emerging field for the development of antibiotics, anticancer drugs, antifungal medications, sedatives, and hazardous material detoxification [396,405,406]. Likewise, a series of 1,4-naphthoquinone-2,3-bis-sulfides, synthesized with the aid of Novozym® 51003 (*M. thermophila* laccase expressed in *Aspergillus oryzae*) catalysis, showed activity against melanoma (UACC62), prostate (PC3), breast (MCF7), and renal (TK10) cancer cell lines, with some compounds having IC_{50} values under 10 μ M [407,408]. Another application has been documented for hair dyeing products in recent years [409]. The principal intermediate (*p*-phenylenediamine, *p*-aminophenol, and its derivatives), the coupler (*m*-phenylenediamines, resorcinol, naphthols, and derivatives), hydrogen peroxide, and ammonia are typically blended to make permanent hair dyes [179]. The oxidant's primary function is to oxidize the primary intermediates; its secondary function, when combined with ammonia, is to lighten the hair's natural color [179,410]. However, these circumstances facilitate adverse interactions with hair protein, resulting in damage to the hair. Therefore, this impact may be lessened by using a different oxidant, such as laccase instead of hydrogen peroxide [179]. It has been reported that alkaline LACs have been used for this purpose as well [409,411].

7. Emerging trends in nano-bio catalyst and immobilization

Functional nanostructures have been shown to be suitable supports for the production of enzyme-nanostructure biocatalysts due to their unique physicochemical properties [412]. The development of new nanocatalysts has been linked to significant improved enzyme activity in a variety of applications in recent years [412–414]. Owing to its unique attributes, such as improved enzyme activity and stability under harsh environments, with relatively low concentrations, nano-biocatalysts have sparked intense interest in the bioremediation of wastewater from industrial sectors [366,415]. Recently, Guo et al. reported LiP immobilized from *Pichia methanolica* on $Fe_3O_4@SiO_2@polydopamine$ (PDA) based nanoparticles for the effective degradation of tetracycline, dibutyl phthalate, 5-chlorophenol, phenol, phenanthrene, fluoranthene,

and benzo(a)pyrene [416]. Singh et al. reported the synthesis of LiP-mediated silver nanoparticles (AgNPs) in *Acinetobacter* sp. for optimal activity of the purified enzyme at pH 2 and 60 °C using *n*-propanol as substrate [417]. Gkantzou et al. reviewed the innovative nanocatalysts for biocatalytic transformation applications, such as the removal of textile dyes from wastewaters employing LAC from *T. versicolor* immobilized on kaolinite [413,418]. In terms of decolorization yield, nano-biocatalysts are often superior to free LAC because to the improved stability brought about by immobilization.

8. Laccase-aided grafting

The use of LAC-mediated grafting on lignocelluloses as an environmentally friendly way to covalently alter wood, paper, and cork has received much attention in recent years [419]. This method has also been used to alter fibers having polysaccharide backbones, including cellulose or chitosan, to impart coloration, antibacterial action, or antioxidant activity. Furthermore, particular attention has been dedicated to the grafting of (bio)-molecules onto surfaces and polymers. Grafting is described as a process in polymer chemistry when one or more species of the block are covalently linked to the main chain of a macromolecule as side chains possessing constitutional or configurationally properties that differ from those in the main chain [419]. A few most recent examples of LAC-mediated grafting have explained in subsequent sections. A descriptive schematic illustration of grafting has portrayed in Fig. 12.

8.1. Lignocellulose grafting through laccase facilitation

A phenolic radical produced by LAC interacts with another radical or an oxidizable moiety in the process of propagation (termination). A scheme is explained in Fig. 13. However, the free radical is delocalized across the aromatic system, which implies several reactive sites, whether it is produced by phenol in solution or lignin [419]. As a result of coupling such delocalized radicals, various substrate-lignin, substrate-substrate, and even lignin-lignin dimers and subsequent oligomers are generated. The inclusion of phenolic extractives in the lignocellulosic matrix, which may potentially function as LAC substrates, makes it more difficult to comprehend the mechanisms behind these activities. Applying mediators to the system changes the reaction pathway further [420].

