American Journal of Environmental Sciences

Review

Microbial Degradation of Paracetamol in Pharmaceutical Wastewater: A Review

[1]Yahya Seun Yisau, [1]Naeif Hamoud Al-Makishah and [1,2]Mohamed Abou El-Fetouh Barakat

[1]Department of Environment, Faculty of Environmental Sciences, King Abdulaziz University, Jeddah, Saudi Arabia
[2]Department of Minning Technology, Central Metallurgical Research and Development Institute, Helwan, Cairo, Egypt

Article history
Received: 23-04-2024
Revised: 27-05-2024
Accepted: 08-07-2024

Corresponding Author:
Mohamed Abou El-Fetouh Barakat
Department of Environment, Faculty of Environmental Sciences, King Abdulaziz University, Jeddah, Saudi Arabia
Email: mabarakat@gmail.com

Abstract: Paracetamol (4′-hydroxyacetanilide or N-acetyl-p-aminophenol or Acetaminophen) is an analgesic and antipyretic over-the-counter commonly used drug. Paracetamol has been detected in, surface waters, wastewater, and drinking water globally because of its significant utilization and unregulated release into the surroundings which have been a great concern and require an urgent approach. Microbial degradation of paracetamol is considered a desirable choice because of its lenient reaction conditions, low-cost operation, and eco-friendly process. This review focuses on summarizing the current processes for the biodegradation of paracetamol. The review includes characteristics and prevalent pharmaceutical drugs in wastewater, toxicity, degrading microorganisms, enzymes, and possible intermediates. Factors affecting the microbial degradation process of paracetamol such as growth pH, microbial cell concentration, temperature, and glucose have also been reported. The wide knowledge of biotransformation sequence and enzymatic processes engaged in the usage of paracetamol will help enable the optimization and simple design of microbial degradation techniques, which are expected to be more efficient in the treatment of paracetamol-contaminated wastewater.

Keywords: Paracetamol, Wastewater, Microbial, Biodegradation Pathway

Introduction

Pharmaceutical compounds are biologically active products that are continuously being used for various forms of prevention, cure, or treatment of diseases and one of the major worrying classes of emergent contaminants are these pharmaceutical contaminants from various pharmaceutical industries (Tiwari *et al*., 2017; Samal and Trivedi, 2020) and these organic pollutants have been identified worldwide in wastewater and surface water (Phillips *et al*., 2010). These pharmaceutical contaminants are consistently introduced into the environment via various emissions stemming from agricultural practices, manufacturing processes, consumption and disposal by consumers, and hospital waste discharge (Mahmood *et al*., 2022). Pharmaceutical compounds are molecules premeditated to be biologically active which thus pose a great effect on aquatic organisms and humans when leached into the environment, even though the contaminants are normally detected at low levels, which range from ng/L (nano-gram per liter) to µg/L micrograms per liter (de Oliveira *et al*., 2020). Varying levels of possible adverse impacts, such effects encompass chronic toxicity and acute damage, endocrine destruction, sexual reproductive damage, and alteration of behavior are detected at these minimal concentrations (Tiwari *et al*., 2017; Samal *et al*., 2022).

It occurs that most common pharmaceuticals detected in wastewater and the environment are usually those that are often obtainable either by prescription or non-prescription and over-the-counter purchase, including a range of substituted acetanilides like paracetamol and its intermediates. Paracetamol (or Acetaminophen) is a non-opioid analgesic, an antipyretic and Non-Steroidal Anti-Inflammatory Drug (NSAID), and a popular over-the-counter pain relief medication (Chiam *et al*., 2015) for headaches, fever, etc. Additionally, during COVID-19 disease outbreak in 2019, the major component of the therapeutic plans was this molecule which was consumed globally for the treatment of symptoms like cough, pain, flu, cold, and sleep disorders (Tony *et al*. 2020). Paracetamol with IUPAC N-(4-hydroxyphenyl) ethanamide, having a benzene ring core with a hydroxyl group and an amide group's nitrogen atom substituted in the para (1, 4) position ($C_8H_9NO_2$) (Maes *et al*., 2016).

Paracetamol has become an issue of concern that couldn't be overlooked due to its prevalent occurrence in drinking water and the environment's continuous documentation of its possible effects on human and environmental wellness. The intake of paracetamol has risen even more following the COVID-19 crisis, it has become the most recommended drug by various healthcare authorities across the world (Leal *et al*., 2021). In America, about 50 million adults utilize products with paracetamol on a weekly basis (Mund *et al*., 2015), and one of the most widely taken pain relief medications in Europe (Varrassi *et al*., 2010). According to previous research, the occurrence of paracetamol concentration was observed in surface water, drinking water, and underground waters (Wadhah Hassan, 2017). Studies have proved that microorganisms play crucial and effective contributions to the degradation of paracetamol in the environment across various conditions, as stated by Rios-Miguel *et al*. (2022). This review aims to consolidate previous and recent studies on microbial degradation of paracetamol, focusing on the occurrence of paracetamol, biodegrading microorganisms, environmental toxicity and health risks of paracetamol in wastewater, factors affecting biodegradation of paracetamol and the proposed metabolic/biodegrading pathways by microorganisms.

The approach of this review stems from an examination of data from both previous and recent investigations into the microbial degradation of paracetamol and other pharmaceutical wastewater pollutants. However, a few articles (4 articles) published from 1975-1996 were considered when describing the microbial degradation and transformation pathway of paracetamol. Also, a few articles published between 2006-2010 were considered, although the majority of the utilized articles were published between 2011-2023 since they presented significant information. The principal database source for these articles was Scopus, accessed with search terms including "paracetamol"; "pharmaceuticals"; "microbial"; "pollutants"; "wastewater"; "biodegradation pathway" and "review". To analyze the range of available studies and highlight literature gaps concerning this topic, a database search was carried out, revealing studies spanning over 10 years between 2014-May 2024 with approximately 1,344 papers on biodegradation of paracetamol comprising 428 review articles and 610 research articles. 340 review articles and 292 research articles publications on the use of bacteria, 191 review articles and 162 research articles on the use of microalgae, and 104 review articles and 82 research articles on the use of fungi were published (Fig. 1). The quest to identify the most efficient microbial degradation method for wastewater polluted with paracetamol has garnered major attention, resulting in an increase in publications over recent years. Several comprehensive reviews exist; however, most of them lack a comprehensive critical analysis of both traditional and high-level techniques, in conjunction with optimizing operational details to enhance the efficiency of microbial processes in the complete removal of paracetamol.

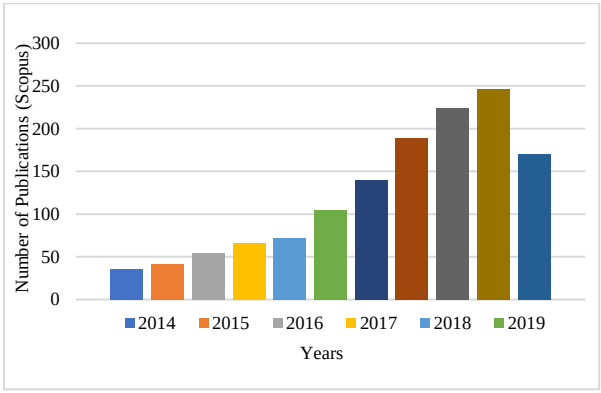

Fig. 1: Quantity of published articles on paracetamol biodegradation in wastewater from the Scopus database between 2014-2024

Characteristics of Pharmaceuticals in Industrial Wastewater

There is a need to characterize and discard effluent from the pharmaceutical industry so that safety standards are maintained before pharmaceutical wastewater discharge. Wastewater contains potent chemicals that are mutagenic, teratogenic, carcinogenic, and have other serious detrimental effects, so it is important to classify the elements and their forms before treatment. It is mainly composed of organic elements which pose greater harm in contrast to their inorganic variants (Kumar *et al*., 2018). It is certain that pharmaceutical companies' generated wastewater streams are not uniform and are always found to contain substances such as active biomass, polyaromatic hydrocarbons, antibiotics, and phenols. (Dixit and Parmar, 2013; Kumar *et al*., 2019). The wastewater could incorporate the following; heavy metals, non-biodegradable organic, biodegradable organic materials, and inorganic materials, and viable inhibitors that may be leached into the groundwater or ultimately flow into a water body. The presence and concentration of this contaminant can be assessed through water analysis by examining a water quality index employing several physicochemical parameters such as pH, turbidity, conductivity, Total Suspended Solids (TSS), Biological Oxygen Demand (BOD), and Chemical Oxygen Demand (COD) amongst others. A comprehensive interpretation of wastewater composition and properties (Table 1) is crucial to the implementation of a particular method and certification of its operation in a wastewater treatment plant (Mhlanga and Brouckaert, 2013).

To devise an efficient method for wastewater treatment, it is crucial to identify the properties of water and its contaminants (Deegan *et al*., 2011). The Pharmaceutical Industries' wastewater characteristic feature shows that it contains several intermediates, catalysts, solvents, and additional raw materials used during the synthesis and development of a certain drug in

its required dosage formula and not just the Active Pharmaceutical Ingredients (APIs) and these materials are quite harmful to the water bodies and environment been discharged in Zaman *et al*. (2014). Previous studies have evaluated the occurrence of the most prevalent drugs in pharmaceutical industrial wastewater and they have been classified into different therapeutic groups. (a) NSAIDs are largely found in Pharmaceutical Industrial Wastewater, such as Paracetamol: Ibuprofen, diclofenac, and Indomethacin, and the likes in their average mean and highest influent concentrations were detected. (b) Antibiotics; another group of prevalent drugs that are found largely consist of Antibiotics such as Ofloxacin, Ciprofloxacin, Trimethoprim, Sulpham ethaxozole, Chloramphenicol and Penicillin (c) Additionally, β-blockers like Propranolol, Metoprolol and Atenolol were also be discovered over the years. (d) Anticonvulsant and psychiatric drugs, for example, Carbamazepine have also been detected as prevalent drug contaminants found in pharmaceutical wastewaters (Petrovic *et al*., 2009; Shah and Shah, 2020). An overview of prevalent drugs in pharmaceutical wastewater is enumerated below in Table 2.

