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Review

Ibuprofen Pollution in the Environment: A Critical Review of Sources, Physicochemical Properties, Ecotoxicological Implications, Human Health Risks, and Bioremediation Technologies

Ali Mohsen Mohammed[1], Aalaa Fahim Abbas[1] and Haider Mashkoor Hussein [1]

[1] Al-Qadisiyah University / College of Science

† Corresponding author: Author Name; nnb893505@gmail.com

https://orcid.org/0009-0001-3142-5699, https://orcid.org/0000-0003-1910-1496 ,https://orcid.org/0000-0001-5853-4871

Abstract: Ibuprofen (IBU) is increasingly recognized as a significant category of emerging micro-pollutants that infiltrate aquatic ecosystems. IBU possesses a significant capacity to inflict ecological harm, adversely affecting both ecosystems and the health of humans and animals. The primary contributors to the environmental presence of IBU encompass the pharmaceutical manufacturing sector, wastewater treatment plants (WWTPs), hospital effluents, and agricultural byproducts. The degradation of IBU is contingent upon various factors, including its chemical and biological persistence, physicochemical properties, and the methodologies employed for their treatment. A multitude of techniques has been employed to mitigate its detrimental effects, involve adsorption, coagulation, bioremediation (constructed wetlands (CWs), membrane bioreactors (MBRs), microalgal-based systems), advanced oxidation processes (AOPs), membrane filtration systems (including reverse osmosis, nanofiltration, and microfiltration), as well as photocatalytic methods, among others. The exploration of more innovative and effective technologies, aimed at IBU degradation, necessitates thorough investigation and should be specifically tailored for cost-efficiency and scalability. Additionally, the assessment of green and eco-friendly alternatives for IBU, characterized by attributes such as negligible bioaccumulation, minimal persistence, environmental compatibility, and low or no toxicity, is equally essential. Bacterial degradation mechanisms constitute a highly promising alternative for the biodegradation of IBU, especially through the application of meticulously chosen strains that have been isolated from contaminated environments.

Key Words	Bioremediation, Emerging Pollutant, Ibuprofen, Microorganisms, Metabolites, HPLC, Excretion
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1. INTRODUCTION

Water is indispensable for all forms of life and should never be underestimated; even though water blankets more than 71% of the Earth's surface, only approximately 1.2% of it is considered potable. This restricted availability underscores the necessity of clean water for maintaining a healthy way of life (Ranjith & Rajeev 2023). Regrettably, various substances like industrial chemicals, personal care products, pesticides, plastic debris, synthetic hormones, and pharmaceuticals have been discharged by rapidly advancing industries and urban areas, leading to the

contamination of a significant portion of drinkable water sources and impacting water quality as well as aquatic life (Parolini & Binelli 2012; Show & Halder 2024; Yuniarto & Hadibarata 2024).

Over the past two decades, developed nations have observed an unparalleled increase in pharmaceutical consumption attributed to the expanding global population, demographic aging, and enhanced investments in health care infrastructure. In the year 2001, worldwide expenditures on pharmaceuticals amounted to 390 billion dollars, which escalated to 1.2 trillion dollars in 2018 and is estimated to reach 1.5 dollars trillion by the year 2023 (IQVIA 2019). Pharmaceutical compounds are frequently identified as significant emerging pollutants within aquatic ecosystems globally (Samal et al. 2022). Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), for instance paracetamol, naproxen, and ibuprofen are among the most widely used pharmaceuticals and consequently, the most significant pollutants. The existence of NSAIDs contamination poses a significant concern within ecosystems due to its extensive magnitude, complex nature, as well as toxic potential (Rastogi et al. 2021; Pawłowska et al. 2023). Ibuprofen (IBU) is a widely familiar anti-inflammatory agent with high substantial rates of human consumption, often prescribed for relieving fever, headaches, toothaches, and more (Mazaleuskaya et al. 2015; Chopra & Kumar 2020; Yılmaz & Goktas 2023). IBU constitutes one of the substances suggested as option 1 for inclusion in the catalog of individual priority compounds within the European Union's initiative for a novel directive revising (Document 52022PC0540, 2022). Anthropogenic activities are accountable for the escalation in the concentration of IBU within the environment. Concentrations of IBU observed in natural aquatic environments vary from 37 ng L-1 to 30 μg L-1, whereas in wastewater systems, concentrations fluctuate between 406 ng L-1 and 2.11 mg L-1 (Thalla & Vannarath 2020; Rastogi et al. 2024). However, improper disposal, industrial facilities, WWTPs, veterinary treatments, among others, also contribute to the introduction of IBU into various environmental compartments. After ingestion by humans and animals, the substance is not entirely metabolized and subsequently eliminated from the body. The enzymes found in humans and animals facilitate the conversion of this substance into a variety of metabolic products. The resultant excretion product encompasses both IBU and its associated metabolic byproducts, which may exhibit greater toxicity than the original compound. Subsequent to excretion, these substances are introduced into WWTPs, lakes, rivers, soil, groundwater, and oceans, among other environments. Additionally, they are consumed by plants and aquatic organisms. Consequently, this process facilitates the incorporation of these substances into the food web (Jan-Roblero & Cruz-Maya 2023; Chopra & Kumar 2020). Some recognized harmful influences associated with heightened exposure to IBU encompass cellular and genetic impairment, disruption of enzymatic equilibrium, reduction in body length and ovum production, deterioration of overall health status, and modifications in hematological parameters across various organisms. Owing to its widespread presence and bioaccumulation within aquatic food structures, eradicating IBU from waters bodies has become an urgent issue for researchers (Du et al. 2016; Wang et al. 2016; Rastogi et al. 2024). IBU's environmental persistence vary when compared to other NSAIDs. For instance, a study comparing the photodegradation rates of IBU and ketoprofen in aqueous solutions revealed that IBU degrades more slowly under light exposure, suggesting a higher environmental persistence relative to ketoprofen (Szabó et al. 2011). In addition, biodegradation studies have demonstrated that IBU is more amenable to microbial breakdown than diclofenac. Using activated sludge systems, it was found that IBU degrades at a faster rate, pointing to its lower persistence in wastewater treatment processes compared to diclofenac (Peng et al. 2019). In contrast, paracetamol exhibits lower environmental persistence compared to IBU due to its higher rate of biodegradation (Quintelas et al. 2020).

The issue of pharmaceutical contamination, particularly that of IBU, is complex because of the insufficient accessibility of effective strategies for capturing, extracting, or eliminating these compounds in a controlled and efficient manner. Conventional wastewater treatment processes are inadequate for eliminating pharmaceutical residues. Furthermore, the diverse chemical composition of pharmaceuticals presents a significant challenge in developing targeted treatment technologies. However, a variety of advanced technologies are available for IBU removal, including advanced oxidation processes (AOPs), membrane processes, membrane bioreactors (MBRs), coagulation-flocculation, UV/H_2O_2, electronic oxidation, adsorption, Fenton and Fenton-like oxidation, O_3/UV, and sonolysis (Chopra & Kumar 2020; Rastogi et al. 2024; Singh et al. 2022).

These methods have some limitation such as operational costs, sludge generation, pre-treatment requirements, operability, reliability, and efficiency. However, many toxicological studies have shown that the intermediate byproducts generated during advanced chemical treatments can exhibit higher toxicity compared to the initial compound. Additionally, these oxidation technologies often have a significant environmental impact due to high energy consumption (Quero-Pastor et al. 2014; Chopra & Kumar 2020; Show & Halder 2024). As a result, IBU biodegradation is emerging as a promising substitute for removing IBU contamination in water bodies. The biodegradation method offers a number of benefits compared to conventional, physical, and chemical techniques, including being a cost-effective, natural process, capable of operating under various circumstances. Microorganisms metabolize IBU, producing carboxylated-ibuprofen and hydroxyl-ibuprofen as byproducts of the biodegradation process (Chopra & Kumar 2020; Show & Halder 2024; Lara-Moreno et al. 2024).

The objective of this review was to conduct a comprehensive evaluation the properties, pathways, ecological and human health effect and possible bioremediation approaches of IBU. IBU has been selected as a focus pollutant owing to its widespread detection in aquatic ecosystems at elevated concentrations and its known eco-toxicological effects. Previous studies on IBU pollution have primarily focused on its environmental presence, human health impacts, and traditional removal methods. However, many of these studies fail to comprehensively explore the mechanisms of IBU biodegradation, particularly the role of specific bacterial strains and their genetic components. Additionally, there is limited discussion on the integration of biological degradation methods with engineering and physical systems to enhance efficiency. While some research has explored IBU detection methods, the development and application of advanced and more sensitive techniques for IBU quantification in environmental samples remain insufficiently addressed. Furthermore, studies often overlook detailed analyses of the main sources contributing to IBU pollution, such as pharmaceutical industries, hospital waste, and domestic sewage. This review addresses these gaps by providing a thorough analysis of IBU's structure, its effects on humans and living organisms, and advanced methods for its removal, including bacterial degradation. It also highlights the latest detection techniques for IBU and examines major environmental sources responsible for its release. Additionally, the review delves into the genetic factors responsible for IBU biodegradation and evaluates the influence of environmental parameters such as temperature, pH, and heavy metals on bacterial efficiency. By combining biological and engineering approaches, this work presents a holistic framework to tackle IBU contamination more effectively than previous studies.

