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Fungal and bacterial species in degrading carbamazepine: a metabolite perspective: Mini-review

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ABSTRACT

Carbamazepine (CBZ) is a ubiquitous pharmaceutical pollutant found in various water environments. This is due to the ineffective CBZ removal, despite employing advanced physiochemical treatment technologies in the current conventional wastewater treatment plants. Thus, bioremediation that utilizes enzymes in microorganisms' systems to bio-mineralize CBZ is suggested as an alternative or complementary technique to remove CBZ more effectively. However, information from published research on the biodegradation of CBZ, the toxicity of metabolites, or toxicity testing was rarely evaluated or assessed cohesively. This aspect is important because if bioremediation of CBZ produces toxic metabolites, it will defeat the main purpose of bioremediation. Thus, the focus of this review is to assess the effectiveness of fungi and bacteria in the biodegradation of CBZ, particularly by looking at the type of enzymes expressed, and the metabolites produced. In this review, information related to the fungal and bacterial species that were reported to degrade CBZ was collated from the published literature and analyzed. Results of the analysis showed that cytochrome P450, laccase, and manganese peroxidase were the common enzymes responsible to degrade CBZ. However, such enzymatic activities can sometimes produce epoxy-CBZ, which is a more toxic compound than the parent compound. Only the fungus *Pleurotus ostreatus* was able to oxidize epoxy-CBZ *via* the acridine pathway into acridone, the latter a metabolite that is susceptible to further biodegradation into nontoxic metabolites. However, the identity of the end metabolites is not reported nor characterized. Further, *Pseudomonas* spp. is the most promising bioremediating agent since it can metabolize CBZ into catechol, the latter can enter the carbon central pathways to generate energy for the bacterial cells.

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1 Introduction

Carbamazepine (CBZ) is an aromatic xenobiotic compound (Figure 1) that contains 98.0% of dibenzoazepine that carries a carbamoyl substituent at the azepine nitrogen (Alrashood 2016). CBZ is frequently detected in wastewater (Arye et al. 2011) because it does not undergo degradation during wastewater treatment (Clara et al. 2004), which leads to contamination of drinking water (Miao et al. 2005). According to a study conducted by Ternes et al. (2004), CBZ was detected in all 30 wastewater treatment plants and, also from 90% of the river water samples studied. Hospital and municipal effluents was the main contributor to CBZ found in the sewage treatment plants (Heberer and Feldmann 2005).

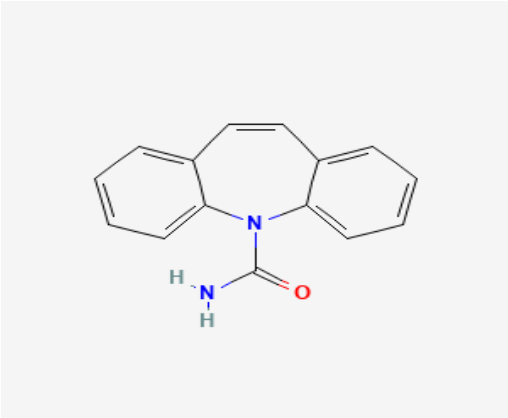

Figure 1 2D chemical structure of carbamazepine (PubChem 2021).

Physiochemical treatment technologies are commonly used to remove CBZ from wastewater (Table 1). The first two techniques which are well known to effectively remove most organic and inorganic compounds from water are nanofiltration and reverse osmosis (Radjenović et al. 2008). Even though nanofiltration and reverse osmosis show high organic and inorganic compounds removal efficiency from water, but the CBZ remains intact with the membranes which require further elimination action (Crini and Lichtfouse 2018). Physiochemical treatment that uses activated carbon also shows high CBZ removal efficiency from wastewater but the issue of disposing of the carbon matrix remains to persist with this (Crini and Lichtfouse 2018). The last type of physiochemical treatment is the advanced oxidation process (AOP) which utilizes the combination of chemical oxidation processes or ultraviolet (UV) irradiation on an added catalyst. This type of treatment can oxidize CBZ (Dai et al. 2012), but it is costly if it is operated on a large scale (Dai et al. 2012). Though the technologies mentioned in Table 1 show a high percentage of CBZ removal from water, the disappearance of CBZ provides only a partial indication of treatment efficiency (Kosjek et al. 2009). The most common transformation products of CBZ formed by such technologies belong to acridine and its derivatives, both being genotoxic (Bleeker et al. 1999). Moreover, the transformation products of CBZ from physicochemical treatments can become more resilient to further degradation (Kosjek et al. 2009). Thus, conventional wastewater treatment plants are found to be not wholly effective (Hai et al. 2018), and if such wastewater escaped into the environment it may cause serious ecological damage (Jos et al. 2003).

