

## White rot fungi and advanced combined biotechnology with nanomaterials: promising tools for endocrine-disrupting compounds biotransformation

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### ABSTRACT

Endocrine-disrupting compounds (EDCs) can interfere with endocrine systems and bio-accumulate through the food chain and even decrease biodiversity in contaminated areas. This review discusses a critical overview of recent research progress in the biotransformation of EDCs (including polychlorinated biphenyl and nonylphenol, and suspected EDCs such as heavy metals and sulfonamide antibiotics) by white rot fungi (WRF) based on techniques with an emphasis on summarizing and analyzing fungal molecular, metabolic and genetic mechanisms. Not only intracellular metabolism which seems to perform essential roles in the ability of WRF to transform EDCs, but also advanced applications are deeply discussed. This review mainly reveals the removal pathway of heavy metal and antibiotic pollutants because the single pollution almost did not exist in a real environment while the combined pollution has become more serious and close to people's life. The trends in WRF technology and its related advanced applications which use the combined technology, including biocatalysis of WRF and adsorption of nanomaterials, to degrade EDCs have also been introduced. Furthermore, challenges and future research needs EDCs biotransformation by WRF are also discussed. This research, referring to metabolic mechanisms and the combined technology of WRF with nanomaterials, undoubtedly contributes to the applications of biotechnology. This review will be of great benefit to an understanding of the trends in biotechnology for the removal of EDCs.

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### Introduction

Biotransformation of endocrine-disrupting compounds (EDCs) is an innovative, alternative, and sustainable removal technology that utilizes enzyme systems and various non-protein thiols from the liquid or soil phase by microorganism. This technology can efficiently degrade or transform many kinds of EDCs into harmless or less toxic forms. Because of the high efficiency and ecofriendly effects, these treatment methods tend to be more appropriate for both industry and agriculture applications [1,2].

EDCs are a category of chemicals which can interfere with endocrine (or hormone) systems and further affect the synthesis and metabolism of inherent hormones and disrupt normal hormone levels and human fertility, when the concentrations reach a certain level. This pollutant is easy to accumulate within the food chain and even has potential risks on the ecological environment and for biodiversity. Many kinds of compounds,

including pharmaceuticals, polychlorinated biphenyls (PCBs), polybrominated diethyl ethers (PBDEs), Di (2-ethylhexyl) phthalates (DEHP), alkylphenols, pesticides, and plasticizers, are deemed to possess the ability to disrupt the endocrine regulation. These endocrine disruptions can cause human and other biology diseases such as cancerous tumors, congenital defects, and other diseases that have not been thoroughly researched [3]. 17-Alpha ethinylestradiol and heavy metals including Pb, Hg, and Cd, are also suspected of endocrine disruptors, which have been thought to either promote or inhibit the biosynthesis of progesterone and crucial metabolic intermediate in the production of other endogenous steroids [4–6]. Some of the suspected EDCs are persistent organic pollutants, including abundant halogenated organic compounds, which can be transported a long way far away from their source and exhibit accumulation performances in the fatty tissues of living organisms for long periods of time and virtually allow the contaminant to be eliminated more slowly.

So, it is time to attach great importance to the EDC pollution and the most promising tools for EDCs treatment are biotechnology and co-treatment by biological-nanomaterials which are called nano-biotechnology.

White rot fungi (WRF) are efficiently capable of degrading lignin and a majority of lignin structure analogs. This occurs via unique extracellular oxidative enzyme systems with a low substrate specificity, and intracellular enzyme systems [7,8]. This micro-organism is related to biogeochemical cycling of metals and carbon in the course of biomineralization and biodegradation. Their high tolerance protects them from high-level concentrations of organic pollutants and heavy metals so that their enzyme system could function normally in harsh environments [9]. The WRF has also been referred to “externalized stomachs” that secrete hydrolytic enzymes and organic acids into the extracellular conditions and transports metabolites and chelates pass through the cell wall. The high removal efficiency of the contaminant is also owing to their extracellular and intracellular enzyme system (Figure 1): (i) CYP450 monooxygenases is an essential part of the intracellular enzyme systems, which could use molecular oxygen as the terminal electron acceptor, (ii) Laccase (Lac), coupled with both electron donating functional groups and electron withdrawing functional groups, is one of the most efficient extracellular non-specific oxidative enzymes besides lignin peroxidase [10], and (iii) superoxide dismutase (SOD) and glucose oxidase, has the ability to degrade lignin cooperating with the WRF enzyme but does not function alone [11]. In general, the EDCs degraded by WRF can pass through two phases so that the one reaction is adding the functional group to the reactants oxidized by intracellular cytochrome P-450 monooxygenase, by groups such as hydroxyl, carboxyl, or an amine group. The phase II reaction is conjugating the sulfates, glucuronides, glucosides, or glutathione (GSH) to the metabolism product by non-specific extracellular oxidizing agents, which

have been reported to exhibit distinct advantage to protect cells against the toxic effects of  $H_2O_2$  [12]. This type of fungus also possesses excellent and efficient performances for heavy metal recovery, via the mechanisms involving (i) the biosynthesis of phytochelatin (PCs) and metallothioneins (MTs) in cells; (ii) phosphate and polyphosphate metabolism; (iii) transformation of heavy metal complexes into vacuoles, chloroplasts, and mitochondria; and (iv) chelation with malate and oxalate [1]. Among all kinds of WRF, *Phanerochaete chrysosporium* is an appropriate species due to its essential intracellular hyper bioaccumulation capacity for removing organic contaminants and recovering heavy metals pollutants [13,14]. Tien and Kirk [15] characterized that the *P. chrysosporium* could degrade DDT, lindane, PCBs, dioxins and benzo[a]pyrene. Recently, extensive research has been reported for its highly efficient biotransformation and inner mechanism for a variety of pollutants by *P. chrysosporium* [16]. So these fungi became the first species to have their complete genome sequenced [17].

With industrial development, allied with pollution, especially heavy metals and organic pollutants, this has become the most closely linked factor to people's livelihood that needs to be addressed. Therefore, co-removal technology of these complicated harmful substances has attracted increasing concern to the public [18–20]. Studies showed that adding a certain concentration of heavy metals may generate a force like a “bridge” to facilitate the synergistic removal of antibiotics, but some details were not clear [21]. Generally, a combined pollution is more severe and more difficult than the remediation of unitary traditional contaminants according to circumstantial evidences [22].

Nowadays, nanomaterials, such as iron-based nanomaterials and photocatalytic nanomaterials, have been widely used to remove various pollutants from water and soil [23,24]. Nanoparticles possess some ideal properties such as (i) near identical strength, which provides

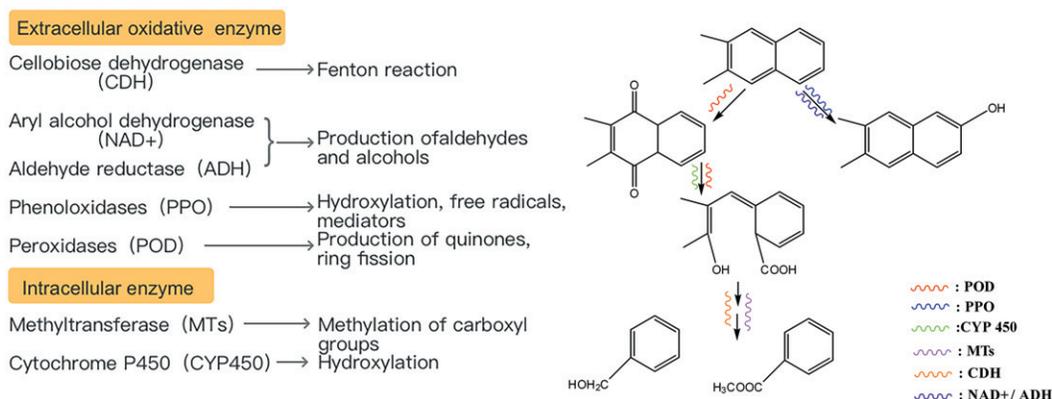


Figure 1. Function of extracellular and intracellular enzyme systems of WRF.

the high tolerance of crushing, (ii) active surfaces, which are benefit to catalytic reactions, (iii) discrete energy levels, which could generate numerous crucial tailoring of electronic properties [25]. These superior properties could contribute to the application prospects of nano-materials. One of the most promising methods is WRF-nanoparticle joint technology which is also called nano-biotechnology. Among them, silver nanoparticles, selenium nanoparticles, and titanium oxide nanoparticles cause extensive concerns for scientists.

