Science of the Total Environment 977 (2025) 179379

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Check for updates

# Bioremediation of emerging pharmaceutical pollutants acetaminophen and ibuprofen by white-rot fungi – A review

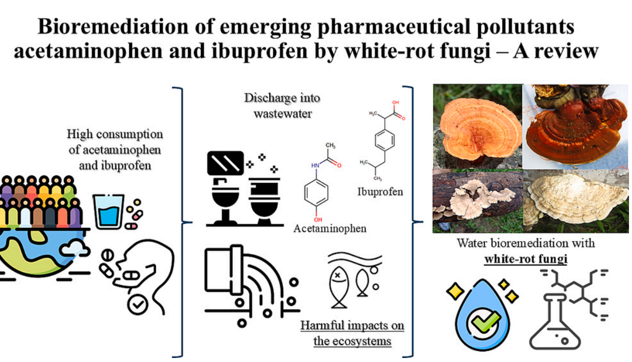
María Alejandra Flórez-Restrepo *, Xiomara López-Legarda *, Freimar Segura-Sánchez

*Biopolimer Research Group, Facultad de Ciencias Farmacéuticas y Alimentarias, Universidad de Antioquia UdeA, Calle 70 No. 52-21, Medellín, Colombia*

## HIGHLIGHTS

- White-rot fungi effectively degrade acetaminophen and ibuprofen in aquatic environments.
- Ligninolytic enzymes play a pivotal role in biotransformation and pollutant removal.
- Bioremediation offers a cost-effective and eco-friendly solution for water pollution.
- Pharmaceutical pollutants exhibit significant toxicity to aquatic ecosystems.
- Fungal enzyme stabilization enhances scalability of water treatment applications.

## GRAPHICAL ABSTRACT




## ARTICLE INFO

Editor: Dimitra A Lambropoulou

*Keywords:*
Pharmaceutical pollutants
White-rot fungi
Biodegradation
Acetaminophen and ibuprofen

## ABSTRACT

Emerging pharmaceutical pollutants, such as acetaminophen and ibuprofen, are frequently detected in aquatic ecosystems due to their widespread use and persistence in the environment. Their continuous discharge into water bodies through municipal wastewater presents significant ecological risks, including bioaccumulation and toxicity to aquatic organisms.

Extensive research on white-rot fungi has highlighted their exceptional capacity to oxidize diverse contaminants, emphasizing their promise for environmental cleanup. This article presents a detailed evaluation of the effectiveness of white-rot fungi and their ligninolytic enzymes in mitigating micropollutants, with a particular focus on pharmaceuticals such as acetaminophen and ibuprofen in aquatic environments. The aim is to provide a foundation for utilizing these fungi and their enzymes in the treatment of commonly used analgesics, discuss the occurrence, fate, and environmental impacts of these two pharmaceuticals, followed by an in-depth examination of white-rot fungi degradation mechanisms, including biosorption and enzymatic oxidation through their ligninolytic enzymes. The review highlights key fungal species, operational parameters influencing degradation efficiency, thereby promoting advancements in fungal enzyme production, and practical applications in pollutant removal.

* Corresponding authors.
*E-mail addresses:* mariaa.florez@udea.edu.co (M.A. Flórez-Restrepo), xiomara.lopezl@udea.edu.co (X. López-Legarda), freimar.segura@udea.edu.co (F. Segura-Sánchez).

https://doi.org/10.1016/j.scitotenv.2025.179379
Received 26 January 2025; Received in revised form 21 March 2025; Accepted 6 April 2025
Available online 15 April 2025

## 1. Introduction

Water, one of Earth's most essential resources, is crucial for maintaining ecosystems, preserving biodiversity, and regulating the climate (WWF, 2018). It also plays a pivotal role in addressing fundamental human needs, including health, food, education, and energy (Chopra and Kumar, 2020; WWF, 2018). However, the demand for high-quality water continues to increase, while environmental pollution intensifies due to enhanced living standards, rising consumer demands, and the growth of industrial and agricultural practices. These factors significantly lead to the release of contaminants, introducing newly identified pollutants such as pharmaceuticals, personal care items, and hormone-disrupting chemicals (González-González et al., 2022; Rasheed et al., 2019; Zhuo and Fan, 2021).

Pharmaceutical substances constitute a significant class of newly identified contaminants frequently found in aquatic systems, primarily due to their widespread use linked to population growth and their persistence against natural degradation processes (Jain et al., 2022; Parra Guardado, 2019). Acetaminophen (paracetamol), for example, is extensively consumed worldwide for its antipyretic and analgesic effects, and its recurrent detection in water bodies highlights the pressing need for remedial research (de Lima et al., 2018). Similarly, ibuprofen—a commonly utilized NSAID valued for its pain-relieving and fever-reducing functions—enters the environment in substantial quantities. Even at trace levels, these pharmaceuticals can negatively impact aquatic ecosystems through biomagnification and bioaccumulation, potentially disturbing ecological food webs (Ding et al., 2017; Gong et al., 2017).

Acetaminophen and ibuprofen, both listed on the World Health Organization's Essential Medicines List, are extensively utilized for pain relief, palliative care, and migraine management (WHO, W. H. O, 2023). In 2023, global demand for acetaminophen was estimated at approximately 145,000 t, with a projected Compound Annual Growth Rate (CAGR) of 4.5 %, potentially reaching 235,000 t by 2034. Similarly, the global market for ibuprofen was estimated at 46,000 t in 2023, with an expected CAGR of 2.3 %, likely growing to around 60,000 t by 2034 (ChemAnalyst, 2024a, 2024b).

The widespread use of pharmaceuticals, including acetaminophen and ibuprofen, poses significant environmental risks when these compounds enter natural ecosystems through usage or improper disposal. Acetaminophen exposure has been associated with neurotoxicity, oxidative stress, enzyme inhibition, DNA damage, and reproductive impairments in aquatic species. Similarly, ibuprofen has been shown to disrupt physiological processes such as circadian rhythms and induce inflammatory responses in fish, while also accumulating through aquatic food chains (Fu et al., 2024; Moro et al., 2014; Ogunwole et al., 2024; Żur et al., 2018). Consequently, investigating their degradation has become a priority in water treatment research.

Pharmaceutical contamination is a growing environmental concern, primarily driven by improper disposal practices, insufficient wastewater treatment, and outdated infrastructure in treatment facilities not originally designed to remove these compounds. Consequently, aquatic ecosystems are consistently exposed to elevated concentrations of pharmaceuticals (Akerman-Sanchez and Rojas-Jimenez, 2021; Barrios-Estrada et al., 2018), posing risks to diverse organisms and potentially raising significant public health concerns. As a result, substantial research efforts have been directed toward removing these emerging contaminants through various remediation methods (González-González et al., 2022).

Bioremediation offers an innovative strategy for pollutant removal, delivering significant benefits related to cost-effectiveness, operational efficiency, and environmental sustainability (Jain et al., 2022). Numerous investigations have highlighted the effectiveness of various microbial species in pollutant biodegradation, with increasing attention to fungal species in recent years. Basidiomycetes—a diverse fungal group that includes white-rot fungi—stand out as particularly advantageous for bioremediation purposes. Key genera within this group, such as *Ganoderma, Trametes, Phanerochaete, Bjerkandera*, and *Pleurotus*, have been thoroughly examined for their potential in such contexts (Bautista-Zamudio et al., 2023; Mir-Tutusaus et al., 2018; Voběrková et al., 2018).

White-rot fungi have been extensively studied for their ability to degrade a wide variety of pharmaceutical compounds, including acetaminophen and ibuprofen, from wastewater, due to their production of ligninolytic enzymes (Akerman-Sanchez and Rojas-Jimenez, 2021; Naghdi et al., 2018). Their enzymatic machinery exhibits broad substrate specificity, enabling the breakdown of complex organic molecules even under low-nutrient conditions and across a wide pH range (Bautista-Zamudio et al., 2023; Chen et al., 2022; Mir-Tutusaus et al., 2018). This highlights their potential as a sustainable bioremediation tool for the treatment of aquatic environments polluted by these commonly used pharmaceuticals.

This review aims to provide a comprehensive overview of the application of white-rot fungi and their ligninolytic enzymes in the bioremediation of aquatic environments contaminated with pharmaceutical micropollutants, with a particular focus on acetaminophen and ibuprofen. The manuscript covers the occurrence, environmental fate, and ecotoxicological effects of these two widely used analgesics, followed by an analysis of the degradation mechanisms employed by white-rot fungi. Additionally, it discusses key fungal species, operational conditions influencing degradation efficiency, and recent advances in enzyme evaluation. While several reviews have addressed the bioremediation potential of white-rot fungi in general, few have specifically focused on the removal of acetaminophen and ibuprofen from aquatic systems. Therefore, this review addresses this gap by critically analyzing the current state of research and highlighting future perspectives for scaling up fungal bioremediation processes in wastewater treatment.

## 2. Emerging pharmaceutical pollutants: characteristics and environmental impacts

Emerging contaminants, also referred to as micropollutants, represent one of the most critical categories of environmental pollutants. This group includes both manufactured materials and substances of synthetic or natural origin that largely remain unregulated within ecosystems. Their increasing prevalence in water bodies raises concerns due to possible threats to human well-being and ecological systems. While the impacts of certain micropollutants are not yet fully understood, they have recently been identified as significant contributors to water pollution (Barrios-Estrada et al., 2018; Morsi et al., 2020; Ogunwole et al., 2024; Rasheed et al., 2019).

Emerging pollutants have been analyzed across various aquatic systems, such as surface water, potable water, groundwater, and treated wastewater (Ogunwole et al., 2024). Micropollutants are compounds identified in environmental samples at concentrations spanning from nanograms to micrograms per liter. These substances present environmental risks due to their bioaccumulative potential, toxicity, and persistence, which can result in significant disruptions to local aquatic ecosystems, even at minimal concentrations. Historically, identifying these pollutants has posed considerable difficulties (Asif et al., 2017; Mir-Tutusaus et al., 2018; Varga et al., 2019; Zhong et al., 2019).