Numerous studies regarding the toxic effects of CBZ and its derivatives on aquatic organisms have been reported (Table 2). Jos et al. (2003) show the proliferation of aquatic algae *Chlorella vulgaris* was significantly inhibited within 48 hours of exposure to CBZ. Bivalve *Ruditapes philippinarum* was found to have its

Table 1 The efficiency of CBZ removal in water by various advanced physicochemical treatment technologies

Physicochemical Treatment	Treatment Type/ Systems	Starting Concentration of CBZ (ng/L)	Period of Treatment (min)	Removal Efficiency (%)	References
Pressure-driven membrane filtration technologies	Nanofiltration	84.5	-	98	Radjenović et al. 2008
	Reverse Osmosis	84.5	-	98	
Adsorption by activated carbon	Granular Activated Carbon	25	30	99	Park et al. 2007
	Powdered Activated Carbon	78	300	95	Snyder et al. 2007
Advanced oxidation processes	Ozonation	9	15	99	Huerta-Fontela et al. 2011
	UV	992×10^3	50	34	Dai et al. 2012
	UV/H_2O_2	210	20	74	Rosario-Ortiz et al. 2010
	UV/Cl_2	59	1.5	60	Sichel et al. 2011
	UV/TiO_2	992×10^3	10	10	Dai et al. 2012
	UV/Fenton	992×10^3	7	78	

Note: (-) means not stated.

Table 2 Toxicological effects of CBZ on aquatic organisms under different exposure conditions

Species	Starting Amount of Inoculum	Starting amount of CBZ (µg/L)	Period of Exposure (days)	EC50 (mg/L)	Effects	References
			Algae			
Chlorella vulgaris	1×10^6 cells/ml	-	2	3.66	Inhibited proliferation	Jos et al. 2003
Desmodesmus subspicatus	1×10^4 cells/ml	-	3	74	Inhibition of average growth rate	Cleuvers 2003
			Plankton			
Daphnia magna	10 neonates	-	1	112.23	Immobilized (Dead)	Jos et al. 2003
Daphnia similis	-	3	21	-	Inhibition of molting, delayed reproduction, and reduced fecundity	Chen et al. 2019
			Bivalve			
Ruditapes philippinarum	18 individuals	0.30 – 9.00	28	-	Inhibition of antioxidant enzymes in glycogen and electron transfer system	Almeida et al. 2015
Scrobicularia plana	10 individuals	0.30 - 9.00	28	-	Cell damage due to high lipid peroxidation	Freitas et al. 2015

Note: EC50 is the effective concentration that gives a half-maximal response; (-) means not available

Table 3 The efficiency of CBZ removal by various species of bacteria

Species	Enzyme Involved	Concentration of CBZ (mg/L)	Incubation Period (days)	Temperature (°C)	Shaking Speed (rpm)	pH	Removal Efficiency (%)	References
Labrys portucalensis F11	-	10.09	30	25	150	-	95.4	Bessa et al. 2019
Streptomyces MIUG 4.89	Laccase Phenoloxidase	0.2	7	25	150	7.2	35	Popa et al. 2014
Streptomyces SNA	Laccase	0.2	7	25	150	7.2	30	
Pseudomonas sp. CBZ-4	-	100	6	10	150	7	46.6	Li et al. 2013
Paraburkholderia xenovorans LB400	Biphenyl dioxygenase	10	1	25	100	7	100	Aukema et al. 2016
Pseudomonas sp. strain NCIB 9816-4	Naphthalene dioxygenase	10	1	25	100	7	>90	