Table 1: Physicochemical parameters of pharmaceutical wastewater adapted (Rana *et al*., 2017)

Physicochemical indicators and heavy metal concentrations in pharmaceutical wastewater

Parameters/Items	Ranges	Heavy metals and toxic compounds	Ranges (mg/L)
Ph	5.8-8.5	Lead	0.03-6.53
Biological oxygen demand	20-1800 mg per liter	Iron	8.5-10.8
Chemical oxygen demand	128-28,640 mg per liter	Selenium	0.428-0.67
TDS	600-20,000 mg per liter	Cadmium	0.036-0.56
TSS	48-7500 mg per liter	Nickel	0.02-2.35
Total phosphate	18-47 mg per liter	Manganese	6.41-8.47
Dissolved organic carbon	775.0 mg per liter	Chromium	0.01-1.11
Total nitrogen	80-164 mg per liter	Chloride	200-2800
Temperature	31-46°C (degree Celsius)	Sulphate	82-360
Phenol	95-125 mg per liter	Arsenic	0.0049-0.0076
Conductivity	157±115.8-1673±119 (μS/cm)	Sulphide	42-100
Turbidity	2.2-138 Nephelometric turbidity units		
Nalidixic acid	45.0 mg per liter		
Alkalinity	50-2500 mg per liter		
Total acidity	300.0 mg per liter		

Table 2: Prevalent drugs in pharmaceutical industrial wastewater (Petrovic *et al*., 2009; Shah and Shah, 2020)

Pharmacological class	Drugs	Chemical class
NSAIDs	Paracetamol	Para-aminophenol derivative
	Ibuprofen	Propionic acid derivative
	ketoprofen	Propionic acid derivative
	Diclofenac	Acetic acid derivative
Antibiotics	Sulphamethaxozole	Sulphonamide
	Amoxicillin	Penicillin
	Sulfadiazine	Sulphonamide
	Ofloxacin	Fluoroquinolone
	Norfloxacin	Fluoroquinolone
	Ciprofloxacin	Fluoroquinolone
	Chloramphenicol	Amphenicol-class antibacterial
	Trimethoprim	Aminopyrimidine
Antihypertensive	Atenolol	Beta blocker
	Metoprolol	Beta blocker
	Propranolol	Beta blocker
	Sotalo	Beta blocker
Anticonvulsant/ Antiepileptic drugs	Carbamazepine	Tricyclic Anti-depressant
Lipid and	Clofibric Acid	Clofibrate metabolite
Cholesterol regulating	Gemfibrozil	Fibric acid derivative

Occurrence of Paracetamol in Industrial Wastewater

Paracetamol was found to be one of the most abundant pharmaceuticals identified with widely varying concentrations in wastewater across the globe (Gracia-Lor *et al*., 2012; Thomas *et al*., 2007). A record has shown a range between 1.75-43.22 μg/L in inflow samples of wastewater purification plants and about 83% of wastewater treatment plant effluent has shown a range between 0.025-4.319 μg/L. Also, from Ulleval University effluent samples between the range 13.87-177.67 μg/L were observed, and 5.42-1368.5 μg/L from wastewater, Norway (Thomas *et al*., 2007).

In Saudi Arabia, paracetamol concentrations of 12 and 0.073 micrograms per liter were observed in influent and effluent in wastewater purification facilities (Al Qarni *et al*., 2016). Also, paracetamol was found with a maximum concentration of 2.086 and 0.0521 μg/L in wastewater treatment plant inflow samples and effluent samples sequentially in the year 2011 in Kuwait (Alajmi, 2014).

In Canada, concentrations between 57.5-77.4 μg/L were found in influent samples of treatment plants and about 90.2 micrograms per liter in inflow samples from the hospital (Ba *et al*., 2014).

Furthermore, in Italy, 246 μg/L paracetamol concentration was found in the raw influent wastewater treatment plant sample (Verlicchi *et al*., 2012a) and in influents from two hospital wastewater varying from 1.4-5.9 μg/L as well as 1.2 and 0.058 μg/L concentration in influent and effluent of wastewater treatment systems accordingly (Verlicchi *et al*., 2012b). However, in Switzerland, a paracetamol concentration of 107 μg/L was recorded in hospital wastewater influent (Kovalova *et al*., 2012). In Taiwan, it was recorded that influents from hospital wastewater samples contain up to 186.5 μg/L and influents from drug production facilities contain about 417.5 μg/L (Lin and Tsai, 2009) and from 1.80-30.967 μg/L in effluents from six wastewater treatment plants (Lin *et al*., 2010), about 2.69 μg/L in inflow and 0.33 μg/L in outflow of sewage water treatment facility (Dutta *et al*., 2014) and 150 μg/L in hospital wastewater sample in China (Wu *et al*., 2012). In North Korea, 41.90 and 6.760 μg/L (influent and effluent samples) of paracetamol were subsequently detected in a hospital wastewater treatment facility. Also, 6.80 μg/L was reported in influent from municipal wastewater purification facility (Sim *et al*., 2010) then 10.234 μg/L in wastewater processing system influent was found in Ulsan (Behera *et al*., 2011).

In the USA, a paracetamol concentration level of 1.06 μg/L was found in the effluent of a wastewater purification system (Glassmeyer and Shoemaker, 2005). A concentration of 61 and 0.86 μg/L in influent and effluent of a wastewater purification facility in New York City (Benotti and Brownawell, 2007), another influent contains 140 μg/L concentration in San Marcos, Texas, from a hospital wastewater purification system (Foster, 2007), in the Back River, a concentration of 0.96 μg/L found inflow of a wastewater treatment facility in Baltimore (Yu *et al*., 2006), Influent concentrations of 182-233 μg/L at five wastewater management plants in the Northwest Pacific (Lubliner *et al*., 2010) and in effluents from fifty wastewater treatment plants, about 150.079 μg/L was recorded (Kostich *et al*., 2014) and in influent of a wastewater purification system in Wisconsin, up to 1000 μg/L was found (Wilcox *et al*., 2009).

In the United Kingdom, the concentration of paracetamol observed ranges between 5.53 to 69.57 μg/L as found in Howdon wastewater treatment plant influent (Roberts and Thomas, 2006), 0.129-0.555 μg/L was also detected from wastewater treatment plant effluent in England (Bound and Voulvoulis, 2006) and between 211.4 and 11.73 μg/L was found in inflow and outflow wastewater treatment plant in Cilfynydd, likewise 178.12 and 0.35 μg/L were found in a treatment facility of inflow and outflow wastewater in South Wales (Kasprzyk-Hordern *et al*., 2009).

In Spain, a concentration of 0.5-29 μg/L was found in wastewater from the hospital, in Almerıa (Gómez *et al*., 2006), a level of 0.123 μg/L concentration was found in the influent of the wastewater treatment facility (Radjenovic *et al*., 2007), influent level of 16.72 μg/L and effluent level of 0.34 μg/L in the wastewater treatment system, from Barcelona and Catalonia was noticed (Gros *et al*., 2012). In Croatian, 0.130-26.10 and 5.990 μg/L inflow and outflow of a wastewater purification system (Gros *et al*., 2006), between 1.13-201 μg/L in the inflow of a wastewater purification system detected in Castellon (Gracia-Lor *et al*., 2012), In Girona hospital wastewater between the range of 109.3-114.4 μg/L concentration (Cruz-Morató *et al*., 2014) and 58.857 μg/L from hospital wastewater influent, concentration of 9.29 and 0.11 μg/L from influent wastewater treatment plant and 0.106 μg/L effluent in Portugal (Santos *et al*., 2013).

Microbial Degradation

Biodegradation or microbial degradation is a biological process that offers an environmentally friendly means of breaking down various compounds found in the environment. This process converts pollutants into carbon dioxide (CO_2) and water (H_2O), which are then released as the final by-products of degradation (Chopra and Kumar, 2020a). Presently, wastewater containing pharmaceuticals is primarily treated using Advanced Oxidation Processes (AOPs), like Fenton and photo-Fenton reactions, photocatalysis employing titanium dioxide, ozonation combined with hydrogen peroxide (H_2O_2), or UV photolysis. However, understanding of the subsequent paracetamol characteristics in the environment is still limited. Studies have summarized the efficiency of chemical, and biological treatment systems

and hybrid approaches in wastewater treatment, reporting that a hybrid system employing zonation and biological activated carbon proved highly efficient in pesticide removal, pharmaceuticals, and beta-blockers (Ahmed *et al*., 2017). However, despite their high efficacy, the significant operational expenses, stringent operational conditions, and the production of secondary compounds with elevated toxic effects often made these procedures undesirable. Hence, the microbial degradation of pharmaceuticals, including NSAIDs, employing microbial strains with high degradation capabilities, portrays a sustainable and promising tool in both the environmental and economic aspects of wastewater treatment. The potential of any microbes to degrade xenobiotics is driven by several environmental conditions (Żur *et al*., 2018a), which impact the degradation process. It is widely understood that temperature, pH, and other environmental factors also contribute significantly to this degradation process, influencing microbial physiology and modulating the enzymatic reaction rate.

Factors Affecting Microbial Degradation Processes

There are substantial numbers of previous studies that have found that pharmaceutical compound degradation is highly dependent on operating factors including pH, temperature, shaking speed, carbon, and energy sources, etc., (Chopra and Kumar, 2020b; Sharma *et al*., 2020).

Effects of Temperature on Paracetamol Biodegradation

The significant impact of temperature on xenobiotic degradation is widely recognized, as it impacts bacterial functioning and the efficiency of enzymatic-driven activities. The optimum xenobiotics biodegradation rate is observed within the temperature range of 30-40°C. In lower temperatures, the rigidity of bacterial membranes increased, leading to heightened viscosity of membrane phospholipids. Conversely, higher temperatures often impede membrane transport due to the alteration of proteins associated with membranes (Żur *et al*., 2018a). However, for biodegradation of paracetamol, a wide range temperature of 25-35°C can still be considered to show a moderately high degradation, although, optimization studies as shown an efficient temperature of 25, 28, and 30°C (Edrees *et al*., 2018; Palma *et al*., 2022; Wadhah, 2018). As shown in Fig. 2, the study observed an optimal temperature of 25°C and the reducing effects of microbial degradation of paracetamol was recorded at temperatures below 20°C and above 30°C.

Effect of pH on Biodegradation of Paracetamol

The pH stands as another critical factor regulating the xenobiotic degradation of paracetamol, impacting membrane properties and microbial cell structure. For paracetamol, in a basic environment, it exists as a phenolate (RO−) form, whereas, at lower pH, it has been observed that there is a formation of a protonated form (ROH). Given that the acid dissociation constant (pKa) of paracetamol is 9.5, under mildly basic conditions, paracetamol exists predominantly in its non-ionic state (Xagoraraki *et al*., 2008). It can be inferred from these findings that the optimal breakdown rate of paracetamol could be observed at a neutral pH level. This assumption was validated for *Pseudomonas aeruginosa* strain DSM 50071, *Pseudomonas aeruginosa* strain NBRC 12689 (Wadhah, 2018), and *Pseudomonas* moorei strain KB4, with an efficient paracetamol biodegradation at an optimal pH of 7.0 (Żur *et al*., 2018b). However, in Fig. 3, a study on fungi degradation efficiency has shown a relatively higher degradation within a 5.5-6.5 pH range and the breakdown rate greatly reduced at a pH >7.0 (greater than 7.0) or 5.0<5.0 (smaller than 5.0) (Edrees *et al*., 2018).