8.2. Acrylic acid grafting with laccase onto lignin for its recovery from wastewaters

By grafting acrylic acid (AA) to lignosulfonate in the presence of LAC and *tert*-butyl hydroperoxide (*t*-BHP), AA in paint production wastewater could be recovered. Interestingly, low *t*-BHP levels do not inhibit LAC activity but instead increase radical production of lignin, which then triggered AA polymerization [421]. LAC plays a substantial part in the AA grafting to lignin. Laccase/*t*-BHP enables 94 % of AA to be polymerized on lignin, but only 32 % of AA is grafted on lignin under the same conditions without laccase [421].

9. Synthesis of bioactive natural compounds and their analogs from LACs

Yet another potential use for LACs is the green and environmentally friendly production of highly valuable organic compounds. I.e. polyphenols, antimicrobial powders, etc. [422–425]. Despite the numerous chemical functionalities including; amination, oxidation, polymerization, dimerization, and cyclization LAC has been focused on the synthesis of numerous chemical compounds [426]. The oxidation of phenolic substrates to the respective quinone structures is a different strategy for using LAC in chemical synthesis, and it has been thoroughly documented [15]. Determining the susceptibility of LAC from fungi,

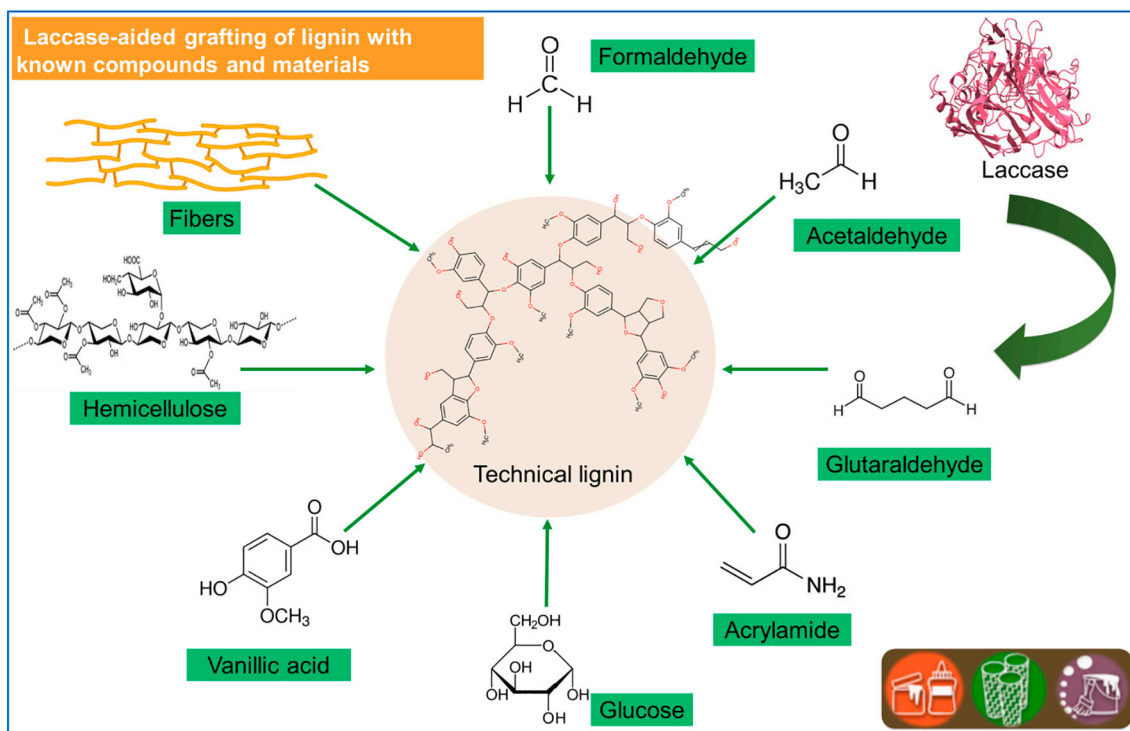


Fig. 12. A basic schematic of laccase-assisted grafting into lignin exploiting different materials.

