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MINI-REVIEW

Bifunctional in vivo role of laccase exploited in multiple biotechnological applications

Abha Sharma[1] · Kavish Kumar Jain[1] · Arti Jain[2] · Mazahir Kidwai[2] · R. C. Kuhad[1]

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Abstract

Laccases are multicopper enzymes present in plants, fungi, bacteria, and insects, which catalyze oxidation reactions together with four electron reduction of oxygen to water. Plant, bacterial, and insect laccases have a polymerizing role in nature, implicated in biosynthesis of lignin, melanin formation, and cuticle hardening, respectively. On the other hand, fungal laccases carry out both polymerizing (melanin synthesis and fruit body formation) as well as depolymerizing roles (lignin degradation). This bifunctionality of fungal laccases can be attributed to the presence of multiple isoforms within the same as well as different genus and species. Interestingly, by manipulating culture conditions, these isoforms with their different induction patterns and unique biochemical characteristics can be expressed or over-expressed for a targeted biotechnological application. Consequently, laccases can be considered as one of the most important biocatalyst which can be exploited for divergent industrial applications viz. paper pulp bleaching, fiber modification, dye decolorization, bioremediation as well as organic synthesis. The present review spotlights the role of fungal laccases in various antagonistic applications, i.e., polymerizing and depolymerizing, and co-relating this dual role with potential industrial significance.

Keywords Laccase · Bifunctional · Isoforms · Polymerization · Depolymerization

Introduction

Laccases are polyphenol multicopper oxidases which catalyze oxidation of various phenols and anilines with the concomitant reduction of molecular oxygen to water (Thurston 1994; Solomon et al. 1996). The enzyme is ubiquitous in nature being found in plants (Berthret et al. 2012), fungi (Baldrian 2006), bacteria (Claus 2003), insects (Dittmer and Kanost 2010) as well as lichens (Lisov et al. 2007) and sponges (Li et al. 2015). The genes that encode for laccases belong to members of a multi-gene family with different isozymes expressed in different space and time (Gianfreda et al. 1999; Kumar et al. 2017). The presence of multiple laccase isoforms explains the diverse and multiple functions of this enzyme within same as well as diverse species (Sharma and Kuhad 2008). In plants, laccases are involved in lignin and polyflavanoid synthesis (Ranocha et al. 2002; Liang et al. 2006), while, in fungi, they have a role in delignification (Eggert et al. 1996), fruit body formation (Zhang et al. 2015, pigmentation (Eisenman et al. 2007), and pathogenesis (Zhu and Williamson 2004). In insects, the function of laccases is sclerotization of cuticle (Gorman et al. 2012) and in bacteria they regulate copper homeostasis, morphogenesis, melanization (Claus 2003), and pathogenesis (Singh et al. 2016). While in lichens, laccases are considered to carry out metabolism of lichen acids and other phenols (Lisov et al. 2007). In sponges, laccase is involved in the antibacterial defense of the sponge organism (Li et al. 2015). Therefore, it can be seen that in vivo function of laccases is synthetic in all the organisms except in fungi (Fig. 1), where they carry out both synthetic (fruit body formation, pigment synthesis) and degradative roles (lignin degradation). In all laccase-mediated catalysis, reaction begins with single electron oxidation of substrate to corresponding radicals, which can then subsequently either repolymerize or lead to depolymerization of the substrate (Madhavi and Lele

Abha Sharma and Kavish Kumar Jain contributed equally to the manuscript.

✉ R. C. Kuhad
kuhad85@gmail.com

[1] Lignocellulose Biotechnology laboratory, Department of Microbiology, University of Delhi South Campus, New Delhi 110021, India

[2] Green Chemistry laboratory, Department of Chemistry, University of Delhi, North Campus, New Delhi 110007, India

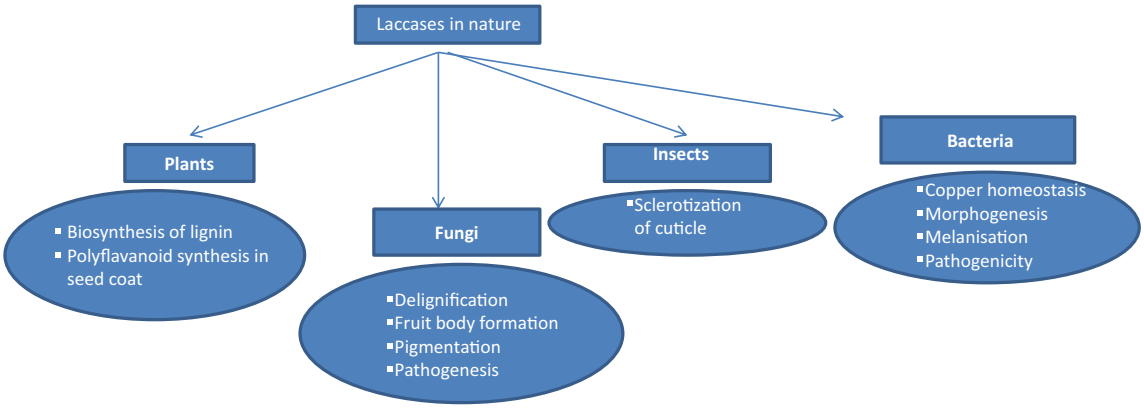

Fig. 1 Occurrence and role of laccases in nature. Except for the role of fungal laccases in delignification, all laccase isoforms carry out the function of polymerization in nature

2009; Jones and Solomon 2015) depending on the reaction conditions, metabolism and half-life of the radicals as well as enzymes redox potential (Jeon and Chang 2013). The polymerizing function of the enzyme occurs by oxidative coupling of the substrate producing dimers and polymers. On the other hand, the depolymerizing role of fungal laccase owe to their higher redox potential (Fig. 2), enabling them to oxidize lignin with the help of small molecular weight mediators (Jeon et al. 2012). It is suggested that parallel polymerization and depolymerization reactions compete during treatment with laccase as phenolic groups in lignin serves as sites for lignin polymerization, which in turn obstruct ligninolysis (Srebotnik and Hammel 2000). Therefore, in order to exploit the depolymerizing role of fungal laccases, various natural/synthetic mediators are added to the reaction mixture, as these mediators act as diffusible electron carriers which enhance substrate conversion (Mate and Alcalde 2016). Synthetic laccase mediators [2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid)], 1-hydroxybenzotriazole, and violuric acid (VA) in conjunction with laccase, called as laccase mediator system (LMS) have been demonstrated to effectively enhance the degradative role of the enzyme (Baldrian 2006). Furthermore, instead of using the abovementioned synthetic mediators, compounds involved in the natural degradation of lignin by fungi can also be used for depolymerizing application of laccase as these natural mediators have an added advantages of being cost effective and eco-friendly (Camarero et al. 2005). These include p-coumaric acid, vanillin, acetovanillone, methyl vanillate, phenol, aniline, 4-hydroxybenzoic acid, and 4-hydroxybenzyl alcohol syringaldehyde and acetosyringone (Johannes and Majcherczyk 2000; Camarero et al. 2005).