This review presents an overview on what is known about the biotransformation of endocrine-disrupting compounds, suspected EDCs, which has not previously been systematically reviewed, by WRF. This study not only focuses on the pollutants' removal behavior but also raises the horizon to the toxicology of microbial systems such as the toxic effects and resistance mechanism. The overall objective brings forward a further novel situation that eliminates the heavy metal-antibiotic compound system by biotechnology, and focuses on the trends in WRF technology and its related to the advanced application – nano-biotechnology.

### Biotransformation of single endocrine-disrupting compounds by white rot fungi

Simulating single pollutants in the laboratory is an essential approach for scientific research. It is also important to make transformation products (TPs) of original environmental contaminants clear because it can help identification of the biotransformation processes and intrinsic reaction mechanisms. Therefore, people could choose the most reasonable treatment method for industrial processes [26]. Currently, the most concerned EDCs, including suspected EDCs, are PCBs, non-ylphenol (NP), sulfonamide antibiotics (SAs), and heavy metals. Despite the mechanisms that degrade the EDCs are not fully understood, some authors have documented that the main biotransformation processes are hydroxylation, dehydroxylation, O-methylation, O-demethylation, glycosylation, deglycosylation, dehydrogenation, hydrogenation, C ring cleavage of the benzo- $\gamma$ -pyrone system, cyclization, and carbonyl

reduction [27]. In addition, some studies have explored the biotransformation of EDCs by genetic analysis. Results showed that genes encoding lytic polysaccharide monoxygenases (LPMOs) were found in WRF. There are three kinds of extracellular electron sources for LPMOs: cellobiose dehydrogenase (CDH), phenols procured by fungi, and glucose-methanol-choline oxidoreductases, which play an important part in EDCs degradation [28].

### Identified endocrine-disrupting compounds biotransformation

#### Mineralization of polychlorinated biphenyls by white rot fungi

PCB, a kind of EDCs (notably blocking thyroid system functioning), is an organic chlorine compound with the formula  $C_{12}H_{10-x}Cl_x$ , which has serious environmental toxicity and can cause cancer. With development of the industry, this chemical had a wide range of applications because of its own thermal and chemical stability, flame resistance and dielectric properties, while the detriment of it was spread all over the world due to the accidental discharge and/or improper methods of control (Table 1). Although the production of PCBs was expressly prohibited by many countries in the late of twentieth century, the concentration of PCBs still kept high levels in many areas. Moreover, the carcinogenesis, tetratogenesis and endocrine disrupting effects of them also threaten the health of public seriously [29]. Therefore, the way to remove it still needs to be aroused extensively in the international community.

Owing to the striking non-specific degradation performance of WRF, it was selected from numerous Basidiomycota phylum microorganisms as a candidate to degrade technical mixture of PCBs and single PCB congeners in a laboratory long time ago. As expected, *P. chrysosporium* was first reported to possess the capacity to degrade PCB pollutants amongst every kind of white rot fungi [38–41]. It was reported that the mineralization ability of PCBs always decreases with an

**Table 1.** Major events of polychlorinated biphenyls pollution.

Location	Time	Incident Intro	References
United States	1954–1982	100,000 tons of PCBs released in the Lakes. Sludge contained PCBs as high as 50%	[30]
Slovenia	1962–1983	PCBs were found in food and Krupa is still the most PCB-polluted river in the world	[31]
Japan	1968–1978	A mixture of dioxins and PCBs entered rice bran oil and cumulatively killed 1684 people	[32]
United Kingdom	1970	The PCBs manufactured by Monsanto were dumped at a disused quarry	[33]
Belgium	1999	Chicken fat exceeded 1500 times. Over 9 million chickens and 60,000 pigs were destroyed	[34]
Italy	2001	The PCB levels of the adult population were 10–20 times higher than reference values	[35]
Brazil	2013	Polychlorinated biphenyls (PCBs) were classified as carcinogenic to humans by the IARC	[36]
China	2016	China has manufactured about 10,000 tons of PCB products in two major categories: printing ink and transformer oil.	[37]

increase in the degree of chlorine but was independent of the position of chlorine [42].

Cameron and Aust [43] once illustrated that hydroxyl radicals were shown to dechlorinate chloro-organic pollutants, which was generated by the oxidizing reaction of oxalate to carboxylate anion radical ( $\text{CO}_2^{\bullet-}$ ), stimulated by CDH. The intracellular cytochrome P450 enzymes, which was always involved in the epoxidation reaction of C=C double bonds and hydroxylation reaction of aromatic compounds, is another important part of the PCBs degradation system [44]. The first step of the degradation reaction of PCBs by WRF was suspected of generating hydroxylated PCBs [40]. Subsequently, the oxidative dechlorination reacts on the metabolite of PCBs by Lac and the reductive reaction with the carboxyl group which stimulates the generation of chlorinated aldehydes and alcohols followed behind oxidative dechlorination (Figure 2). Fujihira et al. [45] elucidated that as the number of chlorine substituents becomes larger, the degradation efficiency of OH-PCB by WRF will decrease. On the contrary, the ionization potential of the molecules could stimulate the degradation performance.

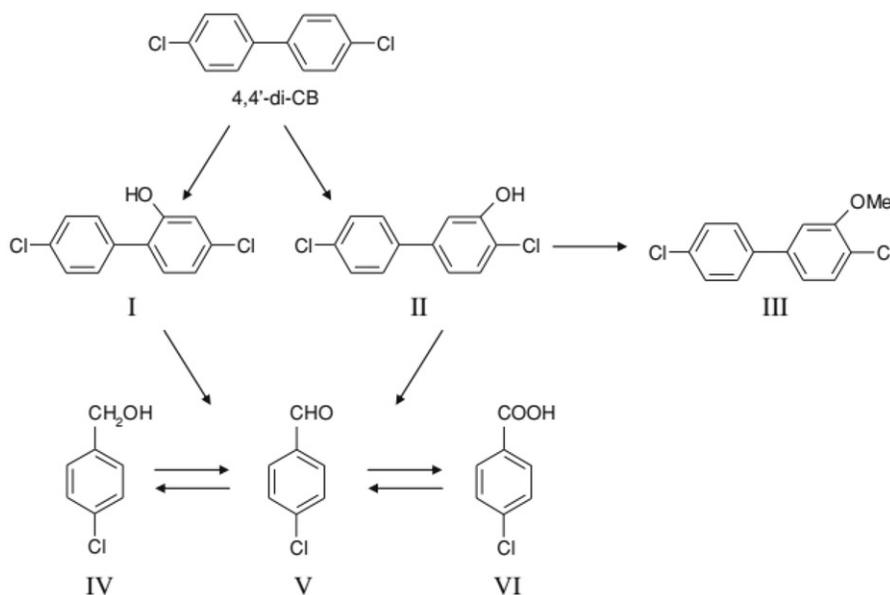
Cvancarova et al. [46] illustrated that *P. chrysosporium* was found that it decomposes 60–70% of PCBs in malt extract-glucose and low-nitrogen mineral media. They also detected the TPs of PCBs by GC-MS, which stimulates, with cytochrome P-450 monooxygenases and methyltransferase system, reactions. The degradation products are mainly methoxy and hydroxy ramifications including CBAs, chlorinated benzaldehydes and chlorinated alcohols.