2.MATERIALS AND METHODS

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and accuracy in the selection and analysis of relevant studies. The following steps were followed in accordance with PRISMA:

1. Protocol: A search protocol was developed prior to the review to ensure consistency in study selection. The main objective was to evaluate the impact of ibuprofen contamination and its removal methods. Inclusion and exclusion criteria were predefined to focus on studies directly related to ibuprofen degradation and bacterial removal processes.

2. Inclusion/Exclusion Criteria: Studies were included if they focused on IBU's degradation, physicochemical properties, bacterial removal methods, and environmental impact. Studies were excluded if they did not provide experimental data, focused on unrelated pollutants, or lacked peer-review status.

3. Search Strategy: A comprehensive search was conducted in databases including PubMed, Scopus, and Google Scholar using keywords such as ibuprofen degradation, bacterial removal of ibuprofen, environmental contamination, bioremediation methods of ibuprofen, and more. The majority of studies were published in the last five years.

4. Study Selection Process: After conducting the search, a total of (170) studies were identified. Following the inclusion and exclusion criteria, (20) studies were excluded for reasons such as unrelated topics or methodological issues. Ultimately, (150) studies were included in the final review.

5. Quality Assessment: The quality of the included studies was evaluated based on their peer-reviewed status and methodological rigor. Preference was given to studies with clear experimental designs and robust data reporting.

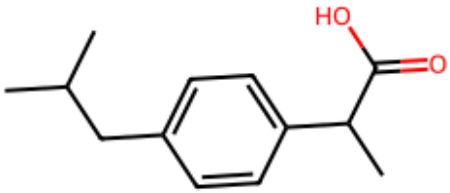
6. Data Synthesis and Analysis: Data from the selected studies were synthesized qualitatively, focusing on the methods of ibuprofen removal and the environmental implications. A comparative analysis was performed to highlight the most effective removal techniques.

7. Discussion of Limitations: While this review followed systematic review principles, some limitations include focusing on recent and relevant studies, which may have excluded some older research or studies that didn't focus directly on research items.

3. THE STRUCTURE AND PHYSICOCHEMICAL PROPERTIES OF IBUPROFEN

IBU is a highly popular over-the-counter medicine, ranking third globally (Murdoch & Hay 2015; Xu et al. 2018; Marchlewicz et al. 2017b). IBU, with the molecular formula $C_{13}H_{18}O_2$, is chemically described as 2-(4-isobutylphenyl) propanoic acid, which encompasses an aromatic ring with isobutyl substituents and propanoic acid, alongside two enantiomeric forms (R and S) (Chopra & Kumar 2020; Show & Halder 2024). The name "ibuprofen" is derived from its structural components: "ibu" for isobutyl, "pro" for propionic acid, and "fen" for phenyl (Show & Halder 2024). IBU exhibits low water solubility and significant mobility in aqueous environments, the main physicochemical characteristics of IBU presented in Table 2.

Table 2: Physicochemical characteristics of IBU (Majeed et al. 2018; Ferreira et al. 2023; Akay et al. 2021)

Item	Ibuprofen
Structure	
Formula	$C_{13}H_{18}O_2$
Molecular weight (g/mol)	206. 28
CAS no.	15687-27-1
Density (g /cm^3)	1.03
Pk_a	4.52
Log K_{ow}	3.97
Log K_d (pH 7.5)	1.00-1.78
Water solubility (mg/L)(at (20 ^{0}C)	21
Boiling point (^{0}C)	157
Melting point	75-77.5

[1] pK_a: dissociation constant; K_d: solid-water distribution coefficient; K_{ow}: octanol-water partition coefficient.

4. THERAPEUTIC USE, CONSUMPTION AND HUMAN METABOLISM OF IBUPROFEN

IBU is a prevalent medicine for both humans and animals' health and is involved in the World Health Organization WHO "Essential Drug List"; it possesses anti-inflammatory, analgesic and antipyretic influences. It available in a variety of dosage forms, such as capsules, tablets, granules, oral suspensions, creams, suppositories, drops, injections, and gels. IBU is a widely used medication across many societies for various

medical purposes. In the United States, United Kingdom, and Poland, people consume a significant amount of IBU each year, at around 300, 162, and 58 tons, respectively (Ferreira et al. 2023; Marchlewicz et al. 2015; Jan-Roblero & Cruz-Maya 2023). Recent years have seen an escalation in IBU use across numerous Nordic countries. Nevertheless, Norway and Denmark have a lower consumption rate compared to other Nordic countries, with figures approximating 2.0 and 1.15 tons annually, in that order (Jan-Roblero & Cruz-Maya 2023; Hudec et al 2012).

IBU is utilized in the therapeutic management of osteoarthritis, migraines, cancer, gout, rheumatoid arthritis, pericarditis, fever, neuritis, muscle soreness, neuropathic pain, dysmenorrhea, and postoperative pain management (Ivshina et al. 2021, Chopra & Kumar 2020; Xu et al. 2018; Yılmaz & Goktas 2023). IBU hinders the activity of cyclooxygenase, an enzyme catalyzes the biotransformation of arachidonic acid into cyclic endoperoxides, subsequently leading to the formation of thromboxanes and prostaglandins, both of which are recognized as key mediators in the inflammatory process. The inhibition of cyclooxygenase, along with the subsequent synthesis of prostaglandins leads to a reduction in the secretion of inflammatory agents and mediators, thereby impeding the nociceptor activation (Upadhyay et al. 2021; Jan-Roblero & Cruz-Maya 2023; Parolini et al. 2011).

Humans metabolize IBU through two distinct pathways: conjugation and hydroxylation. Conjugation involves reactions with glucuronic acid, sulfates, or glutathione (Marchlewicz et al. 2015). The oral administration of IBU leads to its rapid distribution across the human organism, with a considerable fraction (99%) associating with plasma albumin (Marchlewicz et al. 2015). Only a small portion (1-8%) of IBU leaves the body unchanged, after it taken. The majority undergoes a two-step process for excretion: first, the body oxidized IBU in phase one metabolism, then, in phase two, these modified molecules are conjugated, often with glucuronic acid for easier excretion. The roughly 14% of the total IBU dose is excreted as a glucuronide conjugate. Carboxyhydratopic acid (CA-HA), carboxyibuprofen (CA-IBU) and Hydroxyibuprofen (OH-IBU) are the primary metabolites of IBU found in humans (Aissaoui 2017; Aissaoui et al. 2017). In the environmental context, glucuronide-conjugated ibuprofen has the potential to undergo hydrolysis, thereby liberating free IBU (Murdoch & Hay 2015; Marchlewicz et al. 2015). Fig. 1 illustrates the proposed pathway for IBU metabolism in the human body.

