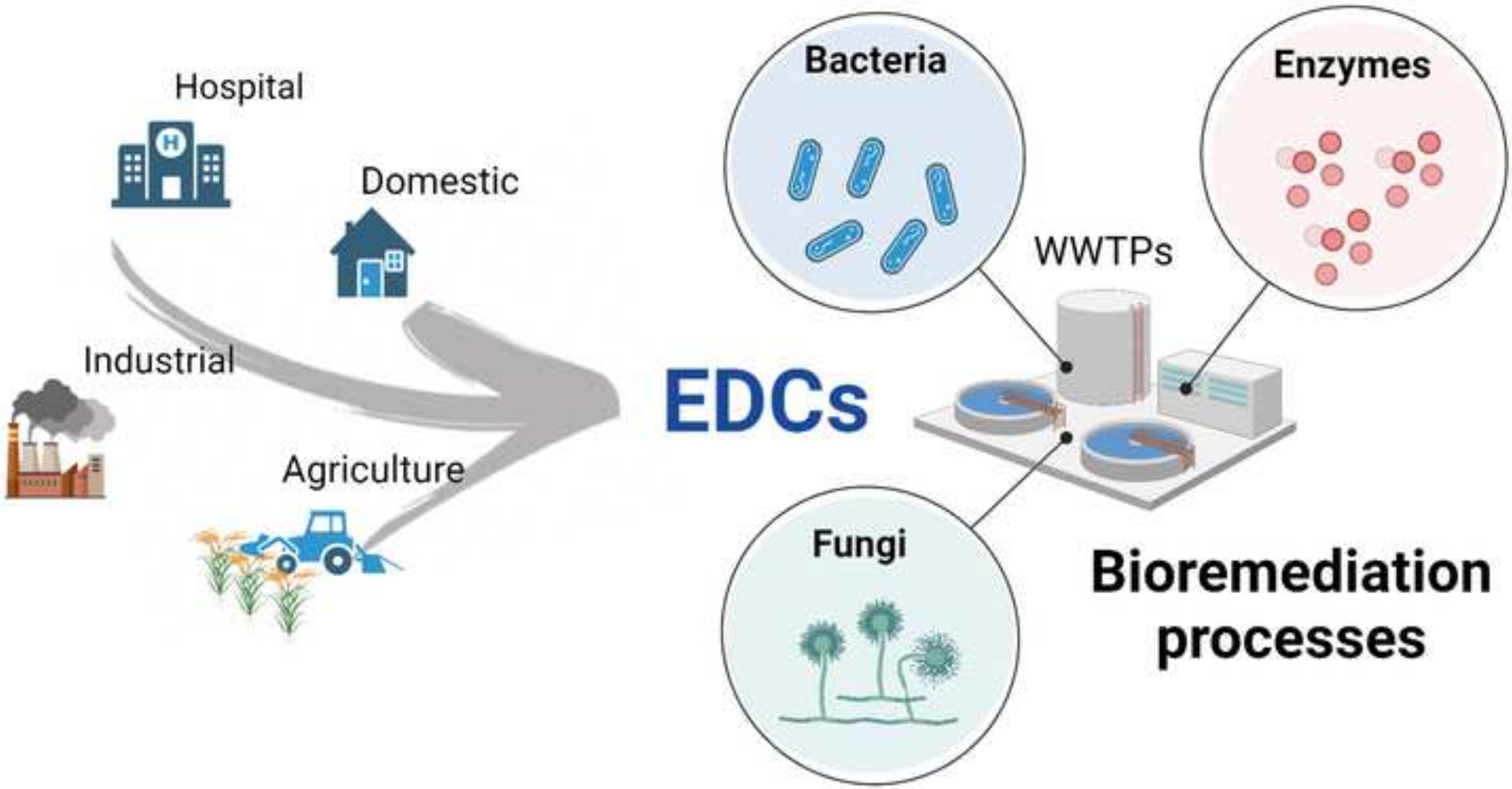
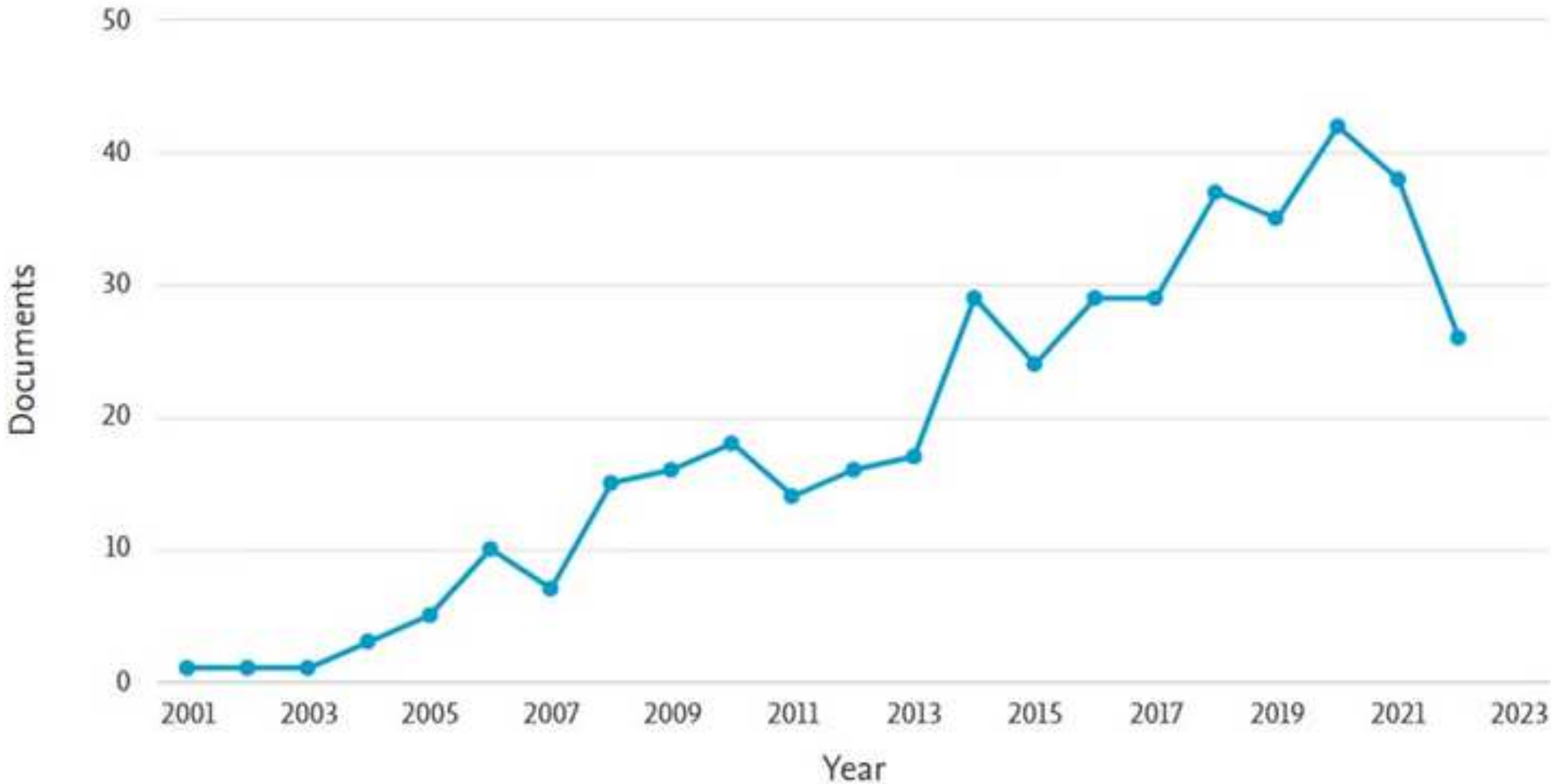
Graphical Abstract