Effects of Cell Concentration on Paracetamol Biodegradation

Several studies have observed that the cell concentration has a high influence on the degradation rate of paracetamol which plays a substantial role in transport elements. Some reports have proven this finding, as observed in *Pseudomonas aeruginosa* strain DSM 50071 and *P. aeruginosa* strain NBRC 12689 (Wadhah, 2018) and *Rhodococcus erythropolis* (Akay and Tezel, 2016) which demonstrated the effect of varying cell concentrations on paracetamol degradation. Microorganisms are supplied with energy and cell-building materials through the degradation of organic substrate and are used up for cell maintenance, regeneration of cells, and co-metabolization of non or less degradable or other materials (Cornelissen and Sijm, 1996). Another optimization study has confirmed that cell concentrations affect the biodegradation rate of paracetamol (Edrees *et al*., 2018). For example, at a higher bacterial concentration of 10^8 CFU/mL an optimal breakdown was achieved within 48 h (Fig. 4). That is, a higher cell concentration led to an increased rate of paracetamol breakdown by microbes.

Effects of Glucose Level on Paracetamol Biodegradation

The role of glucose in paracetamol breakdown, serving as a carbon and energy source for microbial processes. Several studies have proven that the biodegradation of paracetamol glucose medium increased with higher glucose levels. It revealed that glucose acts as a facilitator, providing extra energy to bacteria for paracetamol breakdown. In a similar study, the result was

also the same for the effect of glucose, an optimal degradation was achieved at concentration of 5 g/L within 72 h (Fig. 5). The availability of glucose supplies microbes with energy which subsequently boosts their ability to use up the tolerant aromatic amines (Edrees *et al*., 2018; Palma *et al*., 2021; Wadhah, 2018).

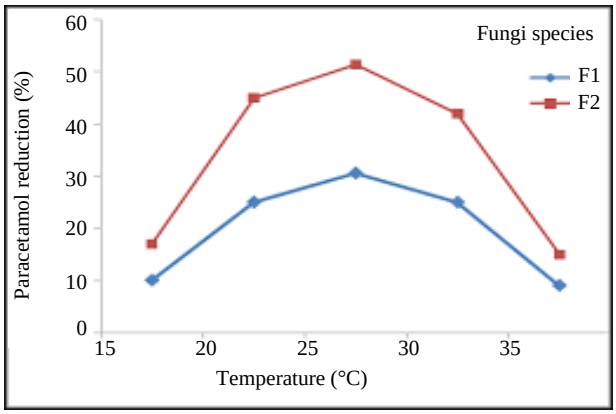

Fig. 2: Effect of temperature (Edrees *et al*., 2018)

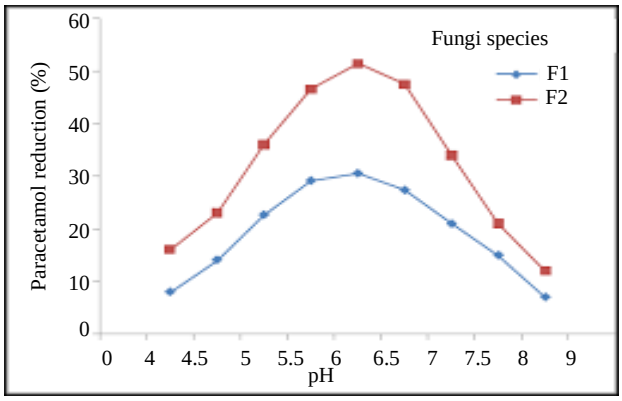

Fig. 3: Effect of pH (Edrees *et al*., 2018)

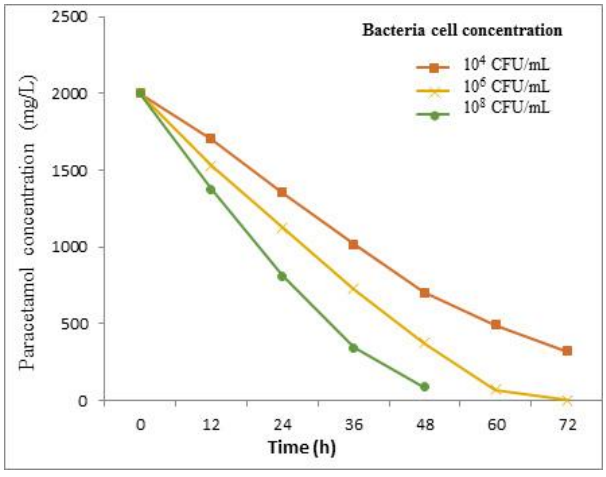

Fig. 4: Effect of Cell concentration (Wadhah, 2018)

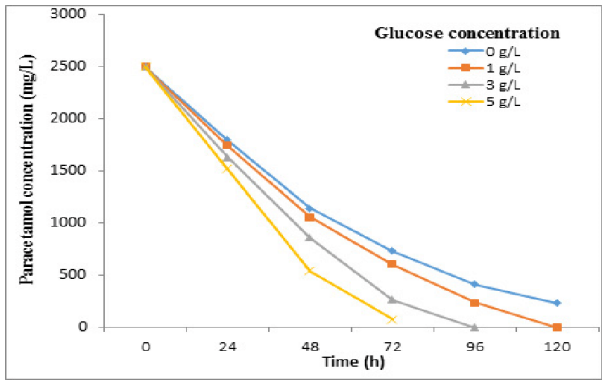

Fig. 5: Effect of glucose concentration (Wadhah, 2018)

Paracetamol Biodegrading Microorganisms

Microorganisms have evolved efficient biodegradation mechanisms, employing unique enzymatic mechanisms and metabolic routes to metabolize paracetamol for carbon and energy utilization. As a result, these microorganisms are efficient in breaking down paracetamol and transforming it into readily metabolizable materials (Hasan *et al*., 2011).

Chlorella vulgaris, Scenedesmus obliquus, and *Chlorella sorokiniana* are frequently utilized microalgae strains in wastewater treatment and have been identified to be efficient in the breakdown of 17-67% of Paracetamol in a study (Escapa *et al*., 2019). Other research has revealed a rapid removal of paracetamol using *Chlorella sorokiniana* strains (Escapa *et al*., 2015; 2017).

The wastewater environment consists of highly variable fungal communities, *Penicillium*, *Geotrichum,* and *Candida* species are the most highly represented then the next are *Trichoderma, Acremonium, Aspergillus, Trichosporon* and *Rhodotorula* (Buratti *et al*., 2022). A study designating fungi as F1 and F2 recognized as *Aspergillus niger* and *Fusarium oxysporium* degraded 26.1 and 35.7% of 2000 and 1000 mg/L of paracetamol concentration respectively at optimum temperature 25°C and pH 6.0 (Sharma *et al*., 2020). *Trichoderma harzianum* and *Pseudomonas* (Shabani *et al*., 2021) and *Scedosporium dehoogii* (Pontié *et al*., 2019) where a combination of bacterial and fungal biofilm having redox-active enzymes capable of electrogenic activity was used as a microbial fuel source and have shown to be effective in elimination of paracetamol contaminated wastewater.

Numerous bacteria with the ability to metabolize paracetamol as a carbon and energy source have been identified, with authors also proposing metabolic pathways for its degradation (Chopra and Kumar, 2020a). The isolation of *Cupriavidus necator* F1 from activated sludge has shown a complete breakdown of paracetamol at a starting concentration of 400.0 mg/L within 2 days. The results indicated that the strain possesses high capability for paracetamol mineralization as reported (Wei *et al*., 2011). A report of 97% degradation by *Delftia tsuruhatensis* was also observed by De Gusseme *et al*. (2011), within 48 h. In addition, the isolation of *Stenotrophomonas* sp. f1,

Pseudomonas sp. fg-2, and *Pseudomonas* sp. f2 from aerobic aggregate breakdown of paracetamol with complete degradation of 400 mg/L, 2,000-2,500 mg/L in 116, 45 and 70 h respectively was reported (Zhang *et al*., 2013). Lately, within 120 h, 79.4 and 88.4% degradation of 3000 mg/L concentration of paracetamol, by *Pseudomonas aeruginosa* strains (labelled as STB2 and STB4) was reported (Abdullah *et al*., 2018). Lastly, two bacteria strains described as *Pseudomonas stutzeri* CSW02 and *Pseudomonas extremaustralis* CSW01 have been shown to be efficient in the breakdown of paracetamol at high concentrations. These bacteria have proven to biodegrade about 500 mg/L concentration of paracetamol in 4 and 6 h, respectively. Hydroquinone and 4 aminophenol the two main paracetamol metabolites that pose high toxicity, were found and eliminated during the degradation process at a faster rate. Both bacterial strains show promise as prospective agents for bioremediation in sewage sludge and water contaminated with paracetamol (Vargas-Ordóñez *et al*., 2023).

Microbial Degradation and Transformation Pathway for Paracetamol

Several researchers were focused on summarizing paracetamol biodegradation studies in aspects such as bacteria degrading paracetamol, their enzymatic mechanisms, proposed biodegradation pathways/metabolic routes in microorganisms, and their possible intermediates. Isolated *Penicillium* sp. was observed to have the ability to degrade paracetamol into 4-aminophenol and acetate, possibly employing arylacylamidase. 4-aminophenol is a non-metabolizable end product (Hart and Orr, 1975) (Fig. 6). Additionally, findings indicate that *Rhodococcus* strains have the capability to decompose paracetamol, resulting in the production of three (3) identifiable metabolites: 4-aminophenol, hydroquinone, and catechol (Ivshina *et al*., 2006).