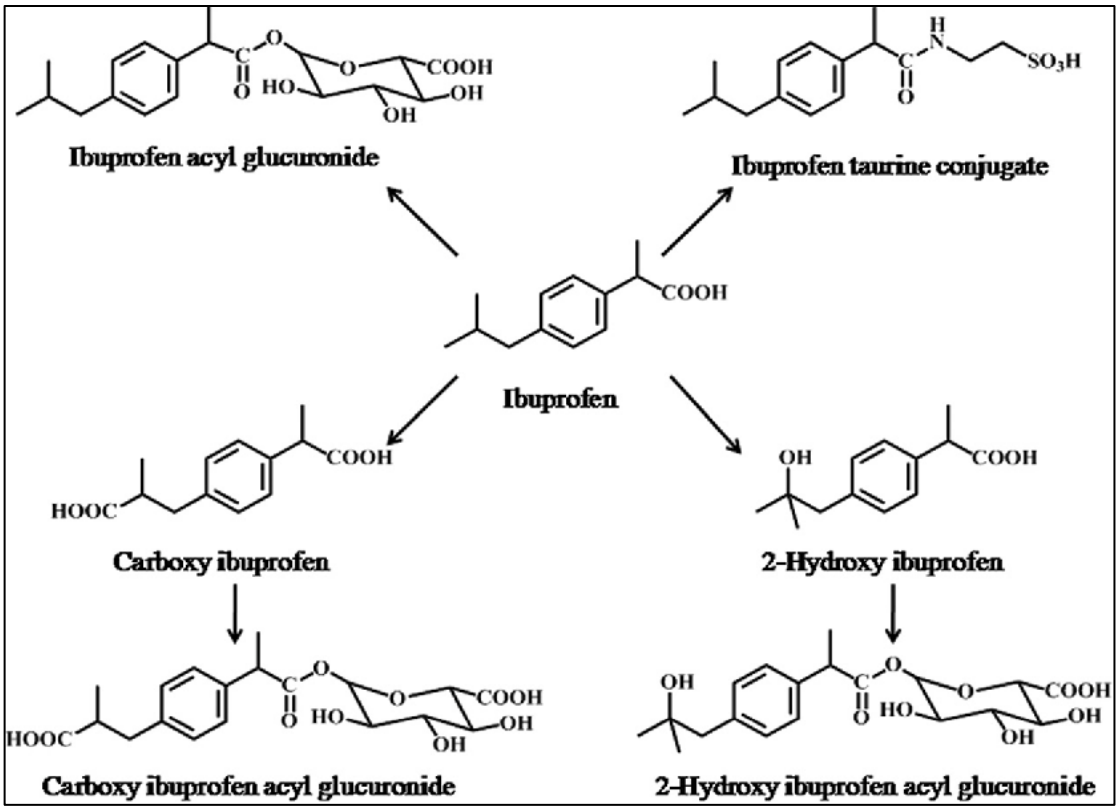


Fig. 1: Metabolic Fate of Ibuprofen in the Human Body (Aissaoui 2017)

5. SOURCES OF IBUPROFEN IN THE ENVIRONMENT (EMERGING POLLUTANT)

IBU production has been estimated at thousands of tons annually, and it has been found in concentrations oscillating from ppt to ppb in the environment (Ma et al. 2018). Small amounts of IBU have been detected in water bodies, soil, sediment, and even agricultural fields (Parolini et al. 2011; Dolu & Nas 2023). It is mostly discharged into the ecosystem via wastewater owing to its well-known utilization, inadequate degradation within human body, and highly stable molecule, as well as the inappropriate disposal method of expired and unused IBU (Sadutto et al. 2021; Chopra & Kumar 2020; Bashaar et al. 2017). Additionally, IBU ends up in the environment through others pathways, such as homes, veterinary clinics, drug factories, and hospitals as shown in Fig. 2 (Wiest et al. 2018; Ebele et al. 2017).

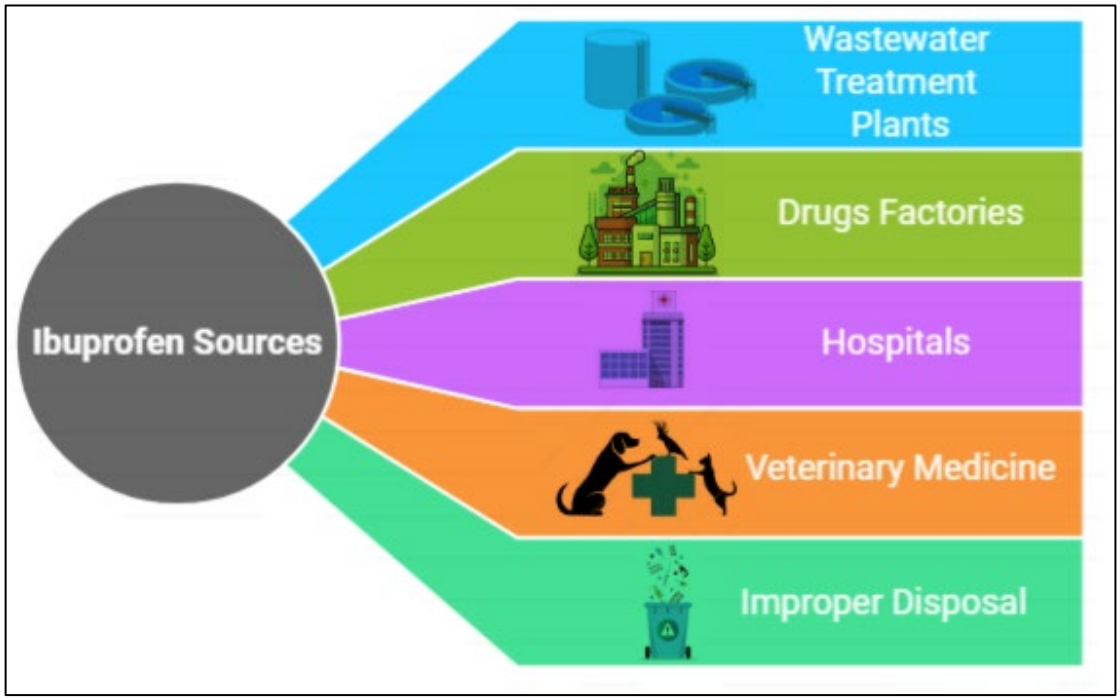


Fig. 2: The Entrance of IBU into Environment by Different Pathways

IBU is introduced into the soil primarily through its incorporation in veterinary medicine, as animals excrete ibuprofen metabolites into the soil. The organic waste can then be turned into sewage sludge or manure-based fertilizers, which have the potential to infiltrate or disperse within agricultural fields. Consequently, the presence of ibuprofen within the soil enables its mobilization, facilitating its migration towards the groundwater (Arpin-Pont et al. 2016). Finally, obtaining IBU without a medical prescription is a prevalent occurrence, resulting in its metabolites entering municipal wastewater via the excretion of feces or urine by individuals. Alternatively, unused or expired ibuprofen is directed towards municipal landfills in certain instances, infiltrating the soil as an environmental contaminant (Jan-Roblero & Cruz-Maya 2023; Marchlewicz et al. 2015). As a result, IBU considered an emerging contaminant because it is ever-present in surface, underground, treated wastewater, drinking water and soils (Aus der Beek et al. 2016; Chopra & Kumar 2020; Singh & Suthar 2021).

6. EFFECT OF IBUPROFEN ON HUMAN HEALTH AND ORGANISMS

IBU is related with several harmful consequences for human well-being. Notably, daily and excessive consumption could cause life-threatening influences, for example mild heart failure, liver failure, kidney problems, renal toxicity, metabolic acidosis, ulceration and gastrointestinal bleeding, hepatic injury, and severe hypersensitive responses and other health disorders for human bodies (Mathias et al. 2018; Volans 2015; Khalil et al. 2020; Rahman et al. 2024). A surplus intake of IBU can induce renal dysfunction by impeding cyclooxygenase, which results in a reduction in the production of renal vasodilators (Volans 2015). Additionally, cutaneous unfavorable responses like generalized bullous fixed drug eruption have been associated with the ingestion of IBU, underscoring the significance of overseeing and addressing such reactions (Bhanja et al. 2020). The safe dose of IBU for humans as a medication depends on medical consultation, the type and severity of the illness, and the patient's age (Lackie et al. 2019). However, regarding the safe exposure to IBU from contaminated water, no specific guidelines or safe exposure limits have been established by the World Health Organization (WHO) or the United States Environmental Protection Agency (EPA). Furthermore, there are currently no studies that have defined or set safe exposure limits for humans regarding consumption of IBU-contaminated water, as IBU is considered an emerging pollutant. Both the WHO

and EPA have raised concerns about the long-term accumulation of such emerging pollutants and their potential adverse effects on human health. Further research is needed to evaluate the potential health risks of such exposure.

The high lipophilicity of IBU, with a log K_{ow} value of 3.97, is attributed to the incorporation of a 2-methylpropyl group and the lack of extra oxygen atoms. This characteristic aids IBU to efficiently permeate biological membranes and reveal an important distribution within living beings, with a value of 0.18 l/kg (Czyrski 2019; Majeed et al. 2018; Oliveira et al. 2015). Accordingly, IBU has a tendency to bio-accumulate in marine (Ericson et al. 2010; Mezzelani et al. 2018) and freshwater (Xie et al. 2015; Parolini 2020) molluscs, fish (Pyhälä & Zandaryaa 2017, Xie et al. 2019), mammals (Richards et al. 2011), plants (Pi et al. 2017), and undergo biomagnification in food chains (Xie et al. 2015; Richmond et al. 2018). Upon accumulating in vertebrates and invertebrates, IBU elicits harmful effects, such as DNA damage, oxidative stress, inhibition of specific enzyme actions (such as protein nitration), lipid peroxidation and disruption of mitochondria (Sánchez-Aceves et al. 2021; Żur et al. 2018; Parolini et al. 2011; Ortiz de García et al. 2014). A severe impact is elicited in living beings following exposure to elevated levels of IBU (>100 mg L-1). Within the concentration spectrum of 10 to 100 mg L-1, it has the potential to induce non-lethal consequences. The typical IBU concentration found in ecosystems falls within the bracket of 0.2 to 8.0 µg/L (Parolini & Binelli 2012; Jan-Roblero & Cruz-Maya 2023).