Highlights

- Environmental contamination by EDCs is a global challenge.
- Conventional physical-chemical methods are not enough efficient to remove EDCs.
- Bioremediation as a promising and sustainable alternative for EDCs removing.
- Bacteria, fungi, and enzyme-based technologies effectively remove EDCs.
- Potential applications of bioremediation approaches are described.



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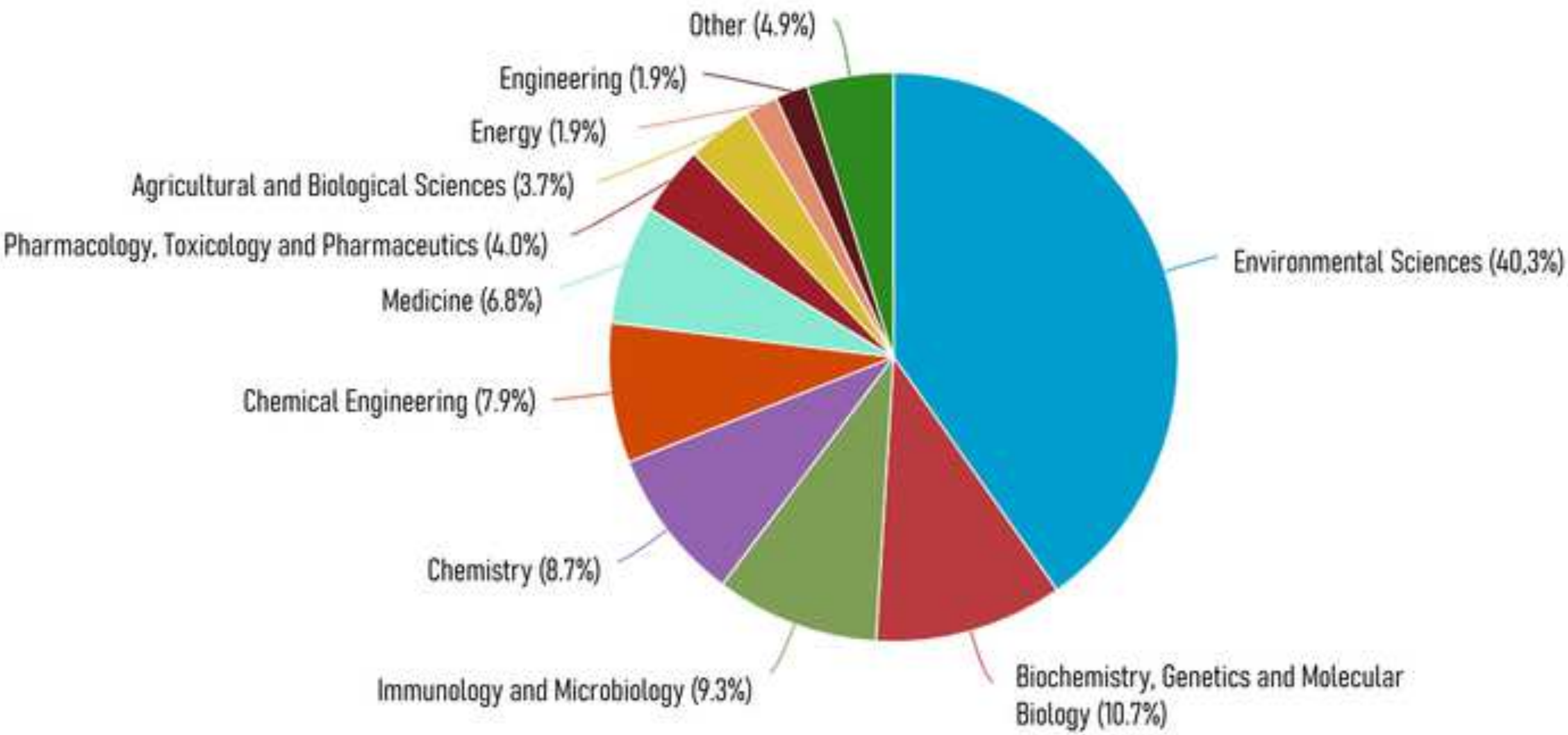