Nonetheless, the in vivo bifunctionality of laccases is also incurred to the presence of numerous laccase isozymes with different induction patterns as well as unique biochemical properties (Fig. 2). Most white rot fungi produce more than one laccase isozyme that differ in the degree of glycosylation, amino acid sequence, molecular weight, pI, and substrate specificity (Mansur et al. 2003; Kumar et al. 2017). As a result, diverse functions of laccase isozymes is dependent on cell type and intra- or extra-cellular conditions in which it gets expressed. Isoforms expressed in the lag or logarithmic phase of fungal fermentation are mainly drawn in degradation of substrate, while the ones detected in the stationary phase are related to pigmentation and morphogenesis (Lettera et al. 2010). The effect of metal ions, phenolic compounds, nutrient nitrogen and carbon are also critical in the expression of a particular laccase isoform (Piscitelli et al. 2011). Some of the isoforms are constitutively expressed, while others are inducible (Soden and Dobson 2001). In this regard, positive induction by nitrogen sources has been reported for two isozymes of laccase (lac2 and lac4) from *Pleurotus sajor-caju*, while the expression of other two (lac1 and lac3) are not affected (Soden and Dobson 2001). While, Galhaup and co-workers (Galhaup et al. 2002) observed that *Trametes pubescens* secrete eight laccase isoforms, with LAP2 being majorly induced in the presence of copper ions in the media. On the other hand, D'souza et al. (2004) found out that two laccase isoforms (lcc1 and lcc2) from *Pleurotus pulmonarius* are produced in non-induced cultures after the depletion of carbon and nitrogen sources, while the other two (lcc3 and lcc4) were detected in cultures induced by various phenolic and aromatic compounds related to lignin and its derivatives,

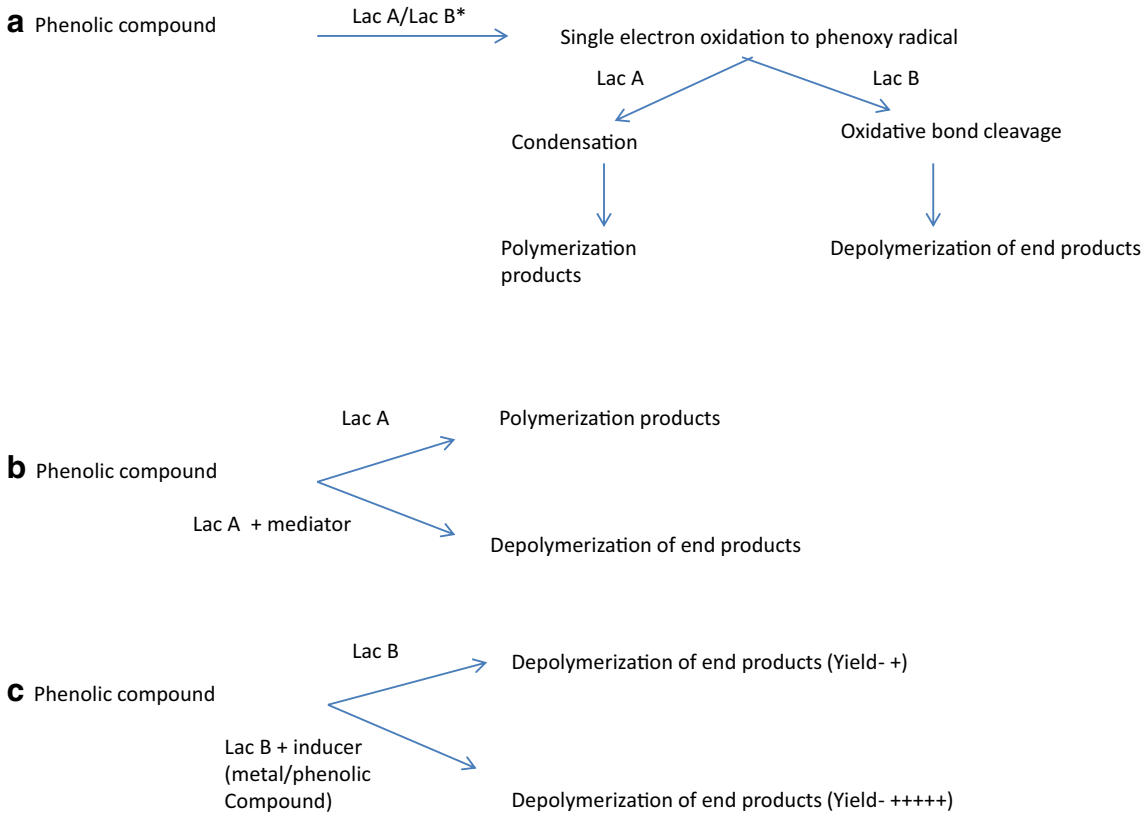

Fig. 2 Mechanism of action of laccase isozymes (*Lac B has higher redox potential than Lac A). Many organics can be converted to their corresponding radicals by laccase-mediated catalysis. These radicals per se can then undergo synthetic or degradative processes. For instance, **a** Lac B with higher redox potential can cause oxidative bond cleavage of substrate, while Lac A with lower redox potential will cause condensation of targets. **b** However, in presence of redox mediators, Lac A can also carry out depolymerization of end products. **c** The inducible nature of laccase isoforms can result in overexpression of a particular isoform, and thus increased catalytic activity

with maximum stimulation with ferulic acid and vanillin. In another study, different electrophoretic profiles of laccase isoforms were observed from *Ganoderma lucidum* in the presence of phenolic and metallic inducers (Kuhar and Papinutti 2014). Similarly, three laccase isoforms were characterized from *Steccherinum ochraceum* with unusual and different biochemical properties (Chernykh et al. 2008). Furthermore, the three laccase isozymes (LacI, LacII, and LacIII) were purified and characterized from white rot fungus, *Trametes* sp. HS-03 with different PIs and thermostabilities. While, LacI and LacII showed similar thermo stability, LacIII showed better thermostability (Guo et al. 2012). Likewise, three laccase isozymes (Lac-2, Lac-3, and Lac-4) with different pH stabilities and thermostabilities were purified from the white rot fungus *Ganoderma* sp. En3 (He et al. 2014). Among the three isolated isonzymes, Lac-2 showed stronger pH stability and thermostability than the other two isoforms. Furthermore, it was found that Lac-2 had a stronger ability to tolerate metal ions and organic solvents compared with the other two isoenzymes. The authors also deciphered a positive synergistic effect of the three isozymes on decolorization of azo dyes, with Lac-3 alone having a negligible effect on dye decolorization but when combined with the other two isoenzymes Lac-2 or Lac-4, enhanced their decolorization potential against the tested dyes (He et al. 2014). Very interestingly, Kumar et al. (2017) observed differential expression of laccase isozymes from *Ganoderma* strains, *G. lucidum* MDU-7, and *Ganoderma* sp. kk-02 in the presence of diverse aromatic compounds and metal salts. While, O-toluidine induced isozyme production from *G. lucidum* MDU-7, it did not have any effect on isozyme pattern of *Ganoderma* sp. kk-02. On the other hand, copper and tannic acid induced laccase production from both the strains. Thus, Kumar and co-workers (Kumar et al. 2017) concluded that the species-specific action of different aromatic compounds on the production of laccase isozymes might be due to differences in ecological habitat, which eventually helps in adaptation