However, recent advancements in analytical methods and laboratory instrumentation have significantly enhanced the ability to detect these compounds in environmental samples, achieving detection limits as low as micrograms—and even picograms—per liter (Aus der Beek et al., 2016).

Emerging contaminants include a diverse array of substances, such as active pharmaceutical compounds (e.g., antibiotics, pain relievers, and hormones), cosmetics, nanomaterials, personal care products, phthalates, plastic additives, pesticides, fluorinated chemicals, industrial compounds, and various non-halogenated materials (Barrios-Estrada et al., 2018; Mir-Tutusaus et al., 2018; Morsi et al., 2020;

Rasheed et al., 2019; Zhong et al., 2019).

Recent advancements in pharmacology and health sciences have resulted in the creation of numerous medications aimed at addressing a broad spectrum of illnesses in humans and animals alike. However, for over 30 years, pharmaceuticals have also been identified as significant environmental pollutants (Akerman-Sanchez and Rojas-Jimenez, 2021; Mulkiewicz et al., 2021). Pharmaceutical residues are particularly worrisome due to their potential long-term effects on both human health and aquatic ecosystems, even at minimal concentrations. Their persistence and bioactivity in natural environments can impair water quality and lead to economic repercussions (Akerman-Sanchez and Rojas-Jimenez, 2021; Chopra and Kumar, 2020; Esterhuizen et al., 2021; Rasheed et al., 2019; Zhong et al., 2019).

### 2.1. Origin and consequences of emerging pharmaceutical pollutants

Understanding the presence, sources, environmental pathways, and impacts of emerging pollutants is crucial. The world is currently grappling with a significant water quality crisis, which is expected to worsen with a global population projected to exceed nine billion by 2050 (Barrios-Estrada et al., 2018).

The sources of pharmaceutical contaminants (Fig. 1) are comparable to those of traditionally recognized pollutants. Micropollutants may enter the environment at various stages, including during production, following consumption, and through the disposal of unused medications. These contaminants are introduced through urban and industrial activities, as well as via wastewater and effluent discharge. Although conventional wastewater treatment facilities address leachates from municipal landfills and agricultural runoff, these systems are primarily designed to eliminate larger pollutants, such as organic matter, nutrients, and suspended particles, and may not effectively remove pharmaceutical residues (Girijan and Kumar, 2020; Mir-Tutusaus et al., 2018; Naidu et al., 2016; Rasheed et al., 2019; Varga et al., 2019).

Widely used pharmaceuticals, whether prescription or over-the-counter, significantly contribute to environmental pollution due to the persistence of their residual compounds. This contamination often stems from the partial bioassimilation of these medications by humans and animals. Medicinal substances are commonly excreted through bodily waste, either unchanged or as metabolites, creating pathways from these sources to environmental receptors (Naghdi et al., 2018; Rasheed et al., 2019; Varga et al., 2019). Notable examples include antihypertensive agents, antibiotics, diuretics, beta-blockers, and anti-inflammatory drugs (Akerman-Sanchez and Rojas-Jimenez, 2021; Varga et al., 2019).


**Fig. 1.** Sources of pharmaceuticals as emergent contaminants – icons from (Flaticon, 2023).

Studies on the impacts of emerging pollutants have highlighted the environmental risks that pharmaceuticals pose to aquatic ecosystems. As bioactive substances, their presence in aquatic environments has demonstrated adverse effects on numerous organisms, potentially disrupting entire ecosystems (Varga et al., 2019). Designed to trigger biological reactions in specific target species, pharmaceutical compounds may also produce similar effects in non-target species, including primary producers, cnidarians, water fleas, mussels, and various fish species. Exposure to these pollutants has been associated with observable abnormalities, with prolonged exposure posing significant risks during critical developmental periods (Rasheed et al., 2019; Wilkinson et al., 2015; Żur et al., 2018).

Pharmaceuticals are commonly identified in wastewater treatment plants at levels ranging from nanograms to micrograms per liter. Medications—including analgesics, psychiatric drugs, antidiabetic treatments, and anti-inflammatory compounds—have been documented at varying concentrations in discharged effluents (Akerman-Sanchez and Rojas-Jimenez, 2021). These levels are considered to pose significant environmental risks, including fostering antimicrobial resistance, disrupting endocrine systems in higher organisms, and contributing to reproductive impairments, physical deformities, and other negative impacts (Morsi et al., 2020).

Exposure of non-target species to pharmaceutical substances can promote the development of drug resistance or tolerance (e.g., antibiotic resistance or analgesic tolerance), alter microbial community structures, and disrupt food chains. Such exposure may also lead to behavioral changes in affected species and long-term health issues (Mir-Tutusaus et al., 2018; Sundararaman et al., 2022). Furthermore, micropollutants can infiltrate aquatic ecosystems via various routes, leading to biomagnification and increased accumulation of these substances in organisms occupying higher trophic levels, eventually transferring to humans through dietary exposure (Mahesh et al., 2022).

### 2.2. Acetaminophen and ibuprofen as emerging pollutants: characteristics, risks, and environmental impact

In an era of heightened public health awareness, a broad range of medications is widely used to treat or manage conditions ranging from headaches to muscle pain and inflammatory disorders. This rising demand is largely driven by the high prevalence of chronic illnesses and an aging population. Growing concerns regarding the accumulation of micropollutants in aquatic environments have prompted extensive research on their impacts and potential biodegradation methods (Marchlewicz et al., 2015; Naghdi et al., 2018).

Over-the-counter (OTC) drugs—medications accessible without a prescription—such as acetaminophen and ibuprofen, are widely used due to their availability and affordability (Marchlewicz et al., 2015). These medications belong to a well-known category of synthetic chemicals and have been detected across various environments, including soil, rivers, wastewater systems, and even drinking water, underscoring the global scope of this issue (Girijan and Kumar, 2020; González-González et al., 2022; Żur et al., 2018).

#### 2.2.1. Acetaminophen: chemical structure, environmental presence, and toxicity

Acetaminophen (commonly referred to as paracetamol, *N*-acetyl-p-aminophenol, N-(4-hydroxyphenyl) ethanamide, 4-acetaminophenol, or 4′-hydroxyacetanilide) is a frequently utilized non-opioid medication with pain-relieving and fever-reducing properties. It can be administered individually or in combination with other pharmaceuticals in various formulations (Chiam et al., 2015; Chu-Wen et al., 2020; Żur et al., 2018). Structurally, paracetamol comprises a benzene ring functionalized with a hydroxyl group and an amide group positioned in the para (1,4) orientation (Fig. 2) (Żur et al., 2018).

This pharmaceutical compound is available over-the-counter and is among the ten most commonly consumed medications worldwide. Annual consumption is estimated at approximately 29 billion doses, with production predominantly occurring in nations including China, India, the United States, Australia, the United Kingdom, and several European countries such as Italy, Spain, Portugal, and Germany, as well as in Colombia, Poland, the Czech Republic, Hong Kong, Thailand, and Indonesia (Poddar et al., 2022; Żur et al., 2018).

Acetaminophen, along with related compounds such as 4-aminophenol and N-(4-hydroxyphenyl)acetamide, is classified as a micropollutant. It has been identified across various environmental media, with levels varying between 5 ng/L and 30 mg/L in different water samples. Harmful effects have been documented at lower trophic levels, and its concentration may increase through biomagnification within ecological food chains, leading to accumulation in aquatic environments and ultimately posing risks to human health (Chang et al., 2018; Chu-Wen et al., 2020; Poddar et al., 2022; Żur et al., 2018).

The toxic mechanisms of acetaminophen appear to be highly conserved, affecting both vertebrate and invertebrate species in similar ways. Environmentally significant outcomes include neurotoxicity and enzyme inhibition, which result in oxidative stress—a common consequence of exposure to this compound. Other harmful effects include DNA damage, tissue accumulation, lipid degradation, and alterations in behavior reported in organisms such as algae, small crustaceans, mollusks, and various fish species. Acetaminophen exposure has also been linked to liver toxicity, impaired biological functions, reduced reproductive capacity, and concerns about bacterial resistance (Fu et al., 2024; Żur et al., 2018).

### 2.2.2. *Ibuprofen: chemical structure, environmental presence, and toxicity*

Ibuprofen, chemically known as α-methyl-4-[isobutyl]phenylacetic acid or 2-(4-methylpropyl)phenyl propanoic acid, ranks as the third most frequently utilized NSAID (non-steroidal anti-inflammatory drug) globally. It is commonly prescribed to reduce fever and alleviate pain or inflammation associated with various conditions, such as headaches, dental pain, back pain, arthritis, menstrual discomfort, and minor injuries (Gong et al., 2017; Zhang et al., 2022; Żur et al., 2018). Structurally, ibuprofen contains an aromatic ring attached to acetate and alkyl groups, which makes its degradation particularly challenging (Fig. 3) (de Melo Pirete et al., 2022).

The widespread occurrence of ibuprofen and its derivatives in natural environments is largely due to its frequently prescribed high doses, typically ranging from 600 to 1200 mg per day. Around 15 % of ibuprofen is eliminated from the body unchanged, as glucuronide or thiol conjugates, or as a variety of metabolites, including hydroxy-ibuprofen, carboxy-ibuprofen, and carboxyhydratropic acid. Notably, some of these metabolites are more toxic than the original compound (Chopra and Kumar, 2020; Marchlewicz et al., 2015; Żur et al., 2018). Once released, ibuprofen enters wastewater systems and spreads throughout the environment—including aquatic habitats like rivers, lakes, and oceans, along with soil and groundwater—where it can be absorbed by plants and aquatic species (Chopra and Kumar, 2020).