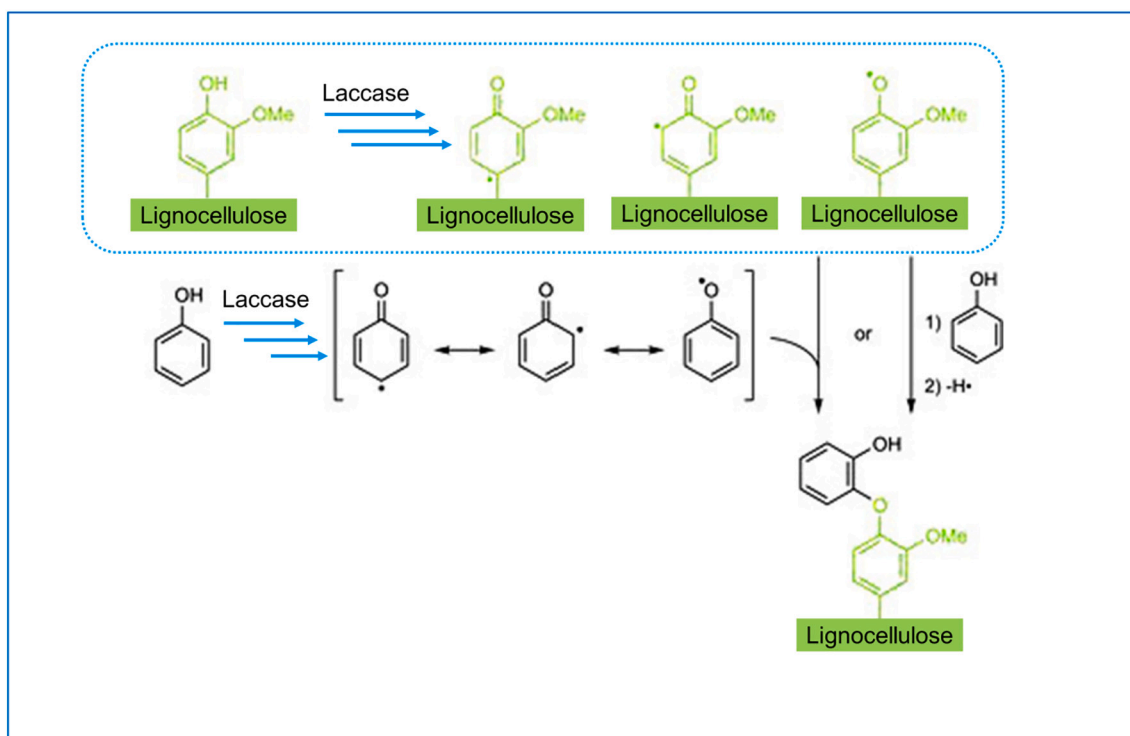


Fig. 13. A basic schematic of laccase-assisted phenol grafting into lignin.

bacteria, and plants to particular substrates and reactions have also been the attention of several investigations. In well-structured publications, comparisons of enzymes from various sources in-depth as well as assessments of several types of LAC from the same source have been reported and discussed [15,427,428]. Most recent, Cardullo et al. reported LACs and peroxidases could be deployed for the synthesis of numerous

organic compounds synthesis i.e. lignans, neolignans, dimeric stilbenoids, dimeric flavonoids, biflavonolignans, biaryl compounds and so on [15,429]. Likewise in another study, Hahn et al. reported LAC mediated ring-closure mechanism for the synthesis of phenothiazines, phenoxazines, and phenazines [422]. LAC's viability may be confirmed through successful lab-to-market products.