of the fungus. However, actual mechanism and purposes of temporal and substrate specific laccase isozyme secretion is unknown and therefore needs to be scientifically elaborated and ecologically related. In contrast, structural studies of two laccase isoforms from *Pycnoporous sanguineus* were performed by Orlikowska et al. (2018) and significant differences were found in their substrate binding pockets, thermal and pH stabilities as well as tolerance against inhibitors. Therefore, it can be concluded that by manipulating culture conditions or adding a specific inducer, a particular laccase isozyme targeted for an application can be expressed or over-expressed (Fig. 2). The approach can also be exploited for increasing total laccase activity in the culture medium, bypassing need of recombinant gene expression. Likewise, two laccase isozymes (Lacc1 and Lacc2) from *Agaricus bisporus* were purified and characterized. While, Lacc1 was found to be thermostable (retaining 80% activity at 60 °C after 90 min), Lacc2 was alkali stable (retaining 93% activity at pH 9.0). Further, the activity of both the isozymes was differently affected by metal ions and the decolorizing activity was also found to be different with Lacc2 more superior in terms of decolorization of Acid blue dye solution (Othman et al. 2018). From the application point of view, co-relating the in vivo duplicate role of enzyme (polymerizing and depolymerizing roles) to the presence of inducible isoforms, the enzyme can be used for divergent biotechnological processes viz. pulp bleaching, fiber modification, dye decolorization, and organic synthesis (Fig. 3). For instance, the lignin polymerization function of laccases can be used for in vitro polymerization of lignocellulosic materials and also for grafting of phenolic compounds onto pulp fibers producing boards with improved properties (Schubert et al. 2015). In contrast, the depolymerizing action of the enzyme can be used for the delignification of wood pulp for paper making (Sharma et al. 2005) with the mediation of synthetic mediators, thereby sinking the consumption of toxic chemicals used for the same purpose. The degradative role of the enzyme can also be exploited for oxidative bond cleavage of toxic xenobiotic compounds (Yang et al. 2017) and synthetic dyes (Vantamuri and Kaliwal 2016) structurally related to lignin and its derivatives. On the other hand, the polymerizing action of the enzyme can be used for polymerization of pollutants which can then be subsequently removed by filtration/sedimentation (Steevensz et al. 2012). In organic synthesis, the polymerization of same or different substrates by laccase result in the formation of homo and heterodimers, respectively, for the production of new antibiotic derivatives and complex products with enhanced physiological properties (Wellington et al. 2013). The present review discusses the synthetic and degradative in vitro applications of laccase viz. paper pulp bleaching and pulp fiber modification in the pulp and paper industry, bioremediation, dye decolorization, and organic synthesis.

Applications of laccase (polymerizing and depolymerizing role)

Organic synthesis (polymerizing role)

Oxidation reactions are an essential part of organic synthesis but the conventional oxidation technologies use environmentally toxic chemicals such as chromium compounds, permanganate, manganese dioxide, and periodate and produce non-specific and undesirable side-reactions (Kidwai et al. 2012b). The growing public concern over the use of such hazardous chemicals has provoked search for new oxidation technologies based on biological systems such as enzymatic oxidation (Sanchez and Demain 2011). In this regard, laccases are of great interest as an enzyme which oxidizes a wide variety of phenolic and aromatic compounds using oxygen from the environment and producing water as the sole by-product, thereby ideal for future sustainable green chemistry (Kidwai et al. 2012b). Since fungal laccases have higher redox potential than laccases from other species, they are more fitted to perform the polymerizing role in organic synthesis (Christopher et al. 2014). For example, laccases secreted by the white rot fungi *Trametes versicolor* and *Neurospora crassa* have a high redox potential of 0.78–0.80 V, whereas the redox potential of laccases from the plant, *Rhus vernicifera* is only 0.42 V (Mikolasch and Schauer 2009). Table 1 lists some fungal laccases used by many research groups for organic synthesis. Furthermore, the application of laccases in the production of pharmaceutically important moieties, synthesis of compounds with increased antioxidant potential, and various valuable polymers is discussed below:

Production of compounds with improved antioxidant potential

Reactive oxygen species (ROS) are produced in the human body as by-products of normal metabolism and are also reduced by the human defense system comprising of glutathione and other thiols. However, in case of oxidative stress, there is an imbalance between ROS formation and cellular antioxidant capacity, leading to the development of various neurogenerative disorders. In such cases, supplementation with external antioxidant agents is needed (Chen et al. 2012). Unfortunately, the clinically effective antioxidant drugs are scarce. As a result, novel compounds are being constantly synthesized chemically and evaluated for their increased antioxidant potential (Gupta et al. 2012; Apotrosoaei et al. 2014). Phenyl propanoid acids and flavonoids (polyphenols) are

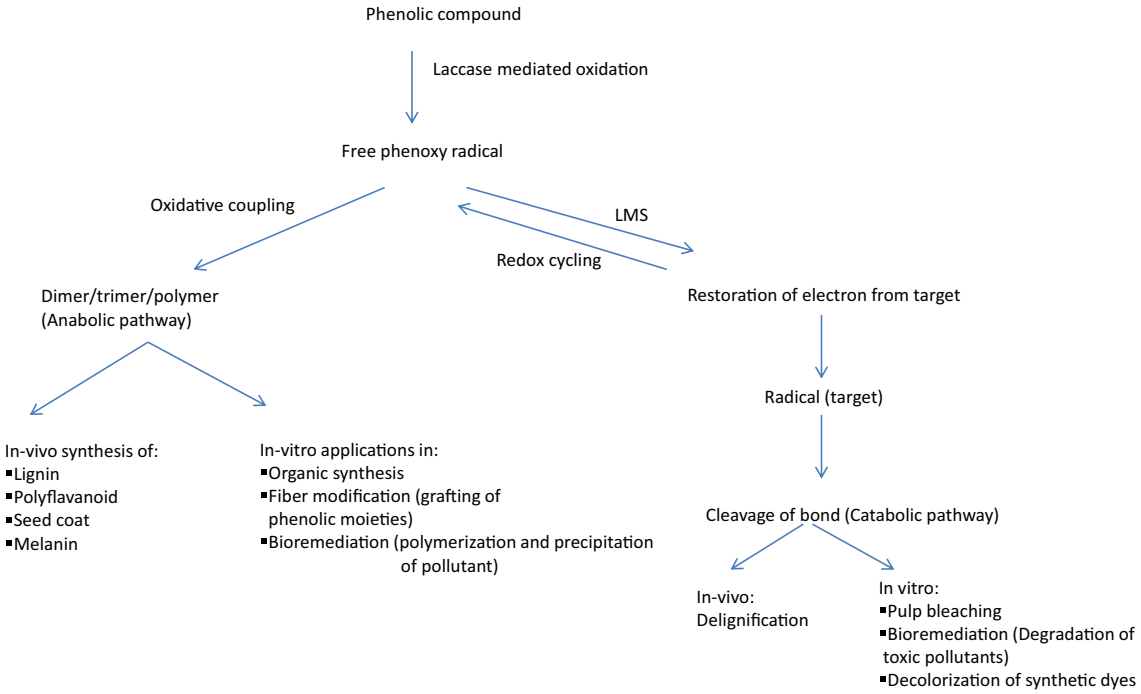

Fig. 3 Bifunctionality of laccases in vivo and in vitro. The catabolic and anabolic in vivo role of laccase isoforms can be exploited in vitro in diverse biotechnological applications