Extended ecological exposure to IBU in aquatic organisms may result in persistent and severe consequences, such as genotoxic and cytotoxic impacts, elevated oxidative stress in cells, and detrimental effects on various aspects including growth rate, reproductive functions, and behavioral patterns. Furthermore, there is a proposition that within living organisms, IBU could undergo biotransformation leading to the formation of intermediary substances possessing greater toxicity compared to IBU alone (Jan-Roblero & Cruz-Maya 2023).

The harmful effect of IBU has been studied by using biological models, such as zebra mussels *(Dreissena polymorpha*). Exposure to IBU for seven days in zebra mussels resulted in the disruption of enzymatic activities and lipid peroxidation (Gonzalez-Rey & Bebianno 2012), as well as long-term exposure to IBU caused a cellular damage, chronic effects, and eliciting genetic (Jan-Roblero & Cruz-Maya 2023; Parolini et al. 2011). Research by Bartoskova et al. 2013 demonstrated that ibuprofen exposure triggered a considerable increase in glutathione peroxidase activity, a crucial antioxidant enzyme, in a manner dependent on the dosage, accompanied by a reduction in malondialdehyde levels, a biomarker of lipid peroxidation. Moreover, Parolini and Binelli's 2012 work underscored that the exposure of zebra mussels to a combination of NSAIDs, including ibuprofen, induced oxidative stress, leading to modifications in enzyme activities and DNA fragmentation, suggestive of genotoxic impacts. Additionally, Schmidt et al. 2014 observed that exposure to diclofenac and ibuprofen resulted in distinct protein expression in marine mussels, impacting proteins associated with the response to oxidative stress, thereby reinforcing the interference with enzymatic activities and oxidative stress prompted by IBU in non-target organisms.

Several investigations have been dedicated to examining the negative impact of IBU on various freshwater fish types. A research conducted by Hodkovicova et al. 2022 identified that exposure to IBU led to notable alterations in the renal systems of *Oncorhynchus mykiss*, such as hyalinosis, modifications in the expression of heat shock protein 70, and heightened oxidative stress levels. Furthermore, the medication also impacted the hepatic function of the fish, leading to dystrophy, inflammatory responses, and cellular congestion. Also, Martyniuk et al. 2022 found that within bivalve mollusks (*Unio tumidus*), the exposure to IBU concentration of 0.8 g/L over a period of 14 days resulted in a decrease in protein carbonyl levels, a decline in integrity of lysosomes within the digestive glands, and the activation of cholinesterase enzyme. Additionally, Wang et al. 2016 detected that the exposure of *Daphnia magna* to IBU levels in natural environments resulted in a marked reduction in both the overall quantity of eggs and broods for each female as well as body size.

In alternative occurrences, the existence of IBU at levels in the nature had adverse effects on tadpoles. A study by Aliko and colleagues 2021 reported that IBU negatively affected the growth of tadpoles by causing a substantial postponement in their metamorphosis duration and a decrease in body mass, as well as, an examination of blood for mutagenic activity indicated a notable rise in the occurrence of nuclear and cellular irregularities in tadpoles of the species *Bufo bufo*. Ibuprofen's damaging impacts extend beyond animals to plants. The study of Wijaya et al. 2020 on cowpea (*Vigna unguiculata*) showed reductions in shoot/root length, leaf area, weight, chlorophyll, carotenoids, minerals (Mg and K), and antioxidant activity, interestingly, calcium (Ca), manganese (Mn), and sodium translocation increased, along with stress markers like hydrogen peroxide and enzymes.

Limited data exists on the adverse impacts of IBU and its metabolites, as well as other NSAIDs, on some processes, including nitrogen fixation, the induction of oxidative stress within microbial populations, and perturbation of cellular membrane integrity (Palyzova´ et al. 2020; Guzik et al. 2019). Recent studies have revealed that IBU can contribute to the dissemination of antibiotic resistance by facilitating the acquisition of exogenous antibiotic resistance genes (Alav & Buckner 2023; Wang et al. 2020). This phenomenon is associated with IBU-induced bacterial competence, oxidative stress distinguished by an excessive generation of reactive oxygen types, and heightened permeability of the cell membrane (Ivshina et al. 2021). These mechanisms enable bacteria to acquire resistance genes more easily, leading to the spread of multi-drug resistant strains. The emergence of resistant bacteria in aquatic environments poses risks to water safety, as standard treatment processes may not fully eliminate resistant strains. This contributes to higher infection rates, treatment failures, and increased healthcare costs (Lajqi Berisha et al. 2024; Adekanmbi et al. 2023). Additionally, the presence of these resistant bacteria disrupts ecosystems, threatening both environmental and human health, as well as affecting biodiversity and the health of various species (Asif et al. 2024). Prior investigations highlighted the influence of IBU on bacterial communities in freshwater environments. Where Hodkovicova et al. 2022 reported that The exposure to IBU altered the intestinal microbiota of fish (*Oncorhynchus mykiss*), leading to increased growth of Gram-positive bacteria and subsequent changes in bacterial ratios of the Fusobacteria/Firmicutes. In addition, Liu et al. 2022 detected in the systems of activated sludge, that ibuprofen considerably altered microbial variety and bacterial community structures; for instance, several denitrifiers (Hyphomicrobium and Denitratisoma) improved notably, whereas Nitrospira considerably reduced; also, distinct IBU responses observed in different phylogenetic bacterial populations, such as a reduction in Proteobacteria and a rise in Chloroflexi.

The IBU structure endows its S-(+)- and R-(-)-ibuprofen enantiomers with distinct pharmacological activities and toxicological profiles; for instance, R-(-)-ibuprofen exhibits stereo-selectivity that inhibits hepatic mitochondrial beta-oxidation in rodent models; nevertheless, both S-(+)- and R-(-)-ibuprofen result in a moderate inhibition of mitochondrial respiration . The S-(+)-ibuprofen enantiomer demonstrates a lack of toxicity towards chondrocytes and synoviocytes. Empirical investigations indicate that S-(+)-ibuprofen possesses superior anti-inflammatory properties compared to R-(-)-ibuprofen, accompanied by reduced toxicity, enhanced clinical efficacy, and diminished variability in therapeutic outcomes. Furthermore, S-(+)-ibuprofen contributes to the mitigation of cancer progression and offers preventive measures against the onset of neurodegenerative diseases (Jan-Roblero & Cruz-Maya 2023; Gliszczyńska & Sánchez-López 2021). IBU, a racemic mixture, was found in various aquatic environments, including the Guadalquivir River basin. Both enantiomers, S-(+) and R-(-), have been found in water and sediment systems, with the R-(-) form exhibiting faster degradation (Qu et al. 2021; López-Serna et al. 2013). Aquatic organisms exhibit differential responses to IBU enantiomers. For instance, rainbow trout metabolize them slowly, while zebrafish exposed to IBU displayed stereoselective alterations in biomarkers. Additionally, ibuprofen enantiomers have varying toxicities to algae and bacteria (Jan-Roblero & Cruz-Maya 2023).

7. ANALYSIS AND DETECTION OF IBUPROFEN IN THE ENVIRONMENT

The detection and analysis of pharmaceutical compounds (PhCs), such as IBU, are crucial for comprehending the properties of their bulk substances and byproducts (Singh et al. 2022). Various methodologies for PhCs detection, including titrimetry, electrochemistry, chromatography and spectroscopy (Femina Carolin et al. 2021; Qarah & El-Maaiden 2023).

In general, the analysis of PhCs involves a series of crucial steps. The sampling process is essential to collect representative samples from water, wastewater, or soil for analysis (Sapingi et al. 2023). Subsequently, extraction procedures like solid-phase extraction (SPE) are commonly employed to isolate and concentrate PhCs from complex matrices, offering advantages over traditional liquid-liquid extraction methods (Badawy et al. 2022). Concentration and cleaning of the extracted samples are vital to increase the sensitivity and accuracy of the analytical measurements, with SPE offering various sorbent technologies for improved selectivity and efficiency (Badawy et al. 2022). Finally, chromatographic methodologies, including liquid chromatography (LC) and gas chromatography (GC), are essential for separating and quantifying PhCs in the samples, ensuring accurate identification and measurement of these composites across diverse environmental media (Badawy et al. 2022; Gulhane et al. 2022; Sapingi et al. 2023).

Recent advancements in combining GC or LC with mass spectrometry (MS) have enabled researchers to detect IBU at much lower concentrations in surface and groundwater, for example Salgado et al. 2020 used gas-chromatography-mass spectrometry (GC-MS) system in their investigation to elucidate the metabolic products through IBU biodegradation process within the reactors.