Note: (-) means not stated.

metabolism inhibited when exposed to CBZ (Almeida et al. 2015; Almeida et al. 2021). Similarly, when the crustacean *Daphnia similis* was exposed to CBZ, it disrupts the endocrine system of *D. similis* (Chen et al. 2019). Since existing studies have reflected that CBZ can bioaccumulate, this indicates that the current wastewater treatments are not effective to remove CBZ, and a better approach to remediate CBZ is crucial to protect the organisms and environment.

Therefore, biological treatment processes such as biodegradation are available for the removal of CBZ and its metabolites in water. Biodegradation is a process whereby microorganisms are employed to degrade organic pollutants such as CBZ and convert them into less toxic or nontoxic forms of products (Zouboulis et al. 2019). Although biodegradation is an effective method to degrade CBZ, the achievement of a complete degradation varies within different types of organisms, particularly in between species (Li et al. 2013) of suitable organisms such as bacteria, fungi, algae, or plants that own the physiological abilities to degrade, detoxify, or render substrate of interest CBZ (Zouboulis et al. 2019).

To this concerning issue, enzymatic activities of microorganisms can be used to biodegrade CBZ more effectively (Singh et al. 2019). However, despite the wealth of information reported, the success to achieve a complete degradation varies within different types of organisms, between species and growth parameters (Li et al. 2013). Therefore, this review is to compare the efficacy of various species of fungi and bacteria in degrading CBZ, by investigating the various enzymes that degrade CBZ, and to determine which species can degrade CBZ into non-toxic metabolites.

In this current review, information n the enzyme expression and pathways involved in CBZ metabolism were summarized from different scientific databases including Google Scholar, PubMed, and Research Gate, etc., and collated in tabular for easy comparison. Available toxicity test studies on the metabolites generated by the enzymes of each species were assessed to achieve the aim of this review which is to determine the most efficacious species in degrading CBZ into non-toxic end metabolites in water.

2 Degradation of Carbamazepine by Bacteria

Table 3 summarizes the various CBZ-degrading bacterial species along with their diverse enzymes and operating parameters. Varying operating experimental conditions make comparison difficult when assessing which organism is the most efficient to degrade CBZ. Thus, it is best to investigate and compare the enzymes involved (Table 4) because different enzymes will produce different intermediate or end metabolites that might be toxic (Brusseau et al. 2019), which is the primary concern of this review. Furthermore, the different operating parameters will not affect the enzymes expressed, which makes the assessment more reliable.

2.1 *L. portucalensis*

It was reported that *L. portucalensis* degrades CBZ to produce OH-iminostilbene and epoxy-CBZ, catalyzed by the enzymes cytochrome 450 and MnP (Bessa et al. 2019). Following that, Epoxy-CBZ is proposed to be metabolized *via* the acridine pathway that resulted in a metabolite with molecular formula $C_{15}H_9NO_2$ and acridone. The latter has the potential to be degraded into nontoxic metabolites. However, a toxicity test conducted using the *Vibrio fischeri* luminescence (Jarque et al. 2016) resulted in an increase in toxicity which implies that the metabolites of CBZ degradation by *L. portucalensis* are more toxic than the parent compound CBZ itself.

2.2 *Streptomyces* spp.

Both strains of *Streptomyces* MIUG 4.98 and *Streptomyces* SNA expressed laccase during the degradation of CBZ (Table 4) to produce Epoxy-CBZ. In addition to laccase, *Streptomyces* MIUG 4.98 also expresses phenoloxidase (PO), although neither a conclusive study on this enzymatic pathway nor the resulting metabolites is available (Popa et al. 2014). Therefore, further identification of metabolites of CBZ degradation by *Streptomyces* spp. and the examination of toxicity after degradation are needed for better assessment.