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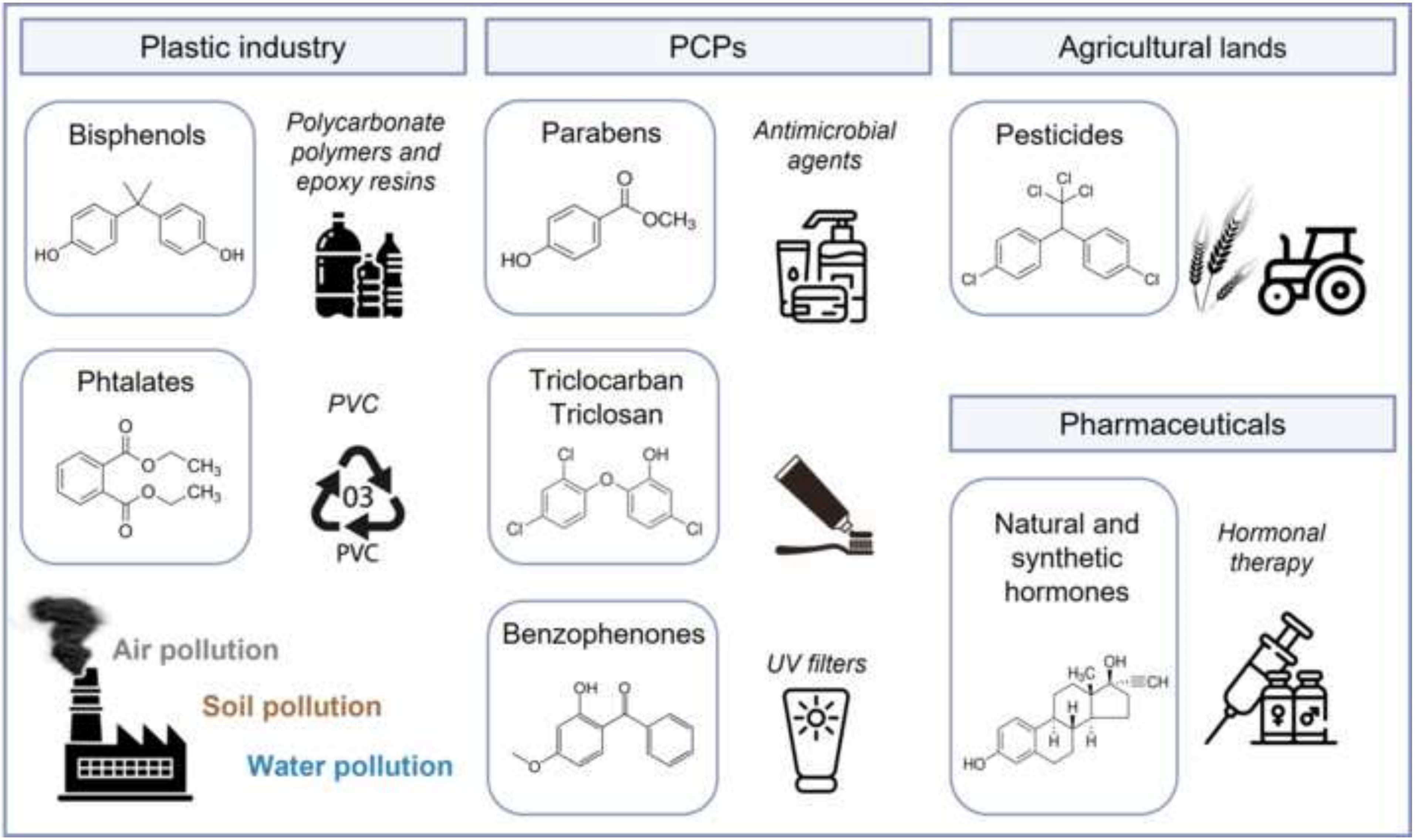
Energy (1.9%)
Agricultural and Biological Sciences (3.7%)
Pharmacology, Toxicology and Pharmaceutics (4.0%)
Medicine (6.8%)
Chemical Engineering (7.9%)
Chemistry (8.7%)
Immunology and Microbiology (9.3%)
Biochemistry, Genetics and Molecular Biology (10.7%)
Environmental Sciences (40,3%)



