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REVIEW

Psychotropic Drugs of Emerging Concerns in Aquatic Systems: Ecotoxicology and Remediation Approaches

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Abstract
Carbamazepine (CBZ) and diazepam (DZP) are often prescribed for the treatment of stress, muscle spasm, anxiety, alcohol withdrawal symptoms, convulsion, and epileptic conditions, but are prone to abuse, which contributes to their environmental fate. According to the European Medicines Agency methods, CBZ and DZP were found to pose environmental risk (RQ > 1) to surface waters. Yet, risk assessment reports carried out on CBZ and DZP exposures in water bodies did not include behavioural or other sub-lethal endpoints and these information are vital. In the last two decades, scientific research has focused on the development of techniques such as biological, chemical, physical, and electrochemical methods for the remediation of pharmaceutical drug-related pollution. Several of the technologies have been implemented on a field/industrial scale, while others remain as pilot studies to date. Existing remediation methods include; nanofiltration, reverse osmosis, chemical oxidation, bioremediation, phytoremediation, photolysis, catalytic photodegradation, and adsorption. Electrochemical remediation, mycoremediation, phycoremediation, green nanoremediation, biocatalytic remediation, and integrated approaches are still at the developmental phase, although they hold great potential. The Sustainable Development Goals (SDGs) emphasized the need for clean and safe water for the sustenance of the ecosystem. This review seeks to bridge information gaps and provide a holistic overview of toxicological reports, as well as existing and emerging techniques, suitable for remediation of these pharmaceuticals in aquatic environments.

Keywords Carbamazepine · Diazepam · Ecotoxicity · Environment · Pollution · Remediation

1 Introduction

Advancement in scientific research and development in the last few decades has resulted in milestone achievements in the development of specialized therapeutic compounds capable of curing many illnesses, diseases, and improving life expectancy [1–4]. These milestones in knowledge acquisition and application has led to the inclusion of pharmaceuticals in the list of emerging contaminants as well, due to an increase in the concentrations found in non-target environmental compartments, exposure routes, and potential ecotoxicity even at very low concentrations [3]. Psychotropic drugs are drugs that affect behavior, mood, thoughts, or perception. They are majorly grouped into five classes, which are; mood stabilizers, antidepressants, stimulants, anti-anxiety medications, and antipsychotics, because of their multiple applications, they are one of the substances most prone to abuse, along with painkillers [5]. Carbamazepine and diazepam are often prescribed sedative, anti-anxiety, and anticonvulsant

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drugs often used to relieve stress, anxiety, and other chronic central nervous system (CNS) issues [3–5].

Carbamazepine (CBZ) is a moderately hydrophobic compound with therapeutic effect against bipolar disorder and epilepsy [6]. CBZ metabolism in humans is dose-dependent and there is a high probability of partial absorption and excretion of unmetabolized CBZ [7]. Certain metabolites of CBZ, such as carbamazepine-10,11-epoxide, carbamazepine-10,11-trans-diol, and phenolic derivatives, are excreted through the urinary tract and released into municipal sewages [8]. Diazepam (benzodiazepine class) is used for the treatment of anxiety, insomnia and highly susceptible to abuse, which could lead to drug addiction [9]. CBZ and DZP are whitish, crystalline, and poorly soluble in water, because of their structure and high octanol–water partition coefficient (Log K_{ow}) (Table 1). Their residues are ubiquitously present in environmental compartments and they are not routinely monitored or regulated, thus they are categorized as emerging contaminants of growing concerns, due to their impact on human health and the ecosystem [10, 11].

Advanced analytical techniques such as liquid chromatography coupled with triple quadrupole, tandem mass spectrometry (LC-MS/MS), and liquid chromatography coupled with triple quadrupole, tandem mass spectrometry (GC-MS/MS) have been used to quantify CBZ and DZP in water samples and concentration as low as part-per-trillion (ppt) can be quantitatively determined [3, 12, 13]. The fate of CBZ, DZP, and their metabolites is not well established, but they are regarded as pseudo-persistent due to incessant indiscriminate discharge into the environment [14, 15]. Psychotropic drugs have been detected in surface water and wastewater treatment plant (WWTPs) influents and effluents, because most WWTPs are not designed for clean-up of pharmaceuticals, thus removal could be as low as 10% for most pharmaceuticals [3]. The uptake of CBZ by cucumber plants exposed to residues via irrigation has been reported with the highest concentration found in plant leaves [14].

This article aims to discuss the ecotoxicology of CBZ and DZP and evaluate advances in the remediation of CBZ and DZP in aqueous media. This study is important in filling knowledge gaps, keeping track of scientific coverage, and charting future perspectives for sustainable remediation approaches and environmental protection.

1.1 Scope of the Review

Several reviews have been published on the occurrence of different pharmaceuticals in waterbodies [16–20], however, exhaustive literature survey carried out by the authors revealed that there is no comprehensive review directed towards the ecotoxicity and remediation of carbamazepine and diazepam in environmental matrices (Table 2), despite their tendency for abuse, ubiquitous nature, activity, and toxicity at very low concentrations. Most of the information discussed in this review were published within the last decade (2012–2022), and they focus on the occurrence, ecotoxicology, and remediation of diazepam and carbamazepine. However, earlier literatures were also included in a bid to provide a robust review of the subject. The literature scope are reports from published articles and books from reputable publishers, as well as thesis from University repositories. A systematic arrangement of the sections of this review was done to ensure clarity and provide up-to-date references for researchers.

Table 1 Physicochemical properties and structures of carbamazepine and diazepam

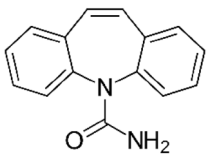
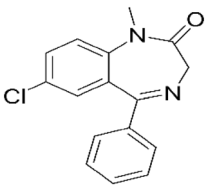
Pharmaceuticals (CAS number)	Therapeutic application	Chemical formula and weight (g/mol)	p*K*a	LogK_{ow}	Structure
Carbamazepine (CBZ) (298-46-4)	Neuropathic pain reliever/ anti-epileptic/anti-psychotic	$C_{15}H_{12}N_2O$ (236.274)	13.9	2.45	
Diazepam (DZP) (439-14-5)	Anti-anxiety/seizures	$C_{16}H_{13}ClN_2O$ (284.743)	3.4	2.82	

Table 2 Reviews published within the last decade on occurrence and remediation of different pharmaceuticals in the aquatic environment

Titles	Scope	Reference
Sources, impacts and trends of pharmaceuticals in the marine and coastal environment	Focused on sources and environmental impact of selected drugs. (*Diazepam and carbamazepine were not captured, and no remediation strategies was discussed*)	Gaw et al. [21]
Status of pharmaceuticals in African water bodies: occurrence, removal and analytical methods	Focused on occurrence, analysis and removal of selected pharmaceuticals in *African water bodies* using articles between 2012–2019	Madikizela et al. [22, 23]
Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment	Provided overview of fate and toxicity of selected PCPPs in waterbodies. (*Diazepam and carbamazepine were not captured and no remediation strategies was discussed*)	Ebele et al. [15]
Adsorption of Pharmaceuticals from Water and Wastewater Using Nonconventional Low-Cost Materials: A Review	Focused only on adsorption method for remediation of selected pharmaceuticals	de Andrade et al. [24]
Pharmaceuticals of Emerging Concern in Aquatic Systems: Chemistry, Occurrence, Effects, and Removal Methods	Focused on the prevalence, toxicity and removal of a wide variety of pharmaceuticals found in aquatic environments, using articles between 1990–2018	Patel et al. [3]
A review on effective removal of emerging contaminants from aquatic systems: Current trends and scope for further research	Focused on sources, detection and treatment of pharmaceuticals, pesticides, personal care product and other emerging chemical pollutants	Rathi et al. [25]
Review on the occurrence and biological effects of illicit drugs in aquatic ecosystems	Focused on the occurrence and toxicity of illicit drugs and metabolites (i.e. cocaine) in water bodies. (*No remediation approach was discussed*)	Fontes et al. [26]
Pharmaceuticals as emerging contaminants in the aquatic environment of Latin America: a review	Focused on the occurrence and risk assessment of several pharmaceuticals in waterbodies in Latin America only. (*No remediation approach was discussed*)	Valdez-Carrillo et al. [27]
Antiretroviral drugs in African surface waters: prevalence, analysis and potential remediation	Focused mainly on the occurrence, ecotoxicity and remediation strategies for antiretroviral drugs in African water waterbodies	Adeola and Forbes [28]
Persistence, environmental hazards, and mitigation of pharmaceutically active residual contaminants from water matrices	Focused principally on the occurrence, classification, potential hazards, and bioremediation of pharmaceutically active compounds in water matrices	González-González et al. [29]

2 Ecological Risk Assessment of Diazepam and Carbamazepine

2.1 Sources and Fate in the Environment

The occurrence of pharmaceutical compounds in water bodies has raised global concern in recent years [30, 31]. Sequel upon their mode of therapeutic action, pharmaceutical compounds are broadly classified into a group of eight namely, lipid regulator, hormone/steroid, beta-blocker, antidepressant, iodinated X-ray contrast media, central nervous system stimulant, analgesic and antipyretic, and antibiotic. These classifications represent the most frequently detected pharmaceuticals in the environment [32–36]. This may be largely due to high production rates and high volumes of prescription in both developing and developed countries of the world. For instance, diazepam, among other benzodiazepines, comes first in terms of production. Other commercialized benzodiazepines such as oxazepam are by-products of the degradation of diazepam [35].

A critical understanding of the sources and fate of pharmaceuticals in water resources is necessary in a bid to preventing their accumulation in groundwaters and surface waters [36]. Reports suggest that the major sources of pharmaceuticals-related contamination include**,** industrial production, farming, and agriculture use, veterinary use, human use, and wastewater discharge, which may contribute to the existence of pharmaceuticals in the environment. Manufacturing and production industries may contribute to the existence of pharmaceuticals via direct pharmaceutical effluent discharge to waterbodies as well as accidental spillage during distribution processes [37, 38]. These pharmaceuticals end up being transported to nearby water sources through leaching processes from municipal landfills and sewage tanks [34, 39]. The pathway for drug contamination of water resources includes the indiscriminate disposal of surplus, expired, and unused pharmaceuticals by humans into sewage and refuse to dump sites [38, 40–42].