10. Deployment of LMEs in pre-screening of degradability or theoretical degradation of environmental pollutants

Enzyme kinetics and other parameters are vital in enzyme-substrate reaction, however, lack underlying molecular interactions, and simultaneously biotransformation information [73]. In recent decades, LME-producing microbes have been widely used for lignin degradation, depolymerization, and a variety of biotechnological applications [5,118,430]. For both environmental and various biotechnological uses, they have been labeled “green biocatalysts” owing to their effectiveness, efficiency, and environmental friendliness. Unfortunately, numerous critical pieces of information are unavailable in LME-assisted degradation, including the complete chemical transformation, underlying chemical interplay between enzyme and pollutant, and specific amino acids that interact as active site residues along with the dominant chemical bondings i.e. H-bond, π - π , sigma, alkyl, and π - π stacking [73]. However, existing shortcomings might be overcome by employing a computational framework in combination with a real-time assay to enhance biodegradation rate. Computational frameworks including docking, MD-simulation, and chemical cleavage prediction have gained the highest influence in predictive biodegradation for revealing the underlying molecular interplay between enzyme and pollutants at atomic level [73,75,431]. In recent years, LMEs has been outlined in computational frameworks for predictive biodegradation that depend on a wide range of aforementioned techniques, including docking and MD-simulation for virtual screening of degradability [73,75]. Even though it is a feasible and robust approach for pre-screening of enzymatic degradation, it has numerous advantages over the inefficient and time-consuming biodegradation process [73]. In contrast to conventional bioremediation, which primarily involves the entire media or the target contaminant of concern, the fate, molecular interactions, and rate of each transformed compound seem to be unidentified, even though the assessment of degradation compounds is based on the analytical probability of GC-MS/MS screening [73,431]. Although computational frameworks have been little documented, they might be considered a green computational tool in the remediation of environmental pollutants for regulatory consideration (Table 7). Over the last several years, several docking and simulation studies have been documented employing lignin and its derivatives as ligand in an effort to elucidate the molecular interaction between LMEs and ligand (pollutants) [77,320,432,433]. Previously, we reported on an *in silico* investigation of bacterial LiP using a set of 12 lignin model compounds to examine

Table 7

Exploitation of lignin modifying enzyme in computational degradation of lignin model compounds for unraveling molecular interactions between enzyme-pollutants.

LMEs member	Substrate/model compounds	Application	Reference
LAC	Lignin model compounds	Structural and functional properties of laccase	[77]
LAC	Lignin model compounds	Molecular basis of lignin binding to laccase	[434]
LAC	Lignin model compounds	Lignin degradation	[435]
LAC	Lignin model compounds	Molecular basis of LAC-lignin binding	[436]
LiP	Different lignin model compounds	Molecular basis of LiP-lignin bindings	[75]
LiP	Multimeric lignin model compounds	Theoretical degradation of model compounds	[74]
LMEs	EDCs	Theoretical basis of degradation mechanism	[79]
LMEs	Priority pollutants	Theoretical basis of degradation mechanism	[80]
LAC	Glyphosate, isoproturon, lignin, parathion	Bioremediation potential of laccase	[78]

molecular binding affinity and get a theoretical understanding of the lignin degradation mechanism at the molecular level [75]. Subsequently lowest XP Gscore as -8.136 (kcal/mol) was found for the trimer model compound, with Pi-Pi stacking and H-bond type bonding interactions corresponding to LiP [75]. Among all model compounds specific binding residues were observed as TYR, HIP (protonated histidine), PHE, VAL, ASP, THR, LYS and GLN. Furthermore, MD-simulation was deployed for validation of docked complex with a simulation ran of 30 ns [75]. A similar analysis was carried out in another investigation to describe the catalytic activity of LiP against multimeric lignin model compounds to comprehend the theoretical degradation potential of selected LiP [74]. Nevertheless, additional investigation of LMEs against a broad range of hazardous compounds for potential catalytic behavior still remains unexplored. A schematic representation of LME-assisted degradability screening of pollutants has been highlighted in Fig. 14. Future views and the incorporation of computational framework for enhancing bioremediation of various pollutants along with joint efforts including *in silico*, and conventional experiments have been outlined in Fig. 15.