Plastic industry
PCPs
Agricultural lands
Bisphenols
HO
OH
Polycarbonate polymers and epoxy resins
Parabens
O
OCH3
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Antimicrobial agents
Pesticides
Cl
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Pharmaceuticals
Natural and synthetic hormones
H3C
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Hormonal therapy
Air pollution
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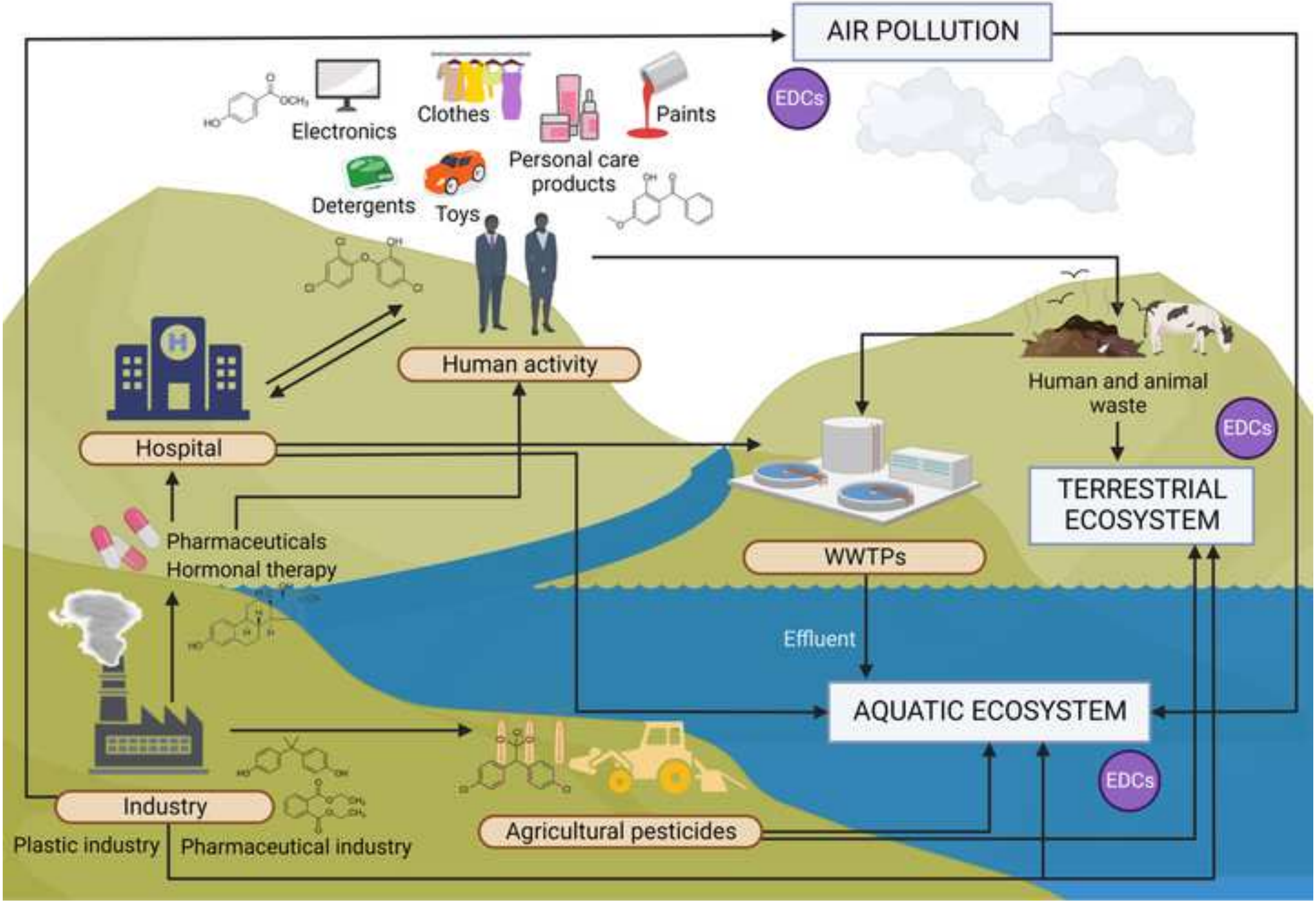
AIR POLLUTION
EDCs
Electronics
Clothes
Paints
Personal care products
Detergents
Toys
Human activity
Hospital
Human and animal waste
EDCs
TERRESTRIAL ECOSYSTEM
WWTPs
Pharmaceuticals
Hormonal therapy
Effluent
AQUATIC ECOSYSTEM
EDCs
Industry
Agricultural pesticides
Plastic industry
Pharmaceutical industry