The annual production of NSAIDs is estimated to reach several thousand tonnes, and their increasing use in medicine is evident in their extensive presence within natural environments. As a result, ibuprofen has been identified in environmental samples worldwide, with levels varying between 0.02 μg/L and up to 703–1673 μg/L in wastewater (Ogunwole et al., 2024; Żur et al., 2018). Due to its bioactive nature, ibuprofen contributes to environmental toxicity and accumulates in wastewater systems (Chopra and Kumar, 2020).

The negative impacts associated with ibuprofen exposure indicate a significant risk of toxicity (Żur et al., 2018). Notably, degrading the parent compound does not necessarily eliminate its environmental hazards. This issue arises because, in some cases, the toxicity of treated wastewater may increase due to the formation of more harmful

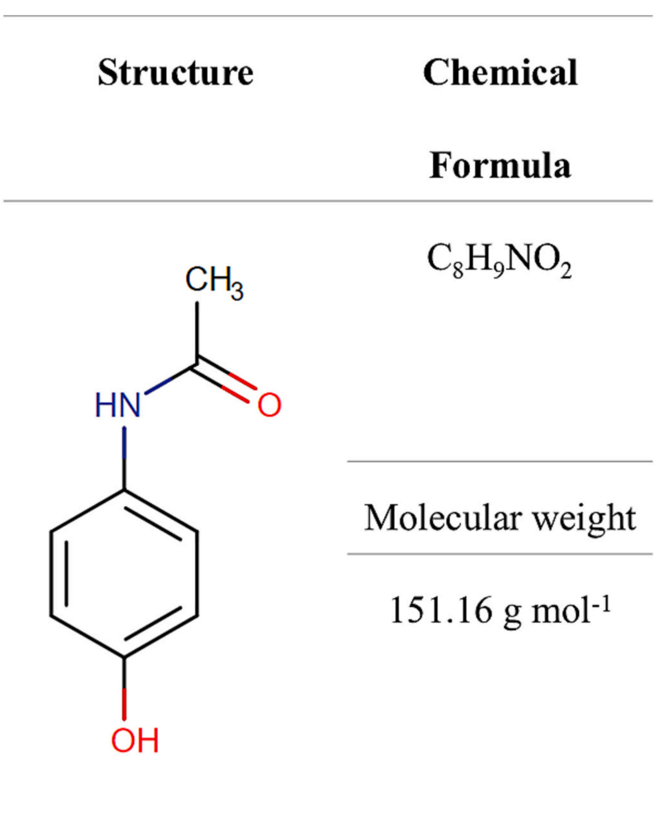



**Fig. 2.** Structure and chemical formula of acetaminophen (DrugBank, 2023a)

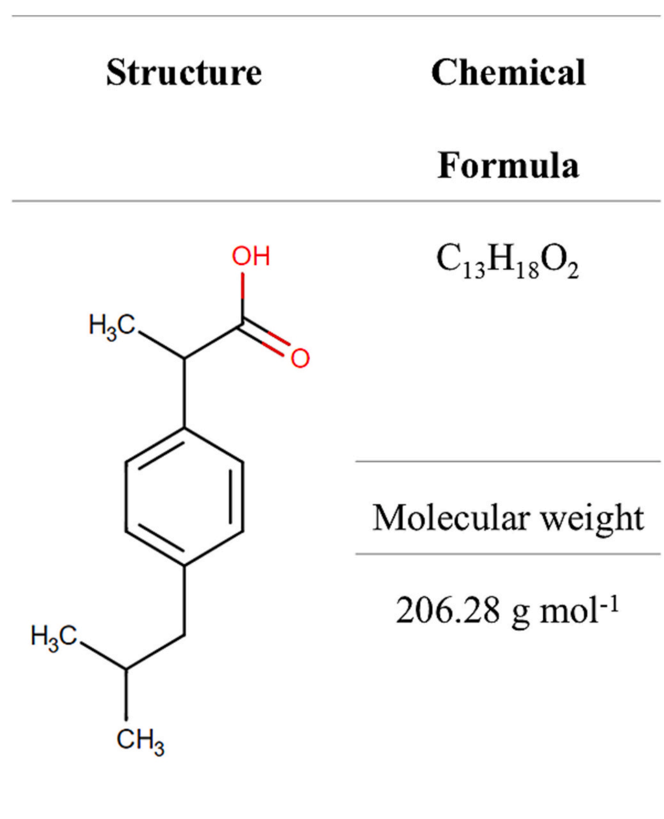



**Fig. 3.** Structure and chemical formula of ibuprofen (DrugBank, 2023b).

intermediate products during standard treatment methods (Gong et al., 2017).

Recent research on the toxic effects of ibuprofen and its metabolites indicates that this drug can induce stress, disrupt sleep cycles in fish, and stimulate the production of inflammatory cytokines in aquatic organisms. This contrasts with its effect in humans, where ibuprofen functions as an inhibitor of inflammatory mediators like prostaglandins. Additionally, ibuprofen tends to accumulate within ecological food chains, leading to negative impacts on both aquatic and land-based ecosystems (Moro et al., 2014; Ogunwole et al., 2024).

## 3. Remediation treatments for pharmaceutical pollutants: Conventional and biological approaches

The partial elimination of pharmaceutical compounds during wastewater treatment processes poses substantial risks to both aquatic ecosystems and human health. Monitoring studies have shown that pharmaceutical pollutants have infiltrated and become widespread in water systems (Ebele et al., 2017). In response, a range of treatment methods has been designed to extract micropollutants from water, aiming to mitigate their environmental impact (Morsi et al., 2020).

Wastewater treatment technologies employ an integrated approach combining chemical, physical, and biological methods to remove contaminants (Kasonga et al., 2021). Given the structural diversity of micropollutants, developing effective treatment methods requires consideration of factors such as molecular saturation, the presence of functional groups (e.g., halogens and sulfates), and structural configurations (e.g., linear or branched forms). Consequently, no single technique can effectively address all emerging contaminants (Żur et al., 2018).

A range of physicochemical methods has been explored for removing contaminants from water, including membrane separation, precipitation, ion exchange, flocculation, liquid-liquid extraction, irradiation, adsorption using materials like activated carbon, advanced oxidative techniques, and photocatalytic breakdown (Morsi et al., 2020; Naghdi et al., 2018; Zhuo and Fan, 2021).

However, despite their widespread application, these techniques have several drawbacks. For instance, the use of chemical agents as coagulants and flocculants can result in significant sludge accumulation. Additionally, these methods often exhibit limited effectiveness in contaminant degradation, involve high operational costs, and may produce harmful by-products, including more toxic intermediates (Naghdi et al., 2018; Sundararaman et al., 2022; Vasiliadou et al., 2016; Zhuo and Fan, 2021).

Biodegradation methods present multiple benefits compared to conventional techniques, such as lower costs, greater public acceptance, reliance on natural degradation processes, fewer toxic by-products, and a wider range of favorable operational conditions (Chopra and Kumar, 2020; González-González et al., 2022). Biological treatments, particularly those employing microbes and enzymes, provide effective solutions for decomposing various types of organic pollutants, making this an increasingly promising area of research in water treatment (Morsi et al., 2020).

### 3.1. Bioremediation: mechanisms and effectiveness of white-rot fungi in pharmaceutical pollutant degradation

Bioremediation is a biological approach that employs living organisms in processes such as phytoremediation, vermicomposting, bioleaching, land farming, and bioventing. This method harnesses the activity of plants, bacteria, fungi, or their enzymes to degrade or remove contaminants—including dyes, metals, organic compounds, and other persistent or toxic substances, as well as micropollutants—from various environmental matrices (Kasonga et al., 2021; Mahesh et al., 2022; Naghdi et al., 2018; Sundararaman et al., 2022).

In these biotreatment processes, microorganisms utilize pollutants as substrates, inducing enzyme production to catalyze their degradation. As a result, pollutants are biotransformed into smaller molecules, with the ultimate goal of achieving mineralization, which produces $CO_2$ and water as final end products (Morsi et al., 2020; Naghdi et al., 2018).

Fungi are acknowledged as key agents in the breakdown of various organic materials within natural environments. White-rot fungi, in particular, are regarded as highly effective because of their ability to metabolize a wide range of compounds, as evidenced by their use in bioremediation applications for soil and water (Akerman-Sanchez and Rojas-Jimenez, 2021; Mir-Tutusaus et al., 2018). Known for their role in wood decay, these fungi have been employed across various industrial and environmental sectors for biotechnological applications, owing to their ability to degrade complex polymers (González et al., 2021).

White-rot fungi exhibit multiple traits that render them highly effective in the degradation of pharmaceutically active substances. These traits include their enzymes' broad specificity, enabling the breakdown of diverse pollutants; their rapid hyphal growth, which improves contact with contaminants; the production of enzymes capable of degrading poorly water-soluble compounds; and their capacity to decompose substances in low-nutrient environments over a wide pH range (Naghdi et al., 2018).

White-rot fungi are part of a physiological group within basidiomycetes recognized for their ability to degrade lignin, which gives wood a bleached appearance (Zhuo and Fan, 2021). In natural environments, these fungi break down complex lignocellulosic biomass into smaller molecules, enabling them to utilize carbohydrates from hemicellulose and cellulose as carbon sources for metabolism. This decomposition process is driven by a synergistic action of extracellular ligninolytic enzymes, organic acids, mediators, and other enzymatic components (Kumar and Chandra, 2020; Mir-Tutusaus et al., 2018).

### 3.2. Biodegradation of acetaminophen and ibuprofen by white-rot fungi

Several species of white-rot fungi have demonstrated notable success in removing emerging pollutants. These microorganisms possess enzymatic systems, including lignin-degrading enzymes, that facilitate lignocellulose degradation and exhibit resilience to xenobiotic compounds. This adaptability and effectiveness make them highly suitable for environmental applications, such as wastewater remediation (González-González et al., 2022; González et al., 2021).