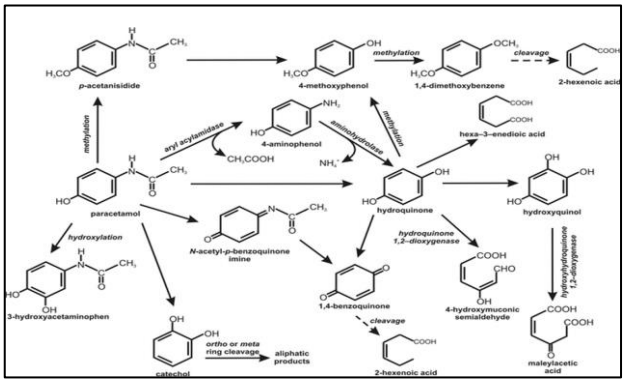

Fig. 6: Microbial transformation of paracetamol pathways (Hart and Orr, 1975; Kolvenbach *et al*., 2011; Takenaka *et al*., 2003; Li *et al*., 2014; Zhang *et al*., 2013)

The procedure involved in the continual breakdown of 1,4-hydroxybenzene could progress in two directions. First, direct cleaving of Hydroquinone through hydroquinone 1,2-dioxygenase along with 4-hydroxymuconic semialdehyde, similar to an aliphatic material (Daubaras *et al*., 1996). As documented in the biotransformation of paracetamol by *Pseudomonas aeruginosa* and *Delftia tsuruhatensis* bacterial strains, the methylation of hydroquinone might yield the mono and di O-methylated intermediates "4-methoxyphenol and 1,4-dimethoxybenzene." (De Gusseme *et al*., 2011). Through an amidohydrolase reaction paracetamol possibly metabolizes and yields 4-aminophenol from the carbonyl group through the cleavage between nitrogen-carbon bond, in which the formation of hydroquinone would result from the nitrogen being removed followed by hydroxylation (Takenaka *et al*., 2003). However, the transformation of 4-aminophenol to 1,4-hydroxybenzene by *Burkholderia* sp. strain AK-4 and then progress to 1,2,4-trihydroxybenzene was detailed. Progressively, hydroxy-hydroquinone 1,2-dioxygenase gradually cleaved 1,2,4-trihydroxybenzene to produce maleylacetic acid, incorporated into the core metabolism process (Kolvenbach *et al*., 2011; Moonen *et al*., 2008) (Fig. 6).

In more detail, the biotransformation of paracetamol to hydroquinone was followed by the conversion to the aliphatic product hexa-3-enedioic acid, this could stem from aromatic ring fission or might suggest the bypassing of intermediate metabolites between aliphatic and aromatic compounds. The Hexa-3-enedioic acid is related to muconic acid, which resulted from ortho-ring cleavage of catechol. A primary pathway of paracetamol biodegradation could be suggested based on reported intermediates. The mechanism may involve the elimination of two carbon atoms as formic acid (Zhang *et al*., 2013) (Fig. 6). Additionally, a sequence of hydroxylation reactions resulted in the transformation of paracetamol to phenols and organic acids by using *Rhodococcus erythropolis* reported (Akay and Tezel, 2016). In the biotransformation course, paracetamol undergoes initial conversion to 4-aminophenol, then was later changed to hydroquinone by replacing the amino group with a hydroxyl and hydroquinone subsequently underwent ring fusion.

Moreover, filamentous fungi that produce glucoside conjugates with paracetamol by O and N linkages in soil were defined (Huang *et al*., 2006). Phase-II xenobiotic detoxication routes for humans are absolutely related to this process (Halling-Sørensen *et al*., 1998). Also, a proposed pathway for paracetamol breakdown by soil microorganisms was explained in depth. The first step indicated that Paracetamol's aromatic ring is hydroxylated to form 3-hydroxyparacetamol, which is followed by methylation to form p-acetanisidide or oxygenation to form N-acetyl-p-benzoquinone imine. Which is a more

stable and significant toxic metabolite i.e., the 1,4-benzoquinone, of the N-acetyl-p-benzoquinone imine, was produced next. Furthermore, the subsequent step transforms p-acetanisidide into 4-methoxyphenol and 1,4-dimethoxybenzene. The occurrence of 2-hexenoic acid in the soil extract is demonstrated by the breakdown of paracetamol's aromatic ring (Li *et al*., 2014). In soil, flavin-containing hydroxylases, and monooxygenases are generally allocated among the microorganisms and as well catalyze several oxidative processes as found in the hydroxylation reaction of phenols to catechols (Sariaslani and Dalton, 1989).

Environmental Toxicity and Health Risk of Paracetamol

Paracetamol is widely prescribed around the world for its analgesic antipyretic properties. However, at high doses, it becomes highly toxic (Nunes *et al*., 2014). The rising levels of paracetamol and other emerging contaminants create the potential for toxic effects on unintended species in aquatic habitats. Lately, the England and Wales Environment Agency recognizing the possible threat of these contaminants to aquatic ecosystems, suggested a ranking scheme identifying the top 10 compounds of significance, with paracetamol listed as the 5th (Ebele *et al*., 2017). The pervasive presence of paracetamol together with its primary product of degradation, 4-aminophenol, in the environment is somewhat linked to their application in the manufacture of azo dyes and photographic materials (Zhang *et al*., 2013). In 2017, the consumption habits of paracetamol by consumers were assessed, and it was found that paracetamol is majorly consumed for fever, headaches, and general pain relief (Chong *et al*., 2017). Even though paracetamol is generally regarded as safe, it is among the top causes of toxicity and liver impairment. Following administration, paracetamol is predominantly and rapidly metabolized in the liver by sulfotransferases and urine 5′-diphosphoglucuronosyltransferase (conjugating enzymes), which convert the drug into non-toxic molecules, biliary and renal excretion then followed. The residual paracetamol undergoes oxidation to form N-acetyl-p-benzoquinone-imine, a reactive electrophilic metabolite during Phase I cytochrome P450 isoenzymes. Glutathione detoxifies N-acetyl-p-benzoquinone-imine, forming conjugates of paracetamol with cysteine and mercapturate. A paracetamol overdose causes glutathione reserves to be depleted, resulting in the accumulation of N-acetyl-p-benzoquinone-imine. This buildup leads to covalent alteration of protein thiol groups, damage to genetic material, cell necrosis, oxidative damage to membrane lipids, and cell lysis (Żur *et al*., 2018a).

Effects on Aquatic Bodies

Several studies as observed the harmful effects connected to countless pharmaceutical contaminants. For example, A study on male fish (*Rhamdia quelen)*, has shown that exposure to paracetamol caused an increase in thrombocytes and Leukocytes, and hemoglobin and hematocrit were reduced upon exposure to paracetamol concentration of 0.25 μg/L, reduced testosterone levels, increased dopamine and serotonin exposure level to 0.25 μg/L, estradiol levels increased at higher concentration and at 0.25 μg/L concentration hepatic genotoxicity arose; leucocytes infiltration and mild blood congestion in hepatic tissue (Guiloski *et al*., 2017). Also, several studies have confirmed the endocrine disruption and hepatotoxicity effect of Paracetamol in zebrafish *(Danio rerio)* (Ayobahan *et al*., 2020; Moreira *et al*., 2023).

Effects on Human Health

Paracetamol, as a non-opioid analgesic, operates through a unique mechanism different from that of other NSAIDs. The action mechanism is not fully comprehended, yet it seems to selectively target cyclooxygenase in the brain to alleviate pain or fever and possibly suppress prostaglandin production in the central nervous system. Paracetamol mode of action generates an antipyretic response by targeting the hypothalamus directly (Ghanem *et al*., 2016). Harmful effects such as histopathological and biochemical alterations in rat livers at 66 mg per kg body weight and 15mg per kg body weight have been attached to exposure to paracetamol, exposure to paracetamol in the primary stages of growth has been linked to the medulla oblongata shown to affect the neurotransmission (Blecharz-Klin *et al*., 2015a) or significantly influence effect on the spinal cord (Blecharz-Klin *et al*., 2015b).

In the past, pregnancy was considered to be safe with the usage of paracetamol but now, it has become debatable that its usage may generate future adverse impacts on the offspring if consumed during pregnancy. A recent report on various epidemiological studies linked to offspring having behavioral syndromes such as attention deficit hyperactivity disorder and Autism spectrum disorder has been connected to exposure to paracetamol despite the limited evidence linking paracetamol use during pregnancy to brain function (Bührer *et al*., 2021).

Current Techniques for Paracetamol Degradation

Several treatment methods have been developed in response to the threat caused by paracetamol as an organic contaminant found in wastewater. Different techniques are used, depending on the structure and properties of the organic component. Four of these methods; adsorption, membrane processes, advanced oxidation processes, and

biodegradation are particularly popular for wastewater treatment. Each method uses a very distinct process to break down paracetamol, even though they are all capable of degrading it. For example, oxidation mechanisms break down a variety of organic contaminants by causing the compounds to undergo radical splitting by in situ formation via oxidation. The chief benefit of oxidation processes is their capability to completely break down pollutants without transitioning them into another phase or producing secondary waste (Lee *et al*., 2020). The adsorption process operates through solutes and adsorbent interaction. Pollutants are attracted to the adsorbent by hydrophobic and electrostatic interactions and are subsequently removed by water. The primary benefit of adsorption is its non-toxic nature. Nevertheless, it has a short lifespan, is somewhat costly, and is ineffective against some pollutants. Regenerating the adsorbent is feasible, however, it frequently results in considerable mass loss, making it unfeasible from an economic standpoint (Cabrita *et al*., 2010; Reungoat *et al*., 2010). Membrane processes use a semi-permeable membrane's charge repulsion, solute adsorption, pressure, and size exclusion to separate solutes from water (Lee *et al*., 2020). The benefit of membrane techniques lies in their capability to effectively eliminate nearly all types of pollutants. However, their operational costs are high due to significant energy consumption and the need for membrane replacement resulting from fouling (Babu *et al*., 2019; Hua *et al*. 2020). Biodegradation is a broader term that encompasses the breakdown of organic compounds by biological processes, including microbial degradation. While microbial degradation is a type of biodegradation, not all biodegradation processes necessarily involve microorganisms. Biodegradation employs either an anaerobic or aerobic microbial process to effectively break down contaminants. Broadly, the resultant products are less harmful and more resilient than the original compound (Rana *et al*., 2017). The flexibility of microbes in targeting a wide array of substrate media is a key advantage of biodegradation. However, microbial growth may be hindered in high-salinity effluents. In addition, biodegradation is a lengthy process and may result in non-biodegradable soluble or cellular residues. The effectiveness of the method is also contingent on the compound's biodegradability.

A closer examination is undertaken to explore the efficiency of microbial degradation of different pharmaceuticals (NSAIDs), sourced from multiple research findings. The focus lies on understanding the efficacy of different microbes in breaking down various pharmaceutical compounds. Table 3 presents a compilation of data sourced from multiple research papers, detailing the origins of these microbes, the pharmaceutical products of the target, and the rates and conditions of biodegradation.