11. Concluding remarks and future perspectives

LMEs have made a significant contribution to their prospective abilities in a wide range of industrial and biotechnological applications over the past few decades. Fungi, particularly WRF, have been reported to outcompete bacteria in the biosynthesis of extracellular LMEs enzymes. Extensive application in *ex-situ* environmental studies has conclusively demonstrated their pollutant removal capability, commercial availability, and biotechnological applications. Environmental research has received far more attention than any other application of LMEs. Despite the aforementioned, lower yield and increased enzyme demand remain major challenges in LMEs synthesis by native microbial species. However, protein engineering or recombinant technologies are being developed to tackle such a pillar to meet the growing demand of LMEs for industrial deployment. LiP, MnP, and VP are H_2O_2 dependent in the catalysis of phenolic and non-phenolic substrates (lignin), whereas LACs are oxidized phenolic substrates using molecular O_2 . LAC plays an important role in the food industries as a stabilizer, and destabilizer, pharmaceutical, biosensor, biobleaching, and medical. As opposed to LiP, this possesses a multipurpose oxidoreductase with uses in both the environmental and biotechnological fields. Recent medical advancements and skin whitening agents have been thoroughly documented, proving that LMEs member (LiP, LAC) have exceptional capabilities. The implementation of LMEs in computer-assisted theoretical degradation solves the complicated, recalcitrant pollutant puzzle in a smarter and greener way has brought us even closer to another deployment. LMEs are still expected to provide a number of opportunities for further investigation into previously unknown domains, such as those of:

- ✓ Exploration of LMEs-assisted depolymerized compounds screening for drugs properties
- ✓ Protein engineering approach for high yield, pH, and stability at harsh temperature
- ✓ A computational framework for green biodegradation
- ✓ Exploration for extended pharmaceutical and medicinal application
- ✓ Computational exploration of homologous enzyme sequence among other origins e.g., plant species

CRedit authorship contribution statement

Listed authors have made equal contribution in this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