One ongoing area of research in environmental analysis focuses on exploring innovative methods for analyzing IBU. For instance, high-performance liquid chromatography (HPLC) has been utilized to ascertain IBU concentrations in environmental samples with exceptional sensitivity and accuracy (Salgado et al. 2020; Kelani et al. 2023). One study highlighted the utilization of HPLC combined with mass spectrometry (HPLC–MS) for evaluating the residual eco-toxicity of IBU degradation products in wastewater, indicating that the number and abundance of these products correlate with toxicity level (Hussain et al. 2024).

Recently, the use of liquid chromatography-tandem mass spectrometry (LC-MS/MS) has surfaced as an innovative and efficacious methodology for the identification of IBU and other pharmaceutical compounds within environmental matrices. This analytical method involves solid phase extraction (SPE) succeeded by (LC-MS/MS), which allows for the simultaneous detection of multiple emerging contaminants at ultra-trace concentrations in different media, including water environments (Ramadan et al. 2024; Yao et al. 2023). Likewise, analytical techniques such as High-Performance Liquid Chromatography with Diode Array Detector coupled with Tandem Mass Spectrometry (HPLC-DAD-MS/MS) and High-Performance Liquid Chromatography with Diode Array Detector (HPLC-DAD) have been utilized by Salgado et al. 2020 to identify and evaluate the metabolic products that produced in bioreactors during the IBU biodegradation. These methodologies are crucial for understanding the metabolic pathways that govern the degradation process, as they enable the comprehensive analysis of intricate mixtures of metabolites.

8. IBUPROFEN REMOVAL BY BIOTRANSFORMATION /BIODEGRADATION MECHANISM

An ecologically sustainable option for pharmaceutical removal involves the biodegradation by microorganisms, for example bacteria (bioremediation) (Wu et al. 2024). The primary processes engaged in biotransformation of the majority of pharmaceuticals are hydroxylation and oxidation catalyzed by cytochrome P450 (CYP). Hydroxylation refers to the addition of a hydroxyl group to a radical or ion typically by replacing hydrogen. This assertion was corroborated by the reduction in pharmaceutical concentrations when microbial cultures are exposed to 1-aminobenzotriazole (an inhibitor of CYP) (Singh et al. 2022; Hata et al. 2010). The capability of microorganisms to break down xenobiotic compounds is attributed to possessing functions akin to mammalian CYP2C9, CYP3A4, and others. These isoforms of cytochrome P450 play a major role in drug metabolism in humans. Purified laccase also serves as a catalyst in the biotransformation of certain

pharmaceuticals; nevertheless, the degradation capabilities of laccase are limited to a specific subset of pharmaceuticals, such as ciprofloxacin and naproxen (Singh et al. 2022).

Besides hydroxylation, microbial pharmaceutical degradation also employs other mechanisms like decarboxylation (carboxyl group elimination), dehydrogenation (hydrogen removal), demethylation (methyl group removal), dealkylation (alkyl group removal), acetylation (introduction of an acetyl group), dechlorination (chlorine elimination), acetate group detachment, hydroxyl and glucuronide group loss, and ester group cleavage. Various enzymes are observed to be upregulated during the degradation process, suggesting their potential involvement in the microbial breakdown of pharmaceuticals (Singh et al. 2022).

The biodegradation of IBU predominantly relies on the particular microbes utilized for biodegradation. Factors such as pH, optimal temperature, appropriate xenobiotic concentrations, and an additional carbon source required for microbial growth significantly influence the efficiency of degradation. IBU contains phenylacetic acid (PAA) in its fundamental composition. The chemical composition of IBU provides strong resilience against biodegradation, attributable to the presence of an aromatic ring featuring branched substitutions located at the para position. Aromatic ring-containing compounds typically exhibit greater resistance to degradation compared to aliphatic compounds. As a result, the structural characteristics of IBU render it resistant to degradation by microorganisms. Despite its physicochemical properties suggesting high mobility in aquatic settings, experimental evidence indicates that IBU's persistence is lower than that of other pharmaceuticals, illustrating its degradability (Jan-Roblero & Cruz-Maya 2023; Parolini et al. 2011).

Generally, IBU biodegradation proceeds through multiple pathways depending on the microorganism involved. Thus far some IBU biodegradation pathways using bacteria have been clarified. The main process involves hydroxylation, either by binding to coenzyme A (CoA) or direct trihydroxylation of the aromatic ring (Jan-Roblero & Cruz-Maya 2023; Murdoch & Hay 2013). Various investigations on the biodegradation of IBU via bacteria demonstrated the hydroxylation on its side chains (isobutyl and propanoic) or aromatic ring. Hydroxylation of the isobutyl chain by aliphatic monooxygenases results in the formation of 2-hydroxyibuprofen or 1-hydroxyibuprofen, which are subsequently dihydroxylated by acyl-CoA synthase to yield hydroquinone byproducts. Similarly, hydroxylation of the propionic acid chain results in the addition of CoA to the carboxylic group of propionic acid by acyl-CoA synthase, generating ibuprofen-CoA, which is further hydroxylated by dioxygenases and deacetylated to create p-isobutylcatechol. An alternative biotransformation route includes reducing the carboxyl group of propionic acid to generate ibuprophenol, which is then acetylated to form ibuprophenol-acetate. Lastly, the hydroxylation of aromatic ring of IBU by aliphatic monooxygenases produces trihydroxyibuprofen, leading to destabilization and cleavage by the meta-cleavage pathway as shown in Fig. 3 (Murdoch & Hay 2013; Jan-Roblero & Cruz-Maya 2023).

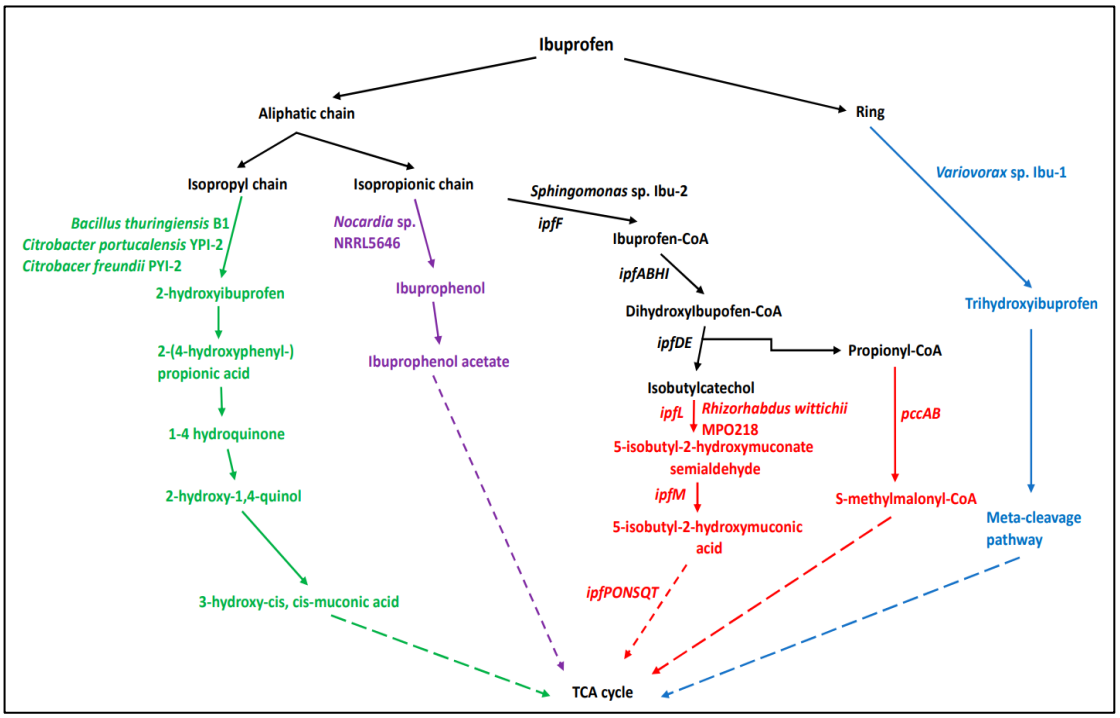


Fig. 3: The bacterial biodegradation of ibuprofen. Colored lines symbolize the metabolic pathways employed by individual bacterial genera. dotted lines indicates the existence of additional steps within the biodegradation process (Jan-Roblero & Cruz-Maya 2023).

8.1 IBUPROFEN-DEGRADING BACTERIA

Although bacteria exhibiting biodegradation potential towards ibuprofen have been recognized in recent years, the quest for novel strains with unique properties persists employing diverse methodologies aimed at acquiring new data and understanding relevant to applied bioremediation.