Table 3: Microbial biodegradation efficiency of some selected pharmaceuticals (NSAIDs)

Microorganism	Habitat/location of isolation	Pharmaceutical products (drugs)	Biodegradation rate (%)	Biodegradation conditions	Reference
Bacillus subtilis	Marseille, France	Diclofenac	Greater than 99% (1,000 mg/L)	Speed: 100 rpm, temp: 20°C, within 17 h	Grandclément *et al*. (2020)
Brevibacterium sp. D4	Wastewater Treatment Plant (WWTP) in, Portugal	Diclofenac	About 90% breakdown (10 mg/L)	A temp: 25°C, speed: 150 rpm within 30 days	Bessa *et al*. (2017)
Klebsiella sp. KSC	Sourced from livestock soil	Diclofenac	90% breakdown (i.e., 70,000 mg/L)	pH 7, 30°C, at a speed 100 rpm within 72 h	Stylianou *et al*. (2018)
Microbacterium paraoxydans	East India pharmaceutical wastewater	Ibuprofen	92.01% breakdown (15 mg/L)	pH 7, 30°C, speed: 150 rpm, 0.3% yeast extract	Show *et al*. (2023)
Patulibacter sp. Strain L11	Lisbon, Portugal, From WWTP activated sludge	Ibuprofen	92% breakdown (0.05 mg/L)	Speed: 110 rpm, temp: 28°C, within 90 h	Almeida *et al*. (2013)
Sphingopyxis granuli RW412	Downstream of the Hamburg harbor on the Elbe River, Germany	Ibuprofen	80% breakdown (800 mg/L)	Speed of 200 rpm, temp. 30°C, within 72 h	Aguilar-Romero *et al.* (2021)
Pseudomonas spp.	Delft, Netherland Hospital WWTP Pharma filter, sludge	Paracetamol	>99% breakdown (250 mg/L)	A pH 7, 500 rpm, temp. 20±1°C, airflow 30 mL/min, within 10 days	Rios-Miguel *et al*. (2022)
Pseudomonas moorei KB4	Poland. Activated sludge from Klimzowiec	Paracetamol (50 mg/L)	99% breakdown within 1.5 h	pH 7, temp. 30°C	Żur *et al*. (2018b)
Pseudomonas	Obtained from a	Paracetamol	About 71.4%	A pH 7, 30°C,	Hu *et al*. (2013)

Table 3: Count.

aeruginosa strain HJ1012	batch reactor microbial colony		breakdown (2,200 mg/L)	within 18 h	
Stenotrophomonas sp. f1	Paracetamol-metabolizing aerobic colony	Paracetamol	100% total breakdown (2,000 mg/L)	Speed of 200 rpm, 30°C, temp. 30°C within 16 h	Zhang *et al*. (2013)
Pseudomonas sp. fg-2	Paracetamol-metabolizing aerobic colony	Paracetamol	100% complete breakdown (2,500 mg/L)	Speed 200 rpm, 30°C within 45 h	Zhang *et al*. (2013)
Pseudomonas sp. f2	Paracetamol-metabolizing aerobic colony	Paracetamol	100% total breakdown (2.000 mg/L)	Speed 200 rpm, 30°C within 70 h	Zhang *et al*. (2013)
Bacillus drentensis estirpe S1	Derived sewage wastewater drains in Sonipat, India	Paracetamol	93% breakdown (300 mg/L)	A pH 7, 40°C, 165 rpm within 48 h	Chopra and Kumar (2020b)
Micrococcus yunnanensis	Derived from marine organisms, obtained	Paracetamol	Greater than 60% (i.e., about 15 mg/L)	At 150 rpm, within 360 h	Palma *et al*. (2022)
TJPT4	from Portugal	Paracetamol	90% (50 mg/L)	At 150 rmp, room temp., within 48 h	
Pseudomonas aeruginosa	WWTPs Sludges from Portuguese				Palma *et al*. (2018)
Micrococcus yunnanensis KGP04	Jaipur industrial Pharmaceutical WWT source	Paracetamol	80% breakdown (1% w/v)	pH 8, temp. 25°C, speed 200 rpm, by 6 h	Sharma *et al*. (2020)
Pseudomonas extremaustralis CSW01	Seville city sewage sludge from WWTP	Paracetamol	100% complete breakdown (500 mg /L)	Speed 150 rpm, ±31°C within 6 h	Vargas-Ordóñez *et al*. (2023)
Pseudomonas stutzeri CSW02	Seville city sewage sludge from WWTP	Paracetamol	100% total breakdown (500 mg/L)	Temp. ±31°C, speed 150 rpm By 4 h.	Vargas-Ordóñez *et al*. (2023)
Pseudomonas sp. PrS10	Sourced from Gujarat Pharmaceutical, India	Paracetamol	96.37% breakdown (3,000 mg/L)	At speed 140 rpm, temp. 30°C within 168 h	Poddar *et al*. (2022)

Research GAP and Future Directions

In spite of the fact that microbial degradation is a well-established process widely used in the treatment of wastewater, the removal of paracetamol and pharmaceuticals, in general, still requires further exploration in both theoretical and practical aspects related to risk assessment and ecological footprint. Key areas needing additional study include (a) Optimizing operational conditions to improve the microbial efficacy of processes in the complete removal of paracetamol; (b) Evaluating the risks associated with paracetamol and its metabolites in order to address legislative gaps; and lastly (c) Conducting direct measurement-based ecological footprint assessments of wastewater treatment systems, taking into consideration all emissions before, during and after treatment.

Conclusion

This review delves into the critical issue of paracetamol contamination in pharmaceutical wastewater and explores microbial degradation as a potential solution. Paracetamol, extensively produced and consumed worldwide, poses a significant environmental threat as it enters water bodies through various sources, including pharmaceutical production, consumer use, and improper disposal. Despite efforts by wastewater treatment plants, current methods fail to efficiently remove paracetamol, leading to its persistence in water sources.

Microbial degradation emerges as a promising approach, leveraging the natural abilities of microorganisms to break down paracetamol into less harmful compounds. Enzymes secreted by these microorganisms are essential in this process, highlighting the potential of biodegradation as an economically viable and environmentally friendly solution.

This review consolidates findings from a wide range of studies, emphasizing the importance of optimizing operational conditions to enhance microbial efficiency in wastewater treatment systems. This review will contribute to the advancement of wastewater treatment practices, safeguarding water quality, and protecting environmental health by addressing these research gaps aspects and focusing on future research directions.

Acknowledgment

Thank you to the publisher for their support in the publication of this research article. We are grateful for the resources and platform provided by the publisher, which

have enabled us to share our findings with a wider audience. We appreciate the efforts of the editorial team in reviewing and editing our work, and we are thankful for the opportunity to contribute to the field of research through this publication.

Funding Information

The authors have not received any financial support or funding to report.

Author's Contributions

Yahya Seun Yisau: Conceptualization data curation, written original drafted.

Naeif Hamoud Al-Makishah: Visualization, supervision, written, reviewed and edited.

Mohamed Abou El-Fetouh Barakat: Investigation, validation, written, reviewed and edited.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

Conflict of Interest

The authors affirm no conflicts of interest.

References

Abdullah, Q. Y., Edrees, W. H., Al-Kaf, A. G., & Naji, K. M. (2018). "Biodegradation of Paracetamol by Native Bacterial Strains Isolated from Yemeni Pharmaceutical Wastewater Plant in Sana'a". *Chronicles of Pharmaceutical Science*, *2*, 512–522.

Aguilar-Romero, I., De la Torre-Zúñiga, J., Quesada, J. M., Haïdour, A., O'Connell, G., McAmmond, B. M., Van Hamme, J. D., Romero, E., Wittich, R.-M., & van Dillewijn, P. (2021). Effluent decontamination by the ibuprofen-mineralizing strain, Sphingopyxis granuli RW412: Metabolic processes. *Environmental Pollution*, *274*, 116536. https://doi.org/10.1016/j.envpol.2021.116536

Ahmed, M. B., Zhou, J. L., Ngo, H. H., Guo, W., Thomaidis, N. S., & Xu, J. (2017). Progress in the biological and chemical treatment technologies for emerging contaminant removal from wastewater: A critical review. *Journal of Hazardous Materials*, *323*, 274–298. https://doi.org/10.1016/j.jhazmat.2016.04.045

Akay, C., & Tezel, U. (2016). *Biotransformation of Acetaminophen by Four Phylogenetically Distinct Bacteria*. Bogazici University.

Al Qarni, H., Collier, P., O'Keeffe, J., & Akunna, J. (2016). Investigating the removal of some pharmaceutical compounds in hospital wastewater treatment plants operating in Saudi Arabia. *Environmental Science and Pollution Research*, *23*(13), 13003–13014. https://doi.org/10.1007/s11356-016-6389-7

Alajmi, H. M. (2014). *Effect of Physical, Chemical and Biological Treatment on the Removal of Five Pharmaceuticals from Domestic Wastewater in Laboratory-Scale Reactors and Full-Scale Plant*. Newcastle University.

Almeida, B., Kjeldal, H., Lolas, I., Knudsen, A. D., Carvalho, G., Nielsen, K. L., Barreto Crespo, M. T., Stensballe, A., & Nielsen, J. L. (2013). Quantitative proteomic analysis of ibuprofen-degrading Patulibacter sp. strain I11. *Biodegradation*, *24*(5), 615–630. https://doi.org/10.1007/s10532-012-9610-5

Ayobahan, S. U., Eilebrecht, S., Baumann, L., Teigeler, M., Hollert, H., Kalkhof, S., Eilebrecht, E., & Schäfers, C. (2020). Detection of biomarkers to differentiate endocrine disruption from hepatotoxicity in zebrafish (*Danio rerio*) using proteomics. *Chemosphere*, *240*, 124970. https://doi.org/10.1016/j.chemosphere.2019.124970

Ba, S., Haroune, L., Cruz-Morató, C., Jacquet, C., Touahar, I. E., Bellenger, J. P., Legault, C. Y., Jones, J. P., & Cabana, H. (2014). Synthesis and characterization of combined cross-linked laccase and tyrosinase aggregates transforming acetaminophen as a model phenolic compound in wastewaters. *Science of the Total Environment*, *487*, 748–755. https://doi.org/10.1016/j.scitotenv.2013.10.004

Babu, D. S., Srivastava, V., Nidheesh, P. V., & Kumar, M. S. (2019). Detoxification of water and wastewater by advanced oxidation processes. *Science of the Total Environment*, *696*, 133961. https://doi.org/10.1016/j.scitotenv.2019.133961

Behera, S. K., Kim, H. W., Oh, J. E., & Park, H. S. (2011). Occurrence and removal of antibiotics, hormones and several other pharmaceuticals in wastewater treatment plants of the largest industrial city of Korea. *Science of the Total Environment*, *409*(20), 4351–4360. https://doi.org/10.1016/j.scitotenv.2011.07.015

Benotti, M. J., & Brownawell, B. J. (2007). Distributions of Pharmaceuticals in an Urban Estuary during both Dry- and Wet-Weather Conditions. *Environmental Science and Technology*, *41*(16), 5795–5802. https://doi.org/10.1021/es0629965

Bessa, V. S., Moreira, I. S., Tiritan, M. E., & Castro, P. M. L. (2017). Enrichment of bacterial strains for the biodegradation of diclofenac and carbamazepine from activated sludge. *International Biodeterioration & Biodegradation*, *120*, 135–142. https://doi.org/10.1016/j.ibiod.2017.02.008