strong antioxidants that protects from oxidative stress caused by surplus ROS. However, the position and stereo-electronic properties of the substituents on the aromatic rings of polyphenols as well as the presence of catechol and pyrogallol pharmacophores tune the antioxidant effect of these compounds (Botta et al. 2017). Therefore, the oxidative effect of laccases on phenols can further enhance their antioxidant potential. In this regard, laccase-catalyzed polymerization of quercetin as well as of kampeferol was performed separately to produce aggregates with higher antioxidant properties than the monomeric quercetin and kampeferol (Desentis-Mendoza et al. 2006). While, silybin dimers were successfully prepared

Table 1 Application of fungal laccases in organic synthesis

Laccase source	Compounds synthesized	Application	Reference
Trametes versicolor	Polycatechol	Valuable polymer used as a chromatographic resin and in the formation of thin films for biosensors	(Aktaş et al. 2003)
Ustilago maydis	Polymerization of quercitin and kampferol	Improved antioxidant properties of the polymers compared to the monomers	(Desentis-Mendoza et al. 2006)
T. versicolor	Benzofuranones	Medicinal chemistry	(Hajdok et al. 2007)
Crinipellis sp.	Oxaflavins	Redox co-enzymes	(Kidwai et al. 2009)
Trametes villosa	Benzofurans	Antimicrobial and anti-inflammatory activities	(Witayakran and Ragauskas 2009)
T. versicolor	Polycatechol	Polymeric film	(Ceylan et al. 2008)
Trametes hirsute	Polyanniline	Conducting polymer	(Streltsov et al. 2009)
T. versicolor	Synthesis of poly allylamine	High antioxidant potential	(Gogoi et al. 2010)
T. versicolor	Dyes	Used in hair dyeing	(Jeon et al. 2010)
T. versicolor	Benzoquinones	Intermediate in pharmaceuticals	(Hajdok et al. 2012)
Pycnoporus cinnabarinus	Benzofuropyroles	Super potent pharmaceutical agent	(Kidwai et al. 2013a)
P. cinnabarinus	6,7-dihydroxy-2,2-dimethyl-1, 3,9-trioxa-fluoren-4-one	Pharmaceutical agent	(Kidwai et al. 2013b)
T. versicolor	Phenazine and phenoxazinone chromopheres	Synthetic dyes	(Sousa et al. 2014)
T. villosa	Polyanniline	Conducting polymer	(de Salas et al. 2016)

by laccase-catalyzed polymerization of silybin derivatives (Gažák et al. 2008). Silybin dimers are commonly used in the treatment of liver dysfunction, as a hepatoprotectant and also as an antioxidant (Agarwal et al. 2006). In another reaction, conjugate of catechin (poly(allylamine)) was synthesized by the polymerization of catechins present in green tea and was found to have improved properties compared to the unconjugated catechin in terms of antioxidant potential (Gogoi et al. 2010). Nemadziva and co-workers (Nemadziva et al. 2018) synthesized a β-β caffeic acid dimer, phellinsin A, using laccase-mediated catalysis and found that the dimer had almost 1.8-fold higher antioxidant property compared to caffeic acid. Fascinatingly, three dimers were synthesized from 2,6-dimethoxyphenol using *Botryosphaeria rhodina* laccase under different reaction conditions (pH and reaction times) and it was found that dimer II, 3,3′,5,5′-tetramethoxybiphenyl-4,4′-diol (TMBP), being synthesized at pH 6.5 in 120 h had high antioxidant activity, similar to the commercial standard, butyl hydroxytoluene (Schirmann et al. 2018). The authors also indicated that TMBP can be used as an alternative antioxidant to stabilize biodiesel (Schirmann et al. 2018).

Production of pharmaceutically and industrially important compounds

Selective oxidations catalyzed by laccase have been applied for the manufacture of pharmaceutically vital compounds (Mogharabi and Faramarzi 2014). For instance, laccase-catalyzed oxidative domino reaction of cylcohexane-1,3-dione with catechol produced 3,4-dihydro-7,8-dihydroxy-2-H-debenzofuran-1-ones with yields ranging from 70 to 97% (Hajdok et al. 2007). Because of their biological chemistry, these dibenzofuranones are of great interest to medicinal chemistry. In another study, dimers were produced by laccase-catalyzed oxidation of catechol. Further, these dimers reacted with chalcones producing oxaflavins, which owe their importance as probable redox co-enzymes (Kidwai et al. 2009). While, benzofurans were synthesized using laccase-catalyzed oxidation of catechol to corresponding dimers (Witayakran and Ragauskas 2009). Benzofurans are known to have good antimicrobial and anti-inflammatory activities but are produced conventionally by lanthanide metal catalysts. In another work, a new series of quinoxaline derivatives have been effectively produced by laccase-mediated oxidative coupling of dihyroxy benzene and diamines (Kidwai et al. 2012b). Quinoxaline derivatives form basic skeleton of many antibiotics (levomycin and actinomycin), synthesized conventionally by electrochemical methods. In another study, aminonapthoquinones were synthesized by laccase-catalyzed nuclear monoanimation of 1,4-hydroquinone with primary aromatic amines (Wellington and Kolesnikova 2012). The authors also demonstrated the cytostatic effects of the produced aminonapthoquinones against cancer cell lines. In yet another reaction, benzoquinones were synthesized by laccase-catalyzed domino reaction between cyclic 1.3-dicarbonyls and hydroquinones (Hajdok et al. 2012). Likewise, laccase-catalyzed coupling of 1,2- ethanedithiol with substituted hydroquinones for the eco-friendly one-pot synthesis of 2,3-ethylenedithio-1,4-quinones was performed (Cannatelli and Ragauskas 2015). Interestingly, an efficient synthesis of benzofuro(2,3-c) pyrazoles by polymerization of catechols with pyrazolin-5-ones in the presence of laccase was also carried out (Kidwai et al. 2013a). The fusion of benzofurans with pyrazoles can lead to superpotent pharmaceutical compounds (Kidwai et al. 2013a). The same research group (Kidwai et al. 2013b) fused meldrum's acid with catechols and flavanoids in the presence of laccase and produced some new superior compounds, thereby making a significant input in the field of biocatalysis (Kidwai et al. 2013b). Meldrum's acid is known to have a depressant effect on the central nervous system and possess low toxicity like barbiturates, whereas, catechols and flavanoids are good antimicrobial agents. Furthermore, laccase was employed in enzymatic derivatization of amino acids, such as L-tryptophan, L-phenyalanine, or L-lysine by Mogharabi and Faramarzi (2014). On the other hand, laccase in association with the water-soluble palladium complex catalyzed aerobic oxidation of alcohols (Mekmouche et al. 2015). Recently, *T. versicolor* laccase was used for aerobic oxidative coupling of 4-substituted urazoles with sodium arylsulphinates for the synthesis of arylsulfonyl triazolidinediones (Rahimi et al. 2018).