2.3 *P. axenovorans*

P. axenovorans was shown to express a dioxygenase enzyme, Biphenyl-2,3-dioxygenase (BPDO) while degrading CBZ (Aukema et al. 2016). BPDO hydroxylates CBZ by oxygenating dihydrodiols which are cis-10,11-dihydroxy-10,11-dihydrocarbamazepine (diOH-CBZ), cis-2,3-dihydroxy-2,3-dihydrocarbamazepine, and carbamazepine-2,3-diol (Table 4). However, these dihydrodiols are toxic and highly reactive towards proteins, DNA, and lipids resulting in mutagenic and carcinogenic effects (Oesch-Bartlomowicz and Oesch 2007).

2.4 *Pseudomonas* spp.

The bacterial strain *Pseudomonas* sp. NCIB 9816-4 expressed a dioxygenase enzyme, Naphtahalene-1,2-dioxygenase (NDO) to degrade CBZ (Table 4) (Aukema et al. 2016). However, NDO's substrate specificity is to bind to naphthalene, a tricyclic aromatic ring compound unlike CBZ (Barry and Challis 2013). This suggests that *Pseudomonas* sp. degrades CBZ into naphthalene by other unidentified enzymes before the involvement of NDO.

Table 4 CBZ degradation by enzymes secreted from various species of bacteria

Species	Enzyme(s) Involved	End Metabolite	References
L. portucalensis F11	-	• $C_{14}H_{11}NO$ (OH iminostilbene) • $C_{15}H_9NO_2$ • $C_{13}H_9NO$ (acridone) • $C_7H_7NO_2$	Bessa et al. 2019
Streptomyces MIUG 4.89	Laccase, Phenoloxidase	-	Popa et al. 2014
Streptomyces SNA	Laccase	-	Popa et al. 2014
Pseudomonas sp. CBZ-4	-	-	Li et al. 2013
P. xenovorans LB400	Biphenyl-2,3-dioxygenases (BPDO)	• *cis*-10,11- dihydroxy-10,11-dihydrocarbamazepine (diOH-CBZ) • *cis*-2,3-dihydroxy-2,3 dihydrocarbamazepine • carbamazepine-2,3-diol	Aukema et al. 2016
Pseudomonas sp. strain NCIB 9816-4	Naphthalene-1,2-dioxygenase (NDO)	-	Aukema et al. 2016

Note: (-) means not stated.

Various species of *Pseudomonas* including *P. putida* (strains: NCIB 9816-4, G7, AK-5, PMD-1, and CSV86), *P. stutzeri* AN10 and *P. fluorescens* PC20 (Mahajan et al. 1994; Resnick et al. 1996; Annweiler et al. 2000; Basu and Phale 2008; Dennis and Zylstra 2004; Izmalkova et al. 2013) can metabolize naphthalene. The NDO catalyzes the oxidation of the aromatic rings of naphthalene into *cis*-dihydrodiol and later into catechol. Catechol is then cleaved to 2-hydroxymuconic semialdehyde following the *meta* route by catechol 2,3-dioxygenase (Yen et al. 1998). Lateroncatechol 2,3-dioxygenase is further hydrolyzed into pyruvic acid and acetaldehyde. Alternatively, catechol can be cleaved *via* the *ortho* route by catechol 1,2-oxygenase to yield *cis, cis*-muconic acid and further oxidized into succinyl-CoA and acetyl-CoA (Nozaki et al. 1968). Both routes produced non-toxic end metabolites that can furnish bacterial cells with energy.

3 Degradation of Carbamazepine by Fungi

Species of fungi that biodegrade CBZ are listed in Table 5. However, the percentages of CBZ's removal vary due to different operating parameters including starting concentration of CBZ, temperature, incubation period, shaking speed, and pH. The toxicity of the metabolites is not known, which defeats the purpose of bioremediation. Thus, a better comparison is by looking at the enzyme expression to deduce whether the metabolites produced are safe. Table 6 summarizes the identified enzymes involved in the degradation of CBZ and the corresponding metabolites in each fungal species.