### Biodegradation of nonylphenol by white rot fungi

NP, a kind of usual alkylphenols which possess strongly endocrine-disrupting activities, can be detected easily in the environment because of the widely use of its original compound nonylphenol ethoxylate in industrial, commercial and household applications [47]. Therefore, NP was easily found in many kinds of aquatic environments even contained in drinking water all over the world. What is more, the concentration of NP is at an obvious level in both plasma and urine of weavers and household service workers [48]. Scientist reported that NP reacts with substances in living organisms according to the imitation of hormone 17- $\beta$ -estradiol, so that this compound could cause abnormal expression of males and their reproductive systems [49,50].

There are many methods have been used to alleviate pollution of NPs such as UV treatment, ozonation, electrochemical degradation, Fenton treatment, and filtration techniques [51]. However, some drawbacks existed in the aforementioned technologies: (i) the expensive infrastructure requirements at incipient stage and operating process and (ii) the generation of toxic intermediate products during degradation process [52,53]. The treatment methods for microorganisms, especially WRF, are an alternative way to curb NPs pollution.

Subramanian et al. [54] showed that NP at a concentration of 100 ppm was degraded completely in both nutrient-limited cultures (LN) and nutrient-sufficient cultures (ME) by *P. chrysosporium*. Furthermore the results indicated that negligible abiotic degradation and mycelial adsorption of NP during this process by comparing

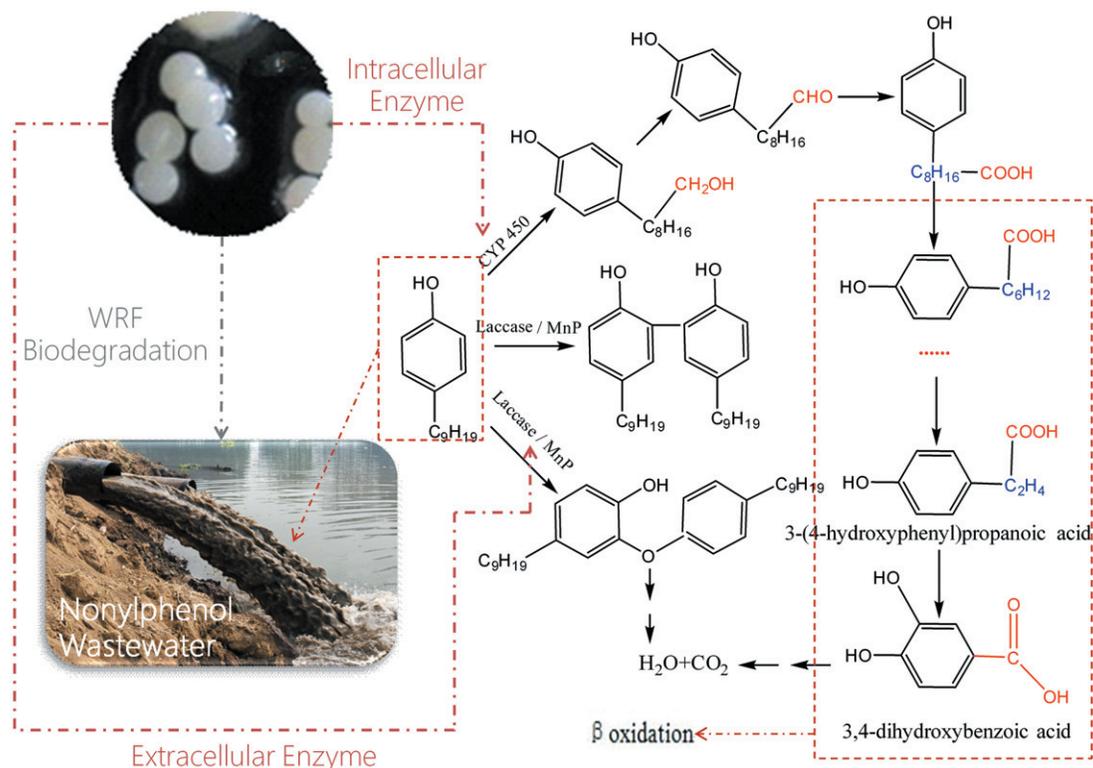


**Figure 2.** Transformation processes of 4,4'-dichlorobiphenyl (4,4'-di-CBP) by *P. Phanerochaete* [40]. Symbols: I: 2-hydroxy-4,4'-dichlorobiphenyl, II: 3-hydroxy-4,4'-dichlorobiphenyl, III: 3-methoxy-4,4'-dichlorobiphenyl, IV: 4-chlorobenzyl alcohol, V: 4-chlorobenzaldehyde, VI: 4-chlorobenzoic acid.

with the uninoculated controls and chemically killed controls. Ting et al. [55] found the addition of NPs could inhibit the activity of Lac in WRF while adding  $\text{CuSO}_4$ , citric acid, gallic acid, tartaric acid, veratryl alcohol, guaiacol could relieve this symptom. The experimental results from García-Morales showed that the biotransformation percentage of NPs was  $93 \pm 2.93\%$  after 6 h treatment by a Lac cocktail (a filtered culture supernatant of WRF) [56]. Méndez-Hernández et al. [57] placed WRF into a two-stage membrane bioreactor to remove NP in wastewater. After 20 min treatment, the biodegradation percentage of NP achieved to 99.5% at an initial concentration of  $454 \text{ nmol L}^{-1}$ . Huang et al. [58] used the composting pathway to bioremove 4-nonylphenol (4-NP) in river sediments by inoculating the *P. chrysosporium*. The result showed that the *P. chrysosporium* inoculation could increase the activity of catalase (CAT) and polyphenol oxidase of compost, and promote the degradation process of 4-NP.

Wang et al. [59] illustrated that the main approach (Figure 3) to degrade NPs by WRF is caused by breakage of C–C and C–H bonds. Moreover, Syed et al. [60] proposed the oxidation of the terminal ( $\omega$ -) alkyl chain which could form aldehyde and hydroxy instead of epoxide, catalyzed by P-450, also make contributions to the metabolic pathway of NPs. Scientists also suggested that the oxidation reaction of the terminal alkyl chain is always followed by removing of the terminal carbons

via the  $\beta$ -oxidation pathway. Apart from the terminal chemical groups reaction, Krupinski et al. [61] illustrated that through a sequence of oxidizing reactions, NPs were degraded to the corresponding carboxylic acids, then exploded to a lower carbon aliphatic chain and finally became 4-hydroxybenzoic acid or carbon dioxide and water. At the genetic level, genome-wide gene technology can be used to reveal various P450s and other peroxidase response behaviors by different kinds of xenobiotics in WRF. The microarray data showed that NP differentially induced several P450 genes in *P. chrysosporium* and their induction levels are significantly affected by the nutritional conditions. The results indicated that 18 genes were induced under ME conditions and 17 genes were induced in LN cultures in NP degradation. The P450 genes Pff 311 b (protein ID 5852) and Pff 4a (protein ID 5001) showed extraordinarily high levels of induction and the P450 oxidoreductase, glutathione S-transferase (GST), and cellulose metabolism genes were also induced in ME cultures [54]. In addition, lignin-degrading enzyme genes (LiP/MnP) were mutated under the conditions of high levels of xenobiotic compounds. According to hybridization signals, LiP genes were downregulated in the presence of NP and MnP genes were expressed at higher levels in LN cultures [62]. Despite a few inhibitory effects of some components on the ligninolytic metabolic machinery, NP addition did not seem to affect the overall



**Figure 3.** Main approach to degrade nonylphenol and its intermediate products by white rot fungi.

NP-degrading potential of the fungus and the biodegradation efficiency of NP by WRF is still considerable. Furthermore, Syed and Porollo [14] found that replacing Trp<sup>129</sup> with Leu and Phe and replacing Leu<sup>324</sup> with Gly apparently inhibited the oxidation of NPs. The results indicated that Trp<sup>129</sup> and Leu<sup>324</sup> in P450 monooxygenases of WRF play an essential part in substrate recognition and regio-selective oxidation of NP. This discovery could improve strategies using P450-based biocatalysts for the biotechnological of WRF.