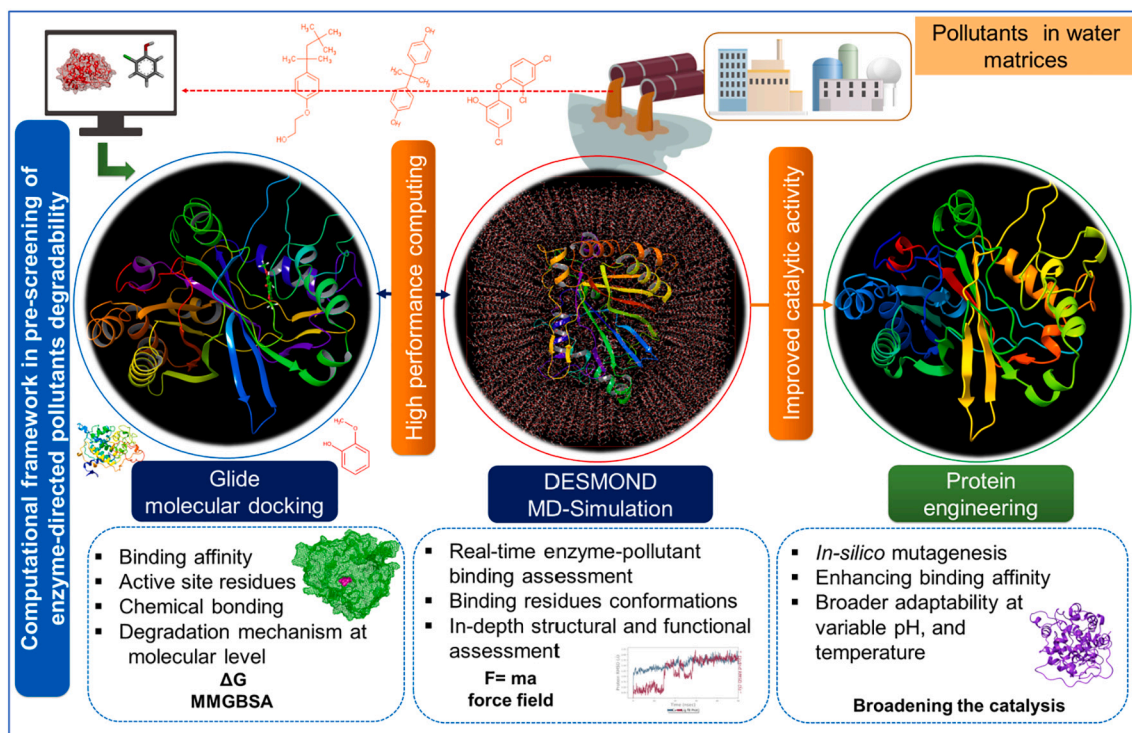


Fig. 14. A most recent breakthrough in water research. A computational framework has been explained, containing molecular docking, MD-simulation, and protein engineering approaches for sustainable smart remediation of pollutants from water matrices. An array of pollutants from wastewaters could be screened and deployed for docking, and simulation for accessing the degradability and therefore such techniques has designated as pre-screening of pollutants degradability. Different oxidoreductase can be used for target pollutant docking, and simulation, and thus obtained results could be transformed into real-time degradation assay for enhancing the degradation rate. However, the protein engineering approach can be exploited for enhancing the catalytic functionalities under unfavorable environmental conditions.

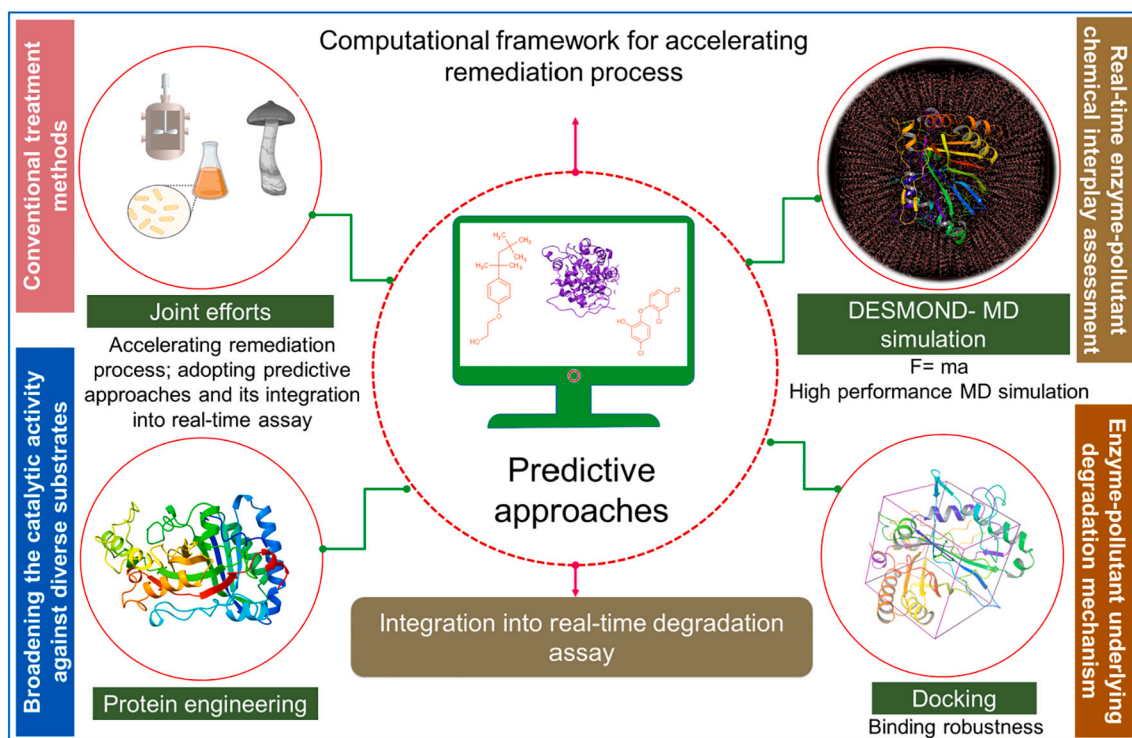


Fig. 15. Future perspective of lignin modifying enzymes (LMEs), for regulatory consideration to access the pre-screening based degradability of pollutants deploying aforesaid member of LMEs. Even though, it would be necessary to confirm the outcomes of the pre-screening methods using a real-time degrading assay.

the work reported in this paper.

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