Microbial processes for biodegrading or biotransforming pharmaceutical compounds operate primarily through two mechanisms: adsorption onto biomass and enzymatic chemical modification. During adsorption, the hyphal network of mycelia contributes to water treatment via biosorption, in which pharmaceutical compounds and other substances attach to the mycelial surface or are absorbed into cells, effectively immobilizing them and restricting their movement within the water flow (Akerman-Sanchez and Rojas-Jimenez, 2021).

Additionally, extracellular enzymes, including laccase, manganese peroxidase, and lignin peroxidase—enzymes predominantly secreted by fungi for lignin degradation—play a crucial role in breaking down persistent contaminants. These enzymes utilize free radical mechanisms to degrade various pollutant molecules, with enzymatic activity occurring both within cells and along the mycelial surface (Mulkiewicz et al., 2021; Naghdi et al., 2018).

The biotransformation of pharmaceuticals, such as ibuprofen and acetaminophen, by certain strains of white-rot fungi enhances degradation processes and offers an environmentally and economically viable solution for treating wastewater (Żur et al., 2018). Tormo-Budowski et al. (2021) described a *Trametes versicolor* strain that successfully degraded acetaminophen and other pharmaceutical compounds at 100 mg/L in a bioreactor utilizing synthetic and hospital wastewater samples. The study demonstrated high removal efficiency, achieving nearly complete elimination of acetaminophen. This method effectively removed contaminants while preserving the original characteristics of the treated matrix, providing a cost-effective solution (Tormo-Budowski et al., 2021).

Additionally, Vasiliadou et al. (2019) demonstrated that *Ganoderma lucidum* and *Trametes versicolor* efficiently removed ibuprofen at 50 μg/L. The success of enhanced bio-oxidation techniques in eliminating pharmaceutical contaminants highlights the remarkable capabilities of white-rot fungi, particularly in the presence of mediators—processes that hold significant potential for bioremediation applications (Vasiliadou et al., 2019). Table 1 provides an overview of research on the biodegradation or biotransformation of acetaminophen and/or ibuprofen by white-rot fungi.

Biodegradation mechanisms in complete cultures of white-rot fungi involve adsorption onto fungal biomass and degradation mediated by both intracellular and extracellular enzymatic processes (Asif et al., 2017). The effectiveness of contaminant elimination may vary based on the range of enzyme systems produced by various fungal species (Yang et al., 2013).

Microorganisms employ various pathways for the biodegradation of acetaminophen and ibuprofen. In the degradation of acetaminophen, the process begins with hydroxylation, leading to hydroquinone formation, the release of acetamide, and cleavage of the aromatic ring. A subsequent decarboxylation step transforms 4-aminophenol, replacing the amino group with a hydroxyl group, which further generates hydroquinone. Intermediates identified during acetaminophen degradation include catechol, 2-hexenoate, succinate, oxalate, malonate, formate, nitrite, and nitrate (Li et al., 2014; Żur et al., 2018).

The biodegradation of ibuprofen involves the incorporation of hydroxyl groups into both the aromatic ring and the aliphatic chain of the molecule, producing intermediates such as 2-hydroxyibuprofen, 2-(4-hydroxyphenyl)propanoic acid, 1,4-benzenediol, and 2-hydroxyquinoline (Marchlewicz et al., 2017; Żur et al., 2018).

### 3.3. *Ligninolytic enzymes of white-rot fungi: targeted biodegradation of acetaminophen and ibuprofen*

Focusing on targeted methods, the application of purified enzymes derived from white-rot fungi offers an effective approach for biodegrading emerging contaminants in aquatic environments. In bioremediation, lignin-degrading enzymes have garnered considerable interest for industrial applications in recent years. These enzymes can operate continuously without additional nutrient inputs, minimize competition with bacterial populations, and address a wide range of contaminants. They also demonstrate high reaction rates under moderate temperature and pH conditions. Furthermore, using isolated enzymes rather than whole microorganisms significantly reduces reaction time, thereby enhancing overall process efficiency (Alvarado-Ramírez et al., 2021; Bilal et al., 2017; Morsi et al., 2020; Naghdi et al., 2018).

Enzymes provide exceptional specificity under mild operating conditions, requiring minimal energy and promoting environmentally sustainable technologies. This benefit has fueled significant progress in biotechnology, particularly in green chemistry. Projections indicate that the global market for industrial enzymes will reach $9.4 billion by 2026 (Alvarado-Ramírez et al., 2021; GlobeNewswire, 2023). The demand for lignocellulolytic enzymes has experienced significant expansion, driven by their versatile applications across multiple industries, including chemical synthesis, degradation of persistent pollutants, healthcare products, renewable energy, textiles, and food and beverage production. These enzymes are vital in supporting the economies of both developing and developed nations, as they heavily influence industrial workflows associated with the creation of various goods and services (Saldarriaga-Hernández et al., 2020).

Key enzymes extensively studied for the degradation of lignocellulosic biomass include laccase (Lac, EC 1.10.3.2), manganese peroxidase (MnP, EC 1.11.1.13), and lignin peroxidase (LiP, EC 1.11.1.14), as well as additional auxiliary enzymes. The molecular weight of these enzymes varies depending on their amino acid composition and associated cofactors. However, not all white-rot fungi species produce every ligninolytic enzyme (Asif et al., 2017; Bilal et al., 2017; Kumar and Chandra, 2020; Mir-Tutusaus et al., 2018; Yang et al., 2013). These biologically derived catalysts efficiently accelerate biochemical reactions and are essential for addressing pollution through sustainable methods (Naghdi et al., 2018).

Laccase and peroxidase enzymes are among the most widely applied in bioremediation due to their efficiency in breaking down various organic pollutants in water. The main difference between them lies in their electron acceptors: laccases rely on molecular oxygen, whereas peroxidases utilize hydrogen peroxide ($H_2O_2$) (Asif et al., 2017; Mir-Tutusaus et al., 2018). These enzymes mediate oxidation-reduction reactions in persistent molecules, producing radicals that degrade the original pollutant into smaller compounds. This ability allows extracellular enzymes derived from white-rot fungi to alter diverse organic substances, including micropollutants such as pharmaceutical residues, cresols, PAHs (polycyclic aromatic hydrocarbons), various phenolic compounds (including chlorinated variants), herbicides, pesticides, dioxins, synthetic textile dyes, and numerous other contaminants (Mir-Tutusaus et al., 2018; Morsi et al., 2020; Zhuo and Fan, 2021).

Enzymes responsible for breaking down pharmaceutical compounds have been widely studied for their roles in bioremediation and commercial uses. The application of isolated enzymes in catalytic environmental processes has been examined under diverse conditions. For instance, Alokpa et al. (2022) investigated the breakdown of acetaminophen and other pharmaceuticals using laccase derived from *Trametes hirsuta*. The study reported a high removal efficiency of 99 % in batch treatments, highlighting significant potential for improving wastewater treatment performance (Alokpa et al., 2022). Similarly, Arca-Ramos et al. (2016) employed laccase from *Trametes versicolor* to investigate the degradation of ibuprofen, acetaminophen, and additional pharmaceuticals, achieving a removal rate close to 80 % (Arca-Ramos et al., 2016).

The biodegradation of emerging contaminants using lignin-degrading enzymes obtained from white-rot fungi represents an innovative and sustainable strategy to address the escalating issue of water pollution. This method offers an efficient and eco-friendly approach to reducing the effects of these compounds on aquatic ecosystems and human health. Table 2 provides an overview of research focused on the biodegradation or biotransformation of acetaminophen and/or ibuprofen using isolated ligninolytic enzymes derived from white-rot fungi.

## 4. Conclusions and future perspectives

The widespread use of medications such as acetaminophen and ibuprofen, coupled with pollution driven by population growth and industrial expansion, has caused a substantial global impact from these emerging pollutants, which is expected to worsen without effective management. Bioremediation research, particularly studies focused on treatment systems employing microorganisms like white-rot fungi and their associated enzymes, presents a promising solution. These fungi have proven effective at breaking down a diverse array of persistent contaminants, offering environmentally sustainable approaches for pollutant removal in water treatment systems.

Studies have demonstrated that specific white-rot fungi, including *Trametes versicolor* and *Ganoderma lucidum*, are highly effective in breaking down pharmaceuticals such as acetaminophen and ibuprofen. Although these fungi have shown promising results, investigating other species within the white-rot group and their enzyme systems could uncover additional candidates for bioremediation. Comparative research on enzyme specificity and degradation pathways may also provide insights into the underlying mechanisms. A key process involves the secretion of extracellular ligninolytic enzymes—such as laccase, manganese peroxidase, and lignin peroxidase—that degrade complex pharmaceutical compounds into less harmful forms. These fungi function efficiently under a variety of environmental conditions, including