However, the behaviour of pharmaceuticals in the environment is affected by several factors, among which are climatic factors, environmental degradation, sorption behaviour, sediment composition, chemical structure, pH, persistence, redox potential, solubility, and organic carbon content [43]. For instance, the oxidative chlorination or ozonolysis of drinking water may lead to the transformation of some pharmaceuticals into toxic products. For example, the reaction of diazepam with chlorine produces derivatives that are more mutagenic and toxic than the precursor drug (Fig. 1) [44]. Also, the photolysis of carbamazepine in a natural water source yielded more toxic reaction products (Fig. 2) [45]. Accumulation of these pharmaceuticals in surface water, groundwater, and soil may affect the dynamic balance of the ecosystem [46].

2.2 Environmental Risk Assessment

The purpose of ecological risk assessment is to evaluate the concentration of a pharmaceutical that may pose harm to given species in the environment upon exposure [49]. There are generally two phases of risk analysis, comprising of predicted environmental concentration (PEC) and measured environmental concentration (MEC). The PEC makes up the first phase of risk assessment and its calculation is based on the highest recommended dose used for a product with the assumption that [50]:

(i) The patient's metabolism will be disregarded;
(ii) There is no occurrence of the substance's retention or biodegradation in the sewage treatment plant;
(iii) The substances' main route of entry into the surface water is the sewage system;
(iv) There is an even distribution of the predicted amount used per year over the geographic area; and
(v) A fraction of the overall market penetration is within the range of existing medicinal products.

The PEC can be calculated using the formula in Eqs. 1 and 2:

$$PEC_{surfacewater} = DOSE_{ai} \times \frac{F_{pen}}{wastewater_{inhab}} \times dilutionfactor \quad (1)$$

$$PEC_{groundwater} = 0.25 \times PEC_{surfacewater} \quad (2)$$

where $DOSE_{ai}$ is the maximum daily dose of a substance (mg/day), F_{pen} is the penetration factor, and $wastewater_{inhab}$ is the amount of wastewater per inhabitant per day (L/inhab/day) [50, 51].

The risk assessment of pharmaceuticals detected in the aquatic environment has been estimated using the risk quotient formula (Eqs. 3 and 4):

$$RQ = \frac{MEC}{PNEC} \quad (3)$$

$$PNEC = \frac{LC_{50}\ or\ EC_{50}}{AF} \quad (4)$$

where RQ = risk quotient, MEC = measured environmental concentration, PNEC = predicted no effect concentration, LC_{50} or EC_{50} = median effective concentration, and AF = assessment factor [52, 53]. When RQ is less than 0.01, it indicates no risk, when RQ is between 0.01–0.1, it is indicative of low risk, when RQ is between 0.1–1, it suggests

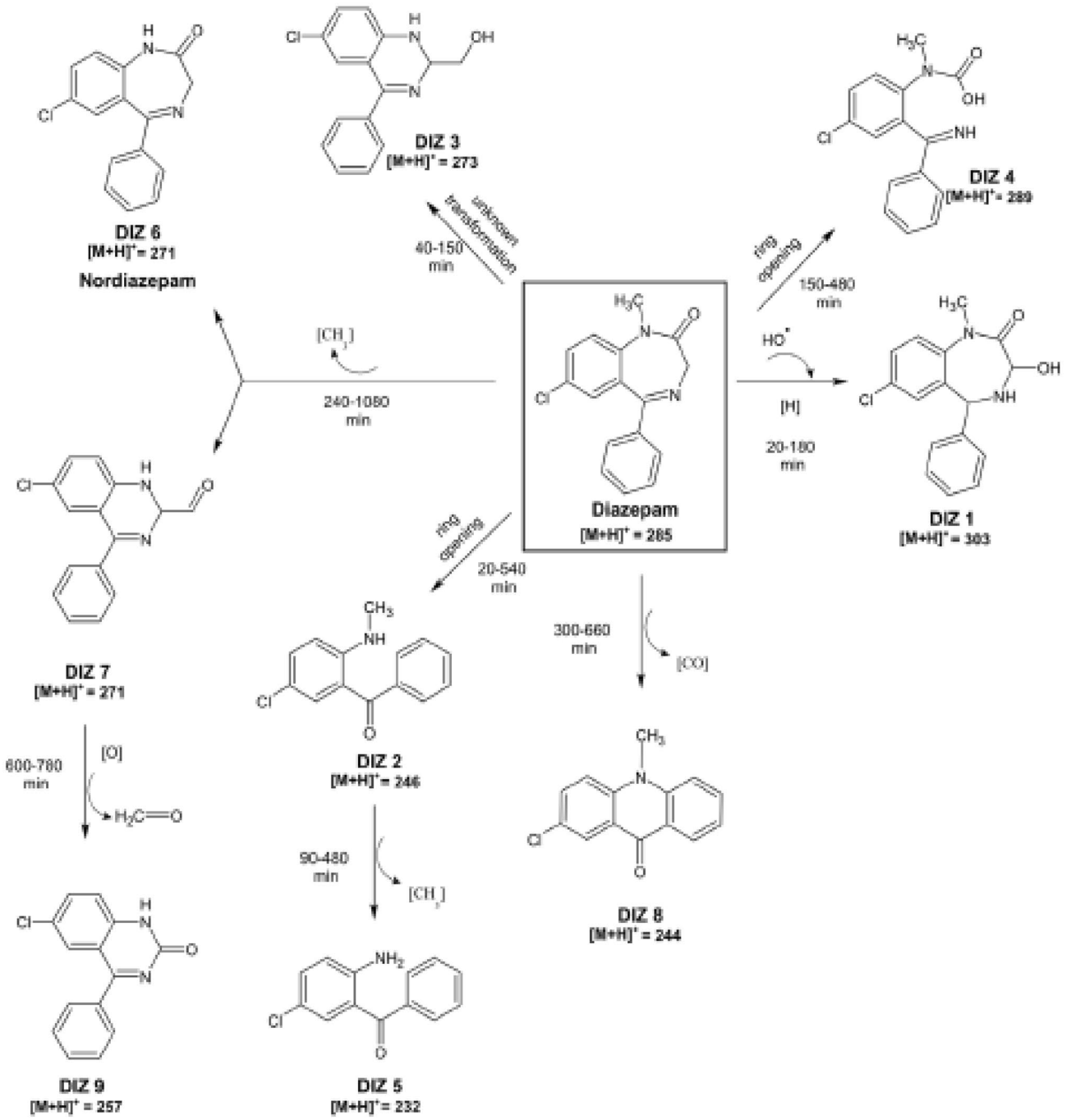


Fig. 1 Photodegradation of diazepam and its degradation products (adapted with permission from Jakimska-Nagórska et al. copyright [47], OMICS)

medium risk, while at RQ values greater than 1, high risk is indicated [54, 55]. In addition, the MEC is usually compared with the PEC to establish the risk quotient associated with exposure to a particular substance in the environment. This procedure ensures that a comparative analysis is carried out to determine the most suitable approach to the ecological risk assessment of psychoactive drugs in aquatic systems [51].

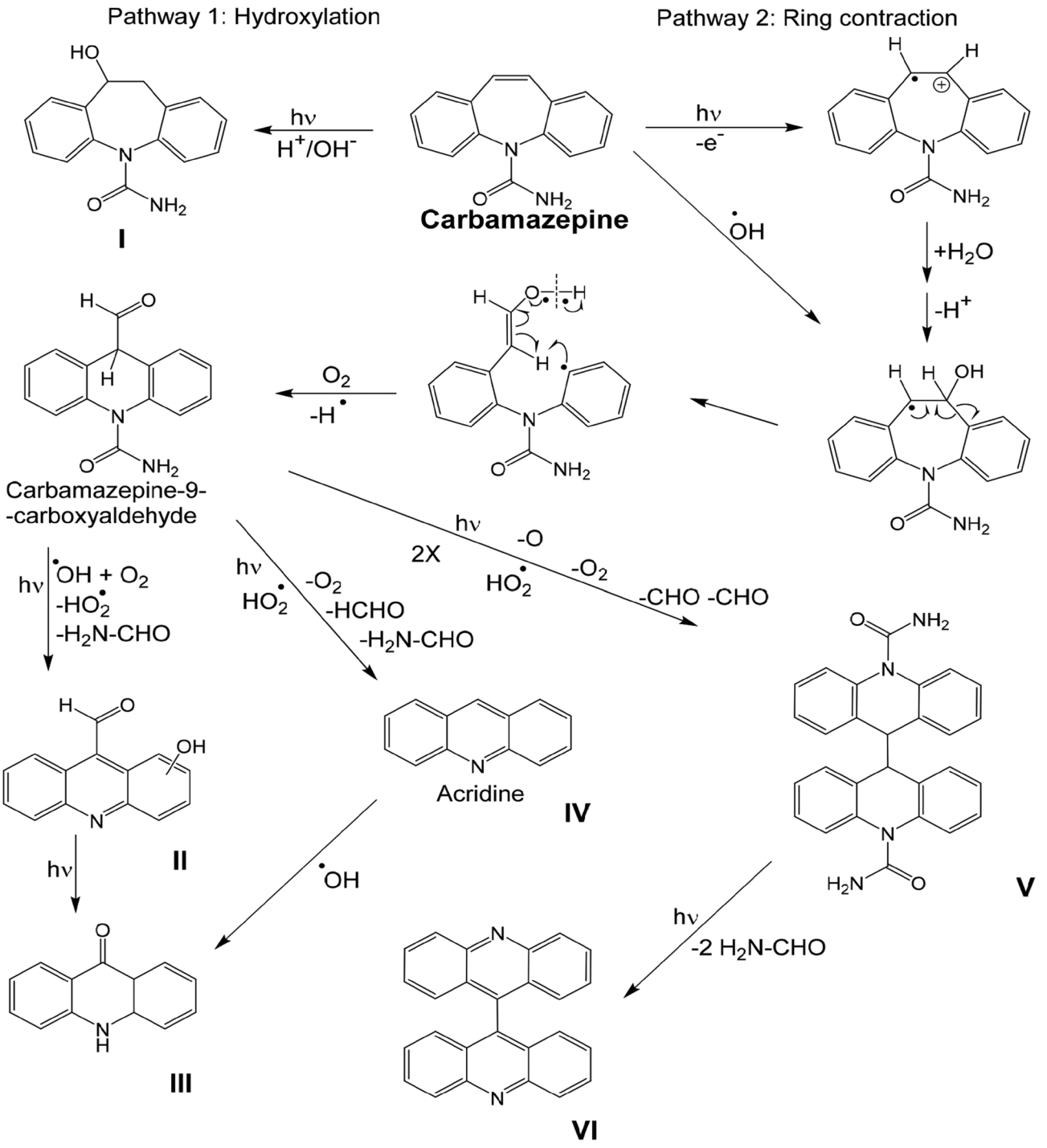


Fig. 2 Photodegradation of carbamazepine and its degradation products (adapted with permission from Calisto et al. copyright [48], Elsevier)