### **Suspected endocrine-disrupting compounds bioaccumulation**

#### ***Detoxification and elimination of sulfonamide antibiotics by white rot fungi***

In the middle of the twentieth century which has been called the “antibiotic era”, the antibacterial agents have been utilized all over the world to protect humans against life-threatening infections successfully and efficiently [63]. At the beginning of the twenty-first century, antibiotics were also mainly used in human and veterinary medicine, with an estimated annual consumption of 100,000–200,000 t [64]. Nowadays, this pharmaceutical is still a serious problem and puzzled us because the practices showed that antibiotics have not been completely metabolized in medicated animals for a long time and have been found the potential adverse effects to humans [65,66]. Sulfanilamide, a group of pervasive and widely applicable antibiotics including furosemide, sulfadiazine and sulfamethoxazole, were firstly clarified by GJP Domagk in 1939 which resulted with him becoming the winner of the Nobel Prize. Following that accolade, Hitchings set his sight on the side-effects of SAs during the development of diuretics and antidiabetogenic agents. Evidence showed that the half-life of SAs is 9.6–833 d; therefore, the time duration of them is too long in water and the sediment of the environment [67–69]. SAs residues are too difficult to remove by conventional wastewater treatment facilities so that they were detected in the sludge of most wastewater treatment plants [70,71]. These organisms, which equip 6-membered heterocyclic rings, were classified as sulfadimethoxine (SDM), sulfapyridine (SPY), sulfathiazole (STZ), sulfamethoxazole (SMX), and so on [72]. They always exhibit high performance to inhibit the enzymatic reaction in bacteria via deferring the synthesis of para-aminobenzoic acid which was the coenzyme influence on the production of purines and pyrimidines.

There are some bacterial and chemical treatment methods, including ozonation, photolysis and photocatalysis, capable of degrading SAs [73–75].

However, the chemical materials treatment always leads to secondary pollution and bacteria will inhibit the pollutant bioremoval in the SAs degradation because of its own production free-hydroxyl phenolic compounds [76]. The OH-SAs have been known as inhibitors for many kinds of organism degradation so that decreasing the production concentration of it in transport processes is essential for the degradation of efficiency. Recently the discovery of O-methyltransferases in WRF, which can accelerate SAs degradation by converting these inhibitors into non-toxic methylated phenolic ones, inspires the academic community [77]. Accordingly, researchers move their horizon to the degradation of the SAs by WRF and suggest that they could make a contribution to degrade antibiotics efficiently.

The reactions catalyzed by Lac alone always couples with high redox potentials which may inhibit the rate of the degradation reaction. So that researchers attempted to combine the WRF-Lac system with some redox mediators such as ABTS and violuric acid (VLA) what we call the mediator system [78]. Recent experiments have illustrated that the Lac-mediator system (LMS) can effectively degrade several antibiotics such as tetracyclines, sulfonamides, and fluoroquinolones also meant that WRF, producing Lac in high yield, have high ability to degrade SAs [79,80]. Rodríguez and García-Galán [72] also make a point of adding purified Lac and Lac-mediators in the pollution system can promote the degrading efficiency to 75%, while the desulfonation rate will move to 94% cooperating with WRF-fluidized bed system. Statistical analysis by the Microtox Analyzer toxicity test showed that adding VLA into medium could reduce the toxicity during the oxidation reaction of SAs by Lac and the detoxifying effect is higher than any other mediators [81]. Not only the degradation efficiency but also the degradation times were remarkably increased. SAs in water and sediment in the dark had  $t_{1/2s}$  of 9.6–833 d [82]. While the  $t_{1/2s}$  of SAs treated with Lac alone is 2.6–96.7 d and the  $t_{1/2s}$  of SAs in LMS is 1.8–131 min. The main reasons for effective oxidation of LMS are an electron transfer route and their high redox potentials. Data showed that the redox potential of Lac oxidation activity is in a range of 0.5–0.8 V which is not high enough to oxidize SAs which possesses 0.858–1.158 V redox potentials. However, the redox potential is increased to 0.68–1.09 V after adding mediators VLA and ABTS in LMS so that the biodegradation ability of SAs can be greatly improved [83,84]. Accordingly, LMS is not a universal method which includes two aspects of limitations: (i) the redox potentials of xenobiotics must be within certain limits; and (ii) different mediators make large differences in LMS

degradation efficiency therefore further studies still need to explore the widespread application of LMS.

In WRF cultures, seven different TPs were found by the SPY degradation processes after 48 h according to the different retention time. Apart from enzymatic desulfonated reaction and hydroxylation, the glycosylated adduct (N4-glycosyl-SPY) was also detected. Similarly, another five signals can be discovered which represents five kinds of organic TPs, produced by hydroxylation, cyclization decarboxylation reactions and oxidative coupling, in the chromatogram of STZ degradation (Figure 4). The difference is STZ which was not fully degraded after 96 h by WRF.

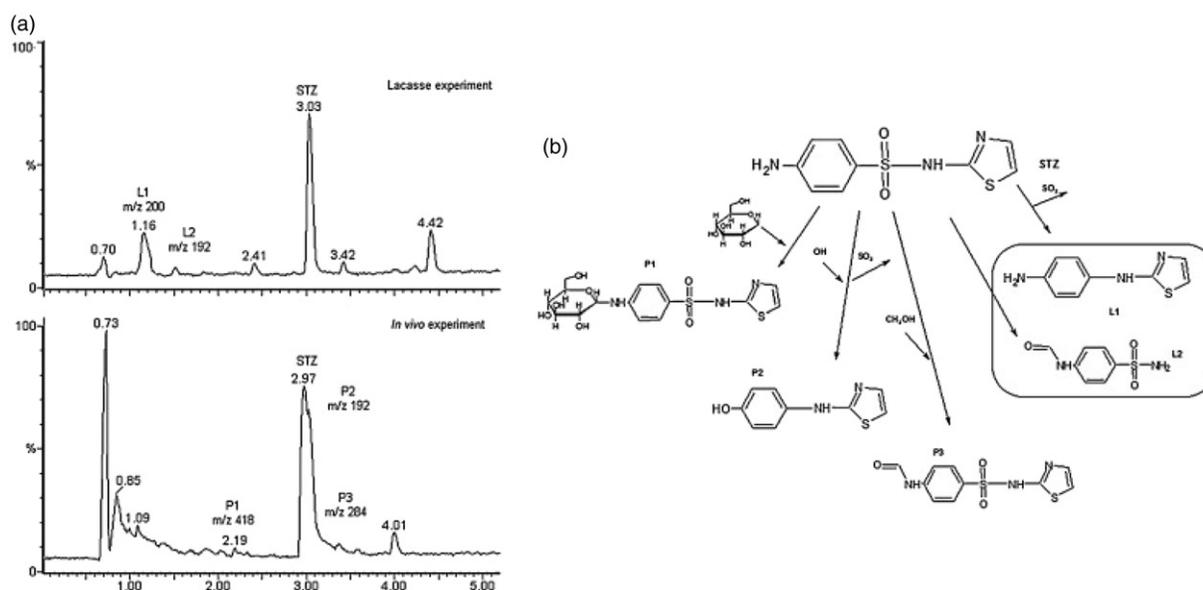
As regard degradation of sulfamethoxazole (SMX), researchers indicated that apart from cytochrome P450, a typical enzyme involved in hydroxylation reactions to produce OH-SMX, N-arylamine acetyltransferase are another crucial active protein in SAs bioremoval processes which can catalyze SMX to N4-acetyl sulfamethoxazole (Ac-SMX) [85]. Due to the O-methyltransferases, heterologous expression in WRF, the WRF-Lac system can decrease the production of HO-SMX which has been known as more recalcitrant than a contaminant than SMX and an inhibitor for the degradation processes in the environment [76]. WRF was also considered as having high tolerance in the concentration range of 10–30 mg L<sup>-1</sup> and a high efficiency for SMX degradation. Data also showed that the Lac activity is higher in the SMX culture medium than in a blank controlled group [86]. Therefore, the WRF-Lac system is more appropriate and a sustainable way for SMX treatment.