Synthesis of valuable polymers and dyes

Polyanniline has good electrical and optical properties as well as remarkable environmental stability and therefore used as an active constituent of organic light weight batteries, optical display, micro-electronics, anti-corrosive protection, and in bioanalysis. Similarly, polycatechol is also a valuable polymer, used as a chromatographic resin and also for the production of thin films in biosensors (Kunamneni et al. 2008). Existing processes for synthesis of these polymers use horseradish peroxidase (HRP) per se, which shows low activity and stability at pH below pH 4.5 and also gets inactivated in the presence of high concentrations of H_2O_2 (Karamyshev et al. 2003). To address this issue, laccases have been used for the synthesis of polyanniline (de Salas et al. 2016) and polycatechol (Aktaş et al. 2003).

Mild conditions of synthesis thereof, as well as a lack of any toxic by-products, constitute advantages of the application of laccase-mediated biocatalysis in the synthesis of dyes (Polak et al. 2016). Laccase-based polymerization of different phenols in different combinations (gallic acid and syringic acid; catechin and catechol; ferulic acid and syringic acid) yielded diverse hair dyes (Jeon et al. 2010). Each of the formulated dye showed resistance to conventional shampooing, thereby showing the potential of laccase-mediated catalysis in the development of non-toxic hair dyes. The conventional hair dyeing methodology uses H_2O_2 as an oxidizing agent and phenylenediamine as a dye precursor. While H_2O_2 can cause

damage to the hair, phenylendiamine is a potential carcinogen. In another work, laccase-catalyzed dimerization of various ortho and meta, para-disubstituted aromatic amines into phenazine and phenoxazinone chromophores was performed (Sousa et al. 2014). Very interestingly, laccases from *Myceliphthora thermophila* were evolved by directed evolution and further expressed in *Saccharomyces cerevisiae* to be finally used for the synthesis C-H heteropolymeric dyes at alkaline pH (Vicente et al. 2016). The study thus provided useful laccase mutant for organic synthesis at basic pH. In another very interesting report, the toxicity and dyeing properties of several orange-red biodyes, which were obtained after laccase-catalyzed biotransformation of aromatic precursors was studied by Polak et al. (2016). The authors found out that the dyes were non-toxic on bioluminescent marine bacterium (*Vibrio fischeri*) as a test organism as well as on cultures of normal human colon epithelial cells (Polak et al. 2016).

Bioremediation (polymerizing and depolymerizing role)

Bioremediation is one such important application of laccase where the enzyme is involved in removal of toxic environmental pollutants either by an oxidative bond cleavage or by oxidative coupling mechanism depending on the reaction conditions. For instance, Murugesan and co-workers (Murugesan et al. 2010) studied transformation as well as detoxification of triclosan (TCS) by laccase in the presence and absence of redox mediators. It was observed that TCS was removed by 56.5% in the absence of redox mediator within 24 h, along with formation of new products (dimers and trimers of TCS) with molecular weights greater than that of the parent compound. However, in the presence of mediators (HBT and syringaldehyde), 90% of TCS was removed and compounds with molecular weight lower than TCS were detected by GC-MS. Hence, involvement of two mechanisms in laccase-mediated reactions was postulated: (i) polymerization or oxidative coupling in the absence of redox mediators, and (ii) bond cleavage as well as dechlorination in the presence of redox mediators (Murugesan et al. 2010). The results also suggest that laccase with redox mediators can be used for detoxification or elimination of pollutants by oxidative bond cleavage while, in the absence of mediators, enzyme polymerizes small organics with pollutants forming adducts that can be subsequently removed by filtration.

Laccase-catalyzed bioremediation by oxidative coupling (polymerizing role)

Oxidative coupling of small organic compounds with pollutants in the presence of laccase lead to their removal by consequent filtration or sedimentation. This is specifically valuable as well as practical in the treatment of water as the pollutant-containing co-polymeric compounds will become insoluble in water (Kulys et al. 2003), thereby making their consequent removal by filtration or sedimentation easier (Lante et al. 2000). In this regard, Han-Ko and Chen (2008) elucidated mechanisms for enhanced removal of common phenolic compounds present in various industrial effluents by laccase polymerization. The authors found out that guaiacol, catechol, and m-cresol got polymerized by laccase to products of average molecular weight of 9600, 8350, and 5400 Da, respectively, and thus can be easily removed by ultra and microfiltration membrane systems. Similarly, transformation of chlorinated hydroxybiphenyls by laccase from *Pycnoporus cinnabarinus* was investigated by Schultz et al. (2001). It was found out that the compounds used were transformed to sparingly water-soluble colored precipitates, identified as oligomerization products of the chlorinated hydroxybiphenyls by gas chromatography-mass spectrometry (Schultz et al. 2001). In another study, cell cultures of a laccase-producing fungus, *T. versicolor*, were compared with the immobilized cultures on nylon mesh in a 2 L bioreactor for transformation and adsorption of pentachlorophenol (PCP) and 2,4- dichlorophenol (2,4-DCP) by Sedarati et al. (2003). The authors observed that the immobilized cultures performed better with 85% of 2,4-DCP and 70% of PCP transformed; 5% of 2,4-DCP and 28% of PCP adsorbed by the biomass; and 10% of 2,4-DCP and 2% of PCP retained in the medium at the termination of the fermentation after 1020 h. While, Gullato and co-workers (Gullotto et al. 2008) exploited combination of two enzymes, namely toluene o-xylene monooxygenase from *Pseudomonas* sp. OX1 and laccase from *P. ostreatus* for the polymerization of mono and poly-aromatic hydrocarbons into polymers with reduced toxicity. Bhattacharya and Banerjee (2008) observed faster biodegradation of 2,4-DCP with Pleurotus sp. laccase compared with whole-cell biodegradation and obtained 98% degradation of the xenobiotic compound in 9 h. Furthermore, Bhattacharya et al. (2009) used RSM with a developed genetic algorithm for reducing contact time of laccase-mediated biodegradation of 2,4-DCP and successfully achieved 99% biodegradation in 8 h.Similarly, laccase-mediated coupling of aromatic amines, produced after decolorization of textile dyes, was performed by Franciscon et al. (2010). In another report, Steevensz and co-authors (Steevensz et al. 2012) studied laccase initiated oxidative coupling of various aromatic phenols and anilines present in water. Likewise, laccase-mediated oxidative coupling of phenol and its derivatives with 4-aminoantipyrene was investigated by Kidwai et al. (2012a). The authors obtained different yields of antipyrilquinoneimine dye as the colored product using laccase isolated from three different organisms (*P. cinnarabanius*, *Ganoderma* sp., and fungal isolate RCK-3), with better catalytic efficiency of *P. cinnabarinus* laccase w.r.t this particular reaction compared to the laccase from *Ganoderma* sp., and isolate RCK-3. The strategy can prove to be useful in estimating phenols in aqueous solutions (Kidwai et al. 2012a).Very interestingly, Sumathi et al. (2016) isolated the laccase-producing fungal strain Cochliobolus sp. from plastic-

dumped soils and found it to be effective in the degradation of low molecular weight polyvinyl chloride. Recently, Huber et al. (2018) performed laccase-catalyzed elimination of morphine from an aqueous system and obtained complete elimination of 60 g/L within 6 h.