3 Ecotoxicology of Diazepam and Carbamazepine

The presence of pharmaceuticals in environmental compartments may pose imminent threat to the ecosystem because of their mobility, activity, and potential to bioconcentrate/bioaccumulate in biological systems [56]. Pharmaceutical compounds were made to easily penetrate cells and tissues for therapeutic actions, however, this biological construct, makes PCPPs very mobile, persistent in non-target environments and may become hazardous with strong binding activity [3]. Hence, they have been detected in aquatic flora

and fauna, soils, agricultural products, and water bodies [14, 57–60].

Ecotoxicology refers to the study of adverse biological responses to the release of chemicals to the environment, which could lead to distortion of biodiversity and ecological balance [61]. CBZ and DZP acts on the central nervous system as a biological tranquilizer with very fast action, however, they have side effects like most pharmaceutical agents [62]. CBZ and DZP can bind to receptors in lower organisms leading to similar or different physiological changes, as those that occur in humans, due to the similarities and differences in animals and humans in terms of cells, tissues, and organs. Unfortunately, current toxicity testing do not take into account the dissimilar modes of actions on exposure to pharmaceuticals that may occur in lower organisms (vertebrates/invertebrates), rather ecotoxicological testing and risk assessment still maintain the traditional guidelines and test organisms for chemical pollutants.

Altered conditions bring about an adjustment in the behaviour of an organism [63]. More specifically, the presence of diazepam in water bodies has been reported to induce prominent behavioural modifications in aquatic lives [64]. Exposure to diazepam has been reported to impair the swimming abilities of zebrafish [65]. Despite the episodic duration of exposure, the studied zebrafish required a long time to recover after exposure [65]. The persistence of such behavioural abnormality infers that the ecosystem may be at risk of diazepam contamination/pollution.

Diazepam is usually prescribed to combat anxiety disorders and this is attributed to its anxiolytic, muscle-relaxant, and sedative effects; while carbamazepine is an established anticonvulsant and mood-stabilizer drug prescribed for the treatment of neuralgia, bipolar disorder, and epilepsy [66, 67]. However, despite the significant importance of these drugs, their harmful effects ranging from endocrine dysfunction, decreased antioxidant status, decreased reproductive output, increased oxidative stress, and impaired energy homeostasis have been reported in non-target organisms in the environment [68–75]. Exposure of Polychaete to diazepam caused impairment to its biochemical and behavioural traits [76]. Hyperactivity and hypoactivity were reported to be associated with acute and chronic exposures, respectively [76].

3.1 Ecotoxicology of Diazepam

In zebrafish, *Danio rerio*, chronic exposure to DZP induced sedation, elicited a reduction in their swimming velocity and mobility (Fig. 3) [65]. Behavioural traits in the females during the mating season were also affected and potentially led to a decline in the rate of reproduction. Another study also suggest that respiration and development of juvenile zebrafish were affected by DZP, and which ultimately decreased the survival rate of the larvae, even at low concentrations [77]. Similarly, another study revealed that diazepam at 1 ng/mL altered the endocrine function and gene expression of catfish (*Ictalurus punctatus*) [78]. However, diazepam was one of the pharmaceuticals that were not detected in the brain and plasma of common roach fish (*Rutilus rutilus*) even after 15 days of exposure to wastewater treatment plant effluent, suggesting possible biotransformation. The report suggests that DZP does not bioconcentrate in catfish but caused harm even at low concentrations [78, 79].

Exposure of the fathead minnow fish to medium (< 10 µg/L) and high concentrations (10 µg/L) of diazepam did not affect their fertility or reproductive behaviour significantly [80]. However, in *Daphnia Magna*, 0.1 µg/L of diazepam enhanced reproduction by increasing the offsprings and a positive phototactic behaviour was elicited in them on DZP exposure [81]. This kind of observation is termed hormesis, where low concentration of toxicant result in high reproduction to improve chances of survival. Rats exposed to DZP were reported to exhibit an oxidative imbalance in some parts of the brain as shown by elevated levels of protein oxidation and lipid peroxidation [82, 83]. The reports suggest that while DZP exposure may potentially cause

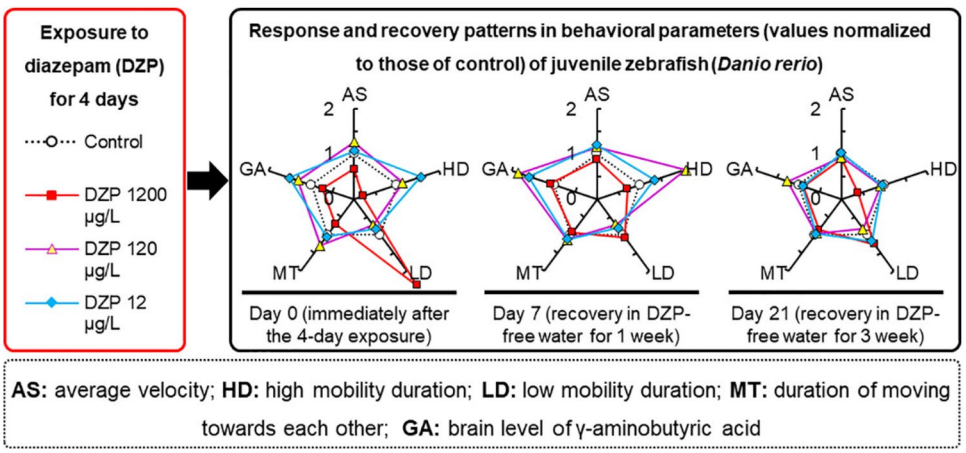


Fig. 3 Dosage and time-dependent response to diazepam exposure by juvenile zebrafish (Adapted from Wu et al., Copyright [65] Elsevier)

positive biological effects in living organisms by increasing their reproduction, exposure to trace to a high concentration of DZP may upset ecological balance, decrease the rate of survival of offspring and cause oxidative stress in aquatic organisms.

3.2 Ecotoxicology of Carbamazepine

Carbamazepine may pose harmful effects on fishes and algae owing to its high risk quotient (RQ) [84]. However, it has been shown that CBZ RQ < 1 indicated that it might not pose significant threat to aquatic lives [85]. Exposure of sea anemones (*Anemonia sulcata* and *Actinia equina*) to 1 and 100 µg/L of carbamazepine for 8 days only resulted in the short-term effects [86]. CBZ bioconcentrate at high concentration only and biochemical parameters such as induced ATPase and glucose level was doubled in *A. equina,* while lactate level was reduced in *A. equina* and increased in *A. sulcate* [86].

Exposure of the bivalves, *Venerupis philippinarum,* and *Venerupis decussata*, to CBZ at environmentally relevant concentrations for 96 h elicited oxidative stress in them [87]. It was discovered that the bioaccumulation level of CBZ in both species was low compared to the concentration they were exposed to; however, a substantial adverse effect still occurred in the clams. A weak accumulation of CBZ was also reported in marine mussels *Mytilus galloprovincialis* [88]. The mussels metabolize CBZ to acridine and carbamazepine-10,11-epoxide, which were detected in their tissues. The clams *Ruditapes decussatus* were found to also bioaccumulate CBZ and metabolize it to 3-hydroxycarbamazepine after exposure to nominal CBZ concentrations of 30 and 50 µg/L for 14 days [89]. CBZ in water bodies is known to degrade in the presence of light, leading to the formation of photoproducts which are also toxic (Fig. 2) [48]. Exposure of edible clams *Scrobicularia plana* to solar irradiated and non-irradiated environmental concentrations of CBZ (0–9 µg/L) for 96 h led to degradation of CBZ [90]. The photodegradation yielded five products, among which are acridine and acridine derivatives. The study revealed that exposure to CBZ and its photoproducts did not lead to higher toxicity in the clams when compared with exposure to CBZ alone however, oxidative stress was induced in both study groups [90].

Another study revealed that CBZ was one of the pharmaceuticals detected in soil [91]. The concentration however was low, hence, has a low RQ and it was concluded that it posed limited ecotoxicological risks to the soil and microorganisms present therein. *Cucurbita pepo* was exposed to soil contaminated with CBZ; there was a decrease in the concentration of CBZ in soil over 14 weeks. Therefore, it could be concluded that this is due to plant uptake since CBZ was present in seeds of *C. pepo* [92]. Reports of the ecotoxicity of CBZ on the duckweed, *Lemna minor* is scarce, but a group reported a half-maximal effective concentration ($EC_{50)}$ value of 25.5 mg/L after exposure for 7 days [93], while another group observed no specific pattern in the response of the duckweed to CBZ [94]. There was a report on reduction in the food intake and phototactic behaviour of *Daphnia magna* that were exposed to carbamazepine for 48 h [75], and this may affect their growth and susceptibility to being preyed on in daylight [81]. Bioconcentration of CBZ led to behavioural changes, inhibition of the acetylcholinesterase activity, and induction of oxidative stress. Similar to DZP, exposure to 1 µg/L of CBZ also caused hormesis [81].