**Table 1**
Degradation of acetaminophen and ibuprofen by white-rot fungi.

| White-rot fungi | Pharmaceuticals | Concentration | Conditions | Determined analytical procedures | Effectiveness of treatment (%) | References |
|---|---|---|---|---|---|---|
| *Trametes versicolor* | Acetaminophen | 60 and 80 mg/L | The treatment of acetaminophen was carried out using a laccase activity of 40 U/L. The reduction of the drug was evaluated with and without the mediator HBT (1-hydroxybenzotriazole) at 0.2 mM. The mixtures were incubated in darkness at 37 °C in a final volume of 5 mL. | Spectrophotometer | 79 % | (Sybuia et al., 2024) |
| *Trametes versicolor* | Acetaminophen, and 16 other pharmaceuticals. | 1 mg/L each | The study evaluated the removal of pharmaceuticals in two types of bioreactors: a 5 L semi-batch stirred tank bioreactor and a 3 L recirculating trickle-bed bioreactor. In both systems, synthetic and hospital wastewater were used, with pH controlled at 4.5 and temperature maintained at 25 °C. Fungal pellets were inoculated, and nutrients were added every 48 h for 14 days. | LC-MS/MS | 90.5 to 99.7 % removal | (Tormo-Budowski et al., 2021) |
| *Phanerochaete chrysosporium* | Acetaminophen | 0.25 mg/L | The study evaluated the remediation capacity of acetaminophen in nutrient-rich and nutrient-poor media. The effects of nitrogen limitation, pH manipulation, and co-cultivation of both species were investigated. The cultures were incubated at 20–30 °C, 130–150 rpm, and samples were taken at specific time intervals to analyse the pH and drug concentration for 7 days. | LC-MS/MS | 99 % removal | (Esterhuizen et al., 2021) |
| *Trametes versicolor* and *Ganoderma lucidum* | Ibuprofen, and other 12 pharmaceuticals | 0.05 mg/L each | The experiments for the treatment of hospital wastewater were carried out in sealed 125 mL glass serum bottles. Each bottle contained 50 mL of a solution of oxidising promoters, 5 mL of wet fungal pellets, and 25 μL of a standard solution containing 13 pharmaceutical compounds. The mixtures were incubated at 25 °C, 150 rpm for 24 h for 1 day. | LC-MS/MS | 70–100 % removal | (Vasiliadou et al., 2019) |
| *Trametes versicolor* | Ibuprofen, and other pharmaceuticals | 10 mg/L of each compound | Experiments were conducted on hospital wastewater, which was pretreated with a coagulation-flocculation process. Following this, bioreactor treatment was performed, where after the pellet growth, the medium was withdrawn, and the bioreactor was filled with pretreated hospital wastewater. Continuous operation and batch degradation experiments were carried out for 21 days. | HPLC-UV | >80 % removal | (Mir-Tutusaus et al., 2018b) |
| *Pleurotus eryngii*, *Pleurotus djamor*, *Lentinus edodes*, *Pleurotus ostreatus*, and *Pleurotus citrinopileatus*, among others. | Acetaminophen, and other pharmaceuticals | 5 to 100 mg/L | Bioreactor experiments were performed in glass reactors with a total volume of 500 mL at a temperature of 25 °C. For the acetaminophen removal, reverse osmosis water was circulated through the reactor for 24 h. Once the reactor reached a steady state, it was continuously fed with either reverse osmosis water or wastewater containing 2 mg/L of acetaminophen. | HPLC-DAD | 30–100 % removal | (Chang et al., 2018) |
| *Trametes versicolor* | Ibuprofen, and other pharmaceuticals | 20 mg/L | The biodegradation study was carried out in a glass air-pulsed fluidised bed bioreactor with a volume of 1.5 L, in continuous and sequential batch reactor modes. The pH was maintained at 4.5, temperature at 25 °C, with synthetic water and pretreated hospital wastewater for 3 days. | HPLC-UV | Almost 100 % removal | (Torán et al., 2017) |
| *Trametes versicolor* | Ibuprofen, and other pharmaceuticals | 20 mg/L of each | An air-pulsed fluidised bed bioreactor was used, with a volume of 1.5 L, in continuous and sequential batch reactor modes. In the pharmaceutical compound treatment experiments, pretreatments | HPLC | 90–100 % removal | (Mir-Tutusaus et al., 2016) |

(continued on next page)

**Table 1** (*continued*)

| White-rot fungi | Pharmaceuticals | Concentration | Conditions | Determined analytical procedures | Effectiveness of treatment (%) | References |
|---|---|---|---|---|---|---|
| | | | such as coagulation-flocculation and UV-C irradiation were evaluated, with untreated or pretreated hospital wastewater for 28 days. | | | |
| *Trametes hirsuta* | Acetaminophen, ibuprofen and other 4 pharmaceuticals | 0.1 mg/L to 0.5 μg/L each | Biodegradation studies were performed in 250 mL Erlenmeyer flasks. Each flask contained 50 mL of sterile medium with 0.5 mL of mycelial solution at 26 °C, 135 rpm, and pH 4.6. After 3 days of fungal growth, 50 μL of a solution containing six pharmaceuticals were added. The treatment lasted for an additional 48 h. | UPLC-MS/ESI | 90 % removal | (Haroune et al., 2016) |
| *Trametes versicolor* and *Ganoderma lucidum* | Ibuprofen, and 13 pharmaceutical | 0.05 mg/L of each pharmaceutical | Biological removal experiments were conducted in 125 mL glass serum bottles using 36 mL of defined medium with a pH of 4.5, at 150 rpm and 25 °C for 7 days. | LC-MS/MS | >98 % removal | (Vasiliadou et al., 2016) |
| *Trametes versicolor* | Ibuprofen, acetaminophen and other pharmaceuticals | Ibu 12.61 μg/L and Ace 3.87 μg/L | A batch mode scale was used in a fluidised bed bioreactor with a volume of 10 L, to carry out both sterile and non-sterile urban wastewater treatments, at pH 4.5, 25 °C, air flow rate: 12 L $h^{-1}$, and the contact time varied in intervals to study the degradation process. | UPLC-MS | 100 % removal | (Cruz-Morató et al., 2013) |
| *Trametes versicolor* ATCC 7731 | Iibuprofen, and 30 trace organic contaminants | Ibu 100 μg/L | A batch mode experimentation scale was used. Experiments were conducted in a 5.5 L membrane bioreactor with a Polyvinylidene Fluoride hollow fiber membrane module. | GC/MS | Low removal | (Nguyen et al., 2013) |
| *Phanerochaete chrysosporium* | Ibuprofen and other pharmaceuticals | 1 mg/L each | A continuous mode experimentation scale was used. Experiments were conducted in a continuous fixed-bed reactor (FBR) operated continuously for 100 days, at 30 °C, and a continuous air flow (1 L/min). | GC–MS | 100 % removal | (Rodarte-Morales et al., 2012) |
| *Phanerochaete chrysosporium* | Ibuprofen, and other pharmaceuticals | 2000 mg/L each | A fed-batch mode experimentation scale was used. Experiments were conducted in a 2 L fermenter at 200 rpm and 30 °C, using modified Kirk medium with a pH of 4.5. Pulses of glucose and pharmaceuticals were added every 3–4 days, with daily additions of pharmaceuticals. | GC–MS | 100 % removal | (Rodarte-Morales et al., 2011) |
| *Trametes versicolor* and its laccase | Ibuprofen, and other 9 pharmaceuticals | 10 μg/L | A batch mode experimentation scale was used. The incubation time was 48 h, at a temperature of 30 °C and 125 rpm. 1 mM ABTS was added as a mediator in some experiments. | GC–MS | 100 % removal | (Tran et al., 2010) |
| *Bejerkandera* sp. *Phanerochaete chrysosporium* | Ibuprofen and other 3 pharmaceuticals | 1 mg/L each | Experiments were conducted in Erlenmeyer flasks containing 90 mL of modified Kirk medium at 30 °C, 150 rpm for 14 days. | GC–MS | 100 % removal | (Rodarte-Morales et al., 2010) |
| *Trametes versicolor*, *Ganoderma lucidum*, *Irpex lacteus* and *Phanerochaete chrysosporium* | Ibuprofen, and other pharmaceuticals | 10 mg/L | Experiments were conducted at pH 4.5, 25 °C, with an incubation time of 7 days at 135 rpm in 10 mL of medium per 125 mL serum bottle. | NMR, HPLC, GC | 100 % removal | (Marco-Urrea et al., 2009) |

different pH levels and nutrient-limited settings, broadening their applicability in wastewater treatment.

Future research should prioritize the optimization of ligninolytic enzyme production from white-rot fungi by exploring genetic and environmental factors that influence enzyme yield and activity. Improving enzyme stability and reusability, both in free and immobilized forms, is essential to enhance reaction rates and overall efficiency in degrading pharmaceutical contaminants. Additionally, feasibility and scale-up studies, including pilot projects and economic evaluations, are crucial to establishing a favorable cost-benefit ratio and validating the practical implementation of fungal bioremediation in large-scale wastewater treatment facilities. Such research is vital for developing effective technological approaches to address diverse contaminated matrices from an environmental perspective.

Ensuring regulatory compliance and achieving public acceptance are critical for the successful implementation of bioremediation technologies. Engaging policymakers, industry stakeholders, and the public to effectively communicate the benefits and safety of fungal bioremediation in wastewater treatment is essential. Addressing these factors will enable future research to advance bioremediation, providing robust, sustainable, and environmentally friendly approaches to eliminate pharmaceutical pollutants from wastewater.