Table 1. Main effects of EDCs in humans and wildlife.

Effects in human health		
Compound	**Effects**	**References**
BPA and analogues	Oestrogenic effect with anti-androgenic properties Breast/prostate cancer Endometriosis in women Infertility in both sexes Diabetes and Obesity Decrease in antibody production during viral infection Increase of cardiovascular problems	Colón et al., 2000; Encarnação et al., 2019; Rocha et al., 2013; Schug et al., 2011; Snyder et al., 2005
Triclosan	Decrease in antibody production during viral infection Reproductive toxicity in both sexes Developmental toxicity Genotoxicity (damages the DNA) Immune and respiratory diseases (asthma)	Clayton et al., 2006, 2011; Kuo et al., 2012; Lan et al., 2015; Yeh et al., 2010; Zhang et al., 2020
Parabens	Breast cancer Sperm genotoxicity	Darbre and Charles, 2010; Meeker et al., 2011
NPs	Interference with IFN-γ signalling during viral infection Supresses cytokine production in dendritic cells	Clayton et al., 2006; Kuo et al., 2012; Hung et al., 2010; Yeh et al., 2010
Phthalates	Inhibits TNF-α expression in macrophages Development of asthma and allergies in children Quality sperm decline in men Pregnancy loss Ovulation issues (anovulation, delays, etc.) Pre-mature thelarche	Chou et al., 2009; Clayton et al., 2006; Kuo et al., 2012; Toft et al., 2021; Yeh et al., 2010; Zhang et al., 2006
Benzophenones	Endometriosis Delayed male puberty	Krause et al., 2012; Kunisue et al., 2012
Organochlorine pesticides	Early onset puberty in girls Delayed puberty in boys and infertility Endometriosis in women Contributes to the early onset of Alzheimer and Parkinson Miscarriage and preeclampsia	Colon et al., 2000; Falconer et al., 2006; Kunisue et al., 2012; Stillerman et al., 2008