Oxidative stress is caused by the production of reactive oxygen species (ROS) with an imbalance with free radicals [95]. CBZ induces lipid peroxidation as a result of the rapid production of ROS [63]. Excess ROS and free radicals cause DNA damage, hinders DNA repairs, and makes cell prone to apoptosis [96]. Growth inhibition was observed when the roots of onion, *Allium cepa*, were exposed to varying concentrations of CBZ, with a half-maximal inhibitory concentration (IC_{50}) of 31.36 µg/L [97]. The roots of *A. cepa* were exposed to 1 and 31.36 µg/L of CBZ for 72 h and the genotoxicity was studied [97]. There was a noticeable increase in the mitotic index (MI) and DNA damage of the group exposed to the nominal concentration of 31.36 µg/L at 48 h followed by a decrease in the MI at 72 h. It was concluded that the cytotoxicity and genotoxicity observed in *A. cepa* models are related to the oxidative stress caused by the production of hydroperoxides and oxidized proteins [97].

Studies have also shown that CBZ may be toxic to algae [98]. The microalgae *Raphidocelis subcapitata* was exposed to carbamazepine of nominal concentrations varying from 1 to 500 µg/L with a significant inhibitory effect on the growth rate only observed at concentrations above 10 µg/L [99]. Another study also reported that the EC_{50} values of the growth rate increased with CBZ exposure time (105 nmol/L after 72 h and 170.3 nmol/L after 16 days) suggesting that the negative effect of CBZ was mitigated over time [99]. Chlorophyll-*a* (Chl-*a*) is monitored in algae toxicity studies because it protects algal cells from damage caused by ROS. The Chl-*a* content of the diatom *Navicula* sp. decreased by 53.5, 81.2, and 100% at CBZ concentrations of 0.01, 0.1, and 0.5 mg/L, respectively [100]. Exposure of CBZ to UV light yielded degradation products (acridine and acridone) regarded more toxic than CBZ [100].

CBZ inhibited the growth of the algae, *Pseudokirchneriella subcapitata* with the lowest observed effective concentration (LOEC) value of 40 mg/L; the UV-photolysis products were more toxic with acridine having an EC_{50} value of 0.61 mg/L, and acridone with LOEC value 1.09 mg/L [45]. A 96-h toxicity study gave the EC_{50} values of CBZ exposed to algal species, *Chlamydomonas mexicana* and *Scenedesmus obliquus* as 797 and 149 mg/L [101]. However, EC_{50}

values reported for *S. obliquus* and *Chlorella pyrenoidosa* in the same time frame were 70.10 and 49.40 mg/L, respectively [102]. *C. mexicana* was observed to be more tolerant of CBZ compared to *S. obliquus*. Short-term exposure of *Chlorococcum* sp. to CBZ induced a change in the green algae's lipids while also affecting proteins that can lead to cell membrane damage [103].

The agile frog, *Rana dalmatina,* and the common toad, *Bufo bufo* were exposed to CBZ at environmentally relevant concentration throughout their larval developmental stage. Treatment with 50 µg/L of CBZ decreased the feeding activity of the toad tadpole but lower concentrations had no significant effect on them. The toxin, bufadienolide's content in the toad larvae reduced in the group exposed to 50 µg/L CBZ [104]. CBZ may affect the immune system in amphibians [105], this was supported by a study which revealed that CBZ at 50 µg/L affected the spleen in both the toads and frogs [104]. Acute exposure of the crustacean *Daphnia similis* to CBZ did not affect their survival whereas, chronic exposure to CBZ led to reduced fecundity, inhibition of molting, and release of chitobiase in *D. similis* [106]. The mild toxicity of CBZ and/or its degradation products on *Vibrio fischeri* has also been reported [107].

Ocean acidification is a phenomenon that is predicted to happen over the coming years [108] and can affect marine organisms negatively [1, 109] This was the rationale behind the study carried out by Freitas et al. [69] in which clams, *S. plana* exposed to CBZ in acidic pH conditions for 96 h were compared. It was observed that clams exposed to CBZ accumulated more concentrations than those at reduced pH conditions. However, the physiology and biochemistry of the clams were altered at reduced pH conditions. It has also been reported that exposure to CBZ at low pH (pH 7.5) induced transcription of immune-related genes and genes related to neurotransmission and biomineralization [110, 111].

Generally, oxidative stress and low bioaccumulation tendency are observed in aquatic organisms when exposed to this class of chemicals, due to the unique ability of CBZ to metabolize to equally hazardous derivatives (mostly hydroxyl, epoxides, and acridine derivatives). Furthermore, CBZ bioaccumulates in soils and plants leading to cytotoxicity and genotoxicity. Overdose associated with the use of benzodiazepines such as diazepam is rarely accompanied by morbidity or mortality. However, effects such as altered mental status, slurred speech, respiratory depression, etc. are possible clinical manifestations [111].

Nauphoeta cinerea (cockroach) were exposed to DZP and CBZ singly and as binary mixtures, combining both in a predetermined ratio [112]. Insects exposed to DZP alone were not affected negatively. Exposure to carbamazepine alone or combination of CBZ and DZP diminished their exploratory activities and mobility, with degenerative impact more prominent in insects exposed to only carbamazepine. The study established that oxidative stress and inflammation were induced in the experimental insects. However, further studies are required to comprehensively establish the role of different environmental variables on the ecotoxicity and bioaccumulation potential of CBZ and DZP in different environmental matrices and organisms.

4 Remediation by Adsorption Technique

Adsorption can be described as a mass transfer process involving the sorption of solutes or gases by liquid or solid surfaces. The mechanism of solid surface adsorption is characterized by the presence of residual surface energy in the atoms or molecules on the solid surface due to unbalanced forces. Upon collision with the solid surface, substances are attracted and glued to the surface. Depending on the forces of attraction (Fig. 4), adsorption is generally categorized into two: physical adsorption and chemical adsorption. The former occurs due to the interaction of intermolecular forces, specifically, van der Waals forces, while the latter involves a process where chemical bonds are formed and destroyed. While physical adsorption is characterized by low adsorption heat, chemical adsorption requires a larger adsorption heat and consequently larger activation energy due to the action of chemical bonds [113].

Adsorption is a method that has found wide applications in the mitigation of organic pollutants in groundwater, surface water, and wastewater. The efficiency of adsorption processes is largely dependent on the physicochemical properties of the solid surface (otherwise referred to as adsorbent) and the soluble substance(s) (otherwise referred to as the adsorbate) [115]. Specifically, the use of adsorption in the mitigation of diazepam and carbamazepine were reported in recent studies [116–120].

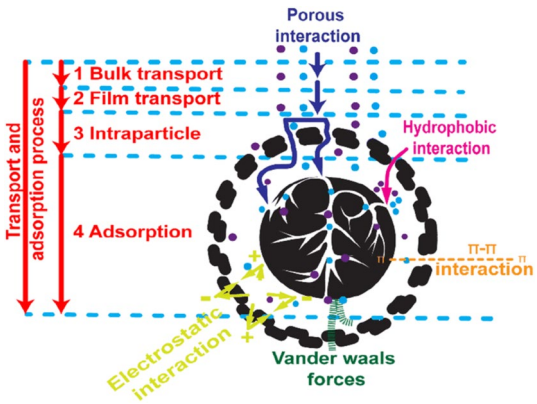


Fig. 4 Various transport and adsorption mechanisms between adsorbents and adsorbates (Adapted with permission from Ndagijimana et al., Copyright [114] Springer BV)

4.1 Recent Advances in Adsorption of Diazepam

The use of some adsorbents in the adsorption of diazepam (DZP) was discussed in this section and summarized in Table 3. In addition to the high efficiency associated with the adsorption process, it is a commonly employed technique due to its ecofriendly nature [121, 122]. Despite the vast array of sorbents, activated carbon continues to find wide applicability due to its large porous structure, high surface area, high efficiency, high adsorption capacity, and low cost [123, 124]. The adsorptive removal of diazepam (DZP) from a drinking water treatment plant using commercial and reused carbon under similar reaction conditions has been reported [125]. As opposed to the sole use of biological treatment which only ensured about 50% removal of DZP, the integration of activated carbon with biological treatment yielded about 68% removal of DZP after 7 days [125]. Comparatively, the study concluded that the use of activated carbon as powder achieved the best adsorptive performance.

The use of titanium dioxide has gained enormous importance in recent decades due to its wide resourcefulness in gas sensors, batteries, and catalysis [131, 132]. More specifically, the design and synthesis of nanostructured titanium dioxide are becoming more important due to their nanoscale properties [133, 134]. For example, efficiency of TiO_2 nanofibers, characterized with a transmission electron microscope (TEM), scanning electron microscope (SEM), and X-ray diffraction (XRD), was employed the removal of DZP from liquids [128]. Isotherm studies indicated a maximum adsorption capacity of 282.3 mg/g. The reaction mechanism was reported to be monolayer adsorption on the vacant adsorptive sites of the TiO_2 nanofibers' surface.

Activated charcoal has been reported to be of use in preventing the absorption of benzodiazepines from the gastrointestinal tract [135]. The capacity of activated charcoal to adsorb drugs is regulated by its internal pore volume and the type of activation [136]. For example, the influence of the internal structures of activated charcoal and natural Na-montmorillonite (geosorbent) on the adsorption of diazepam had been earlier investigated [120]. Both adsorbents were characterized using X-ray fluorescence (XRF), Fourier transform infrared spectrophotometer (FTIR), SEM, and XRD. Adsorption studies revealed that activated charcoal has a comparatively higher adsorption capacity (611 mg/g) than geosorbent (13 mg/g); which is attributed to its relatively greater pore volume.