The initial documentation of microbial IBU biotransformation was presented by Chen & Rosazza 1994 concerning *Nocardia sp*. NRRL 5646, which utilized IBU as the exclusive energy and carbon source, resulting in the formation of intermediates such as IBU acetate, ibuprofenol, and benzoic acid byproducts. Besides the investigations conducted by Chen and Rosazza, all efforts to elucidate the bacterial catabolic route of IBU have relied on the reports carried out by Murdoch and Hay in 2005 and 2013. These studies unveiled the microbiological biodegradation process of IBU through *Sphingomonas* sp. Ibu-2 strain isolated from a wastewater treatment plant. The bacterium exhibited the capacity to degrade IBU by enzymatically removing the propionic acid chain, resulting in the formation of catechols or methylocatechols like isobutylcatechol. Similar transformations were observed with other PAA derivatives, including 2-phenylpropionic acid, 3- and 4-tolylacetic acids, and 2-(4-tolyl) propionic acid.

Biochemical and genetic analyses conducted on *Sphingomonas* sp. Ibu-2 led to the determination of its IBU degradation constituents. The establishment of a comprehensive DNA library for *Sphingomonas* sp. Ibu-2, which was inserted into fosmids, facilitated the discovery of the *ipfABDEFHI* operon consisting of seven genes involved in the biodegradation route of IBU and other PAA compounds. The functionalities of the operon genes were elucidated: *ipfA* and *ipfB* genes encode two dioxygenase subunits targeting the aromatic ring; *ipfD* gene encodes a sterol carrier protein X thiolase; and *ipfF* gene encodes a CoA ligase enzyme. Nonetheless, the role of the protein produced by the *ipfE* gene remains undisclosed. Furthermore, *ipfH* and *ipfI* genes encode a ferredoxin reductase and aromatic dioxygenase, respectively (Fig. 3). Upon the identification of these genes, it was postulated that the mechanism of IBU biodegradation in *Sphingomonas* sp. Ibu-2 unfolds as follows: the enzyme CoA ligase (*ipfF*) conjugates CoA to IBU; the multicomponent oxygenase IpfABHI subsequently

dihydroxylates ibuprofen-CoA to generate 1,2-cis-diol-2-hydroibuprofen-CoA; *IpfD* and *IpfE* then decompose this compound to yield 4-isobutylcatechol and propinyl-CoA (Kagle et al. 2009; Murdoch & Hay 2013; Murdoch & Hay 2005). Presently, the pathway of IBU biodegradation is believed to consist of dual phases. The initial (upper) phase involves the production of 4-isobutylcatechol and propinyl-CoA (Aguilar-Romero et al. 2021; Murdoch & Hay 2013; Murdoch & Hay 2005). The subsequent (lower) phase encompasses the cleavage of the IBU ring, producing substances that enter the tricarboxylic acid (TCA) cycle.

IBU biodegradation by *Patulibacter* sp. I11 was solely noticed in the existence of tryptone and yeast extract. Through the utilization of proteomic analysis, the proteins responsible for the biodegradation of ibuprofen were successfully identified. These proteins encompass acyl-CoA synthetase, a protein containing a Rieske (2Fe-2S) iron-sulfur cluster, enoyl-CoA hydratase, and ATP-binding cassette (ABC) transporter proteins. Specifically, the protein featuring a Rieske (2Fe-2S) iron-sulfur cluster is acknowledged for its role in the initial oxidation of the aromatic ring, while enoyl-CoA hydratase facilitates the hydroxylation of double bonds subsequent to ring union. Furthermore, ABC transporters are actively engaged in the transportation of compounds (Almeida et al. 2013a). The identification of these proteins strongly implies their potential involvement in the IBU biodegradation with the bacterium *Patulibacter*.

The biotransformation of IBU to trihydroxyibuprofen through the meta-cleavage route was demonstrated in the *Variovorax* sp. Ibu-1 strain isolated from activated sludge by Murdoch and Hay (Murdoch & Hay 2015). In contrast to the known degradation *ipf* route of the Ibu-2 strain, which involves coenzyme A ligation followed by dioxygenation and deacetylation steps leading to isobutylcatechol formation, the *Variovorax* sp. Ibu-1 strain directly trihydroxylates the aromatic ring of ibuprofen to produce a substrate for ring cleavage. The presence of 3-fluorocatechol, a recognized inhibitor of the meta-ring fission enzymes pathway, resulted in the detection of only poly-hydroxylated IBU metabolites. This study marked the first instance of utilizing the inhibitor 3-fluorocatechol to accumulate short-lived catecholic intermediates. These same metabolites were found in sewage sludge polluted with IBU, indicating that the meta-ring fission pathway is likely the primary catabolic route for ibuprofen decomposition in the environment (Toyama 2010; Murdoch & Hay 2015).

Marchlewicz et al. 2017a recently delineated a new pathway for the degradation of ibuprofen in the Gram-positive bacterium, *Bacillus thuringiensis* B1(2015b). The substantial activity of aliphatic monooxygenases, along with phenol and hydroquinone monooxygenases, confirmed the hydroxylation of both the aromatic ring and aliphatic chain of IBU, resulting in the establishment of various intermediates, such as 2-hydroxyibuprofen, 2-(4-hydroxyphenyl)-propionic acid, 1,4-hydroquinone, and 2-hydroxyquinol (Fig. 3). The product of acyl-CoA synthase, 1,4-hydroquinone, might undergo additional transformation via hydroquinone monooxygenase to yield 2-hydroxy-1,4-quinol, which exhibits a favorable binding affinity for hydroxyquinol 1,2-dioxygenase, an enzyme implicated in the ortho-cleavage of the aromatic ring, ultimately leading to the formation of 3-hydroxy-cis, cis-muconic acid. The biodegradation of IBU by *Bacillus thuringiensis* B1(2015b) can be augmented by co-contaminants. Notably, the addition of phenol and benzoate as co-contaminants enhanced the efficiency of IBU biodegradation by *Bacillus thuringiensis* B1(2015b) (Marchlewicz et al. 2017a; Marchlewicz et al. 2017b). Furthermore, the bacterial strain *Bacillus siamensis* DSI-1, isolated from wastewater treatment facilities, exhibits considerable efficacy in the bioremediation of ibuprofen concentrations present in effluent (Chopra & Kumar 2022).

Likewise, the bacterial strain *Rhodococcus cerastii* IEGM 1278 represents an additional bacterium capable of biodegrading IBU converting it into decarboxylated and hydroxylated derivatives. It is noteworthy that the presence of IBU induced a transition from single- to multi-cellular forms, as detailed by Lvshina et al. 2021.

A novel mechanism for enzymatic-nonenzymatic coupling degradation was postulated, utilizing the widespread marine *Pseudoalteromonas* sp. This newly proposed IBU degradation pathway involves the initiation of degradation through exposure to extracellular reactive oxygen species, leading to the formation of

the intermediate 4-ethylresorcinol, which is subsequently broken down by intracellular enzymes. The treatment of IBU with extracellular hydroxyl and superoxide anion radicals, along with hydrogen peroxide, results in the generation of 4-ethylresorcinol. Subsequently, 4-ethylresorcinol is enzymatically degraded intracellularly until complete mineralization, facilitated by enzymes such as 4-hydroxyphenylpyruvate dioxygenase, homogentisate 1,2-dioxygenase, long-chain acyl-CoA synthetase, acetyl-CoA acyltransferase, and enoyl-CoA (Li et al. 2022).

In recent times, *Sphingomonas wittichii* MPO218 exhibited the capability to biodegrade IBU employing it as its exclusive source of carbon. Subsequent investigations revealed that the genomic structure of this strain comprised a singular circular chromosome alongside two circular plasmids. Furthermore, this plasmid demonstrated conjugative properties, facilitating the horizontal transfer of the IBU degradation capacity to Sphingopyxis granuli TFA, thereby indicating that gene transfer is a crucial factor within bacterial communities engaged in biodegradation (Aulestia et al. 2021). A summary of IBU biodegradation by different bacteria is presented in Table 2.