Effects in wildlife (marine and terrestrial)		
Compound	**Effects**	**References**
BPA and analogues	Development inhibition in marine crustaceans Infertility in marine and death molluscs Delayed larval emergence in insects Sex reversal in frogs Feminization of male testes in birds	Aarab et al., 2006; Andersen et al., 1999; Berg et al., 2001; Levy et al., 2004; Oehlmann et al., 2006; Watts et al., 2003
Triclosan	Reproductive and developmental disruption in fish Decreases survival ratio and changes behaviour in amphibian tadpoles	Dann et al., 2011; Nassef et al., 2009
NPs	Increase of vitellogenin levels, alteration of sex ratio in offsprings, development of testis-ova and decreased fecundity in fish Induction of intersex in molluscs Inhibition of metamorphosis in amphibians	Christensen et al., 2005; Hara et al., 2007; Langston et al., 2007
Phthalates	Genotoxicity in molluscs Oestrogenic and induces vitellogenin synthesis in male fish Alteration of expression of sex steroid synthases	Baršienė et al., 2006; Harries et al., 2000; Liu et al., 2005
Organochlorine pesticides	Masculinized sex ratio in molluscs (both marine and terrestrial) Gain of weight and advanced puberty in fish Neurobehavioral changes in birds by binding to sex hormones receptors Poor immune response in amphibians (immunosuppression)	Gahr et al., 2001; Gilbertson et al., 2003; Kidd et al., 2012
EE2	Induction of intersex in molluscs Disruption of brain development during ontogeny and male reproductive disorders in fish	Langston et al., 2007; Kidd et al., 2007; Vosges et al., 2012

BPA, bisphenol A; EE2, 17α-ethynylestradiol; IFN-γ, interferon gamma; NPs, nonylphenols; TNF-α, tumor necrosis factor.

Table 2. Overview of current treatment methods used for the removal of EDCs (Azizi et al., 2022; Surana et al., 2022).

Treatment process		**% Removal**
Physical treatments		
Adsorption	Activated carbon	BPA (99%), EPB (90%), diethyl phthalate (99%), E2 (96%)
	Carbon nanotubes	BPs (44–99%), EE2 (98%)
	Zeolite	Bisphenols (82%)
Membrane and filtration	Microfiltration	BPA (25%), E1 (<20%), E2 (30), phthalates <50%
	Ultrafiltration	BPA (27–79%), E3 (10–17%)
	Nanofiltration	BPA (>98%), PBs (93–99%)
	Reverse and forward osmosis	BPA (99%), EE2 (87–91%), E1 (>95%), E2 (75–95%)
Chemical and electrochemical		
	Chlorination	BPA (>80%)
	Ozonation	Parabens (96–100%), EE2 (60–70%), testosterone (>97%)
	Photocatalysis	4-octylphenol (97%), BPA (92%), triclosan (90%), MPB (88–92%)
	Electro coagulation	E1, E2, EE2, E3, BPA, NP (42–98%)
Biological methods		
Aerobic treatments	Activated sludge treatment process	BPA (92%), triclosan (94%), NP ethoxylates (83–90%), E1, E2, E3, EE2 (61– 95%)
	Membrane bioreactors	BPA (>95%), steroids (>90%), (comparable % removal to activated sludge treatment)
	Aerated lagoons	E1, E2, EE2, E3 (88–100%)
Anaerobic treatments		BPA (25–53%), steroids (34–53%), NP ethoxylates (>50%)

BPA, bisphenol A; E1, estrone; E2, estradiol; E3, estriol; EE2, 17α-ethynylestradiol; EPB, ethylparaben; MPB, methylparaben; NP, nonylphenol.