Table 3 Removal efficiency of some adsorbents used in the removal of diazepam

Adsorbent	Removal efficiency (%)	Reference
Molecularly imprinted polymer	63.98	. [9]
Activated charcoal	611 mg/g*	[120]
Natural Na-montmorillonite	13 mg/g*	
Granular activated carbon	93.7	[126]
	40	[127]
TiO_2 nanofibers	282.3 mg/g*	[128]
Activated carbon	97.61	[129]
H_2O_2/UV/granulated activated carbon	99.99	. [130]

*Indicates maximum adsorption capacity

4.2 Recent Advances in Adsorption of Carbamazepine

Recent studies carried out in the last 5 years were discussed in this section and summarized in Table 4. The adsorption of CBZ using nanosorbents is believed to be the most economical and effective method of removal according to literature [137–139]. This is attributed to their high stability, accessible pores, large surface area, and suitable particle size. The magnetic nanoparticles were prepared by co-precipitation route and characterized using a scanning electron microscope, x-ray diffraction, Fourier transform infrared spectrophotometer and vibration sample magnetometer was used for the adsorption of CBZ [139]. The study reported that the synthesis of the iron oxide nanoparticles from the plant extracts was robust, simple, and eco-friendly [139]. A maximum removal efficiency of 52% CBZ using 5 ppm nanosorbent was recorded. The removal efficiency of the green-synthesized nanosorbent was attributed to the presence of bioactive compounds or phytochemicals in them [139]. However, higher pH levels may not enhance the adsorption rates of magnetic nanosorbents. This is because of possible interaction(s) between the nanoparticle's negatively charged surface and OH^- ions, causing repulsion of similar charges and subsequently leading to steric hindrance [138].

The use of hybrid nanocomposites (a blend of organic and inorganic nanocomposites) for the remediation of organic pollutants in natural waters and/or wastewaters has been investigated [140]. The integration of several compounds is believed to possess enormous advantages attributed to multifunctionality [141]. The inorganic component of the hybrid nanocomposite is usually responsible for its photocatalytic activity while the organic component (comprising of cellulose, chitosan, pectin, etc.) aid the improvement of the mechanical properties of the inorganic component, whilst increasing the surface area for adsorption [140]. For example, a synergistic adsorption/photodegradation technique was employed for remediation of CBZ contaminants in aqueous solutions [142]. A pectin/chitosan/zinc oxide nanocomposite was prepared by the inotropic gelation method. Under optimum conditions of pH 4 and 0.5 g/L dose of the nanocomposite, 69.5% degradation of CBZ was achieved. The study reported only a slight decrease in the removal efficiency of

Table 4 Removal efficiency of some adsorbents used in the removal of carbamazepine

Adsorbent	Removal efficiency (%)	Reference
Iron oxide modified-diatomaceous earth	88.2	[149]
Graphene oxide nanoplatelets	99	[150]
UiO-67	95	[146]
Pec/CS/ZnO nanocomposite	69.5	[142]
Green-synthesized magnetic nanosorbents	52	[139]
Phosphate rock	80.46	[151]
Porcelanite	79.61	
Granite	54.10	
Granular activated carbon	43.44	
Activated biochar	286.5 mg/g*	[152]
Bentonite clay	80	[153]
UiO-66 derived zirconia/porous carbon nanocomposites	190.2 mg/g*	[145]
Magnetic activated carbon	60 mg/g*	[154]
Natural clay	40 mg/g*	[155]
Molecular imprinted adsorbents	28.40 mg/g*	[156]
Alternative activated carbon	209 mg/g*	[157]
CuO/Cu_2O/Cu-biochar	93.02	[158]
$CoFe_2O_4$/rGO	90	[159]
Biosynthesized hematite nanoparticles	100	[160]
MWCNTs	224.6 mg/g*	[161]
Meso-AC1	191.5 mg/g*	
Nanobiochar	95	[162]
Saponite clay	35	[163]
Activated charcoal	> 99	[164]
Iron oxide nanoparticles	68.34	[165]

*Indicates maximum adsorption capacity

CBZ after the third reuse of the hybrid nanocomposite thus confirming its reusability and potential stability.

Although the excellent performance of synthesized carbon nanocomposites is well documented, traditional methods of synthesis are imprecise, time-consuming, and complex. This facilitated the development of a new synthetic pathway involving the direct calcination of metal–organic framework (MOF). The resulting carbon nanocomposite is expected to possess superior advantages of modifiable shape, adjustable pore size, and abundant porosity [143, 144]. This development is attracting the widespread attention of researchers. Zirconium metal–organic framework UiO-66 as a precursor in the preparation of ZrOx/porous carbon nanocomposite had been employed for CBZ adsorption [145]. Upon application, the synthesized carbon nanocomposite reached a maximum adsorption removal of 190.2 mg/g CBZ [145]. Little or no variation in adsorption efficiency was observed over a wide range of pH thus indicating the effectiveness of the adsorbent over a wide solution pH range. Similarly, the adsorptive removal of CBZ using metal–organic frameworks UiO-66 and UiO-67 were compared with a commercial activated carbon F400 [146]. Under the same reaction conditions, UiO-67 showed better removal efficiency (95%) as opposed to UiO-66 and F400 [146]. The relatively smaller pore size and narrow pore aperture of UiO-66 may have been responsible for its low adsorptive efficiency in the removal of CBZ. Generally, UiO-67 are known to have longer linkers in their structural setups which subsequently accounts for their larger tetrahedral and octahedral pores (12 and 16 Å respectively) [147]. In addition to the small-sized crystalline particles, high pore volume, and surface area, the missing linker defects of the UiO-67 were deemed responsible for its relatively faster and more efficient adsorption.

Diatomaceous earth structures are known to have cavities and this is believed to enable them to have capabilities to trap pollutants. In addition to the advantage of low economic cost due to natural occurrence, they have other attributes such as low thermal conductivity and high permeability [148]. A novel study was carried out to adsorb CBZ from synthetic wastewater using iron-oxide modified diatomaceous earth. Adsorption studies indicated that CBZ maximum removal reached 88.2% using the modified diatomaceous earth. Variations in pH did not hinder the adsorptive removal of CBZ during the process [149].

Despite the varying efficiencies of many studied adsorbents, the use of graphene-based materials is receiving

wide attention, and this is because of its relatively high specific surface area coupled with its chemical and mechanical stabilities [166, 167]. The other advantages accrued to the use of graphene-based materials are cost-effectiveness, efficiency in low dosage, and convenient process of synthesis [167–170]. The surface of graphene bears significant quantities of carboxyl and hydroxyl groups. This renders it hydrophilic and makes it suitable for the removal of pharmaceuticals from groundwater, surface water, and wastewater [166]. The use of graphene oxide nanoplatelets in the adsorptive removal of CBZ has been reported to be successful [150]. The graphene oxide nanoplatelets were synthesized using already described methods. Under optimum conditions of pH (2), contact time (120 min), initial CBZ concentration (5 mg/L), and adsorbent dosage (1 g/L), adsorption studies showed 99% removal of CBZ. After eight consecutive cycles, only an infinitesimal decline in adsorption efficiency was observed in the last two cycles (95% and 90% respectively) [150], thus confirming the reusability of the adsorbent.

5 Other Remediation Approaches

The application of other techniques for the remediation of CBZ and DZP in several environmental matrices has been reported in several research articles [126, 129, 179]. These technologies are reviewed in this section and Table 5 present a summary of these remediation strategies, efficiency, materials, and process conditions.

5.1 Flocculation and Coagulation

Coagulation–flocculation is a water treatment technique often applied to remove dissolved and suspended particles as part of the water treatment process. Flocculation is the aggregation and of soluble particles in removal the form of flocs and coagulation is the destabilization of the colloidal system leading to aggregation of colloidal particles [180, 181]. These two terms have been used interchangeably in the literature and the agents that carry out the process of flocculation and coagulation are known as flocculants and coagulants, respectively [3]. These could be metallic salts (e.g., $FeCl_3$ and $Fe_2(SO_4)_3$ organic polymers [180, 182]. Flocculation and coagulation have been commonly employed over the years for water treatment moreover, the methods have been improved upon. For instance, the use of ferric salts such as $FeCl_3$ and Fe_2SO_4 has been replaced by the use of polyferric sulfate $Fe_2(SO_4)_3$ which consists of a large quantity of complex ions such as $(Fe_2(OH)_3)_3C$, $(Fe_2(OH)_2)_4C$, and $(Fe_8(OH)_{20})_4C$, thereby enhancing higher efficiency performance [183–185].

CBZ is not effectively remediated through conventional treatment of drinking water as it has a low partition coefficient between the aqueous and secondary sludge phase [168, 186]. Ternes et al. [187] discovered that coagulation using $FeCl_3$, followed by flocculation and sedimentation, resulted in only 12% removal of CBZ. Furthermore, the complex spatial structure of CBZ (a three-ring phenolic base compound) requires high activation energy in order to react with oxidants. Oxidation using chlorine dioxide ($ClO_{2)}$ did not result in any removal of CBZ as it showed a low reaction

Table 5 Summary of other remediation strategies employed for diazepam and carbamazepine decontamination

Remediation approach	Pollutant	Target environment	Efficiency (%)	Agent/contact/reaction time	References
Reverse osmosis	DZP	Wastewater and sludge	100	UF-HF + UF-SW + GAC + RO	[126]
Nanofiltration	DZP	Deionized water Deionized water Wastewater	18.98 91.28 99.69	UF NF UF-NF	[129]
Photolysis	DZP	Wastewater		TiO_2 100 h + Humic acids, fluvic acids and XAd4 (28 h)	[171]
Mycoremediation	DZP		50–60	*Phanerochaete chrysporium*	[172]
Biocatalysis	DZP		Partial	Laccase	[173]
Nanofiltration	CBZ	Wastewater	80	MF-GAC + NF	[174]
Bacterial culture	CBZ		47	*Pseudomonas* sp. (20 days)	[175]
Mycoremediation	CBZ	Water	94 57 96 54 60–80	*T. versicolor* (6 days) Aerobic degradation *T. versicolor* in closed Erlenmeyer flask *T. versicolor* Batch mode *T. versicolor* continuous mode *Phanerochaete chysosporium*	[176] [176] [177] [177] [178] [178]
Biocatalysis	CBZ	Water	100	Laccase (12 h)	[173]
Phytoremediation	CBZ	Soil	70 90	Sunflower Maize	[179]

rate constant ($< 0.015\ M^{-1}\ s^{-1}$) [188, 189]. Ferric chloride ($FeCl_3$) displayed the best removal for diazepam in a study conducted by Carballa et al. [190]. In summary, flocculation and coagulation yield better results in conjunction with other remediation strategies, which is one of the reasons for advances in water treatment approaches and the advent of an integrated approach.