Table 2: Summary of IBU Biodegradation by Bacteria

Bacteria	Isolation place	Reference
Sphingopyxis granuli RW412	River	Aguilar-Romero et al. 2021
Sphingobium yanoikuyae	WWTP	Balciunas et al. 2020
Bacillus thuringiensis	Soil	Marchlewicz et al. 2016
Patulibacter sp. Strain L11	WWTP	Almeida et al. 2013a
Gordonia amicalis EU266486.1	WWTP	Almeida et al. 2013b
Acinetobacter bouvetti JF681285	WWTP	Almeida et al. 2013b
Bacillus siamensis DSI-1	WWTP	Chopra & Kumar 2022
Microbacterium paraoxydans	Pharmaceutical wastewater	Show et al. 2023
Variovorax Ibu-1	WWTP	Murdoch & Hay 2015
Patulibacter medicamentivorans	WWTP	Salgado et al. 2020
Nocardioides carbamazepini sp. nov. CBZ_1T	Groundwater	Benedek et al. 2022
Sphingomonas wottichii MPO218	Sewage sludge	Aulestia et al. 2021
Pseudoalteromonas sp	Marine environment	Li et al. 2022

Rhodococcus cerastii IEGM 1278	Regional Specialized Collection of Alkanotrophic Microorganisms	Ivshina et al. 2021
R. cercidiphylli IEGM 1184	Regional Specialized Collection of Alkanotrophic Microorganisms	Ivshina et al. 2021
Pseudoxanthomonas sp. DIN-3	WWTP	Lu et al. 2019
R. erythropolis IEGM 501	Regional Specialized Collection of Alkanotrophic Microorganisms	Ivshina et al. 2021
Paracoccus aminophilus NR_042715.1	WWTP	Almeida et al. 2013b
Patulibacter americanus NR_042369	WWTP	Almeida et al. 2013b

9. FACTORS AFFECTING IBUPROFEN BIODEGRADATION

IBU biodegradation is influenced by various environmental factors that can impact both the metabolic pathways of degradation and the overall growth of microbial communities. For instance, elevated temperatures can stimulate metabolic rates, leading to increased biomass and potentially accelerated IBU degradation. Conversely, factors hindering microbial growth by inhibiting core metabolic processes may indirectly affect IBU breakdown. Understanding how environmental conditions influence ibuprofen biodegradation is crucial for predicting the degradation capacity of a given strain in natural settings (Marchlewicz et al. 2017a; Chopra & Kumar 2022).

9.1. INFLUENCE OF PH ON IBUPROFEN DEGRADATION

In case of the elimination of acidic pharmaceuticals, such as ibuprofen, the pH level is the critical variable that affects the rate of drug removal (Zembrzuska et al. 2019). pH represents a critical determinant that profoundly affects bacterial cell morphology, membrane properties, and microbial functionality (Sanguanpak et al. 2015). Furthermore, pH may exert influence over biosorption, toxicity, and the ionization states of pharmaceuticals found within environmental contexts (Boström et al. 2015). In specific scenarios, a diminished degradation rate may be associated with the ionic state of the molecule when situated at alkaline pH levels. In such circumstances, the surface of bacterial cell acquires a negative charge, thereby resulting in diminished electrostatic interactions between negatively charged compounds and the binding sites on the surface of biomass. IBU, possessing a pKa of 4.52, exists in anionic form when the pH exceeds 6.5, with over 99% of the drug being in this state. Consequently, at pH levels of 7.2 and 8.0, variations in the efficiency of degradation possibly will not correlate with distinct ionic species of IBU. An additional consideration is that the identified discrepancies could be pertain to the active status of proteins involved in the biodegradation mechanism. At lower pH values (4.0–5.0), IBU exists in a neutral state and engages with the surfaces of bacteria (Aksu et al. 2004; Marchlewicz et al. 2017a). This may imply a more facile and rapid degradation process for IBU; however, it is important to note that this uncharged state can exhibits heightened toxicity to microorganisms (Boström et al. 2015).

9.2. INFLUENCE OF TEMPERATURE ON IBUPROFEN DEGRADATION

It is widely recognized that temperature constitutes one of the most significant factors influencing biodegradation processes. In accordance with van't Hoff's principle, the rate of a chemical reaction is expected to increase by a factor of (2-4) for every increment of 10°C in temperature (Horel & Schiewer 2011; Marchlewicz et al. 2017a; Kruglova et al. 2016). As the temperature of water is raised, the polarity of water molecules decreases consequently enhancing the solubility of hydrophobic organic compounds, included pharmaceuticals (Akay et al. 2017; Akay et al. 2021; Emire et al. 2017). The aqueous solubility of PhCs is

crucial in determining their bioavailability and therapeutic efficacy, in addition to influencing their removal from wastewater and contaminated environments. IBU solubility was observed to increase with rising temperatures, attributable to the establishment of hydrogen bonds between the oxygenated groups present in IBU and the water molecules (Akay et al. 2021).

Nevertheless, within biological processes, the temperature effect on degradation mechanisms is considerably complex. This complexity arises from the interplay between temperature variations and cellular membrane function. Elevated temperatures may induce denaturation of proteins associated with cellular membranes, while excessively low temperatures can lead to increased viscosity of membrane phospholipids. Such changes may ultimately lead to an increase in the membrane rigidity, thereby obstructing transport processes within cellular membrane (Akulava et al. 2024; Kim et al. 2013). Furthermore, temperature also impacts the metabolic processes and growth rate of bacteria, affecting their efficiency and community dynamics (Aguilar-Romero et al. 2021; Marchlewicz et al. 2017a).

9.3. INFLUENCE OF HEAVY METALS ON IBUPROFEN DEGRADATION

In landfills, wastewaters, and various ecological settings, a multitude of contaminating agents are identified. The introduction of aromatic compounds, including non-steroidal anti-inflammatory drugs, into the environment is frequently associated with the occurrence of heavy metals, which may significantly affect biodegradation mechanisms. The impact of heavy metals on these mechanisms is contingent upon the specific type of metal and its chemical and physical states, such as separated-phase solids, soil-adsorbed species, colloidal solutions, soluble complexed species, or ionic solutes (Marchlewicz et al. 2017a). Environmental parameters, including pH, the cation exchange capability of the soil, the redox potential of the aqueous state, and the content of organic material, play a crucial role in determining the physical and chemical properties of metals (Olaniran et al. 2013). Additionally, the effect of metallic elements on biodegradative processes is fundamentally contingent upon their interactions with microbial entities (Marchlewicz et al. 2017a). Consequently, the influences of the metal ions Co+2, Cd+2, Cu+2, Hg+2 or Cr+6 on Bacillus thuringiensis B1(2015b) has been ascertained (Marchlewicz et al. 2016).

9.4. INFLUENCE OF AROMATIC COMPOUNDS ON DEGRADATION OF IBUPROFEN

Pharmaceutical contaminants exist concurrently in the environment alongside other pollutants, including aromatic compounds that infiltrate ecosystems as a result of both natural phenomena and anthropogenic activities (Kumar et al. 2022, Pierre et al. 2015). Due to their analogous chemical composition to IBU, these aromatic compounds possess the potential to activate enzymes that facilitate the degradation of IBU. Conversely, these aromatic compounds may engage in competitive interactions with IBU for binding sites within the enzyme's active site, thereby diminishing the degradation efficiency (Greń et al. 2010). A reduction in the rate of biodegradation may be attributed to the competitive interactions among reactants for the limited active sites of a singular enzyme. Conversely, an augmentation in degradation efficiency could be attributed to the upregulation of shared enzymes involved in this degradation process. In instances where these degradative enzymes are components of distinct metabolic pathways, the observed increase in degradation rate may be ascribed to improved biomass proliferation in the occurrence of Nutrients, consequently leading to the synthesis of vital reducing equivalents (Nowak & Mrozik 2016; Wojcieszyńska et al. 2011). In research carried out by Marchlewicz and others 2017a, it has been discerned that phenol was the only aromatic compound that exhibited no significant effect on the IBU degradation. Concurrently, a reduction in phenol concentration was noted alongside the degradation of IBU, indicating that phenol may not have impeded the breakdown of its para-substituted derivatives (Nowak & Mrozik 2016).

10. BIOREMEDIATION APPLICATIONS FOR IBUPROFEN REMOVAL

Traditional WWTPs were typically not engineered to effectively eliminate pharmaceutical micro-pollutants present in aquatic systems (Couto et al. 2019; Priya et al. 2022). It required innovative methodologies for the

elimination of these chemicals (Zhou et al. 2023; Varma et al. 2020). To mitigate the prevalence of these contaminants (such as IBU) within the ecosystem, a variety of biological approaches have been innovatively developed e.g., membrane bioreactor (MBR), attached growth MBR, stabilization ponds, constructed wetlands (CWs), Immobilized Cells Bioreactors, and others (Tiwari et al. 2017; Gharibian & Hazrati 2022; Serna-Galvis et al. 2019).