Laccase mediator system catalyzed bioremediation by oxidative bond cleavage (depolymerizing role)

It has been widely reported that laccases alone can carry out degradation of only low-redox-potential phenolic compounds, and not the oxidation of the most recalcitrant nonphenolic contaminants (Xu et al. 1996). However, in the presence of mediators, small molecules that act as electron shuttles between enzymes and target molecules, rate of reaction, and the range of substrates oxidized can be enhanced (Vallecillos et al. 2017). Several polluting substances like textile dyes, pesticides, PAHs, and cholorophenols can be degraded effectively by the laccase mediator system (Camarero et al. 2005). Recently, laccase was also found competent in degradation of lipids as well as oxidation of olefin units present in plastic (Zhang et al. 2002). Therefore, the enzyme in combination with other existing techniques can also be implicated in plastic degradation (Durán et al. 2002). Since, substrate specificity of laccases vary from one to another laccase secreted from different sources and thus can be applied for degrading a variety of environmental contaminants in the presence of synthetic/natural mediators (Table 2).

Pulp and paper industry (polymerizing and depolymerizing role)

The in vivo degradative role of fungal laccases in delignification can be exploited for removal of lignin from paper pulp in the presence of redox mediators, while the in vivo polymerizing role of the enzyme can be used for grafting functional groups on pulp fibers, producing fiber boards with improved properties. Andreu and Vidal (2011) compared the effect of laccase treatment on kenaf pulp in conjunction with a number of diverse natural mediators (vanillin, syringaldehyde, acetosyringone, p-coumaric acid, acetovanillone) and a synthetic mediator (HBT). Interestingly, both the treatments showed opposite results with increase in kappa no. (delignification) and decrease in pulp brightness after enzymatic treatment in the presence of natural mediators. On the other hand, laccase treatment in conjunction with HBT (synthetic mediator) decreased the kappa no. and increased brightness of the pulp. The effect was explained by the authors as partial condensation reactions by laccase on kenaf pulp, leading to grafting of moieties on the fiber, thereby concluding that the effect of the laccase natural mediator system on substrate depends on the delicate equilibrium between reactions of oxidative degradation and polymerization (grafting) (Andreu and Vidal 2011).

Laccase mediator system catalyzed delignification of paper pulp (depolymerizing role)

Conventionally, pulp bleaching was carried out using chlorine, which the released bulk of halogenated organic compounds, measured as adsorbable organic halogens (AOX), in the effluents (Sharma et al. 2014). However, growing public concern and strict legislative laws over the harmful effects of AOX generated in the pulp bleaching processes lead paper mills to replace chlorine from their bleaching sequence with chlorine dioxide in an elemental chlorine-free bleaching (Bajpai et al. 2007). However, many new technologies, such as enzyme-mediated pulp treatment (bio-bleaching) and ozone-based bleaching, have also been studied and used to further reduce the environmental impact of pulp bleaching using chlorine dioxide (Singh et al. 2014). In this regard, application of laccases in bio-bleaching has been thoroughly studied by many researchers (Table 3). Along with reducing the consumption of chemicals for pulp bleaching sequence, the enzyme also helps in improving properties of the resultant paper (Sharma et al. 2014). Nevertheless, it was observed that laccase-mediated delignification of pulp without the addition of synthetic mediators was unsuccessful. The large size as well as lower redox potential limits action of the enzyme on the fiber surface. While, low molecular weight mediators act as a shuttle in transferring electrons from laccase to lignin (Oudia et al. 2007; Morozova et al. 2007). It was also seen by some researchers that introduction of a xylanase stage prior to treatment of pulp with laccase results in a noteworthy reduction of bleaching chemicals (Kapoor et al. 2007; Bajpai et al. 2007; Valls and Roncero 2009). This effect was explained by the action of xylanase on xylan, which lies between lignin and cellulose, thereby increasing the exposure of lignin in the pulp to laccase mediator system (Kapoor et al. 2007). The increased bleach response by introducing a xylanase stage before laccase treatment of the pulp can also be explained by increased accessibility of laccase to hexauronic acid after xylanase treatment and thereby facilitating their removal and thus reducing the kappa number of the pulp (Valls et al. 2010a). The fact was supported by a further study (Valls et al. 2010b) which reported more efficient removal of hexauronic acids by XLMS sequence than by laccase alone. Similarly, Aracri and Vidal (Aracri and Vidal 2011) also concluded that if xylanase treatment was applied before LMS treatment, better quality pulps were retained at the end of the bleaching sequence in terms of lower kappa number and higher cellulose content. Recently, Sharma and co-workers (Sharma et al. 2014) observed that sequential xylanase and laccase treatment of pulp at pilot scale (50 Kg pulp) saved 35% chlorine dioxide in the bleaching sequence to obtain the same targeted brightness as in the control pulp, resulting in 34% decreased AOX levels in bleach effluents along with improvement in properties of the formed paper (reduction in post color number by 50% and increase in tear index by 15.71%).

Table 2 Application of laccases for removal of environmental pollutants in the presence of mediators