5.2 Reverse Osmosis

Reverse osmosis (RO) involves the application of high-pressured selectively permeable membrane in water treatment processes [191]. It is dependent on the properties, type, pore sizes, chemical properties of the membrane used, and the physicochemical properties of the pharmaceutical/compound to be remediated [192]. Several reports revealed that RO can achieve up to 90% removal efficiency of many pharmaceuticals (> 90%), which is quite promising [193–196], however, the activity of pharmaceuticals at every low residual concentration still calls for optimization and advanced research.

Studies have shown that advanced water treatment technology, which adopts the integration of multiple remedial options can enhance the efficiency of treatment protocols [167]. DZP and CBZ can be removed from wastewater effluent via advanced water treatment technology (WWTP), which consist of, (i) activated sludge reservoir (ii) hollow fiber ultrafiltration membrane (UF-HF) (iii) spiral wound ultrafiltration membrane (UF-SW) (iv) granular activated carbon filter (GAC) (v) reverse osmosis. With RO as the last treatment step in the WWTP, diazepam showed 100% removal from the wastewater and CBZ recorded over 95% removal [126, 197].

Overall, RO is a very good remediation approach for both psychotropic drugs under consideration, but RO has disadvantages that limit its public and industrial use. Some of these include water loss, membrane cost, operational cost and the membranes used in the process are likely to decay, which will require frequent replacement. Furthermore, hard water can reduce the durability of RO membrane. Therefore, contaminated water should be pre-treated to soften it to improve the lift span of RO membrane.

5.3 Nanofiltration

Nanofiltration has been reportedly used for the removal of pharmaceuticals such as sulfamethoxazole [198, 199]. However, this method cannot effectively remove many pharmaceuticals hence it is combined with other methods. Generally, ultrafiltration (UF) and low-pressure microfiltration (MF) membranes possess pore sizes that are sometimes inappropriate for the retention of pharmaceuticals [200]. Moreover, some hydrophobic compounds such as CBZ briefly adsorbs onto MF and UF membranes thereby causing a low removal rate [200]. Micro-, nano- and ultrafiltration have been used extensively for the remediation of pharmaceuticals, however, nanofiltration is regarded more efficient amongst the trio [167, 201]. This can be attributed to the lower operating pressures applied in nanofiltration and the nature of membrane [129].

MF-GAC dual hybrid systems have been coupled with the use of nanofiltration. In this technique, nanofiltration was used as a post-treatment tool and this method achieved more than 80% removal of CBZ [174]. Comparison of various removal techniques for some selected pharmaceuticals including DZP has been done [129]. It was observed that diazepam was removed from deionized water containing pharmaceuticals at 18.98% with ultrafiltration and 91.28% with nanofiltration [129]. It was also reported that when ultrafiltration and nanofiltration were combined (UF-NF) the removal efficiency for DZP from wastewater was 99.69% [129]. In summary, Nanofiltration is an effective mitigation approach against DZP and CBZ, but not without drawbacks such as fouling and formation of concentrated filtrate that will require further treatment.

5.4 Advanced Oxidation Processes (AOPs)

These processes are carried out in the aqueous medium in the presence of free radicals. Examples of such radicals are $HO^{\cdot}$, $O_2^{\cdot}$, and $HO_2^{\cdot}$ [3]. These reactive species are generated using UV irradiation, hydrogen peroxide, γ rays, or ozone combined with catalysts. The high reactivity of these species potentiates the oxidation of many pharmaceuticals with high reaction rate constants. Oxidants employed in AOPs include O_3 alone [202], O_3 in combination with UV/H_2O_2 [203], O_3/H_2O_2 [204], Fe^{2+}/H_2O_2 [205], photo-Fenton oxidation [205], and electro-Fenton degradation [206]. Several AOPs have achieved a high remediation rate of diverse pharmaceuticals from water up to 99%, including CBZ [207–209].

However, the challenge with AOPs is the production of harmful metabolites which may be retained in treated water. For instance, advanced oxidation of CBZ forms epoxycarbamazepine, and many other products including acridine that is well known for their ability to cause mutagenesis and carcinogenesis [210]. In general, several advanced oxidation processes (AOPs) are employed with varying degrees of success in mitigating CBZ including ozonation (> 90%) [186], direct photolysis with the aid of Fe (III), and Cl^- species (> 95%) [210], UV/H_2O_2-induced photodegradation (90%) [211], and photocatalytic degradation using TiO_2 as a catalyst (78.4%) [212]. Despite their demonstrated effectiveness for the removal of CBZ, these AOPs have some disadvantages, including incomplete mineralization, required continuous supply of O_3 or H_2O_2, required O_2 and/or H_2O_2 storage thereby introducing long-term stability and corrosion

issues, required removal of potentially toxic catalysts after treatment, and the risk of adsorption on the catalyst surface instead of mineralization [213–216]. However, integrated/hybrid approach involving photocatalytic degradation and adsorption have reported complete remediation of this pollutants, and mitigate deficiencies of single techniques (Fig. 5) [217].

5.4.1 Photolysis and Photocatalytic Degradation

Photolysis is the breaking down of molecules under the influence of artificial or natural light and can either be direct or indirect photolysis [218]. Direct photolysis is characterized by a direct absorption of UV light by an organic compound and its subsequent decomposition in the process. In contrast, indirect photolysis takes place with the aid of catalyst or reactive intermediates and radicals which are formed by photosensitization (Fig. 6) [5, 219]. Some factors that affect the efficiency of a photolytic process and they include radiation intensity and frequency, the compound's absorption spectra, quantum yields, presence of oxidants or free radicals, and the composition of the solution matrix used [220], similarly, pH also influences photocatalysis. Photolysis of CBZ with the aid of TiO_2, N-doped TiO_2, and ZnO_2 has been reported in the literature [221, 222]. The photocatalytic degradation of CBZ with N-doped TiO_2 membrane plunged by 40% with an increase in pH with the increase in calcium trioxocarbonate (V) (100 mg/L as $CaCO_3$) [221].

Under simulated solar radiation, direct photolysis of CBZ in water at variable oxygenation level and pH values was investigated [48]. The result findings indicated that CBZ was most photosensitive at low oxygenation level and lowest pH level (2.9). Although the drug was reported to be most stable at pH 9, it was observed that its photodegradation was not dependent on solution oxygenation at that pH [48]. Diazepam photodegradation occurred in water and sludge producing nordiazepam and temazepam [171]. The results also indicated that combining the adsorption method (clay-micelle complex) with AOPs would achieve complete elimination of DZP from the wastewater body [171].

5.4.2 Ozonation

Ozonation is the use of ozone to oxidize pharmaceuticals. Ozone is a strong oxidant and can act directly or indirectly in the presence of hydrogen peroxide, catalyst, and irradiation. Ozone is an electrophile that reacts with nucleophiles [223]. Direct ozonation takes place in compounds having C=C or C≡C aromatic groups, or with elements such as O, N, P, or S [223]. On the other hand, when ozonation takes place in the presence of catalyst or irradiation, it is considered an advanced oxidation process [224].

Ozonation degrades CBZ at its C=C at a removal rate of 105–106 $Lmol^{-1}$ S^{-1}, while diazepam is poorly remediated via ozonation [203]. Kinetic studies on DZP revealed that hydroxyl radical reactions contributed most to its degradation ($K_{OH} = 7.2 \times 10^9$ $M^{-1}S^{-1}$). It has been suggested that imine group (–C=N–) deactivated the aromatic rings and the presence of chlorine atom may be responsible for the weak reactivity of DZP in ozonation process [225].

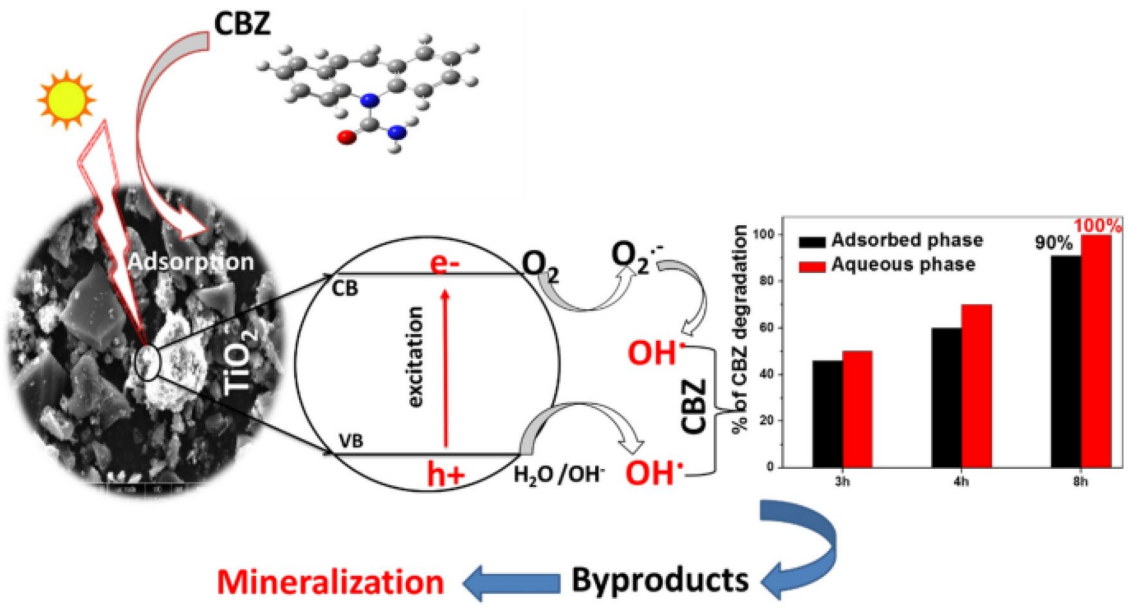


Fig. 5 Adsorption and photodegradation of carbamazepine as hybrid remediation techniques (adapted with permission from El Mouchtari et al. Copyright [217], Elsevier)