10.1 MEMBRANE BIOREACTORS (MBRS)

Membrane bioreactors (MBRs), which represent an integration of conventional biological methodologies (biodegradation using activated sludge) with advanced membrane filtration (MF), have been deemed suitable for the wastewater treatment, exhibiting numerous advantages including a reduced spatial footprint, the production of superior-grade effluent, and diminished sludge generation (Nhut et al. 2020; Ren et al. 2022; Park et al. 2018). Membrane-based separation systems exhibited noteworthy efficacy in the elimination of pharmaceuticals, particularly in the context of antibiotics, NSAIDs, and others (Alshehri et al. 2022; Maryam et al. 2020). The amounts of degradable PhCs removed in MBRs are superior to that in activated sludge facilities, attributable to extended sludge retention times, which facilitate the development of different and diverse microbe populations within the MBR framework, high level of activated sludge, and enhanced microbial activity (Tiwari et al. 2017; Song et al. 2022).

Regarding mechanisms employed within MBRs, the elimination of pharmaceuticals encompasses both biodegradation and the adsorption to sludge (Gharibian & Hazrati 2022). Microorganisms possess the capacity to alter the pharmaceutical structure either directly or indirectly through the production of specific enzymes. Both the transformation and degradation processes of PhCs via microbial communities, particularly bacteria, predominantly happen by two principal routes: co-metabolism (in which PhCs are partially transformed and/or decomposed without serving as a primary source of carbon), and mixed matrix growth/development (in which PhCs are completely mineralized and utilized as an energy and carbon source) (Wittich et al. 2023; Nguyen et al. 2024). The population of denitrifying bacteria within MBRs has exhibited a significant increase, accompanied by enhanced denitrification activities, which collectively contribute to the effective elimination of PhCs (Gharibian & Hazrati 2022). The activated sludge has shown considerable efficacy in adsorbing PhCs, thereby facilitating the contaminants elimination from aqueous phases (Nguyen et al. 2024).

MBRs exhibit numerous improvements in treatment of wastewater, such as their exceptional efficacy in the elimination of a diverse array of PhCs (Gouveia et al. 2022; Wang et al. 2018). The implementation of MF enhances the effectiveness of water purification processes. Nevertheless, it is essential to acknowledge certain limitations associated with MBRs. Among these limitations is the phenomenon of membrane fouling, which poses a substantial challenge in the operation of MBR systems. Gradually, the buildup of microorganisms, particulates, and various substances on the surface of membrane can result in diminished permeability and operational efficiency. Furthermore, MBRs typically necessitate greater energy consumption in comparison to traditional wastewater treatment methodologies (Li et al. 2020a; Nguyen et al. 2024).

10.2. CONSTRUCTED WETLANDS

Constructed wetlands (CWs) have demonstrated significant efficacy in removing various emerging PhCs, including IBU, prior to their release and discharge to the environmental ecosystem (García et al. 2020; Khan et al. 2023). The CW represents an engineered approach that operates without the necessity for supplementary chemical additives and generates minimal sludge mass, thereby achieving benefits that include efficiency, economical, and environmental sustainability in the elimination of aquatic pollutants (Liu et al. 2019; Nguyen et al. 2023; Ky et al. 2020; Zhang et al. 2023). CW consists of a specially designed wetland pool in conjunction with immobilized microorganism plates, where the constructed wetland pool is stratified into five distinct layers arranged sequentially from the top to the bottom: a sand layer, a sand-gravel layer, an immobilized microorganism layer, an artificially mixed matrix layer, and a gravel layer (Stefanakis 2020).

The predominant processes involved in the elimination of PhCs in CWs can be encompass biodegradation, precipitation, plant uptake, substrate sorption, hydrolysis, and photolysis (Vo et al. 2018; ´Avila et al. 2017; García et al. 2020). Microbial-mediated degradation has assumed a pivotal role in the breakdown and elimination of PhCs inside the CWs system (Chen et al. 2019). The availability of specific kinds of plants or vegetation further influences the functional dynamics and composition of the microbiota (e.g., bacteria), thereby impacting their overall efficacy of treatment (Zhang et al. 2023). The filter materials utilized in CWs can also significantly contribute to PhCs removal, attributed to their unique physical and chemical characteristics that enhance sorption processes, biological activities, and precipitation within these systems. Furthermore, the elimination efficiency of various PhCs families (e.g., IBU) in CWs demonstrates variability that relates with their inherent characteristics, such as Kow coefficient and water solubility, among others (Nguyen et al. 2024). Elevated specific surface area (SSA), silanol (Si–OH) configurations, retention time (HRT), hydraulic hydraulic loading rate (HLR), and a variety of microporous structures facilitate microbial adhesion and promote chemical adsorption, thereby enhancing the eradication of PhCs (Anderson et al. 2013; Al Falahi et al. 2022).

CWs exhibit significant benefits, such as environmentally sustainable, economically viable solutions characterized by reduced maintenance and operational expenditures alongside low usage of energy (Ravikumar et al. 2022; Li et al. 2020b). Despite their numerous advantages, they are also associated with certain constraints, notably the requirement for extensive spatial allocation, prolonged retention periods, and the inadequate eradication of specific PhCs (Ravikumar et al. 2022; Nguyen et al. 2023).

10.3. IMMOBILIZED CELLS BIOREACTORS

Immobilized cell bioreactors signify a significant advancement in bioprocessing technology, improving the efficiency and stability of biocatalysts across diverse applications. These systems employ immobilization methodologies to restrict microorganisms within a permeable polymeric gel matrix, wherein the immobilized microorganisms are subjected to polluted media in the gel matrix indirectly, thereby enhancing their reusability and mechanical robustness for the elimination of targeted pollutants, including IBU compounds, from wastewater (Lapponi et al. 2022; Das & Adholeya 2015). A range of techniques such as encapsulation, entrapment, and covalent bonding are utilized for cell immobilization, each presenting distinct advantages pertinent to specific biocatalytic processes (Lapponi et al. 2022).

Many researches have displayed that microorganisms residing in fixed systems exhibit superior efficacy in pollutants degradation, less sensitivity to adverse environmental fluctuations (like temperature and pH), as well as an enhanced growth rate compared to those in suspended cultures. Various fixed bioreactors were applied in the wastewater treatment, including but not limited to fluidized bed bioreactors (FBR), semi-fluidized bed bioreactors, packed bed bioreactors (PBR), anaerobic membrane bioreactors (AnMBR), and hybrid bioreactors (HBR). Bioactive beds within these systems are comprised of biocarriers that are densely populated with microorganisms (biomass). These biocarriers, distinguished by their porous and rough surfaces, facilitate the retention and attachment of a diverse microbial community (Mehrotra et al. 2021; Aissaoui 2017). However, a research of Navrozidou et al. 2019 demonstrated that bioreactors utilizing immobilized cells are capable of efficiently eliminating IBU, attaining removal efficiencies as high as 98.4%. The existence of particular microbial communities that are adept at degrading IBU, such as *Novosphingobium* and *Rhodanobacter*, significantly enhanced the degradation process.

11. CONCLUSIONS

An elevation in the concentration of IBU in both domestic and hospital sewage systems is anticipated as a consequence of the population’s utilization of this pharmaceutical for the management of various infections and ailments. This phenomenon results in its release into the environment, thereby engendering significant ecological concerns.

Microbial degradation mechanisms represent a promising alternative for the biodegradation of IBU, particularly through the utilization of specifically selected strains isolated from contaminated habitats. Furthermore, comprehensive investigations into the biodegradation pathways are imperative for elucidating the fate of this compound, which includes an understanding of the genetic and enzymatic factors implicated in these biochemical methods.

The proliferation of microbial degradation research focusing on IBU, predominantly involving bacterial species, is noteworthy; however, the ecotoxicological implications of the biodegradation byproducts remain largely unexplored. Consequently, several areas necessitate substantial advancements, including the methodical surveillance of IBU along with its biodegradation byproducts within in vivo experimental settings. Additionally, the identification and implementation of strains exhibiting high efficiency for the advancement of applied biotechnological procedures must be prioritized. Moreover, evaluations concerning the cost-effectiveness and energy efficiency of various degradation methodologies should also be investigated.

To address the growing environmental pollution caused by ibuprofen (IBU), it is essential to implement comprehensive strategies. First, effective pharmaceutical waste management policies should be established, encouraging proper disposal practices in both households and healthcare settings to prevent improper release into the environment. Additionally, advancements in microbial biodegradation techniques, particularly using efficient bacterial strains, should be prioritized to improve the breakdown of IBU in wastewater. Further research is also needed to investigate the ecotoxicological effects of biodegradation byproducts, as their potential impacts on ecosystems and human health remain largely unexplored. Continuous monitoring of IBU concentrations and its degradation products in vivo is crucial to assess their long-term environmental and biological consequences. Finally, the evaluation of cost-effective and energy-efficient degradation technologies should be a key focus to ensure that these methods are both sustainable and economically viable for widespread application. By addressing these areas, it will be possible to reduce the ecological impact of IBU and contribute to the preservation of ecosystem health.

11. PATENTS

There are no patents resulting from the work reported in this manuscript.

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