Strategies based on the use of microorganisms for the elimination of pollutants with endocrine-disrupting activity in the environment

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ABSTRACT

The continuous contamination of the environment by a high variety of pollutants is an alarming problem worldwide that requires prompt, effective and sustainable solutions. Among these pollutants, endocrine disrupting chemicals (EDCs) are of special concern due to their persistence and toxicity, interfering with the hormonal homeostasis of humans and wildlife. In addition, conventional physical-chemical treatments are not efficient enough to completely remove EDCs. This review aimed at compiling all the available information about the bioremediation processes capable of transforming EDCs into more environmentally friendly chemicals, focusing on microorganisms, enzymes and fungi. The review outlines the principal sources of EDCs, the problems associated with their presence in the environment, their harmful effects on wildlife, as well as providing an overview of bioremediation as an alternative and efficient strategy for their elimination. The proposed mechanisms to minimize the persistence of EDCs based on the use of microorganisms are described, as well as their potential implementation in wastewater treatment plants. Although the use of bioremediation processes is relatively unexplored, research has shown that microbial communities, enzymes, or fungi are a promising alternative thanks to their ability to efficiently transform EDCs into non-hazardous end products. Aerobic bacteria belonging to the genus *Sphingomonas*, *Achromobacter* or *Pseudomonas*, among others, have proven to be highly effective in the removal of EDCs, such as nonylphenols, bisphenols, and parabens.

Keywords: Endocrine disrupting chemicals (EDCs); Xenobiotics; Degradation; Wastewater treatment plant (WWTP); Bioremediation; Microorganisms

Abbreviations: AMO, ammonium monooxygenases; BBP, benzyl butyl phthalate; BPA, bisphenol A; BPB, butylparaben; DBP, dibutyl phthalate; DEHP, diethyl hexyl phthalate; DIBP, diisobutyl phthalate; E1, estrone; E2, estradiol; E3, estriol; EE2, 17α-ethynylestradiol; EDCs, endocrine disrupting chemicals; EPB, ethylparaben; H_c, Henry's law constant; IFN-γ, interferon gamma; K_{oc}, organic carbon-water partition coefficient; K_{ow}, octanol-water partition coefficient; LC, liquid chromatography; MPB, methylparaben; NP, nonylphenol; OpdA, octylphenol-4-monooxygenase; PAH, polycyclic aromatic hydrocarbon; PCPs, personal care products; REACH, Registration, Evaluation and Authorization of Chemicals; ROS, reactive oxygen species; TAC, tricarboxylic acid cycle; TNF-α, tumor necrosis factor; TSS, two system stage; UHPLC, ultra-high performance liquid chromatography; WWTP, wastewater treatment plant.

1. Introduction

During the last decades, the presence of micropollutants in the environment has increased considerably worldwide as a consequence of growing anthropogenic activity and industrialization (chemical industry, plastics manufacturing, pesticide synthesis and use, the manufacturing and use of pharmaceutical and personal care products, PCPs) (Mohapatra et al., 2021). The main sources of pollutants in natural environments are from industrial effluents, wastewater treatment plants (WWTPs), leaching processes in agricultural soils, as well as via accidental discharges into aquifers and oceans (Barrios-Estrada et al., 2018).

Emerging pollutants are defined as unregulated chemical substances that are suspected of affecting the environment or whose effects are unknown at very low concentrations, usually in the range of μg L^{-1} to ng L^{-1} (Deblonde et al., 2011). Furthermore, many of these compounds are persistent and ubiquitous in the environment (Combalbert and Hernandez-Raquet, 2010; García-Fernández et al., 2022; Hashim et al., 2017). Persistence of pollutants in ecosystems is a direct consequence of their resistance to degradation due to their physical-chemical properties, making them more bioavailable to living beings (Petrie et al., 2015). In addition, some of these pollutants are xenobiotics and micropollutants capable of altering the normal physiology of organisms (metabolism, reproduction, and behavior) since they have the potential to simulate endogenous hormones and stimulate or inhibit their responses in the body. These specific substances are commonly known as endocrine disrupting chemicals (EDCs) (Kidd et al., 2012).