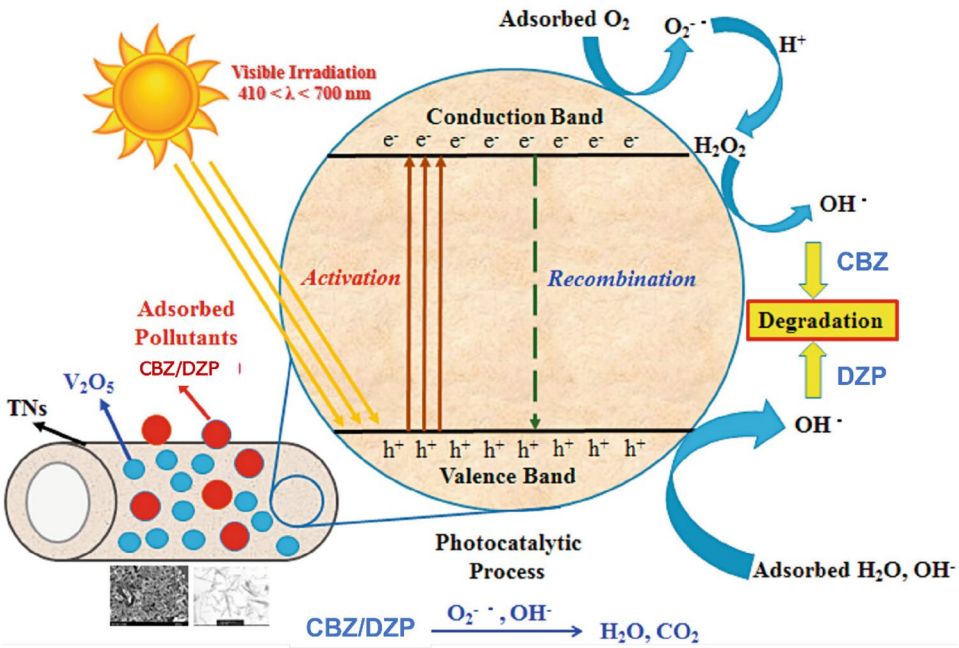


Fig. 6 Schematic representation of photolysis of CBZ and DZP (Adapted with minor adjustments from Bello and Raman, Copyright [219] Springer BV)

Ozonation records > 90% removal of drugs, but those in trace concentrations (ng/L) may persist in potable water after the treatment [226]. Ozonation efficiency is influenced by presence of chloride, temperature, suspended solids, alkalinity, organic matter, and pH [204]. Ozonation is often simply applied in the treatment of wastewater to disintegrate complex compounds to simpler degradable ones but this objective is not always reached [227]. CBZ for example releases harmful oxidation products and the operational cost of the ozonation technique is high [228, 229].

5.5 Bioremediation

Bioremediation involves the utilization of microbes and their enzymes for the biotransformation of recalcitrant pollutants to less toxic products. Biochemical reduction of the half-life of pollutants or outright elimination from contaminated sites is bioremediation strategies [121, 229]. Bioremediation of organic compounds has been extensively studied on a laboratory scale, with an established pathway for the biotransformation/degradation for some drugs [230, 231]. Certain factors affect bioremediation and they include the physicochemical properties, toxicity and concentration of the pollutant, potency of the microbial strain, pH and temperature of the system and surrounding, retention time, and the concentration of co-existing compounds [232]. Some bacteria can metabolize recalcitrant pharmaceuticals and they use them as carbon and nitrogen sources [233]. Dawas-Massalha et al. [234] revealed from their study that CBZ was poorly removed. Similarly, it was reported that only 47% of CBZ was degraded in 20 days with Pseudomonas species [175].

Advantages of bioremediation include; relative safety of the process, the complete transformation of pollutants, cost-effective and ecofriendly, without extensive use of chemicals [235]. Although the technique has its merits, optimization is required to overcome some limitations of the process [233]. These limitations include an incomplete transformation of some pollutants, long treatment time, and the specificity of microorganisms and involves tedious control of bacteria culture. Some of these setbacks could be circumvented with the use of genetically modified enzymes.

5.6 Mycoremediation

Mycoremediation is gotten from the Greek root word "mikes" meaning Fungi. They are eukaryotic organisms and examples are molds, yeasts, and mushrooms. Some fungi are chemoheterotrophs, parasites or saprophytes [236]. Fungi are efficient in the remediation of drug water [237, 238]. The efficiency of mycoremediation is associated with the biotransformation of various classes of compounds via nonspecific oxidative enzymatic reaction [239]. The possible mechanisms of mycoremediation appear to involve biodegradation, biomineralization, precipitation, biosorption, bioaccumulation, photodegradation, and volatilization [273–275]. Volatilization is considered negligible in mechanism of mycoremediation for most pharmaceuticals [276].

The fungi that have been extensively studied for their remediation potential against pharmaceuticals are the White-rot fungi (WRF). They are classified under the phylum Basidiomycota. WRF have been successfully applied for remediation of CBZ contamination [239–245]. WRF can bleach dark-colored lignin of wood to white color and utilize

this same mechanism to degrade a lot of xenobiotic contaminants. An earlier report revealed that WRF has enzymes that non-substrate specific, non-stereo selective, and these properties among others, equip them with the capacity to mineralize broad groups of contaminants [246]. WRF enzyme systems are both intracellular and extracellular. They employ either of these two classes of enzymes to degrade pollutants. The intracellular enzymatic system involves the cytochrome P450 (CYP450) system while the extracellular enzymatic system includes lignin peroxidases and laccases [246–248]. Both enzymatic systems play key roles in pharmaceutical degradation. Cytochrome P450 enzymes of *T. Versicolor were reported to be very* important in CBZ remediation [177].

It has been reported that laccases are produced during the primary metabolism of WRF while peroxidases are secreted during secondary metabolism during production of extracellular enzymatic systems [249]. Other researchers compared these two enzymes (peroxidases and laccases) [250–252]. For instance, it was reported that peroxidases have higher redox potential than laccases but they are deactivated by H_2O_2 [250–252]. Laccases are not deactivated by H_2O_2 but they are influenced by Cl^- [253]. Peroxidase can either be lignin or manganese peroxidases [254]. Lignin peroxidase catalyzes one-electron oxidation of aromatic compounds, resulting in the spontaneous formation of aryl cation radicals that are mineralized via several pathways [254]. Manganese peroxidase enhances the oxidation of Mn^{2+} to Mn^{3+}, leading to the oxidation of several phenolic substrates [255–260]. Laccases are more researched and studied. This is due to the fact that they have broad substrate specificity. They employ O_2 as their ultimate electron acceptor with H_2O as their only by-product [255–260]. In general, the key reactions involved in WRF remediation of pollutants include formylation, hydroxylation, dehalogenation, and deamination [261].

CBZ in an aqueous solution of an air pulsed fluidized bioreactor was removed using *T. versicolor in both* batch and continuous process [177]. In the batch process, CBZ concentration decreased by 96%, while, in the continuous mode, its concentration decreased by 54% [177]. The authors could not establish a correlation between extracellular laccase activity and CBZ removal since laccase and manganese peroxidase levels were negligible during the initial period. *T. versicolor* generates four major metabolites such as acridine, acridone, 10,11-epoxy-carbamazepine, and 10,11-dihydro-10,11 dihydroxycarbamazepine. Similarly, the products were reported in CBZ degradation by *Umbelopsis ramanniana* and *Cunninghamella elegans* species [264]. Unfortunately, microtox tests revealed that these metabolites pose greater risk than parent compound [177, 261]. Another group studied the remediation of six pharmaceuticals (citalopram, sulfamethoxazole, diclofenac, ibuprofen, naproxen, and carbamazepine) from an initial mixture by three WRF strains, *Bjerkandera* sp. R1, *Bjerkandera adusta*, and *Phanerochaete chrysosporium. The team confirmed* the presence of the activity of manganese peroxidase [172].

Phanerochaete chrysosporium has been employed in a nonsterile bioreactor in continuous process for > 100 days to remediate CBZ [178]. The efficiency of the process was 60–80% with 5 mg/L CBZ initial concentration. The same fungus was used in a fixed-bed bioreactors and continuously stirred tank containing psychotropic drugs (DZP and CBZ) and other NSAIDs. It was reported that all the NSAIDs were completely removed, but DZP and CBZ were partially remediated at 50–60% [262]. Some WRF has been employed to bioremediate ibuprofen, clofibric acid, and CBZ, where reported *T. versicolor* was able to degrade 58% of CBZ, and resulting solution after mycoremediation was nontoxic considering microtox toxicity test result [176].

Another WRF that had been used for remediation is *Trichoderma harzianum* [242]. A seven days' study discovered that *Trichoderma harzianum* degraded CBZ at 57% with the initial concentration of 0.03 µg/L and clarithromycin at 72% with an initial concentration of 4 µg/L by co-metabolic oxidation at low concentrations to 10,11-epoxycarbamazepine as the major product [242]. CBZ degradation by *T. versicolor* varies depending on the environment where the remediation takes place. CBZ remediation under three conditions was done to understand the influence of environmental condition [176]. The first experiment was conducted in a closed Erlenmeyer flask for 7 days which yields 57% removal of CBZ. The same process was carried out under aerobic conditions for 6 days and the result showed the removal of 9 mg/L CBZ at 94%. This improvement was believed to be a result of the continuous circulation of oxygen which supports the growth of *T. versicolor*. The third experiment was carried out in a bioreactor which led to 95.6% removal of CBZ [176].

The Pleurotus ostreatus specie of fungi was reported to remove CBZ efficiently than other fungi. It oxidizes CBZ and its metabolites to alcohols, making degradation products less toxic [263]. It is clear from the literature that mycoremediation does not give a 100% removal rate for DZP and CBZ. However, this process can be optimized to yield desired results.