Blecharz-Klin, K., Joniec-Maciejak, I., Jawna, K., Pyrzanowska, J., Piechal, A., Wawer, A., & Widy-Tyszkiewicz, E. (2015a). Developmental exposure to paracetamol causes biochemical alterations in medulla oblongata. *Environmental Toxicology and Pharmacology*, *40*(2), 369–374. https://doi.org/10.1016/j.etap.2015.07.001

Blecharz-Klin, K., Joniec-Maciejak, I., Jawna, K., Pyrzanowska, J., Piechal, A., Wawer, A., & Widy-Tyszkiewicz, E. (2015b). Effect of prenatal and early life paracetamol exposure on the level of neurotransmitters in rats Focus on the spinal cord. *International Journal of Developmental Neuroscience*, *47*, 133–139. https://doi.org/10.1016/j.ijdevneu.2015.09.002

Bound, J. P., & Voulvoulis, N. (2006). Predicted and measured concentrations for selected pharmaceuticals in UK rivers: Implications for risk assessment. *Water Research*, *40*(15), 2885–2892. https://doi.org/10.1016/j.watres.2006.05.036

Bührer, C., Endesfelder, S., Scheuer, T., & Schmitz, T. (2021). Paracetamol (Acetaminophen) and the Developing Brain. *International Journal of Molecular Sciences*, *22*(20), 11156. https://doi.org/10.3390/ijms222011156

Buratti, S., Girometta, C. E., Baiguera, R. M., Barucco, B., Bernardi, M., De Girolamo, G., Malgaretti, M., Oliva, D., Picco, A. M., & Savino, E. (2022). Fungal Diversity in Two Wastewater Treatment Plants in North Italy. *Microorganisms*, *10*(6), 1096. https://doi.org/10.3390/microorganisms10061096

Cabrita, I., Ruiz, B., Mestre, A. S., Fonseca, I. M., Carvalho, A. P., & Ania, C. O. (2010). Removal of an analgesic using activated carbons prepared from urban and industrial residues. *Chemical Engineering Journal*, *163*(3), 249–255. https://doi.org/10.1016/j.cej.2010.07.058

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.

Chong, C., Tan, S., & Chooi, W.-T. (2017). An evaluation on consumers' usage pattern of acetaminophen (paracetamol): A multicenter study from Penang, Malaysia. *Archives of Pharmacy Practice*, *8*(1), 15–21. https://doi.org/10.4103/2045-080x.199617

Chopra, S., & Kumar, D. (2020a). Biodegradation and Kinetic Analysis of Acetaminophen with Co-culture of Bacterial Strains Isolated from Sewage Wastewater. *Current Microbiology*, *77*(10), 3147–3157. https://doi.org/10.1007/s00284-020-02137-6

Chopra, S., & Kumar, D. (2020b). Characterization, optimization and kinetics study of acetaminophen degradation by Bacillus drentensis strain S1 and waste water degradation analysis. *Bioresources and Bioprocessing*, *7*(1), 1–18. https://doi.org/10.1186/s40643-020-0297-x

Cornelissen, G., & Sijm, D. T. H. M. (1996). An energy budget model for the biodegradation and cometabolism of organic substances. *Chemosphere*, *33*(5), 817–830. https://doi.org/10.1016/0045-6535(96)00237-8

Cruz-Morató, C., Lucas, D., Llorca, M., Rodriguez-Mozaz, S., Gorga, M., Petrovic, M., Barceló, D., Vicent, T., Sarrà, M., & Marco-Urrea, E. (2014). Hospital wastewater treatment by fungal bioreactor: Removal efficiency for pharmaceuticals and endocrine disruptor compounds. *Science of the Total Environment*, *493*, 365–376. https://doi.org/10.1016/j.scitotenv.2014.05.117

Daubaras, D. L., Saido, K., & Chakrabarty, A. M. (1996). Purification of hydroxyquinol 1,2-dioxygenase and maleylacetate reductase: the lower pathway of 2,4,5-trichlorophenoxyacetic acid metabolism by Burkholderia cepacia AC1100. *Applied and Environmental Microbiology*, *62*(11), 4276–4279. https://doi.org/10.1128/aem.62.11.4276-4279.1996

De Gusseme, B., Vanhaecke, L., Verstraete, W., & Boon, N. (2011). Degradation of acetaminophen by Delftia tsuruhatensis and Pseudomonas aeruginosa in a membrane bioreactor. *Water Research*, *45*(4), 1829–1837. https://doi.org/10.1016/j.watres.2010.11.040

de Oliveira, M., Frihling, B. E. F., Velasques, J., Filho, F. J. C. M., Cavalheri, P. S., & Migliolo, L. (2020). Pharmaceuticals residues and xenobiotics contaminants: Occurrence, analytical techniques and sustainable alternatives for wastewater treatment. *Science of the Total Environment*, *705*, 135568. https://doi.org/10.1016/j.scitotenv.2019.135568

Deegan, A. M., Shaik, B., Nolan, K., Urell, K., Oelgemöller, M., Tobin, J., & Morrissey, A. (2011). Treatment options for wastewater effluents from pharmaceutical companies. *International Journal of Environmental Science & Technology*, *8*(3), 649–666. https://doi.org/10.1007/bf03326250

Dixit, D., & Parmar, N. (2013). Treatment of Pharmaceutical Waste Water by Electro-Coagulation and Natural Coagulation Process: Review. *VSRD International Journal of Technology & Non-Technology Research*, *4*(5), 79–88.

Dutta, K., Lee, M.-Y., Lai, W. W.-P., Lee, C. H., Lin, A. Y.-C., Lin, C.-F., & Lin, J.-G. (2014). Removal of pharmaceuticals and organic matter from municipal wastewater using two-stage anaerobic fluidized membrane bioreactor. *Bioresource Technology*, *165*, 42–49. https://doi.org/10.1016/j.biortech.2014.03.054

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

Edrees, W. H., Abdullah, Q. Y., Naji, K. M., & Al-Kaf, A. G. (2018). Biodegradation of paracetamol by native fungal species inhabiting wastewater of a pharmaceutical factory in sana'a, Yemen. *Universal Journal of Pharmaceutical Research*, *2*(6), 35–41. https://doi.org/10.22270/ujpr.v2i6.r7

Escapa, C., Coimbra, R. N., Neuparth, T., Torres, T., Santos, M. M., & Otero, M. (2019). Acetaminophen Removal from Water by Microalgae and Effluent Toxicity Assessment by the Zebrafish Embryo Bioassay. *Water*, *11*(9), 1929. https://doi.org/10.3390/w11091929

Escapa, C., Coimbra, R. N., Paniagua, S., García, A. I., & Otero, M. (2015). Nutrients and pharmaceuticals removal from wastewater by culture and harvesting of Chlorella sorokiniana. *Bioresource Technology*, *185*, 276–284. https://doi.org/10.1016/j.biortech.2015.03.004

Escapa, C., Coimbra, R. N., Paniagua, S., García, A. I., & Otero, M. (2017). Paracetamol and salicylic acid removal from contaminated water by microalgae. *Journal of Environmental Management*, *203*, 799–806. https://doi.org/10.1016/j.jenvman.2016.06.051

Foster, A. L. (2007). *Occurrence and Fate of Endocrine Disruptors through the San Marcos Wastewater Treatment Plant*. Texas State University.

Ghanem, C. I., Pérez, M. J., Manautou, J. E., & Mottino, A. D. (2016). Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity. *Pharmacological Research*, *109*, 119–131. https://doi.org/10.1016/j.phrs.2016.02.020

Glassmeyer, S. T., & Shoemaker, J. A. (2005). Effects of Chlorination on the Persistence of Pharmaceuticals in the Environment. *Bulletin of Environmental Contamination and Toxicology*, *74*(1), 24–31. https://doi.org/10.1007/s00128-004-0543-5

Gómez, M. J., Petrović, M., Fernández-Alba, A. R., & Barceló, D. (2006). Determination of pharmaceuticals of various therapeutic classes by solid-phase extraction and liquid chromatography–tandem mass spectrometry analysis in hospital effluent wastewaters. *Journal of Chromatography A*, *1114*(2), 224–233. https://doi.org/10.1016/j.chroma.2006.02.038

Gracia-Lor, E., Sancho, J. V., Serrano, R., & Hernández, F. (2012). Occurrence and removal of pharmaceuticals in wastewater treatment plants at the Spanish Mediterranean area of Valencia. *Chemosphere*, *87*(5), 453–462. https://doi.org/10.1016/j.chemosphere.2011.12.025

Grandclément, C., Piram, A., Petit, M.-E., Seyssiecq, I., Laffont-Schwob, I., Vanot, G., Tiliacos, N., Roche, N., & Doumenq, P. (2020). Biological Removal and Fate Assessment of Diclofenac Using *Bacillus subtilis* and *Brevibacillus laterosporus* Strains and Ecotoxicological Effects of Diclofenac and 4′-Hydroxy-diclofenac. *Journal of Chemistry*, *2020*, 1–12. https://doi.org/10.1155/2020/9789420

Gros, M., Petrović, M., & Barceló, D. (2006). Development of a multi-residue analytical methodology based on liquid chromatography–tandem mass spectrometry (LC–MS/MS) for screening and trace level determination of pharmaceuticals in surface and wastewaters. *Talanta*, *70*(4), 678–690. https://doi.org/10.1016/j.talanta.2006.05.024

Gros, M., Rodríguez-Mozaz, S., & Barceló, D. (2012). Fast and comprehensive multi-residue analysis of a broad range of human and veterinary pharmaceuticals and some of their metabolites in surface and treated waters by ultra-high-performance liquid chromatography coupled to quadrupole-linear ion trap tandem mass spectrometry. *Journal of Chromatography A*, *1248*, 104–121. https://doi.org/10.1016/j.chroma.2012.05.084

Guiloski, I. C., Ribas, J. L. C., Piancini, L. D. S., Dagostim, A. C., Cirio, S. M., Fávaro, L. F., Boschen, S. L., Cestari, M. M., da Cunha, C., & Silva de Assis, H. C. (2017). Paracetamol causes endocrine disruption and hepatotoxicity in male fish Rhamdia quelen after subchronic exposure. *Environmental Toxicology and Pharmacology*, *53*, 111–120. https://doi.org/10.1016/j.etap.2017.05.005

Halling-Sørensen, B., Nors Nielsen, S., Lanzky, P. F., Ingerslev, F., Holten Lützhøft, H. C., & Jørgensen, S. E. (1998). Occurrence, fate and effects of pharmaceutical substances in the environment- A review. *Chemosphere*, *36*(2), 357–393. https://doi.org/10.1016/s0045-6535(97)00354-8