**Table 2**
Degradation of acetaminophen and ibuprofen by enzymes from white-rot fungi.

| White-rot fungi enzyme source | Pharmaceuticals | Concentration | Conditions | Determined analytical procedures | Effectiveness of treatment (%) | Reference |
|---|---|---|---|---|---|---|
| *Trametes versicolor* laccase | Acetaminophen | 30 mg/L | A batch mode experimentation scale was used, with studies conducted in 15 mL Falcon flasks, using 10 mg of biochar incubated with 5 mL of acetaminophen solution for 24 h at 25 °C and 80 rpm in an orbital shaker. | HPLC | 20 % removal | (Hoinacki Da Silva et al., 2022) |
| *Trametes hirsuta* laccase | Acetaminophen and other pharmaceuticals | 10 μg/L | A batch mode experimentation scale was used, with studies conducted at pH 7, temperature of 22 °C, and a contact time of 24 h. | UPLC-MS/MS | 99 % removal | (Alokpa et al., 2022) |
| *Trametes versicolor* laccase | Acetaminophen and other pharmaceuticals | 1 mg/mL | A batch mode experimentation scale was used. Studies were conducted at pH 5.0, with contact times for acetaminophen removal of 1, 2, 4, and 18 h. | SEM, FT-IR, AFM, NMR, UV-VIS | Up to 99 % removal | (Pylypchuk et al., 2018) |
| *Trametes versicolor* laccase | Acetaminophen | 30.232 mg/L | A batch mode experimentation scale was used, with experiments conducted in 50 mL glass flasks, the initial pH of the enzymes at pH 7.4 and the substrate at pH 4.2, temperature: 25 °C, and contact time with samples taken at intervals of 60 s, 150 s, 250 s, and 1000 s. | UV–vis and LC-MS | 63.7 % removal | (Wang et al., 2018) |
| *Lentinus polychrous* laccase | Acetaminophen | 1–100 mg/L | A batch mode experimentation scale was used, with a reaction mixture of 50 g of immobilized laccase and 300 mL of acetaminophen solution in 500 mL conical flasks, with a contact time of 4 h at room temperature. | UV-VIS | 94 % removal | (Ratanapongleka and Punbut, 2017) |
| *Trametes hirsuta* laccase | Acetaminophen and other pharmaceuticals | 1 mg/L | A batch mode experimentation scale was used with biobead-entrapped laccase, initial pH 7.0, temperature: 20 °C, 150 rpm, and contact time: samples collected at intervals of 1, 2, 3, 4, 5, 6, 24, and 48 h. | UPLC-MS/MS | 30 %–70 % removal | (Hachi et al., 2017) |
| *Trametes versicolor* laccase | Ibuprofen, Acetaminophen, and other pharmaceuticals | 10–50 μg/L | A batch mode experimentation scale was used for 6 h, co-aggregation with BSA (laccase ratio of 1:1 w), at room temperature: 24 ± 2 °C. | UPLC-MS/MS | 80 % removal of acetaminophen | (Arca-Ramos et al., 2016) |
| *Trametes versicolor* laccase | Acetaminophen and others 12 pharmaceuticals | 100 μg/L | A batch mode experimentation scale was used for 6 h and 12 h, with a core-shell system composed of copper alginate for laccase immobilisation. | UPLC-MS | 85–97 % removal | (Kumar and Cabana, 2016) |
| *Trametes versicolor* laccase | Acetaminophen | 100 μg/L and 177.4 μg/L | Crosslinked enzyme aggregates (combi-/CLEA) reaction with samples of municipal wastewaters, hospital wastewater, and Milli-Q ultrapure water reaction during 8 h | UPLC/MS/MS | About 99 % and 80 % transformations. | (Ba et al., 2014a) |
| *Trametes versicolor* laccase | Acetaminophen and other pharmaceuticals | 100 μg/L | A hybrid bioreactor (HBR) combining a polysulfone hollow fiber microfiltration membrane and cross-linked enzyme aggregates of laccase (CLEA-Lac) was used at pH 7.5 for 8 h. | UPLC/MS/MS | Nearly 90 % removal | (Ba et al., 2014b) |

## CRediT authorship contribution statement

**María Alejandra Flórez-Restrepo:** Writing – original draft, Investigation, Conceptualization. **Xiomara López-Legarda:** Writing – review & editing, Supervision, Conceptualization. **Freimar Segura-Sánchez:** Writing – review & editing, Supervision, Project administration.

## Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

## References

Akerman-Sanchez, G., Rojas-Jimenez, K., 2021. Fungi for the bioremediation of pharmaceutical-derived pollutants: s bioengineering approach to water treatment. Environmental Advances 4, 100071. https://doi.org/10.1016/J.ENVADV.2021.100071.

Alokpa, K., Lafortune, F., Cabana, H., 2022. Application of laccase and hydrolases for trace organic contaminants removal from contaminated water. Environmental Advances 8, 100243. https://doi.org/10.1016/J.ENVADV.2022.100243.

Alvarado-Ramírez, L., Rostro-Alanis, M., Rodríguez-Rodríguez, J., Castillo-Zacarías, C., Sosa-Hernández, J.E., Barceló, D., Iqbal, H.M.N., Parra-Saldívar, R., 2021. Exploring current tendencies in techniques and materials for immobilization of laccases – a review. Int. J. Biol. Macromol. 181, 683–696. https://doi.org/10.1016/j.ijbiomac.2021.03.175.

Arca-Ramos, A., Kumar, V.V., Eibes, G., Moreira, M.T., Cabana, H., 2016. Recyclable cross-linked laccase aggregates coupled to magnetic silica microbeads for elimination of pharmaceuticals from municipal wastewater. Environ. Sci. Pollut. Res. 23, 8929–8939. https://doi.org/10.1007/s11356-016-6139-x.

Asif, M.B., Hai, F.I., Singh, L., Price, W.E., Nghiem, L.D., 2017. Degradation of pharmaceuticals and personal care products by white-rot fungi—a critical review. Current Pollution Reports 2017 3:2 3 (2), 88–103. https://doi.org/10.1007/S40726-017-0049-5.

Aus der Beek, T., Weber, F.A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016. Pharmaceuticals in the environment—Global occurrences and perspectives. Environ. Toxicol. Chem. 35 (4), 823–835. https://doi.org/10.1002/ETC.3339.

Ba, S., Haroune, L., Cruz-Morató, C., Jacquet, C., Touahar, I.E., Bellenger, J.P., Legault, C.Y., Jones, J.P., Cabana, H., 2014a. Synthesis and characterization of