5.7 Phycoremediation

Phycoremediation is derived from the Greek root word "phyco" meaning Algae. Algae have chlorophyll which they use to carry out photosynthesis. Cyanobacteria which are prokaryotes are also classified as algae. Most algae are microscopic but some are macroscopic. They could be unicellular, colonial, or filamentous [265]. They could also be autotrophs, heterotrophs, or mixotrophs. It has earlier been suggested that algae distinguished based on their

pigmentation [266]. The difference in colouration is as result of the combined effect of different auxiliary photosynthetic pigments and green chlorophylls. Certain features that algae possess make them suitable agents for bioremediation. For instance, they can easily adapt to different environmental conditions. They have a high degree of tolerance for low nutritional levels, and unusual pH, temperature, light, and salinity. These adaptive features to unusual conditions are attributed to genetic evolution which are potentiated by spontaneous mutation or physiological adaptation [267–272].

There are few studies on the utilization of algae as remedial alternative for environmental contamination. This has limited the understanding of the mechanism involved in phycoremediation. The bioconcentration of drug compounds in the cellular structure of algae can catalyze the production of free radicals and reactive oxygen species. These species often aid molecular signaling for control of cellular metabolic activities; however, when in excess, they can cause cellular damage, mutagenesis and cell death [173]. Algae appear to employ both intracellular and extracellular enzymatic systems to carry out bioremediation. Intracellular degradation of pharmaceuticals takes place with the aid of phase I enzymes (cytochrome P450 system) [101, 273, 277–279] and a phase II enzyme (e.g., glutathione-*S*-transferases) [278]. Extracellular degradation of drug compounds occurs via release of various extracellular polymeric substances, such as polysaccharides, proteins, lipids and enzymes, that externally digest pharmaceuticals in their environment. *Chlamydomonas mexicana* and *S. obliquus to remediate CBZ* and both species synergistically employed adsorption, bioconcentration and biodegradation for phycoremediation of CBZ [101].

5.8 Biocatalysis

Biocatalysis (also known as enzymatic bioremediation) involves the isolation specific enzymes and its application, as against the use of the whole microorganism for bioremediation. Some of the enzymes employed in biocatalysis are; bacterial mono- or dioxygenases, cytochrome P450 monooxygenases, dehalogenases, reductases, laccases, lignin- and manganese peroxidases, and bacterial phosphotriesterases [280]. Biocatalysis is done to reduce treatment time, over challenges associated with microbial growth, minimize sludge generation, and enhance process control [239]. This remediation technique reflects a major advancement in bioremediation technique in the field of environmental chemistry. Most xenobiotics including pharmaceuticals can be treated with biocatalysis [281]. However, field application of biocatalysis is constrained due to high operational costs and lack of reactor systems that can facilitate the separation of enzyme and treated wastewater [280, 281]. Fungal laccases (multicopper oxidoreductases) remain the most effective and widely used biocatalysts employed in wastewater bioremediation [282]. Laccase biodegradations of pharmaceuticals such as diclofenac, sulfonamides, tricyclic antidepressants, CBZ, and tetracycline have been well researched [265, 283–287].

Laccase functionalized with immobilized magnetic nanoparticles and chitosan/1-ethyl-3-(3-(dimethylamino) propyl)-carbodiimide hydrochloride were employed to degrade 13 pharmaceuticals [173]. The researchers used hybrid catalysts to degrade 13 pharmaceuticals. The result showed complete removal of CBZ metabolite (epoxy-carbamazepine) in 12 h, while DZP was partially removed. CBZ degradation increased to 60% in 48 h when augmented by a redox mediator, 1 hydroxybenzotriazole [176, 287]. Moreover, peroxidases are also prominent enzymes used in biocatalysis apart from laccases. Zhang and Geiβen [288] reported that lignin peroxidase from *P. chrysosporium* achieved just < 10% CBZ removal. Manganese peroxidase from *Bjerkandera* sp. could not degrade CBZ appreciably except when Mn^{2+} and glucose peptone were introduced to the medium, which recorded 99% degradation of CBZ [176]. Similarly, peroxidase introduced by *Pleurotus ostreatus* can degrade CBZ [263]

5.9 Phytoremediation

Phytoremediation is a technique that uses plants and rhizospheric microbes to biotransform, bioaccumulate and remediate toxic organic and inorganic pollutants present in different compartments such as ground water and surface water, sediments, and soil [289]. Plants can accumulate and degrade pollutants by transforming these xenobiotics without high energy or technological demand [290]. Plant chemicals released by its roots interact with pollutants through conjugation and degradation reactions thereby transforming them to less hazardous form [291]. The process is economically feasible, ecologically sustainable, and globally accepted.

Constructed wetlands have been implemented for remediation of chlorinated organics, metals, pesticides, explosives, radionuclides, and pharmaceuticals [167, 179, 292]. Although, it has been postulated that wetland degradation is a result of photo- and microbial degradation and not phytoremediation [293], and using hydroponics with plants to remove pharmaceuticals [294]. Study on phytoremediation of three pharmaceuticals in wastewater: diltiazem, diazepam and ethinyl estradiol, using sandbar willow (*Salix exigua*). 40 ng/L was the initial concentration for each compound and it was discovered that 20-days old willow cuttings with an average length of 10 cm, were able achieve 56% DZP removal from contaminated aqueous medium after 24 h [295].

Phytoremediation of CBZ and its metabolite 10,11-epoxyCBZ using two plants: sunflower (*Helianthus annuus*) and maize (*Zea may*) yielded positive results [179]. Sunflower

and maize took up CBZ and its metabolite preferentially compared with polar xenobiotics ibuprofen and acetaminophen [179]. Maize plant however showed more potential to eliminate CBZ metabolite [179]. CBZ concentration diminished by 70% and 90% of the initial concentration after 4 days in sunflower and maize media, respectively. Hydroponically grown *Typha species* remediate 56% of 2.0 mg/L CBZ contamination and 52% for CBZ initial concentration of 0.5 mg/L [296]. Wetlands cultivated with *Typhia species* and *Phragmites australis* showed a moderate CBZ removal of 24–36% in winter season and 48% remediation in summer [297], which unveiled the importance of climatic conditions in phytoremediation. It has been stated CBZ uptake in constructed wetlands with *Acorus* and *Typha* plants is strongly dependent on seasons, where plants showed 66% uptake of CBZ in May and zero uptake in August [298].

Some of the advantages and the limitations inherent in the use of technologies highlighted in this review are highlighted in Table 6. Since these compounds are continuously reported in the environment [16–20], more attention should be given to them to ensure the negative effect of their exposure to untargeted communities reduce significantly.

Table 6 Advantages and challenges of remediation techniques used for water contaminated with psychotropic drugs and other organic pollutants

Remediation technique	Merits	Challenge(s)	Reference
Adsorption	- No dangerous metabolites are formed - Retrievable, potentially regenerable and reusable - High adsorption capacity - Efficient towards wide range of pollutants - Low-cost adsorbents are available	- Nanomaterials may also have limited re-use potential, as they tend to lose activity with time as a result of aggregation, fouling, or side reactions - Sensitive to process conditions such as pH, dosage, temperature etc	[299]
Advanced oxidation process (Fenton)	- Do not transfer pollutants from one compartment to another - Able to degrade a wide range of organic contaminants - Iron is highly abundant and non-toxic - Relatively shorter treatment - Heat released from reactions enhances reaction rate, and microbial activity	- Operational cost due to oxidant required - Complete mineralization must be ensured to prevent harmful secondary pollutants	[300]
Bioremediation	- Readily available resource - Relatively cheaper - Not rigid and quite robust	- Microbial growth and action are highly sensitive to temperature and pH changes - Requires long treatment time - Large amount of sludge is generated	[233]
Coagulation and flocculation	- Helps remove suspended solids - Improved efficiency in conjunction with other remediation techniques	- Low removal efficiency against CBZ and DZP	[187]
Nanofiltration	- No chemicals involved - Lower energy consumption compared to reverse osmosis	- Membrane fouling - Operational cost	[174]
Photolysis	- Do not transfer pollutants from one compartment to another - No chemicals involved	- Operational cost due to short lifetime of UV lamps - Complete mineralization must be ensured to prevent the generation of harmful secondary pollutants	[45, 218]
Photocatalytic degradation	- Do not transfer pollutants from one compartment to another - Able to degrade a wide range of organic contaminants - Quite efficient	- Loss of catalytic activity over time	[216]
Phytoremediation	- Ecofriendly - Simple to implement - Suitable for organic and inorganic pollutants	- Not all plants can grow in aquatic environment - Long treatment time - Not desirable for edible plants	[179, 291]
Reverse Osmosis	- No chemicals involved - Very compact, and it requires little space	- Membrane fouling - Operational cost	[126, 191]

6 Conclusion

Carbamazepine (CBZ) and diazepam (DZP) are amongst the most investigated psychotropic drugs with respect to the relative abundance of articles relating to their ecotoxicity and remediation, published globally. Based on European Medicines Agency methods, carbamazepine and diazepam were reported to pose an environmental risk (RQ > 1) to surface waters. Thus far, risk assessment reports carried out on CBZ and DZP exposures in water bodies did not include behavioural or other sub-lethal endpoints in ecological risk assessments of psychotropic drugs, which are vital information. Therefore, it is recommended that behavioral endpoints should be included in the risk assessment framework for holistic assessment of flora and fauna exposure to psychotropic drugs in the environment. There is a need for public enlightenment and sensitization of patients, physicians, and veterinarians about the damning consequences of the indiscriminate release of psychotropic drugs into the ecosystems. The need for effective waste management protocols and efficient wastewater treatment plants in urban and rural communities cannot be over-emphasized. This study describes various techniques for the removal of CBZ and DZP from wastewater and highlights their merits and limitations. Several technologies discussed in this review have not undergone field trials, while others have been implemented industrially. Common drawbacks observed in many of the methods include high cost, membrane fouling, non-regenerable, non-ecofriendly, long treatment duration, generation of harmful metabolites, etc. Therefore, new technologies must seek to improve on current deficiencies in order to proffer enduring solutions to environmental pollution, caused by this ubiquitous class of pharmaceutical drugs.

Declarations

Conflict of Interest The authors declare that there is no conflict of interest regarding the publication of this article.

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