In conclusion, degradation of SAs by WRF has its own obvious advantages and applying this method in contamination treatment has good potential. It is also necessary to explore WRF individually or by a combine mechanism which can help to eliminate the secondary pollution production such as hydroxylated SAs and to promote the degradation efficiency.

### Immobilization of heavy metals by white rot fungi

What are commonly called “heavy metals” is defined as extensive toxic metals, for instance Pb, Cd, and Hg [87,88]. These metals, named non-essential heavy metals as well, are highly toxic and cause numerous symptoms and pathologies, such as neurological effects and endocrine dyscrasia [89]. Among these, cadmium (Cd) is the most common pollutant which can enrich easily in the food chain and dissolve readily in water so that it is listed as a chief pollutant by the US Environmental Protection Agency (EPA) [90,91]. Heavy metals bioaccumulated *in vivo* could induce several kinds of damages by thiol-binding, protein denaturation, displacement of essential metals, and side effect of oxidative stress [92]. Some heavy metals are reported that can impair reproductive organs including degeneration, necrosis, inflammation, edema, etc. [93]. After that, Choe et al. [94] illustrated that antimony, barium, and chromium may disrupt the balance of hormone in the organism.

The reactions of heavy metal bioaccumulation can be divided into several steps: (i) adsorbed heavy metal by plasma membrane transporters which involved in



**Figure 4.** Total ion chromatogram (TIC) in STZ degradation processes after 8 h response time (a) and the primary transformation products (b) [72].

the movement of ions, small molecules, or macromolecules; (ii) increased activities of plasma membrane sulfate transporters, metal ion plasma membrane transporters, ATP sulfurylase, adenosine 5'-phosphosulfate reductase (APSR), and  $\gamma$ -glutamylcysteine synthetase ( $\gamma$ -ECS) based on increasing gene transcription; (iii) improved activities of PCs synthase induced by heavy metal; (iv) bio-transferred metal-GSH and metal-PCs chelates into vacuoles and other organelles; and (v) synthesized Metal High Molecular Weight Complexes in cytosol or inside organelles [95].

It is generally known that GSH and some low molecular weight sulfur-containing peptides, derived from GSH, are two main chelating agents for heavy metals intracellular biotransformation. GSH is an antioxidant tripeptide which is rich in cellular sulfhydryl. It could also prevent damage to the oxidizing stress induced by reactive oxygen species (ROS) including free radicals, lipid peroxides, peroxides, and heavy metals in a variety of ways [96]. Metal sequestration and antioxidant response are the major ways and mechanisms involved in metal resistance systems by fungi [97]. GSH can react with Cd to form a kind of chelate cadmium-bis-glutathionate ( $\text{Cd-GS}_2$ ), which has two characteristic structures: (i) thiol groups can react with  $\text{Cd}^{2+}$  but amino groups cannot; (ii)  $\gamma$ -Glu residue is not related to the formation of the metal-hydro sulfonyl chelate [98].

Apart from GSH, PCs is another one of the greatest chelation polymers induced by  $\text{Cd}^{2+}$  stress. PCs are some kind of small cysteine-rich peptides which have 2–11 repeats of a dimeric amino acid. Because of the character of the thiol-rich structure, they could bind with different heavy metals and reduce their toxicity by separation [99]. Studies reported that synthesis of the PCs are related to a kind of individual dipeptidyl transferase from GSH and the vacuolar serine carboxypeptidases can also be responsible for it [100,101]. Schneider et al. [102] found that the subunits of the vacuolar  $\text{H}^+$ -ATPase V1 sector (a kind of enzyme can transport the conjugated phytochelatin-heavy metal compound into the vacuole) were significantly upregulated when *P. chrysosporium* was induced by Cu after 8 h. The two steps that compartmentalized and stored metal-PCs chelates is an important process to promote the resistance mechanisms of heavy metals [103]. The formation of the Cd-PCs chelate and their biotransformation are obviously another integrant intermediate step in the cellular detoxification reaction induced by heavy metals. *In vitro* experiments showed that one  $\text{PC}_2$  molecule could generate four bonds in the combined reaction of  $\text{Cd}^{2+}$  through oxygen and sulfur interactions [104].

Previous studies found that adding the Zn element with from the external source will promote the

synthesis of Cd-PCs and Cd-MTs, while it could also accelerate the transfer of Cd to move this pollutant into the vacuole and reduce the toxicity of microorganisms. The related reason is that Zn from an external source increases the activity of SOD, CAT, peroxidase, and ascorbate peroxidase in fungi with Cd stress. Therefore, the content of malondialdehyde and proline were decreased which indicated that the membrane lipid peroxidation symptom and the toxicity of Cd was relieved [105]. However, other experimental data showed that Zn promoted Cd absorption meanwhile enhancing the Cd toxic reaction. This difference depends on the concentration ratio of Cd and Zn. Wang et al. [106] considered that adding Zn into the system with low concentrations of Cd will accelerate the biotransformation of Cd by microorganisms. Under the low concentration conditions of Cd ( $2.5 \text{ mg kg}^{-1}$ ), the adsorption of Cd increased with the addition of Zn. The results are reversed at high concentrations of Cd ( $5 \text{ mg kg}^{-1}$ ). These results are essential for us to realize how the extraneous Zn can be used in the biotransformation of Cd. Evidence showed that the coexpression of phytochelatin synthase in the cells may produce the CdSe quantum dot in the inocula with  $\text{Cd}^{2+}$  and  $\text{Se}^{+}$  [107]. These reactions or affections of metal-metal and metal-non-metal are another important way to relieve heavy metal physiological and biochemical toxicity.

Similar to PCs, MTs were other important thiol-rich peptides, which can motivate the metal accumulation capacity of WRF by synthesizing metallo-chelate in different cell compartments [108,109]. The structure of MTs consists of many kinds of small sized ( $< 7 \text{ kDa}$ ) cysteine rich proteins, which could provide more binding sites of heavy metals in microorganisms [110]. There exist two domains in MTs: (i)  $\alpha$ -domain containing 11 cysteine residues could react with four  $\text{Cd}^{2+}$ , four  $\text{Zn}^{2+}$  or six  $\text{Cu}^+$  ions, and (ii)  $\beta$ -domain including nine cysteine residues could segregate three  $\text{Cd}^{2+}$ , three  $\text{Zn}^{2+}$ , or six  $\text{Cu}^+$  ions [111]. Das et al. [112] illustrated that the concentration of metallothionein protein obviously revealed higher level induced by heavy metals. It means that MTs are related to heavy metal tolerance metal homeostasis and oxidative stress along with numerous cellular functions. It also can make fungi survive well in the conditions of high heavy metal concentration.

### Biotransformation of combined endocrine-disrupting compounds by white rot fungi

A successful technology must be applied in the actual production process and close to people's life. Therefore, especially heavy metals, combine with organic

pollutants, is becoming more serious than traditional contaminants.