3.1 *T. harzianum*

T. harzianum degrades CBZ by expressing cytochrome P450 system (Table 6). Cytochrome P450, a wide-ranging superfamily of monooxygenases, is one of the important intracellular enzymatic defense systems that protect fungi from toxic compounds including CBZ (Črešnar and Petrič 2011). However, the degradation of CBZ *via* cytochrome P450 might produce toxic daughter compounds (Buchicchio et al. 2016), such as 10,11-epoxy-carbamazepine (epoxy-CBZ) (Miao et al. 2005; Heye et al. 2016). Epoxides are common oxidation products that can inhibit glycosidase enzymes in the carbohydrate metabolism; or covalently bind to cellular proteins and nucleic acids resulting in mutations (Kallemeijn et al. 2014; Golan-Rozen et al. 2011; Di and Kerns 2016; Cajthaml et al. 2002).

However, a study by Buchicchio et al. (2016) showed that the toxic epoxy-CBZ is not present in the water samples treated by *T. harzianum*. This suggests that a variety of other enzymes including epoxidase within the cytochrome P450 system pathway (Olicón-Hernández et al. 2017) facilitated the degradation of epoxy-CBZ. However, the toxicity and the identity of the end metabolites are not known.

3.2 White Rot Fungi

White rot fungi (WRF) are known to biodegrade various types of aromatic pollutants (Gold and Alic 1993), including CBZ (Asif et al. 2017). Three WRFs with such potentials have been identified, namely *Trametes versicolor*, *Pleurotus ostreatus*, and *Phanerocheate chrysosporium*.

3.2.1 *T. versicolor*

Various enzymes including laccase (Rodríguez-Rodríguez et al. 2010), cytochrome P450 (Mir-Tutusaus et al. 2019), lignin peroxidase (LiP), and manganese peroxidase (MnP) are expressed

Table 5 The efficiency of CBZ removal by various species of fungi

Species	Enzyme(s) Involved	Concentration of CBZ	Incubation Period (days)	Temperature (°C)	Shaking Speed (rpm)	pH	Removal Efficiency (%)	References
Trichoderma harzianum	Cytochrome P450	4000 ng/L	15	25	100	7.6	72	Buchicchio et al. 2016
Pleurotus ostreatus	Cytochrome P450	4000 ng/L	15	25	100	7.6	68	
Trametes versicolor	Laccase	0.067 mg/g	2	25	135	4.5	57	Rodríguez-Rodríguez et al. 2010
Pleurotusostreatus strain PC9	Laccase, Manganese peroxidase, Cytochrome P450	0.025 mg/g	60	28	200	-	99	Golan-Rozen et al. 2015
Phanerochaete chrysosporium strain BKM-F-1767	Lignin Peroxidase, Manganese peroxidase	2×10^7 ng/L	7	30	90	4.5	62	Li et al. 2015

Note: (-) means not stated

Table 6 CBZ degradation by enzymes secreted from various species of fungi

Species	Enzyme(s) Involved	End Metabolite	References
T. harzianum	Cytochrome P450	-	Buchicchio et al. 2016
P. ostreatus	Cytochrome P450	-	Buchicchio et al. 2016
T. versicolor	Cytochrome P450, Laccase, Lignin peroxidase, Manganese peroxidase	• 2-hydroxycarbamazepine (2-OH-CBZ), • epoxy-carbamazepine (Epoxy-CBZ) • acridone, • acridine, • dihydroxycarbamazepine (diOH-CBZ)	Rodríguez-Rodríguez et al. 2010; Mir-Tutusaus et al. 2019; Jelic et al. 2012
Pleurotusostreatus strain PC9	Laccase, Manganese peroxidase, Cytochrome P450, Epoxide hydrolase, Aldehyde oxidase	• 10-methoxycarbamazepine (10-methoxy-CBZ) • TP 251 • Acridone • TP254 • 1-(2-Benzaldehyde)-(1H,3H)-quinazoline-2,4-one (BaQD) • TP 281 • TP 297 • TP 286 • 10-hydroxycarbamazepine (10-OH-CBZ) • TP 208	Golan-Rozen et al. 2015; Golan-Rozen et al. 2011
P. chrysosporium strain BKM-F-1767	Lignin peroxidase, Manganese peroxidase, Cytochrome P450	-	Li et al. 2015