Hart, A., & Orr, D. L. J. (1975). The degradation of paracetamol (4-hydroxyacetanilide) and other substituted acetanilides by a*Penicillium* species. *Antonie van Leeuwenhoek*, *41*(1), 239–247. https://doi.org/10.1007/bf02565059

Hasan, S. A., Ferreira, M. I. M., Koetsier, M. J., Arif, M. I., & Janssen, D. B. (2011). Complete Biodegradation of 4-Fluorocinnamic Acid by a Consortium Comprising *Arthrobacter* sp. Strain G1 and *Ralstonia* sp. Strain H1. *Applied and Environmental Microbiology*, *77*(2), 572–579. https://doi.org/10.1128/aem.00393-10

Hu, J., Zhang, L. L., Chen, J. M., & Liu, Y. (2013). Degradation of paracetamol by Pseudomonas aeruginosa strain HJ1012. *Journal of Environmental Science and Health, Part A*, *48*(7), 791–799. https://doi.org/10.1080/10934529.2013.744650

Hua, P., Sellaoui, L., Franco, D., Netto, M. S., Luiz Dotto, G., Bajahzar, A., Belmabrouk, H., Bonilla-Petriciolet, A., & Li, Z. (2020). Adsorption of acid green and procion red on a magnetic geopolymer based adsorbent: Experiments, characterization and theoretical treatment. *Chemical Engineering Journal*, *383*, 123113. https://doi.org/10.1016/j.cej.2019.123113

Huang, H. H., Lin, L. H., Zhang, P., Qi, X. L., & Zhong, D. F. (2006). Formation of glucoside conjugate of acetaminophen by fungi separated from soil. *European Journal of Drug Metabolism and Pharmacokinetics*, *31*(2), 103–108. https://doi.org/10.1007/bf03191126

Ivshina, I. B., Rychkova, M. I., Vikhareva, E. V., Chekryshkina, L. A., & Mishenina, I. I. (2006). Catalysis of the biodegradation of unusable medicines by Alkanotrophic rhodococci. *Applied Biochemistry and Microbiology*, *42*(4), 392–395. https://doi.org/10.1134/s0003683806040090

Kasprzyk-Hordern, B., Dinsdale, R. M., & Guwy, A. J. (2009). The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. *Water Research*, *43*(2), 363–380. https://doi.org/10.1016/j.watres.2008.10.047

Kolvenbach, B. A., Lenz, M., Benndorf, D., Rapp, E., Fousek, J., Vlcek, C., Schäffer, A., Gabriel, F. L., Kohler, H.-P. E., & Corvini, P. F. (2011). Purification and characterization of hydroquinone dioxygenase from *Sphingomonas* sp. strain TTNP3. *AMB Express*, 1–11. https://doi.org/10.1186/2191-0855-1-8

Kostich, M. S., Batt, A. L., & Lazorchak, J. M. (2014). Concentrations of prioritized pharmaceuticals in effluents from 50 large wastewater treatment plants in the US and implications for risk estimation. *Environmental Pollution*, *184*, 354–359. https://doi.org/10.1016/j.envpol.2013.09.013

Kovalova, L., Siegrist, H., Singer, H., Wittmer, A., & McArdell, C. S. (2012). Hospital Wastewater Treatment by Membrane Bioreactor: Performance and Efficiency for Organic Micropollutant Elimination. *Environmental Science & Technology*, *46*(3), 1536–1545. https://doi.org/10.1021/es203495d

Kumar, V., Singh, J., Saini, A., & Kumar, P. (2019). Phytoremediation of copper, iron and mercury from aqueous solution by water lettuce (*Pistia stratiotes* L.). *Environmental Sustainability*, *2*(1), 55–65. https://doi.org/10.1007/s42398-019-00050-8

Kumar, V., Sonkar, M., Pooja, & Shukla, S. K. (2018). Recent Advancement on Bioaugmentation Strategies for Process Industry Wastewater (PIWW) Treatment. In *Water Remediation* (pp. 189–209). Springer. https://doi.org/10.1007/978-981-10-7551-3_11

Leal, N. S., Yu, Y., Chen, Y., Fedele, G., & Martins, L. M. (2021). Paracetamol Is Associated with a Lower Risk of COVID-19 Infection and Decreased ACE2 Protein Expression: A Retrospective Analysis. *COVID*, *1*(1), 218–229. https://doi.org/10.3390/covid1010018

Lee, W. J., Goh, P. S., Lau, W. J., & Ismail, A. F. (2020). Removal of Pharmaceutical Contaminants from Aqueous Medium: A State-of-the-Art Review Based on Paracetamol. *Arabian Journal for Science and Engineering*, *45*(9), 7109–7135. https://doi.org/10.1007/s13369-020-04446-1

Li, J., Ye, Q., & Gan, J. (2014). Degradation and transformation products of acetaminophen in soil. *Water Research*, *49*, 44–52. https://doi.org/10.1016/j.watres.2013.11.008

Lin, A. Y.-C., Lin, C.-F., Tsai, Y.-T., Lin, H. H.-H., Chen, J., Wang, X.-H., & Yu, T.-H. (2010). Fate of selected pharmaceuticals and personal care products after secondary wastewater treatment processes in Taiwan. *Water Science and Technology*, *62*(10), 2450–2458. https://doi.org/10.2166/wst.2010.476

Lin, A. Y.-C., & Tsai, Y.-T. (2009). Occurrence of pharmaceuticals in Taiwan's surface waters: Impact of waste streams from hospitals and pharmaceutical production facilities. *Science of the Total Environment*, *407*(12), 3793–3802. https://doi.org/10.1016/j.scitotenv.2009.03.009

Lubliner, B., Redding, M. B., & Ragsdale, D. (2010). *Pharmaceuticals and Personal Care Products in Municipal Wastewater and Their Removal by Nutrient Treatment Technologies*. Washington State Department of Ecology.

Maes, M., Vinken, M., & Jaeschke, H. (2016). Experimental models of hepatotoxicity related to acute liver failure. *Toxicology and Applied Pharmacology*, *290*, 86–97. https://doi.org/10.1016/j.taap.2015.11.016

Mahmood, T., Momin, S., Ali, R., Naeem, A., & Khan, A. (2022). Technologies for Removal of Emerging Contaminants from Wastewater. In *Wastewater Treatment*. IntechOpen. https://doi.org/10.5772/intechopen.104466

Mhlanga, F., & Brouckaert, C. (2013). Characterisation of wastewater for modelling of wastewater treatment plants receiving industrial effluent. *Water SA*, *39*(3), 403–408. https://doi.org/10.4314/wsa.v39i3.9

Moonen, M. J. H., Synowsky, S. A., van den Berg, W. A. M., Westphal, A. H., Heck, A. J. R., van den Heuvel, R. H. H., Fraaije, M. W., & van Berkel, W. J. H. (2008). Hydroquinone Dioxygenase from *Pseudomonas fluorescens* ACB: a Novel Member of the Family of Nonheme-Iron (II)-Dependent Dioxygenases. *Journal of Bacteriology*, *190*(15), 5199–5209. https://doi.org/10.1128/jb.01945-07

Moreira, D. P., Ribeiro, Y. M., Ferreira, C. S., dos Santos Nassif Lacerda, S. M., & Rizzo, E. (2023). Exposure to acetaminophen impairs gametogenesis and fertility in zebrafish (Danio rerio). *Archives of Toxicology*, *97*(1), 263–278. https://doi.org/10.1007/s00204-022-03390-3

Mund, M. E., Quarcoo, D., Gyo, C., Brüggmann, D., & Groneberg, D. A. (2015). Paracetamol as a toxic substance for children: aspects of legislation in selected countries. *Journal of Occupational Medicine and Toxicology*, *10*(1), 1–7. https://doi.org/10.1186/s12995-015-0084-3

Nunes, B., Antunes, S. C., Santos, J., Martins, L., & Castro, B. B. (2014). Toxic potential of paracetamol to freshwater organisms: A headache to environmental regulators? *Ecotoxicology and Environmental Safety*, *107*, 178–185. https://doi.org/10.1016/j.ecoenv.2014.05.027

Palma, T. L., Donaldben, M. N., Costa, M. C., & Carlier, J. D. (2018). Putative Role of Flavobacterium, Dokdonella and Methylophilus Strains in Paracetamol Biodegradation. *Water, Air, & Soil Pollution*, *229*(6), 1–23. https://doi.org/10.1007/s11270-018-3858-2

Palma, T. L., Magno, G., & Costa, M. C. (2021). Biodegradation of Paracetamol by Some Gram-Positive Bacterial Isolates. *Current Microbiology*, *78*(7), 2774–2786. https://doi.org/10.1007/s00284-021-02543-4

Palma, T., Valentine, J., Gomes, V., Faleiro, M., & Costa, M. (2022). Batch Studies on the Biodegradation Potential of Paracetamol, Fluoxetine and 17α-Ethinylestradiol by the Micrococcus yunnanensis Strain TJPT4 Recovered from Marine Organisms. *Water*, *14*(21), 3365. https://doi.org/10.3390/w14213365

Petrovic, M., de Alda, M. J. L., Diaz-Cruz, S., Postigo, C., Radjenovic, J., Gros, M., & Barcelo, D. (2009). Fate and removal of pharmaceuticals and illicit drugs in conventional and membrane bioreactor wastewater treatment plants and by riverbank filtration. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *367*(1904), 3979–4003. https://doi.org/10.1098/rsta.2009.0105

Phillips, P. J., Smith, S. G., Kolpin, D. W., Zaugg, S. D., Buxton, H. T., Furlong, E. T., Esposito, K., & Stinson, B. (2010). Pharmaceutical Formulation Facilities as Sources of Opioids and Other Pharmaceuticals to Wastewater Treatment Plant Effluents. *Environmental Science & Technology*, *44*(13), 4910–4916. https://doi.org/10.1021/es100356f

Poddar, K., Sarkar, D., Chakraborty, D., Patil, P. B., Maity, S., & Sarkar, A. (2022). Paracetamol biodegradation by Pseudomonas strain PrS10 isolated from pharmaceutical effluents. *International Biodeterioration & Biodegradation*, *175*, 105490. https://doi.org/10.1016/j.ibiod.2022.105490

Pontié, M., Jaspard, E., Friant, C., Kilani, J., Fix-Tailler, A., Innocent, C., Chery, D., Mbokou, S. F., Somrani, A., Cagnon, B., & Pontalier, P. Y. (2019). A sustainable fungal microbial fuel cell (FMFC) for the bioremediation of acetaminophen (APAP) and its main by-product (PAP) and energy production from biomass. *Biocatalysis and Agricultural Biotechnology*, *22*, 101376. https://doi.org/10.1016/j.bcab.2019.101376