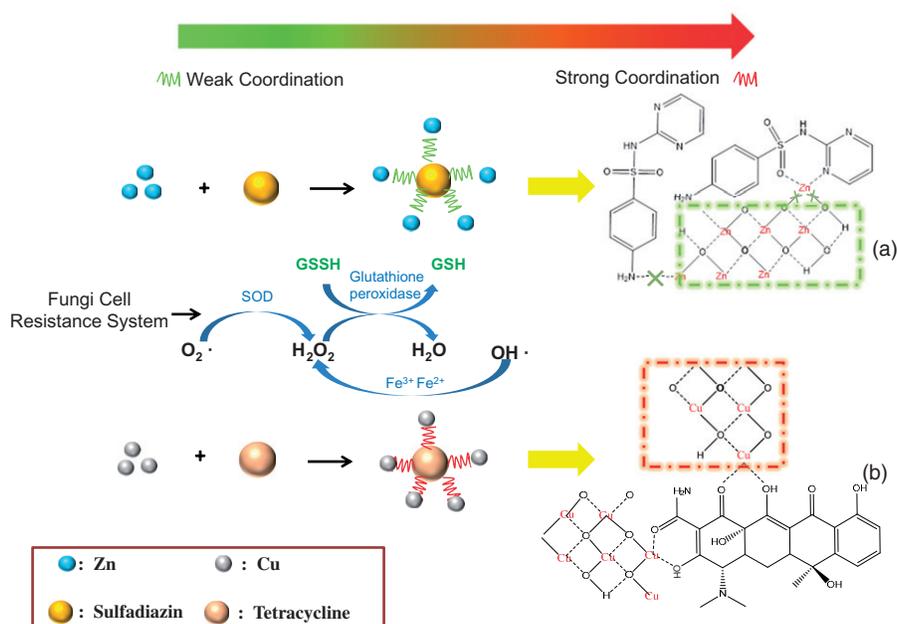
Berg and Thorsen [22] investigated the selective driving force of Cu for the transmission of antibiotic resistance in soil. At the same time, they first monitored the microbial communities and the results showed that exposing to high concentrations of Cu can not only select Cu-tolerant microbial communities but also co-select the microorganisms which have high tolerance to tetracycline and vancomycin. A theory has been enunciated that some kinds of metals could react with heavy metals as a “bridge” to facilitate the synergistic removal efficiency of antibiotics. They used the dialysis equilibrium technique to analyze the different effects and the phenomenon of dissolved organic matter-ofloxacin (DOM-OFL) by  $\text{Cu}^{2+}$  and  $\text{Mg}^{2+}$  and the result showed that  $\text{Cu}^{2+}$  could increase the removal of DOM-OFL while  $\text{Mg}^{2+}$  did not [21]. Yang and Jia [18] studied two types of combined pollution Cu-tetracycline and Zn-sulfadiazine (Figure 5). The result showed that adding a certain concentration of  $\text{Cu}^{2+}$  could promote the removal of coexisted antibiotic molecules but  $\text{Zn}^{2+}$  did not lead to the same phenomenon, because the bond force of Zn-sulfadiazine is too weak. Pan et al. [113] presented the bond between N atom and Zn atom seated in the pyridine ring of Zn-SDZ combined pollutant is not as stable as which occurs between oxygen tom and Cu in Cu-tetracycline combined pollutant.

Very few scientists until now have studied the bio-transformation of the metal-antibiotic compound contaminant by WRF. But from what has been discussed above, WRF does not have the ability to degrade organic pollutants including antibiotics but also can bio-remove the heavy metal pollution efficiently. This review concludes that it could be a feasible solution to improve serious situation of metal-antibiotic compound systems. It is high time to explore the bio-removal pathway of combined pollution by a kind of high-effectively fungal species WRF.

### Toxicity induced by endocrine-disrupting compounds of white rot fungi and their adaptive mechanisms

#### Reactive oxygen species toxicity and resistance mechanisms induced by endocrine-disrupting compounds of white rot fungi

Several kinds of EDCs, especially heavy metals, could inhibit enzyme activities, such as LiP and MnP, by chelating the substrate and interacting with protein-active radical of enzymes [114]. The oxidative stress will be generated induced by various heavy metals especially Pb and Cd in WRF. However, during short-time adaptation, a thorough oxidant-antioxidant system, including antioxidant enzyme and non-enzymatic scavengers, will be established in the cell of the micro-organism [115].



**Figure 5.** Schematic illustration of the role (weak coordination and strong coordination) of heavy metals in antibiotics' removal in (a) Zn (II)-SDZ and (b) Cu (II)-TC systems.

ROS is always seen just like an initiator of an antioxidative defense system and the most common ones of them are superoxide ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), and the hydroxyl radical ( $\bullet OH$ ). These species can make living organisms, including fungi, secrete several kinds of intracellular antioxidase (SOD, CAT, GSH peroxidase, GSH reductase) and non-enzymatic antioxidants (ascorbic acid, GSH, MTs, carotenoids, etc.). It has been published that the concentration of  $O_2^{\bullet -}$  would rise if  $Pb^{2+}$  was added into the culture medium of *P. chrysosporium*. After that, rapid generation of  $O_2^{\bullet -}$  could increase the concentration of  $\bullet OH$  by the Fenton and Haber-Weiss reactions [116]. In the iron-catalyzed Haber-Weiss reaction,  $O_2^{\bullet -}$  could reduce the concentration of  $Fe^{3+}$  to  $Fe^{2+}$  to increase the production of  $\bullet OH$ . During the pathway of the Fenton reaction, increasing one of the products:  $O_2^{\bullet -}$  ( $H_2O_2 + Fe^{3+} \rightarrow Fe^{2+} + O_2 + 2H^+$ ,  $O_2 + Fe^{3+} \rightarrow Fe^{2+} + O_2^{\bullet -}$ ) would promote the generation of another product:  $\bullet H$  ( $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^\bullet$ ) [117].

Because of this, the concentration of ROS remains at a high level in the preliminary stage induced by heavy metals. But the long-term effects of the antioxidative enzyme system, ROS will finally be converted to oxygen and water to relieve the damage to the microorganism [118]. Evidences showed that WRF could keep a balance between oxidation and antioxidation in cells.

### **DNA damage toxicity induced by endocrine-disrupting compounds and the repair pathway of white rot fungi**

Besides ultraviolet light, ionizing radiation, and thermal disruption, Erill et al. [119] and Godon et al. [120] illustrated that the oxidation and alkylation induced by EDCs, especially antibiotic and heavy metals also have the ability to cause DNA damage. There are two types of methods in DNA repair: nucleotide excision repair and base excision repair pathway which was demonstrated by Tomas Lindahl et al. Apart of these, Hakem [121] classified the DNA repair methods into six types in detail: (i) the direct reversal pathway, (ii) the mismatch repair (MMR) pathway, (iii) the nucleotide excision repair (NER) pathway, (iv) the base excision repair (BER) pathway, (v) the homologous recombination (HR) pathway, and (vi) the non-homologous end joining (NHEJ) pathway.

Hakem et al. [121] found that firstly the glycosylases including Ogg1 (8-oxoguanine DNA glycosylase) and Myh (mutyh DNA glycosylase) can be used to obliterate damaged portion which was followed by strand incision of the apurinic or apurimidinic site by the endonuclease APE1, and finally a new crevice was filled by DNA

polymerase-b (Pol b) in the BER pathway [121]. Shen et al. [122] identified the GST genes from fungi which could increase the antioxidizing capacity against the oxidative stress of heavy metals. Jin and Robertson [123] proposed the DNA methyltransferase (DNMT) 1 and the neotype methyltransferases DNMT3A and DNMT3B, which can transfer the methyl group from S-adenosyl-l-methionine to the 5-position of cytosine residues. All are necessary to maintain the balance of the genome in microorganisms and other creatures. Martejn [124] demonstrated that the NER pathway based on cdk-activating kinase (CAK) and RNA polymerase II include two patterns: (i) global genome-NER: avoiding generation of gene mutation by monitoring the spiral damage; (ii) transcription coupled-NER: maintaining genetic expression by removing transcription retardation damage. Jasin and Rothstein [125] used a homologous DNA sequence to repair the DNA double-strand breaks (DSBs) and experimental results show that the HR pathway can reduce the probability of gene mutation. Darja Žgur-Bertok [126] proposed that the repair of DNA damage in the microorganism depends largely on the SOS response which has two key proteins: LexA (a repressor) and RecA (an inducer). The SOS error-prone polymerase has the ability to improve the mutation rate and generate the adaptability of antibiotics and other recalcitrant pharmaceutical compounds. Zheng et al. [127] found a mononuclear Fe (II) – containing enzyme for the first time which can oxidatively reverse DNA methylation damage. Luna et al. [128] carried out research with a family of deacylase-Sirtuin, which is also called mono-ADP-ribosyltransferase, and supported that SIRT1 can regulate the genomic stability by arresting the cell cycle and repairing the DNA damage.

In general, research on the gene damage and the influence factor of WRF, induced by EDCs, is essential to find better ways and optimum conditions, which can make a contribution to alleviate the EDCs pollution. It is also beneficial to deeply understand the resistance and reaction mechanisms in micro-organisms.