combined cross-linked laccase and tyrosinase aggregates transforming acetaminophen as a model phenolic compound in wastewaters. Sci. Total Environ. 487 (1), 748–755. https://doi.org/10.1016/J.SCITOTENV.2013.10.004.
Ba, S., Jones, J.P., Cabana, H., 2014b. Hybrid bioreactor (HBR) of hollow fiber microfilter membrane and cross-linked laccase aggregates eliminate aromatic pharmaceuticals in wastewaters. J. Hazard. Mater. 280, 662–670. https://doi.org/10.1016/J.JHAZMAT.2014.08.062.
Barrios-Estrada, C., de Jesús Rostro-Alanis, M., Muñoz-Gutiérrez, B.D., Iqbal, H.M.N., Kannan, S., Parra-Saldívar, R., 2018. Emergent contaminants: endocrine disruptors and their laccase-assisted degradation – a review. Sci. Total Environ. 612, 1516–1531. https://doi.org/10.1016/J.SCITOTENV.2017.09.013.
Bautista-Zamudio, P.A., Flórez-Restrepo, M.A., López-Legarda, X., Monroy-Giraldo, L.C., Segura-Sánchez, F., 2023. Biodegradation of plastics by white-rot fungi: a review. Sci. Total Environ. 901, 165950. https://doi.org/10.1016/J.SCITOTENV.2023.165950.
Bilal, M., Asgher, M., Parra-Saldivar, R., Hu, H., Wang, W., Zhang, X., Iqbal, H.M.N., 2017. Immobilized ligninolytic enzymes: an innovative and environmental responsive technology to tackle dye-based industrial pollutants – a review. Sci. Total Environ. 576, 646–659. https://doi.org/10.1016/J.SCITOTENV.2016.10.137.
Chang, B.V., Fan, S.N., Tsai, Y.C., Chung, Y.L., Tu, P.X., Yang, C.W., 2018. Removal of emerging contaminants using spent mushroom compost. Sci. Total Environ. 634, 922–933. https://doi.org/10.1016/J.SCITOTENV.2018.03.366.
ChemAnalyst, 2024a. Ibuprofen Market Analysis: Industry Market Size, Plant Capacity, Production, Operating Efficiency, Demand & Supply Gap, End Use Applications, Distribution Channel, Regional Demand, Company Share, Manufacturing Process, 2015-2034 marzo.
ChemAnalyst, 2024b. Paracetamol Market Analysis: Industry Market Size, Plant Capacity, Production, Operating Efficiency, Demand & Supply Gap, End Use Applications, Distribution Channel, Regional Demand, Company Share, Manufacturing Process, 2015-2034. Decode the future of Paracetamol. marzo. https://www.chemanalyst.com/industry-report/paracetamol-market-3152.
Chen, L., Zhang, X., Zhang, M., Zhu, Y., Zhuo, R., 2022. Removal of heavy-metal pollutants by white rot fungi: mechanisms, achievements, and perspectives. J. Clean. Prod. 354, 131681. https://doi.org/10.1016/J.JCLEPRO.2022.131681.
Chiam, E., Weinberg, L., Bellomo, R., 2015. Paracetamol: a review with specific focus on the haemodynamic effects of intravenous administration. Heart, Lung and Vessels 7 (2), 121. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4476766/#:~:text=The haemodynamic effects of the,paracetamol may cause iatrogenic hypotension.
Chopra, S., Kumar, D., 2020. Ibuprofen as an emerging organic contaminant in environment, distribution and remediation. Heliyon 6 (6), e04087. https://doi.org/10.1016/J.HELIYON.2020.E04087.
Chu-Wen, Y., Yi-En, C., Bea Ven, C., 2020. Microbial communities associated with acetaminophen biodegradation from mangrove sediment. Sustainability 12 (13), 5410. https://doi.org/10.3390/SU12135410, 2020, Vol. 12, Page 5410.
Cruz-Morató, C., Ferrando-Climent, L., Rodriguez-Mozaz, S., Barceló, D., Marco-Urrea, E., Vicent, T., Sarrà, M., 2013. Degradation of pharmaceuticals in non-sterile urban wastewater by Trametes versicolor in a fluidized bed bioreactor. Water Res. 47 (14), 5200–5210. https://doi.org/10.1016/J.WATRES.2013.06.007.
Ding, T., Yang, M., Zhang, J., Yang, B., Lin, K., Li, J., Gan, J., 2017. Toxicity, degradation and metabolic fate of ibuprofen on freshwater diatom Navicula sp. J. Hazard. Mater. 330, 127–134. https://doi.org/10.1016/J.JHAZMAT.2017.02.004.
DrugBank, 2023a. Acetaminophen: Uses, Interactions, Mechanism of Action. DrugBank Online. https://go.drugbank.com/drugs/DB00316.
DrugBank, 2023b. Ibuprofen: Uses, Interactions, Mechanism of Action. DrugBank Online. https://go.drugbank.com/drugs/DB01050.
Ebele, A.J., Abou-Elwafa Abdallah, M., Harrad, S., 2017. Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. Emerging Contaminants 3 (1), 1–16. https://doi.org/10.1016/j.emcon.2016.12.004.
Esterhuizen, M., Behnam Sani, S., Wang, L., Kim, Y.J., Pflugmacher, S., 2021. Mycoremediation of acetaminophen: culture parameter optimization to improve efficacy. Chemosphere 263, 128117. https://doi.org/10.1016/J.CHEMOSPHERE.2020.128117.
Flaticon, 2023. Iconos vectoriales y stickers - PNG, SVG, EPS, PSD y CSS - designed by bsd, cube29, Puckung, Freepik, Eucalyp and yoyonpujiono from Flaticon. https://www.flaticon.es/.
Fu, X., Yang, X., Lin, X., Zhu, L., Yang, P., Wang, F., Shen, Z., Wang, J., Ling, Y., Qiu, Z., 2024. Environmental concentrations of acetaminophen and its metabolites promote the spread of antibiotic resistance genes through pheromone signaling pathway. Chem. Eng. J. 488, 150994. https://doi.org/10.1016/J.CEJ.2024.150994.
Girijan, S., Kumar, M., 2020. Microbial degradation of pharmaceuticals and personal care products from wastewater. In: Shah, M. (Ed.), Microbial Bioremediation & Biodegradation. Springer Singapore, pp. 173–201. https://doi.org/10.1007/978-981-15-1812-6_8/FIGURES/4.
GlobeNewswire, 2023. 13. Enzymes Global Market Report 2023. https://www.globenewswire.com/news-release/2023/02/13/2607038/0/en/Enzymes-Global-Market-Report-2023.html. (Accessed 3 December 2023).
Gong, H., Chu, W., Lam, S.H., Lin, A.Y.C., 2017. Ibuprofen degradation and toxicity evolution during Fe2+/Oxone/UV process. Chemosphere 167, 415–421. https://doi.org/10.1016/J.CHEMOSPHERE.2016.10.027.
González, C., Wu, Y., Zuleta-Correa, A., Jaramillo, G., Vasco-Correa, J., 2021. Biomass to value-added products using microbial consortia with white-rot fungi. Bioresource Technology Reports 16, 100831. https://doi.org/10.1016/J.BITEB.2021.100831.
González-González, R.B., Flores-Contreras, E.A., Parra-Saldívar, R., Iqbal, H.M.N., 2022. Bio-removal of emerging pollutants by advanced bioremediation techniques. Environ. Res. 214, 113936. https://doi.org/10.1016/J.ENVRES.2022.113936.
Hachi, M., Chergui, A., Yeddou, A.R., Selatnia, A., Cabana, H., 2017. Removal of acetaminophen and carbamazepine in single and binary systems with immobilized laccase from Trametes hirsuta. Biocatal. Biotransform. 35 (1), 51–62. https://doi.org/10.1080/10242422.2017.1280032.
Haroune, L., Saibi, S., Cabana, H., Bellenger, J.P., 2016. Intracellular enzymes contribution to the biocatalytic removal of pharmaceuticals by Trametes hirsuta. Environ. Sci. Technol. 51 (2), 897–904. https://doi.org/10.1021/ACS.EST.6B04409/SUPPL_FILE/ES6B04409_SI_001.PDF.
Hoinacki Da Silva, Polidoro, A.S., Cabrera Ruschel, Thue, P.S., Jacques, R.A., Lima, É.C., Bussamara, R., Fernandes, A.N., 2022. Laccase covalently immobilized on avocado seed biochar: a high-performance biocatalyst for acetaminophen sorption and biotransformation. J. Environ. Chem. Eng. 10 (3), 107731. https://doi.org/10.1016/J.JECE.2022.107731.
Jain, M., Khan, S.A., Sharma, K., Jadhao, P.R., Pant, K.K., Ziora, Z.M., Blaskovich, M.A.T., 2022. Current perspective of innovative strategies for bioremediation of organic pollutants from wastewater. Bioresour. Technol. 344, 126305. https://doi.org/10.1016/J.BIORTECH.2021.126305.
Kasonga, T.K., Coetzee, M.A.A., Kamika, I., Ngole-Jeme, V.M., Benteke Momba, M.N., 2021. Endocrine-disruptive chemicals as contaminants of emerging concern in wastewater and surface water: a review. J. Environ. Manage. 277, 111485. https://doi.org/10.1016/J.JENVMAN.2020.111485.
Kumar, V.V., Cabana, H., 2016. Towards high potential magnetic biocatalysts for on-demand elimination of pharmaceuticals. Bioresour. Technol. 200, 81–89. https://doi.org/10.1016/J.BIORTECH.2015.09.100.
Kumar, A., Chandra, R., 2020. Ligninolytic enzymes and its mechanisms for degradation of lignocellulosic waste in environment. Heliyon 6 (2), e03170. https://doi.org/10.1016/J.HELIYON.2020.E03170.
Li, J., Ye, Q., Gan, J., 2014. Degradation and transformation products of acetaminophen in soil. Water Res. 49, 44–52. https://doi.org/10.1016/J.WATRES.2013.11.008.
de Lima, D.P., dos Santos, E. dos A., Marques, M.R., Giannesi, G.C., Beatriz, A., Yonekawa, M.K.A., Montanholi, A. dos S., 2018. Fungal bioremediation of pollutant aromatic amines. Current Opinion in Green and Sustainable Chemistry 11, 34–44. https://doi.org/10.1016/J.COGSC.2018.03.012.
Mahesh, N., Balakumar, S., Danya, U., Shyamalagowri, S., Babu, P.S., Aravind, J., Kamaraj, M., Govarthanan, M., 2022. A review on mitigation of emerging contaminants in an aqueous environment using microbial bio-machines as sustainable tools: progress and limitations. Journal of Water Process Engineering 47, 102712. https://doi.org/10.1016/J.JWPE.2022.102712.
Marchlewicz, A., Guzik, U., Wojcieszyńska, D., 2015. Over-the-counter monocyclic non-steroidal anti-inflammatory drugs in environment - sources, risks, biodegradation. Water Air Soil Pollut. 226 (10), 1–13. https://doi.org/10.1007/s11270-015-2622-0.
Marchlewicz, A., Guzik, U., Smułek, W., Wojcieszyńska, D., 2017. Exploring the degradation of ibuprofen by Bacillus thuringiensis B1(2015b): the new pathway and factors affecting degradation. Molecules 22 (10), 1676. https://doi.org/10.3390/MOLECULES22101676, 2017, Vol. 22, Page 1676.
de Melo Pirete, L., Camargo, F.P., Dornelles, H.S., Granatto, C.F., Sakamoto, I.K., Grosseli, G.M., Fadini, P.S., Silva, E.L., Varesche, M.B.A., 2022. Biodegradation of diclofenac and ibuprofen in fluidized bed reactor applied to sanitary sewage treatment in acidogenic and denitrifying conditions. Journal of Water Process Engineering 49, 102964. https://doi.org/10.1016/J.JWPE.2022.102964.
Marco-Urrea, E., Pérez-Trujillo, M., Vicent, T., Caminal, G., 2009. Ability of white-rot fungi to remove selected pharmaceuticals and identification of degradation products of ibuprofen by Trametes versicolor. Chemosphere 74 (6), 765–772. https://doi.org/10.1016/J.CHEMOSPHERE.2008.10.040.
Mir-Tutusaus, J.A., Baccar, R., Caminal, G., Sarrà, M., 2018a. Can white-rot fungi be a real wastewater treatment alternative for organic micropollutants removal? A review. Water Research 138, 137–151. Elsevier Ltd. https://doi.org/10.1016/j.watres.2018.02.056.
Mir-Tutusaus, J.A., Caminal, G., Sarrà, M., 2018b. Influence of process variables in a continuous treatment of non-sterile hospital wastewater by Trametes versicolor and novel method for inoculum production. J. Environ. Manag. 212, 415–423. https://doi.org/10.1016/J.JENVMAN.2018.02.018.
Mir-Tutusaus, J.A., Sarrà, M., Caminal, G., 2016. Continuous treatment of non-sterile hospital wastewater by Trametes versicolor: how to increase fungal viability by means of operational strategies and pretreatments. J. Hazard. Mater. 318, 561–570. https://doi.org/10.1016/J.JHAZMAT.2016.07.036.
Moro, I., Matozzo, V., Piovan, A., Moschin, E., Dalla Vecchia, F., 2014. Morpho-physiological effects of ibuprofen on Scenedesmus rubescens. Environ. Toxicol. Pharmacol. 38 (2), 379–387. https://doi.org/10.1016/J.ETAP.2014.06.005.
Morsi, R., Bilal, M., Iqbal, H.M.N., Ashraf, S.S., 2020. Laccases and peroxidases: the smart, greener and futuristic biocatalytic tools to mitigate recalcitrant emerging pollutants. In: Science of the Total Environment, 714. Elsevier B.V, p. 136572. https://doi.org/10.1016/j.scitotenv.2020.136572.
Mulkiewicz, E., Wolecki, D., Świacka, K., Kumirska, J., Stepnowski, P., Caban, M., 2021. Metabolism of non-steroidal anti-inflammatory drugs by non-target wild-living organisms. Sci. Total Environ. 791. https://doi.org/10.1016/J.SCITOTENV.2021.148251.
Naghdi, M., Taheran, M., Brar, S.K., Kermanshahi-pour, A., Verma, M., Surampalli, R.Y., 2018. Removal of pharmaceutical compounds in water and wastewater using fungal oxidoreductase enzymes. Environ. Pollut. 234, 190–213. https://doi.org/10.1016/j.envpol.2017.11.060 marzo 1.
Naidu, R., Arias Espana, V.A., Liu, Y., Jit, J., 2016. Emerging contaminants in the environment: risk-based analysis for better management. Chemosphere 154, 350–357. https://doi.org/10.1016/J.CHEMOSPHERE.2016.03.068.
Nguyen, L.N., Hai, F.I., Yang, S., Kang, J., Leusch, F.D.L., Roddick, F., Price, W.E., Nghiem, L.D., 2013. Removal of trace organic contaminants by an MBR comprising a