Laccase source	Pollutant	Mediator	% degradation	Reference
Pyricularia oryzae	Model industrial wastewater (phenol solution containing 18 phenolic substrates	Syringaladehyde	Phenol: 19; 3-methoxyphenol: 15; 4-methoxyphenol: 47; 2,6-dimethoxyphenol: 69; 2,4-dichlorophenol: 68; 4-cloro-3-methylphenol: 49; p-nitrophenol: 32; 2-chlorophenol: 47; 3-chlorophenol: 38; 4-chlorophneol: 43; α-napthol: 56; β-napthol: 18; guaiacol: 40; chlorogenic acid: 7; caffeic acid: 18; m-cresol: 43; p-cresol: 49; o-cresol: 39	(Lante et al. 2000)
Coriolus versicolor	Bisphenol A p-nonylphenol 4-chlorophenol 2,4-dichlorophenol 2,4,5-trichorophenol 2,4,6-tricholorophenol	1-HBT	100 100 65 92 82 100	(Okazaki et al. 2002)
T. versicolor	Hydroxy polychlorinated biphenyls	2,2,6,6-tetramethylpiperidine-*N*-oxy radical	~78	(Keum and Li 2004)
Ganoderma lucidum	PAHs	1-HBT	Anthracene-100 Benzopyrene-100 Fluorine- 98.6 Acenapthene-95.4 Acenapthylene-90.1 Benzoanthracene-85.3	(Punnapayak et al. 2009)
T. versicolor	Brominated phenols	ABTS	65–80	(Uhnáková et al. 2009)
T. versicolor	Anthracene	1-HBT	42	(Hu et al. 2009)
G. lucidum	Triclosan	1-HBT	90	(Murugesan et al. 2010)
Recombinant laccase from *Lentinula edodes* expressed in *Pichia pastoris*	Anthracene	TEMPO	> 70	(Wong et al. 2012)
Rhodococcus ruber	Polyethylene	Copper	75	(Santo et al. 2013)
Myceliphthora thermophila	Estrogens	Oxygen	97	(Lloret et al. 2012)
T. versicolor	2-chlorophenol and 4-chlorophenol			(Menale et al. 2012)
P. ostreatus	Bisphenol A, nonylphenol, methylparaben, butylparaben	ABTS	95, 80, 50, 50	(Macellaro et al. 2014)
T. versicolor	Pesticides (chlorpyrifos, chlorothalonil, pyrimethanil, atrazine, and isoproturon)	Violuric acid for pyrimethanil and isoproturon, vanillin for chlorpyrifos, and acetosyringone and HBT for chlorothalonil and atrazine	Pyrimethanil and isoproturon degraded up to nearly 100% after 24 h while the other three pesticides reached up to 90%	(Jin et al. 2016)
T. versicolor	Isoproutron (herbicide)	HBT	100	(Zeng et al. 2017)
P. ostreatus	Chlorophenols, nitrophenols, and sulfonmaide antibiotics		75, 60, 98	(Zhuo et al. 2018)

Table 3 Laccases used in combination with mediators for bio-bleaching

Laccase source	Mediator	Substrate	Advantage	Reference
P. cinnabarinus	HBT	Flax pulp	Decrease in kapp no. (4 U) and increase in brightness (24%)	(Sigoillot et al. 2005)
P. cinnabarinus	HBT	Eucalyptus kraft pulp	4-point decrease in kappa no. and 6% ISO increase in brightness	(Ibarra et al. 2006)
Trametes sp.	ABTS	Eucalyptus kraft pulp	45% reduction in ClO_2 usage for achieving same pulp brightness as in the control	(Bajpai et al. 2007)
T. villosa	HBT	Eucalyptus kraft pulp	20% decrease in kappa no., 3- to 4-fold reduction in peroxide usage to obtain same pulp brightness as in the control pulp	(Moldes and Vidal 2008)
T. villosa	HBT	Flax pulp	1.8 unit decrease in kappa no.	(Fillat and Blanca Roncero 2009)
Trametes trogii	No mediator, addition of a peroxide stage	Loblolly pine kraft pulp	Achieved totally chlorine-free (TCF) bleaching	(Da Re et al. 2010)
Pycnoporus sanguineus	Acetosyringone, TCF bleaching with addition of hydrogen peroxide stage	Eucalyptus kraft pulp	Increase in brightness by 15 and 7% reduction in hydrogen peroxide consumption	(Eugenio et al. 2010)
T. villosa	HBT, addition of a reductive treatment with sodium borohyride	Flax fiber	Achieved TCF bleaching	(Fillat et al. 2010)
T. villosa	HBT	Flax pulp	Increase in brightness by 9% ISO	(Fillat and Roncero 2010)
Trichoderma harzianum	No mediator	Wastewater pulp	Reduction in Kappa no. by 18.6%	(Sadhasivam et al. 2010)
T. villosa	HBT	Eucalyptus kraft pulp	Reduction in Kappa no. by 2.1 units and increase in brightness by 10% ISO	(Valls et al. 2010a)
M. thermophila	Methyl syringate	Eucalyptus kraft pulp	Increase in brightness by 8.3 points and decrease in kappa no. by 2.7 points	(Babot et al. 2011)
T. villosa	HBT and xylanase pre-treatment	Eucalyptus kraft pulp	Improved effluent properties	(Valls et al. 2012)
P. cinnabarinus	Syringaldehyde, acetosyringone, p-coumaric acid, vanillin, acetovanillone	Kenaf pulp	Synringaldehyde and acetosyringone provided delignification, while the others caused grafting of moieties	(Andreu and Vidal 2011)
G. lucidum	HBT	Eucalyptus kraft pulp	25% reduction in ClO_2 consumption	(Sharma et al. 2014)
Aspergillus niveus	Xylanase pre-treatment	Cellulose pulp	Increase in whiteness by 17.2 points and kappa efficiency of around 56%	(de Carvalho Peixoto-Nogueira et al. 2015)

Laccase-catalyzed fiber modification (polymerizing role)

Laccase with its property to oxidize lignin can be applied in the manufacture of composites like liner and fiber boards and thus replacing toxic chemicals (urea, formaldehyde, isocyanate, and petrochemical resins) used for the purpose (Euring et al. 2011). By this way, laccase from *Trametes villosa* was used for grafting a variety of amino acids onto high-lignin softwood kraft pulp and it was observed that the strength properties of the paper formed from pulp treated with laccase-histidine were increased significantly (Witayakran and Ragauskas 2009). While, LMS was used to activate lignin on wood fiber surfaces by Euring et al. (2011). Two different mediators (vanillic acid (VAN) and 4-hydroxybenzoic acid (HBA)) were tested in the study, of which HBA performed better. ^{13}C-NMR revealed more structural changes in the wood fibers using LMS with HBA than LMS with VAN. Similarly, ESR spectroscopy also indicated a higher amount of phenoxy radicals on the fiber surface after treatment with LMS containing HBA as a mediator. But VAN also performed well, which showed a high potential to produce eco-friendly MDF (medium-density fiberboards) by using LMSs in the future (Euring et al. 2011). On the other hand, laccase-catalyzed grafting of protein-flavanoid conjugates was performed onto flax fiber, resulting in better color and increased antioxidant activity of the final product (Kim and Cavaco-Paulo 2012). In another study, Li et al. (2013) observed increased carboxyl group and surface lignin content of pulps treated with laccase and ferulic acid compared to the untreated pulps. Interestingly, commercial laccase from *Myceliophtora thermophila* was used along with latex to catalyze the surface modification of thermo-

Table 4 Laccases used for fiber modification

Laccase source	Fiber modified	Moiety grafted	Reference
Trametes villosa	High-lignin softwood kraft pulp	Amino acids	(Witayakran and Ragauskas 2009)
Myceliophthora thermophila	Flax fiber	Protein-flavanoid conjugates	(Kim and Cavaco-Paulo 2012)
Flammulina velutipes	Kraft pulp	Ferulic acid	(Li et al. 2013)
Myceliophthora thermophila	Thermo-mechanical pulp	Phenolic compounds from process water	(Schubert et al. 2015)
Commercial laccase	Bleached eucalyptus kraft pulp	Increase in carboxyl and aldehyde groups	(Zhang et al. 2016)