### **Latest advance of nano-biotechnology: combining white rot fungi with nanomaterials**

Currently, biotechnology is one of the eco-friendliest treatments for the removal of environmental pollutants. However, some problems should not be overlooked, for example: (i) a longer incubation time than the traditional chemical approach, and (ii) the degradation efficiency by microorganisms still has an improved potential. To tackle this situation, we need to exploit innovative methods as well as traditional

biotechnology, such as nanotechnology [129]. Apart from biotechnology, nanotechnology is divided into two types and is another hot issue in environment remediation. The first one is photocatalytic nanomaterials such as graphene oxide, BiOCl nanoparticles and TiO<sub>2</sub> nanoparticles. Other materials are ordinary nanomaterial including silver nanoparticles (AgNPs), selenium nanoparticle, etc. [130–134]. Recent studies have shown that combined with nanoparticles could increase the biotransformation efficiency and reduce the processing times of WRF biotechnology. This study also showed that nanoparticles could be synthesized by microorganisms including WRF. Consequently, this method is called nano-biotechnology [135]. An interesting finding is that the resistance system caused by extraneous pollutants in the cells of micro-organisms is responsible for its nanoparticle synthesis [136,137]. Studies showed that other important contributors for nanoparticle synthesis in fungi are (i) the low molecular peptides such as GSH, MTs, and PCs, and (ii) some enzymes including oxidoreductases, NADH-dependent reductases, NADH-dependent nitrate reductases, and cysteine desulfhydrases.

#### **White rot fungi combining with silver nanoparticles**

Recently, AgNPs are widely used in a variety of areas, such as catalysts, optical sensors, and electronics. Because of their special properties, the composite effect and combining application between AgNPs and microorganisms has received considerable attention.

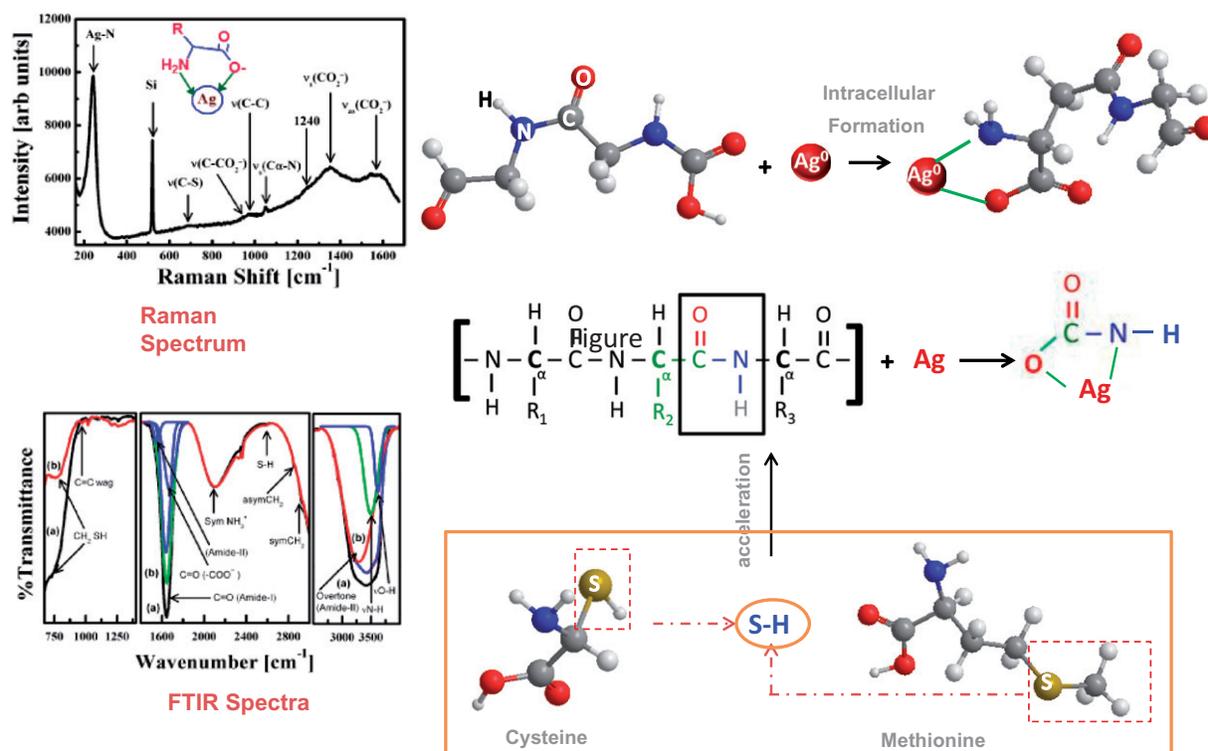
Zuo et al. [138] have researched the concentration variation of Cd under the influence of *P. chrysosporium* while adding AgNPs (hydrodynamic diameter about  $24.3 \pm 0.37$  nm) to promote removal rate and efficiency. Results showed that when the added concentration of AgNPs is in the range 0.1–1 mg/L, bio-removal of Cd<sup>2+</sup> was increased than with separate treatment by WRF. This result proved evidence that nanoparticles exhibited a positive effect on heavy metal biotransformation. The phenomenon that a relatively low concentration of AgNPs could stimulate microorganism activity and found that Guo et al. [139] reported that this rule is also appropriate for WRF, by using the same method. Similar facilitative phenomena also could be noticed by using treatment of microorganisms with AgNPs when the concentration of AgNPs remains at a light stage [140]. This phenomenon may be part of the repair function in fungi cells which could resist or relieve toxicity on the condition of low levels of AgNPs concentration, which is called overcompensatory behavior.

With the improvement of pollutant removal efficiency, the concentration of AgNPs in the WRF cell is increasing. The enrichment course of AgNPs involves two key points: firstly bio-transforming AgNO<sub>3</sub> into AgNPs in fungal cells, and after that, using a matched capping agent to stabilize and encapsulate the chemically active AgNPs. These two steps pave the way to reduce the pollutants efficiently and enhance the stability of some accessory substances which could avoid secondary contamination of the environment. FTIR spectra could illustrate the functional mechanism during the process of AgNPs formation by modifying the wavelength between cell-free extracts and AgNO<sub>3</sub> added extracts. The results revealed that the formation of the C=C double bond could make a contribution to the combination of AgNPs with fungal cells. Furthermore, evidence showed that the sulfhydryl bond is of great importance to nanoparticle reduction reactions, because the number of amino acid with sulfhydryl bonds such as cysteine and methionine was increased in fungi cells. Raman spectrum definitely showed that C=O bonds from the carboxylate ions and Ag–N bonds (Figure 6) of free amine groups are distributing vertically in the surface of AgNPs [141]. These reaction mechanisms may be related to the concentration of Ag<sup>0</sup> increased in fungi cells and the removal efficiency for pollutants improved.

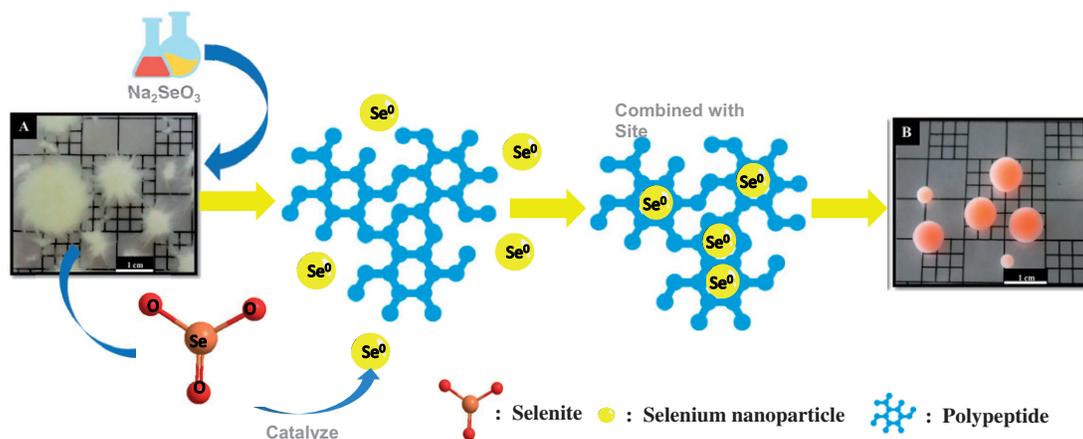
#### **White rot fungi combining with selenium nanoparticle**

Selenium, which has unique semiconducting, photoelectric, and X-ray sensing properties, has been widely applied in several areas such as medicine, chemistry, and electronics. Nowadays, the synthesis of selenium nanoparticles has become a hot topic for researchers. The significant difference between Se nanoparticles and other conventional nanoparticles is that it could not make negative effects for environment and human beings at low concentrations. Therefore, it possesses great application potentials for us to explore.