mixed culture of bacteria and white-rot fungi. Bioresour. Technol. 148, 234–241. https://doi.org/10.1016/J.BIORTECH.2013.08.142.
Ogunwole, G.A., Adeyemi, J.A., Saliu, J.K., Olorundare, K.E., 2024. A computational analysis of the molecular mechanisms underlying the effects of ibuprofen and dibutyl phthalate on gene expression in fish. Heliyon 10 (11), e31880. https://doi.org/10.1016/J.HELIYON.2024.E31880.
Parra Guardado, A.L., 2019. *Enzymatic degradation of recalcitrant pharmaceutical micropollutants* [Université de Montpellier]. https://tel.archives-ouvertes.fr/tel-02286745.
Poddar, K., Sarkar, D., Chakraborty, D., Patil, P.B., Maity, S., Sarkar, A., 2022. Paracetamol biodegradation by Pseudomonas strain PrS10 isolated from pharmaceutical effluents. Int. Biodeter. Biodegr. 175, 105490. https://doi.org/10.1016/J.IBIOD.2022.105490.
Pylypchuk, I.V., Kessler, V.G., Seisenbaeva, G.A., 2018. Simultaneous Removal of Acetaminophen, Diclofenac, and Cd(II) by Trametes versicolor Laccase Immobilized on Fe3O4/SiO2-DTPA Hybrid Nanocomposites. ACS Sustain. Chem. Eng. 6 (8), 9979–9989. https://doi.org/10.1021/ACSSUSCHEMENG.8B01207/SUPPL_FILE/SC8B01207_SI_001.PDF.
Rasheed, T., Bilal, M., Nabeel, F., Adeel, M., Iqbal, H.M.N., 2019. Environmentally-related contaminants of high concern: potential sources and analytical modalities for detection, quantification, and treatment. Environ. Int. 122, 52–66. https://doi.org/10.1016/j.envint.2018.11.038.
Ratanapongleka, K., Punbut, S., 2017. Removal of acetaminophen in water by laccase immobilized in barium alginate. Environ. Technol. (United Kingdom) 39 (3), 336–345. https://doi.org/10.1080/09593330.2017.1301563.
Rodarte-Morales, A.I., Feijoo, G., Moreira, M.T., Lema, J.M., 2011. Biotransformation of three pharmaceutical active compounds by the fungus Phanerochaete chrysosporium in a fed batch stirred reactor under air and oxygen supply. Biodegradation 23 (1), 145–156. https://doi.org/10.1007/S10532-011-9494-9.
Rodarte-Morales, A.I., Feijoo, G., Moreira, M.T., Lema, J.M., 2012. Operation of stirred tank reactors (STRs) and fixed-bed reactors (FBRs) with free and immobilized Phanerochaete chrysosporium for the continuous removal of pharmaceutical compounds. Biochem. Eng. J. 66, 38–45. https://doi.org/10.1016/J.BEJ.2012.04.011.
Rodarte-Morales, A.I., Moreira, M.T., Feijoo, G., Lema, J.M., 2010. Evaluation of two fungal strains for the degradation of Pharmaceutical and Personal Care Products (PPCPs). Chem. Eng. Trans. 20, 31–36. https://doi.org/10.3303/CET1020006.
Saldarriaga-Hernández, S., Velasco-Ayala, C., Leal-Isla Flores, P., de Jesús Rostro-Alanis, M., Parra-Saldivar, R., Iqbal, H.M.N., Carrillo-Nieves, D., 2020. Biotransformation of lignocellulosic biomass into industrially relevant products with the aid of fungi-derived lignocellulolytic enzymes. Int. J. Biol. Macromol. 161, 1099–1116. https://doi.org/10.1016/J.IJBIOMAC.2020.06.047.
Sundararaman, S., Aravind Kumar, J., Deivasigamani, P., Devarajan, Y., 2022. Emerging pharma residue contaminants: occurrence, monitoring, risk and fate assessment – a challenge to water resource management. Sci. Total Environ. 825, 153897. https://doi.org/10.1016/J.SCITOTENV.2022.153897.
Sybuia, P.A., Contato, A.G., de Araújo, C.A.V., Zanzarin, D.M., Maciel, G.M., Pilau, E.J., Peralta, R.M., de Souza, C.G.M., 2024. Application of the white-rot fungus Trametes sp. (C3) laccase in the removal of acetaminophen from aqueous solutions. J. Water Process Eng. 57, 104677. https://doi.org/10.1016/J.JWPE.2023.104677.
Torán, J., Blánquez, P., Caminal, G., 2017. Comparison between several reactors with Trametes versicolor immobilized on lignocellulosic support for the continuous treatments of hospital wastewater. Bioresour. Technol. 243, 966–974. https://doi.org/10.1016/J.BIORTECH.2017.07.055.
Tormo-Budowski, R., Cambronero-Heinrichs, J.C., Durán, J.E., Masís-Mora, M., Ramírez-Morales, D., Quirós-Fournier, J.P., Rodríguez-Rodríguez, C.E., 2021. Removal of pharmaceuticals and ecotoxicological changes in wastewater using Trametes versicolor: A comparison of fungal stirred tank and trickle-bed bioreactors. Chem. Eng. J. 410, 128210. https://doi.org/10.1016/J.CEJ.2020.128210.
Tran, N.H., Urase, T., Kusakabe, O., 2010. Biodegradation Characteristics of Pharmaceutical Substances by Whole Fungal Culture Trametes versicolor and its Laccase. J. Water Environ. Technol. 8 (2), 125–140. https://doi.org/10.2965/jwet.2010.125.
Varga, B., Somogyi, V., Meiczinger, M., Kováts, N., Domokos, E., 2019. Enzymatic treatment and subsequent toxicity of organic micropollutants using oxidoreductases - a review. J. Clean. Prod. 221, 306–322. https://doi.org/10.1016/J.JCLEPRO.2019.02.135.
Vasiliadou, I.A., Sánchez-Vázquez, R., Molina, R., Martínez, F., Melero, J.A., Bautista, L.F., Iglesias, J., Morales, G., 2016. Biological removal of pharmaceutical compounds using white-rot fungi with concomitant FAME production of the residual biomass. J. Environ. Manage. 180, 228–237. https://doi.org/10.1016/J.JENVMAN.2016.05.035.
Vasiliadou, I.A., Molina, R., Pariente, M.I., Christoforidis, K.C., Martinez, F., Melero, J.A., 2019. Understanding the role of mediators in the efficiency of advanced oxidation processes using white-rot fungi. Chem. Eng. J. 359, 1427–1435. https://doi.org/10.1016/J.CEJ.2018.11.035.
Voběrková, S., Solčány, V., Vršanská, M., Adam, V., 2018. Immobilization of ligninolytic enzymes from white-rot fungi in cross-linked aggregates. In: Chemosphere, Vol. 202. Elsevier Ltd, pp. 694–707. https://doi.org/10.1016/j.chemosphere.2018.03.088.
Wang, K., Huang, K., Jiang, G., 2018. Enhanced removal of aqueous acetaminophen by a laccase-catalyzed oxidative coupling reaction under a dual-pH optimization strategy. Sci. Total Environ. 616–617, 1270–1278. https://doi.org/10.1016/J.SCITOTENV.2017.10.191.
WHO, W. H. O, 2023. *WHO Model List of Essential Medicines - 23rd list, 2023*. Web Annex A. The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines. abril 24. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02.
Wilkinson, J.L., Hooda, P.S., Barker, J., Barton, S., Swinden, J., 2015. Ecotoxic pharmaceuticals, personal care products, and other emerging contaminants: A review of environmental, receptor-mediated, developmental, and epigenetic toxicity with discussion of proposed toxicity to humans. Crit. Rev. Environ. Sci. Technol. 46 (4), 336–381. https://doi.org/10.1080/10643389.2015.1096876.
WWF, W. W. forum B, 2018. Susteinability declaration - Documents | World Water Forum 8. Susteinability declaration, 2018, marzo 23. http://8.worldwaterforum.org/en/documents-1.
Yang, S., Hai, F.I., Nghiem, L.D., Price, W.E., Roddick, F., Moreira, M.T., Magram, S.F., 2013. Understanding the factors controlling the removal of trace organic contaminants by white-rot fungi and their lignin modifying enzymes: a critical review. Bioresour. Technol. 141, 97–108. https://doi.org/10.1016/J.BIORTECH.2013.01.173.
Zhang, J., Cai, Q., Chen, J., Lu, Y., Ren, X., Liu, Q., Wen, L., Mateen, M., 2022. Enhanced removal of ibuprofen in water using dynamic dialysis of laccase catalysis. Journal of Water Process Engineering 47, 102791. https://doi.org/10.1016/J.JWPE.2022.102791.
Zhong, C., Zhao, H., Cao, H., Huang, Q., 2019. Polymerization of micropollutants in natural aquatic environments: a review. Sci. Total Environ. 693, 133751. https://doi.org/10.1016/J.SCITOTENV.2019.133751.
Zhuo, R., Fan, F., 2021. A comprehensive insight into the application of white rot fungi and their lignocellulolytic enzymes in the removal of organic pollutants. Sci. Total Environ. 778. https://doi.org/10.1016/J.SCITOTENV.2021.146132.
Żur, J., Piński, A., Marchlewicz, A., Hupert-Kocurek, K., Wojcieszyńska, D., Guzik, U., 2018. Organic micropollutants paracetamol and ibuprofen—toxicity, biodegradation, and genetic background of their utilization by bacteria. Environmental Science and Pollution Research 25 (Número 22), 21498–21524. Springer Verlag. https://doi.org/10.1007/s11356-018-2517-x.