Radjenovic, J., Petrovic, M., & Barceló, D. (2007). Analysis of pharmaceuticals in wastewater and removal using a membrane bioreactor. *Analytical and Bioanalytical Chemistry*, *387*(4), 1365–1377. https://doi.org/10.1007/s00216-006-0883-6

Rana, R. S., Singh, P., Kandari, V., Singh, R., Dobhal, R., & Gupta, S. (2017). A review on characterization and bioremediation of pharmaceutical industries' wastewater: an Indian perspective. *Applied Water Science*, *7*(1), 1–12. https://doi.org/10.1007/s13201-014-0225-3

Reungoat, J., Macova, M., Escher, B. I., Carswell, S., Mueller, J. F., & Keller, J. (2010). Removal of micropollutants and reduction of biological activity in a full scale reclamation plant using ozonation and activated carbon filtration. *Water Research*, *44*(2), 625–637. https://doi.org/10.1016/j.watres.2009.09.048

Rios-Miguel, A. B., Smith, G. J., Cremers, G., van Alen, T., Jetten, M. S. M., Op den Camp, H. J. M., & Welte, C. U. (2022). Microbial paracetamol degradation involves a high diversity of novel amidase enzyme candidates. *Water Research X*, *16*, 100152. https://doi.org/10.1016/j.wroa.2022.100152

Roberts, P., & Thomas, K. (2006). The occurrence of selected pharmaceuticals in wastewater effluent and surface waters of the lower Tyne catchment. *Science of the Total Environment*, *356*(1–3), 143–153. https://doi.org/10.1016/j.scitotenv.2005.04.031

Samal, K., Mahapatra, S., & Hibzur Ali, M. (2022). Pharmaceutical wastewater as Emerging Contaminants (EC): Treatment technologies, impact on environment and human health. *Energy Nexus*, *6*, 100076. https://doi.org/10.1016/j.nexus.2022.100076

Samal, K., & Trivedi, S. (2020). A statistical and kinetic approach to develop a Floating Bed for the treatment of wastewater. *Journal of Environmental Chemical Engineering*, *8*(5), 104102. https://doi.org/10.1016/j.jece.2020.104102

Santos, L. H., Gros, M., Rodriguez-Mozaz, S., Delerue-Matos, C., Pena, A., Barceló, D., & Montenegro, M. C. B. (2013). Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals. *Science of the Total Environment*, *461*, 302–316. https://doi.org/10.1016/j.scitotenv.2013.04.077

Sariaslani, F. S., & Dalton, H. (1989). Microbial Enzymes for Oxidation of Organic Molecules. *Critical Reviews in Biotechnology*, *9*(3), 171–257. https://doi.org/10.3109/07388558909036736

Shabani, M., Pontié, M., Younesi, H., Nacef, M., Rahimpour, A., Rahimnejad, M., & Bouchenak Khelladi, R. M. (2021). Biodegradation of acetaminophen and its main by-product 4-aminophenol by Trichoderma harzianum versus mixed biofilm of Trichoderma harzianum/Pseudomonas fluorescens in a fungal microbial fuel cell. *Journal of Applied Electrochemistry*, *51*(4), 581–596. https://doi.org/10.1007/s10800-020-01518-w

Shah, A., & Shah, M. (2020). Characterisation and bioremediation of wastewater: A review exploring bioremediation as a sustainable technique for pharmaceutical wastewater. *Groundwater for Sustainable Development*, *11*, 100383. https://doi.org/10.1016/j.gsd.2020.100383

Sharma, K., Kaushik, G., Thotakura, N., Raza, K., Sharma, N., & Nimesh, S. (2020). Enhancement effects of process optimization technique while elucidating the degradation pathways of drugs present in pharmaceutical industry wastewater using Micrococcus yunnanensis. *Chemosphere*, *238*, 124689. https://doi.org/10.1016/j.chemosphere.2019.124689

Show, S., Sarkar, P., Barman, S., & Halder, G. (2023). Microbial remediation of ibuprofen contaminated water using novel isolate Microbacterium paraoxydans. *Chemical Papers*, *77*(1), 517–531. https://doi.org/10.1007/s11696-022-02499-0

Sim, W.-J., Lee, J.-W., & Oh, J.-E. (2010). Occurrence and fate of pharmaceuticals in wastewater treatment plants and rivers in Korea. *Environmental Pollution*, *158*(5), 1938–1947. https://doi.org/10.1016/j.envpol.2009.10.036

Stylianou, K., Hapeshi, E., Vasquez, M. I., Fatta-Kassinos, D., & Vyrides, I. (2018). Diclofenac biodegradation by newly isolated Klebsiella sp. KSC: Microbial intermediates and ecotoxicological assessment. *Journal of Environmental Chemical Engineering*, *6*(2), 3242–3248. https://doi.org/10.1016/j.jece.2018.04.052

Takenaka, S., Okugawa, S., Kadowaki, M., Murakami, S., & Aoki, K. (2003). The Metabolic Pathway of 4-Aminophenol in Burkholderia sp. Strain AK-5 Differs from That of Aniline and Aniline with C-4 Substituents. *Applied and Environmental Microbiology*, *69*(9), 5410–5413. https://doi.org/10.1128/aem.69.9.5410-5413.2003

Thomas, K. V., Dye, C., Schlabach, M., & Langford, K. H. (2007). Source to sink tracking of selected human pharmaceuticals from two Oslo city hospitals and a wastewater treatment works. *Journal of Environmental Monitoring*, *9*(12), 1410. https://doi.org/10.1039/b709745j

Tiwari, B., Sellamuthu, B., Ouarda, Y., Drogui, P., Tyagi, R. D., & Buelna, G. (2017). Review on fate and mechanism of removal of pharmaceutical pollutants from wastewater using biological approach. *Bioresource Technology*, *224*, 1–12. https://doi.org/10.1016/j.biortech.2016.11.042

Tony, A. A., Tony, E. AE., Ali, S. B., Ezzeldin, A. M., & Mahmoud, A. A. (2020). COVID-19-associated sleep disorders: A case report. *Neurobiology of Sleep and Circadian Rhythms*, *9*, 100057. https://doi.org/10.1016/j.nbscr.2020.100057

Vargas-Ordóñez, A., Aguilar-Romero, I., Villaverde, J., Madrid, F., & Morillo, E. (2023). Isolation of Novel Bacterial Strains Pseudomonas extremaustralis CSW01 and Stutzerimonas stutzeri CSW02 from Sewage Sludge for Paracetamol Biodegradation. *Microorganisms*, *11*(1), 196. https://doi.org/10.3390/microorganisms11010196

Varrassi, G., Müller-Schwefe, G., Pergolizzi, J., Orónska, A., Morlion, B., Mavrocordatos, P., Margarit, C., Mangas, C., Jaksch, W., Huygen, F., Collett, B., Berti, M., Aldington, D., & Ahlbeck, K. (2010). Pharmacological treatment of chronic pain – the need for CHANGE. *Current Medical Research and Opinion*, *26*(5), 1231–1245. https://doi.org/10.1185/03007991003689175

Verlicchi, P., Al Aukidy, M., Galletti, A., Petrovic, M., & Barceló, D. (2012a). Hospital effluent: Investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment. *Science of the Total Environment*, *430*, 109–118. https://doi.org/10.1016/j.scitotenv.2012.04.055

Verlicchi, P., Al Aukidy, M., & Zambello, E. (2012b). Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment -A review. *Science of the Total Environment*, *429*, 123–155. https://doi.org/10.1016/j.scitotenv.2012.04.028

Wadhah, H. E. (2018). Isolation and Identification of a New Bacterial Strains Degrading Paracetamol Isolated from Yemeni Environment. *Clinical Biotechnology and Microbiology*, *1*, 257–270.

Wadhah Hassan, A. E. (2017). Occurrence of Paracetamol in Aquatic Environments and Transformation by Microorgan-Isms: A Review. *Chronicles of Pharmaceutical Science*, *1*, 341–355.

Wei, F., Zhou, Q. W., Leng, S. Q., Zhang, L. L., & Chen, J. M. (2011). Isolation, Identification and Biodegradation Characteristics of a New Bacterial Strain Degrading Paracetamol. *Environmental Science*, *32*(6), 1812–1819.

Wilcox, J. D., Bahr, J. M., Hedman, C. J., Hemming, J. D. C., Barman, M. A. E., & Bradbury, K. R. (2009). Removal of Organic Wastewater Contaminants in Septic Systems Using Advanced Treatment Technologies. *Journal of Environmental Quality*, *38*(1), 149–156. https://doi.org/10.2134/jeq2007.0365

Wu, S., Zhang, L., & Chen, J. (2012). Paracetamol in the environment and its degradation by microorganisms. *Applied Microbiology and Biotechnology*, *96*(4), 875–884. https://doi.org/10.1007/s00253-012-4414-4

Xagoraraki, I., Hullman, R., Song, W., Li, H., & Voice, T. (2008). Effect of pH on degradation of acetaminophen and production of 1,4-benzoquinone in water chlorination. *Journal of Water Supply: Research and Technology-Aqua*, *57*(6), 381–390. https://doi.org/10.2166/aqua.2008.095

Yu, J. T., Bouwer, E. J., & Coelhan, M. (2006). Occurrence and biodegradability studies of selected pharmaceuticals and personal care products in sewage effluent. *Agricultural Water Management*, *86*(1–2), 72–80. https://doi.org/10.1016/j.agwat.2006.06.015

Zaman, M. F., Akter, M. S., & Muhit, I. B. (2014). Pharmaceutical Waste Water Management (WWM): A Review. *2nd International Conference on Advances in Civil Engineering*, 201–206.

Zhang, L., Hu, J., Zhu, R., Zhou, Q., & Chen, J. (2013). Degradation of paracetamol by pure bacterial cultures and their microbial consortium. *Applied Microbiology and Biotechnology*, *97*(8), 3687–3698. https://doi.org/10.1007/s00253-012-4170-5

Żur, J., Piński, A., Marchlewicz, A., Hupert-Kocurek, K., Wojcieszyńska, D., & Guzik, U. (2018a). Organic micropollutants paracetamol and ibuprofen toxicity, biodegradation, and genetic background of their utilization by bacteria. *Environmental Science and Pollution Research*, *25*(22), 21498–21524. https://doi.org/10.1007/s11356-018-2517-x

Żur, J., Wojcieszyńska, D., Hupert-Kocurek, K., Marchlewicz, A., & Guzik, U. (2018b). Paracetamol – toxicity and microbial utilization. Pseudomonas moorei KB4 as a case study for exploring degradation pathway. *Chemosphere*, *206*, 192–202. https://doi.org/10.1016/j.chemosphere.2018.04.179