Recent reports described that Se<sup>0</sup> nanoparticles have greater bioavailability [143]. *P. chrysosporium* could synthesize Se<sup>0</sup> nanoparticles in cells (Figure 7) to alleviate the toxicity of SeO<sub>3</sub><sup>2-</sup> and the synthesis mechanism of Se<sup>0</sup> in WRF may be related to GSH metabolism [144]. Jain et al. [145] considered that removal efficiency of Zn could reach 70% by biogenic elemental selenium nanoparticles (BioSeNPs). Moreover, their further study found that Cu can be preferentially adsorbed from an equimolar mixture including Cu, Cd and Zn by BioSeNPs. This feature of BioSeNPs is beneficial to obtain Cu easily



**Figure 6.** Formation mechanisms of silver nanoparticles based on Macro-Raman spectrum and FTIR spectra analysis by Mukherjee et al. [141] in fungi cell.



**Figure 7.** Characterization of Se nanoparticle synthesis in white rot fungi. Macroscopic image of (a) single fungi pellets and (b) nSe<sup>0</sup>-pellets (adapted from Espinosa-Ortiz et al. [142]).

which is the most extensively utilized heavy metal in industries. Espinosa-Ortiz and Shakya [142] used selenium nanoparticles immobilized in pellets of *P. chrysosporium*. The results showed that fungi containing Se<sup>0</sup> nanoparticles have higher biotransformation efficiency of Zn (88.1 ± 5.3%) than single fungal systems (56.2 ± 2.8%) at pH 4.5 and an initial Zn concentration of 10 mg L<sup>-1</sup>. This appearance enhanced the adsorption capacity of Zn and may depend on a higher

concentration of adsorption sites and a more negative surface charge density.

Although the addition of Se can increase the adsorption property of WRF, mycelial growth and the activity of Lac were declined significantly at higher concentrations of 1000 μM and above. At the genetic level, gene transcript expressions were also concerned. In spite of the measured laccase activity it showed depreciation, the transcript expression showed a significant

upregulation of 2–2.4-fold in Se supplementation of 1000 and 10,000  $\mu\text{M}$ . This different trend between Lac activity and Lac RNA transcripts can be considered as an indication of oxidative stress. The expression advantage conferred by the Lac gene at higher levels of Se is directed towards scavenging  $\text{H}_2\text{O}_2$  and protecting cells from oxidative damage [146]. Besides, the increased Lac gene expression was thought to be correlated to increased levels of glutathione-based antioxidative activity, including intracellular glutathione levels and the enzymatic activity of glutathione peroxidase, glutathione reductase, and c-glutamyl cysteine synthetase. Recently, fungal-pelleted reactors loaded with various nanomaterials have been popularly applied to environmental pollution [147]. Therefore, these effect factors are valued for us to pay more attention in the application of  $\text{Se}^0$  nanoparticles and WRF combined technology.

### White rot fungi combining with titanium dioxide nanoparticle

Nowadays, titanium dioxide has become the most close and useful material in people's daily life owing to its excellent traits, such as photocatalysis, solar cell devices, gas sensors, and biomaterials. The nontoxic and biocompatible properties of  $\text{TiO}_2$  are significantly highlighted in the field of pollutant treatment [148]. Because of its promising photocatalytic performance, it has received increasing attention in the environmental applications of EDCs degradation. The nanoparticles of  $\text{TiO}_2$  are a promising material in biotechnology especially combining with WRF.

Tan et al. [149] discovered that *P. chrysosporium* loaded with  $\text{TiO}_2$  nanoparticles possess a surprising ability to adsorb cadmium and biodegrade 2,4-dichlorophenol. Fourier transform infrared spectroscopy showed that carboxyl, amino, and hydroxyl groups on the surface of PTNs are higher than that of *P. chrysosporium*. These factors are responsible for the biosorption, therefore, PTNs showed higher performances for the biotransformation of EDCs. They also focus on the real-time changes in  $\text{H}^+$ ,  $\text{O}_2$ , and  $\text{Cd}^{2+}$  fluxes to explore the inner mechanism by using the non-invasive microtest technique. The results indicated that  $\text{TiO}_2$  nanoparticles have changed the structure of the *P. chrysosporium* plasma membrane; therefore, the  $\text{Cd}^{2+}$  flux of PTNs is enhanced as compared with that of *P. chrysosporium*. Furthermore, in a virtuous cycle, the  $\text{Cd}^{2+}$  removal of PTNs was facilitated with the functional groups and hyphae of *P. chrysosporium* and large surface area of  $\text{TiO}_2$  [150]. *Phanerochaete chrysosporium* has been investigated with nitrogen-doped  $\text{TiO}_2$  nanoparticles applied

in the governance process of raw landfill leachate. The result showed that this combined method could not only efficiently remove TOC and change the ratio ( $\text{BOD}_5/\text{COD}$ ) in wastewater but also fully reduce the proportion of heavy metals and organic compounds. Kamwilaisak and Wright [151] discussed the combined treatment including photocatalysis technology ( $\text{TiO}_2$  and UV light) and biocatalysis technology (Lac from WRF-*Trametes versicolor*) to degrade lignin. The results showed that the removal efficiency of lignin could be improved with this combined treatment than with separate applications.

In conclusion, the superiority of  $\text{TiO}_2$ -WRF combined technology is obvious. A network structure surrounded on the surface of PTNs by WRF provides some propitious adsorption sites. The combination of a photocatalytic and biocatalytic process, with  $\text{TiO}_2$  first and Lac second, played an important role and exhibits a good application foreground during pollutant removal.

### Conclusions and perspectives

Academic research considering organic pollutant degradation with high-efficiency, heavy metals immobilization, and enzymology engineering by WRF has been very productive. There is no doubt that white rot fungi metabolism and their related novel advanced technologies with nanomaterials are promising tools for EDCs removal. However, many questions remain unanswered: the deficiency of basic perceiving in metabolic biotransformation pathways, in the application to a complex environment and in genomic changes related to these reactions.

By combining recent novel findings, this review described the biodegradation or biotransformation of EDCs, including PCBs and NPs, and suspected EDCs such as heavy metals and SAs by WRF. Molecular, metabolic and genetic analysis offers novel information about the biotransformation pathways and their degradation mechanisms which are critical to improve the application of bio-technology. This information will be important to predict how WRF will respond to the changes created by EDCs pollutant. In this context, the formation of intermediate products, the function of different enzymes and the resistance mechanisms during EDCs metabolic process by WRF are introduced in detail. By the reason that single pollution almost did not exist in a real environment, the removal of heavy metal-antibiotic compound pollutants by WRF or their combined technologies with nanomaterials has also been discussed in depth. The conclusion was that the combined treatment with WRF and nanomaterials can be regarded as a novel and competitive technology.

Even through the results from some successful experiments have showed a better degradation efficiency of combined pollution by microorganisms in the laboratory, there still remains many problems to solve their practical applications. Further studies are needed to develop the combination of WRF and nano-materials for being an efficient, economical and sustainable treatment technology in the whole environmental network.

## Disclosure statement

The authors report no declarations of other interest.

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