Table 5 Laccases used for decolorization of synthetic dyes

Laccase source	Dye	Reference
Commercial laccase	Remazol Brilliant Blue (RBBR)	(Soares et al. 2001)
Trametes modesta	Anthrachinonic, azo dyes, indigo carmine, triphenylmethane	(Kandelbauer et al. 2004)
Daedalea quecina	Chicago Sky Blue, reactive blue 2, trypan blue, Poly B-411, Remazol Brilliant Blue R	(Baldrian 2004)
Trametes hirsute	Sella solid red and luganil green	(Couto et al. 2004)
T. versicolor	Xylidine, Congo red, malachite green, Azure B, Poly R-478, anthraquinone blue	(Levin et al. 2004)
Irpex lacteus	Reactive blue 19, reactive black 5	(Máximo and Costa-Ferreira 2004)
Pleurotus pulmonarius	Congo red, amido black, methyl green, trypan blue, Remazol Brilliant Blue R, ethyl violet, methyl violet, brilliant cresyl blue, methylene blue, Poly R-478	(Tychanowicz et al. 2004)
T. trogii	Malachite green, xylidine, Ponceau 2R, anthraquinone blue	(Levin et al. 2005)
Funalia trogii	Reactive black 5	(Mazmanci and Ünyayar 2005)
T. villosa	Azo dyes	(Zille et al. 2005)
I. lacteus	Reactive orange 16	(Tavčar et al. 2006)
Funalia trogii	RBBR, Drimaran blue CL-BR	(Erkurt et al. 2007)
Scyzophyllum commune	Solargold yellow R	(Asgher et al. 2008)
I. lacteus	Reactive orange, RBBR	(Svobodová et al. 2008)
Cerrena unicolor	Acid blue 62, acid blue 40, acid red 27, direct black 22, reactive blue 81, direct black 22	(Michniewicz et al. 2008)
T. versicolor	Triphenylmethane dyes	(Casas et al. 2009)
G. lucidum	RB-5, RBBR	(Murugesan et al. 2009)
Trametes pubescens	Simulated textile effluent	(Osma et al. 2010)
T. versicolor	Reactive red 2 and reactive brown 10	(Bayramoğlu et al. 2010)
T. versicolor	Reactive blue 198, dispersed blue 3, acid blue 74, acid red 27, reactive black 5	(Champagne and Ramsay 2010)
T. trogii	Remazol Brilliant Blue R, indigo carmine, malachite green, gentian violet, bromophenol blue, indigo carmine, xylidine	(Grassi et al. 2011)
Funalia trogii	Mixture of Azo and anthraquinone dyes	(Tilli et al. 2011)
Ganoderma sp.	Textile effluent (real and simulated), methyl orange, malachite green, bromophenol blue, crystal violet	(Zhuo et al. 2011)
T.versicolor	Azo dyes	(Dhillon et al. 2012)
P. ostreatus	Triphenylmethane, azo and indigo dyes	(Kumar et al. 2012)
T. trogii	Mixture of azo and anthraquinone dyes	(Zeng et al. 2012)
Paraconiothyrium variabile	Acid yellow 36, acid red 18, disperse red 177, reactive yellow 15, direct blue 71, disperse blue 56, reactive orange 16, reactive black 5	(Ashrafi et al. 2013)
Paraconiothyrium variabile	Acid blue 2, acid orange 7	(Mirzadeh et al. 2014)
Cerrena sp.	Malachite green	(Yang et al. 2015)
Paraconiothyrium variabile	Direct black 166, acid orange 67, disperse yellow 79, direct yellow 107, basic yellow 28, basic red 18	(Forootanfar et al. 2016)
Cyathus bulleri	Reactive blue 21 and textile effluent	(Vats and Mishra 2018)

mechanical pulp (TMP) in process water obtained from the production of low-density wood fiber, which is known to contain natural phenolic extractives (Schubert et al. 2015). The researchers observed changed surface chemistry of the fiber due to grafting of phenolic compounds present in process water onto it by laccase, thereby enhancing mechanical strength properties of the resultant boards (Schubert et al. 2015). Table 4 lists laccases from different sources used for fiber modification.

LMS-catalyzed dye decolorization (depolymerizing role)

The prevalent use of synthetic dyes in a number of industries has resulted in the production of more than 100,000 hazardous dyes of different types such as heterocyclic, anthraquinone, phthalocyanine, triphenylmethane, and azo-based chemical structures (Cristóvão et al. 2008; Ayed et al. 2011). However, there is an urgent need to treat the strong and intense color of dyes discharged in the water from these industries (Cristóvão et al. 2008). This is because even lower concentration of dyes (less than 1 ppm) is distressing for the receiving water bodies as it severely affects the penetration of light and the gas solubility. The dyes are also found to be toxic for aquatic life, microorganisms as well as food chain organisms (Husain 2006). Therefore, treatment technologies need to be investigated for degradation of dyes in water bodies. Many physicochemical techniques are being used for dye removal (Saratale et al. 2011). However, these methods are economically unfeasible, generate large amounts of sludge, causing secondary pollution problem, and are also unable to remove recalcitrant azo dyes (Anjaneyulu et al. 2005). The enzymatic degradation of synthetic dyes provides an environment-friendly and cost effective process for dye removal of waste waters (Forootanfar et al. 2010; Telke et al. 2011). In this regard, laccases have gained much attention as they oxidize a broad range of aromatic compounds including synthetic dyes (Kuhad et al. 2004). During recent decades, many studies have been done on LMS-catalyzed degradation of synthetic dyes (Table 5).

Concluding remarks

The bifunctional roles of laccases owing to the presence of multi-gene families of the enzyme make them useful in diverse biotechnological applications of industrial significance. In addition, with their lesser reaction requirements as well as broad substrate specificity, laccases can be seen as model green catalysts for various industrial processes. Successful application of lignin-degrading ability of the enzyme in pulp bleaching in paper mills will reduce the use of hazardous chemicals to a sizeable extent. Further, the dye decolorizing ability of laccase can be exploited for developing a process for decolorization of textile effluents. On the other hand, the polymerizing ability of the enzyme used for coupling of various phenolic moieties on fiber-boards will help enhance their properties in an eco-friendly manner. While, application of enzyme in organic synthesis for the development of pharmaceutically important compounds as well as valuable polymers and dyes represent a milestone along the path of future sustainable chemistry. Bifunctionally, the enzyme can also be used in bioremediation, wherein it can remove recalcitrant toxic compounds from the environment either by oxidative bond cleavage (depolymerizing role) or by oxidative polymerization (polymerizing role). Nevertheless, the existence of multiple inducible isoforms of the enzyme gives added advantage of selectively expressing a particular isozyme for a desired application using definite inducers. Furthermore, altering reaction conditions (use of natural/synthetic laccase mediators) can also help laccase-based catalysis in either the polymerization/depolymerization direction. Thus, the in-depth knowledge of bifunctionality of this wonderful enzyme and future research on laccase-catalyzed biochemical reactions can definitely pave the way for designing novel biocatalysts with customized features.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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