Note: (-) means not stated. TP stands for unidentified transformation product.

by *T. versicolor* (Asif et al. 2017). The predominant degradation pathway taken by *T. Versicolor* is to degrade CBZ *via* laccase. Laccase enzyme oxidizes CBZ into Epoxy-CBZ and dihydroxycarbamazepine (diOH-CBZ), both are more toxic compared to CBZ (Naghdi et al. 2018). Both lignin peroxidase (LiP) and manganese peroxidase (MnP) are also known to oxidize CBZ into epoxy-CBZ (Asif et al. 2017).

In a field study, water polluted by CBZ was treated using *T. versicolor* and analyzed using a Microtox kit to assess toxicity in the water (Johnson 2005). Results of the study revealed that the treatment by *T. versicolor* reduces water toxicity by 50%. It was postulated the cytochrome P450 further metabolized the toxic epoxy-CBZ into non-toxic acridone (Golan-Rozen et al. 2015), although the reaction seems limited. Despite the wealth of enzymes expressed by *T. versicolor*, no conclusive study was shown that the species can biodegrade CBZ into a complete non-toxic metabolite.

3.2.2 *P. ostreatus*

In addition to cytochrome P450 and laccase, *P. ostreatus* was found to express MnP, epoxide hydrolase (EH), and aldehyde oxidase (AO) (Golan-Rozen et al. 2015). The extracellular enzyme MnPoxidizes can degrade CBZ into epoxy-CBZ or other aryls derivatives (Hildén and Mäkelä 2018). The epoxy-CBZ is then metabolized into acridine by EH *via* the acridine pathway to produce acridone (Golan-Rozen et al. 2015). The conversion of toxic acridine to acridone is mediated by AO (Kosjek et al. 2009). The acridone was found to be further metabolized into unidentified non-toxic end-metabolites (Golan-Rozen et al. 2015).

3.2.3 *P. chrysosporium*

Cytochrome P450 and MnP that can degrade CBZ into epoxy-CBZ are also expressed in *P. chrysosporium* (Table 6). Lignin peroxidase (LiP) is also present in *P. chrysosporium* (Li et al., 2015), and this enzyme metabolizes CBZ by a variety of reactions including benzylic alcohol oxidations, side chain cleavages, ring-opening reactions, demethoxylations, and oxidative de-chlorinations to producearyl compounds (Gold and Alic 1993). Unfortunately, there is no further data to suggest *P. chrysosporium* can degrade the toxic aryls formed *via* LiP into non-toxic metabolites. Aryls are highly oxidative and can react with macromolecules such as nucleic acids causing DNA mutations, deactivates proteins and enzymes such as cytochrome P450 and ribonucleotide reductase in DNA synthesis (Schweigert et al. 2001; Anku et al. 2017).

Conclusion

Despite the wealth of information, various gaps exist in terms of enzymatic pathways, metabolites, and toxicity evaluation as highlighted in this mini-review. So based on the existing information and data available, among all the investigated bacterial species, *Pseudomonas* spp. found most promising and has the highest CBZ degrading capability as it can generate biodegradable naphthalene, and the downstream product catechol than can enter

carbon central pathways to generate energy for the bacterial cells. The ability to degrade the toxic metabolites epoxy-CBZ and acridine into acridone *via* the acridine pathway mediated by EH and AO suggests that *P. ostreatus* is the best within the investigated fungal species. However, considering that CBZ degradation by *P. ostreatus* resulted in unidentified end metabolites, this will need further study to confirm the identity and characterization of such metabolites. Further studies on co-contaminant like heavy metals negatively impacting the enzymatic action and the metabolites should be investigated. This brings us to conclude that *Pseudomonas* spp. is the best candidate between the two species to treat CBZ-contaminated water without producing toxic waste.

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Conflict of Interest Statement

There are no conflicts of interest.

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