According to the official definition of the US Environmental Protection Agency, an endocrine disruptor is *"an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes"* (Kavlock et al., 1996). EDCs are a group of compounds with diverse molecular structures. Despite this, they share common characteristics, such as their high rate of persistence in the environment. They are generally highly resistant to degradation (both oxidative and UV), to elevated temperatures (high thermal stability) and to a wide ranges of pH (extreme pHs). As a result, these compounds tend to accumulate in the environment, posing a risk to the health of animals and humans (Hashim et al., 2017). Some of these substances have low solubility in water and a fat-soluble nature, and they tend to accumulate within biological tissues, particularly in adipose tissue. Thus they become inaccessible to the organs in charge of detoxifying (mainly the liver) and eliminating them (the kidneys) and, therefore, have a tendency to bioaccumulate (Gómez-Regalado et al., 2021; Kidd et al., 2012). Bioaccumulation has another consequence at the environmental and ecosystem level since it leads to the phenomenon of biomagnification, the increasing concentration of a contaminant in organism tissues at successive levels of the trophic chain (Martín et al., 2020).

The negative impact, high persistence and ubiquity of EDCs in the natural environment are a matter of great concern today. Efforts are being made to reduce their presence, but their elimination is a major challenge that requires innovative and more sustainable strategies. Conventional WWTPs are inefficient at completely removing EDCs which are consequently prevalent in wastewater effluents and the marine waters they're ultimately discharged into (Azizi et al, 2022; Ben et al., 2017; Liu et al., 2009; Surana et al., 2022). Such technologies are typically based on physical, chemical, electrochemical and biological processes, highly related to the EDCs properties (Azizi et al, 2022). In this context, the scientific community has proposed several mechanisms for better eliminating EDCs from either from industrial effluents and urban waste, or contaminated environments. Advanced oxidation techniques have been proposed, applied directly in the treatment of industrial and urban wastewater, to enhance the removal efficacy of these micropollutants. Although these processes are effective, both the high associated cost and the volume of generated waste that is potentially harmful to the environment make it difficult to put into practice on a large scale (Ben et al., 2017; Liu et al., 2009).

The use of microorganisms or fungi as tools for EDCs elimination is therefore an interesting, sustainable and eco-friendly alternative. The idea is to use microorganisms capable of efficiently degrading EDCs, thanks to their enzymatic mechanisms, to improve the effectiveness of conventional activated sludge systems (Roccuzo et al., 2021).

The aim of the present review article is to give an overview of the bioremediation of EDCs using bacterial communities, fungi, and their enzymes. The first part is devoted to general aspects of EDCs (main sources, physicochemical characteristics and factors that influence their elimination). Then the bioremediation mechanisms of EDCs proposed by the scientific community are reported on and discussed. Finally, practical considerations and selected application approaches in WTPPs are suggested, with emphasis placed on the advantages of using microorganisms in conventional techniques.

2. Methods for literature search

In this review, different databases (Scopus, Web of Science (WoS), PubMed, CAS Finder) have been consulted for the search of information. The scientific articles that have been selected for the elaboration of this bibliographic work have been obtained by using the search keywords ("Endocrine Disruptor" OR "EDC" OR "WWTP EDC" OR "Emerging Contaminants") AND ("Bioremediation" OR "Micropollutants Bioremediation" OR "Bacterial degradation" OR "Removal enzymes" OR "Microorganism degradation"). In addition, the reference list of these articles was reviewed to identify other potential published studies on the topic.

Figure 1

As shown in Figure 1, the available information and published reports focused on bioremediation are relatively scarce (a total of 413 documents have been reported since 2001 – data from Scopus). Consequently, the selected articles that provided useful information for the present review were mainly limited to a 10-year period. Given the scarcity of available scientific reports on EDC bioremediation processes, certain works from previous years (up to 15 years ago) were also included, providing relevant contextual information.

A large part of the selected articles belongs to environmental sciences, although journals from other areas have also been consulted (Figure 2). From the bibliographic reviews on EDCs, an attempt has been made to obtain and synthesize the maximum information available on the mechanism of action of endocrine disruptors in humans and in ecosystems (at the molecular, cellular, physiological, and metabolic levels), their physicochemical properties and their behavior in the environment (mobility, persistence, and bioavailability).

Figure 2

A more specific search was made for experimental articles on bioremediation methods. These lay the groundwork for the development of new methods based on the use of microorganisms or their enzymes as tools for the removal of EDCs from WWTPs and environments contaminated by these compounds, but also to better understand the degradation reactions of these compounds at the molecular (biochemical) level. For the search of the proposed degradation-bioremediation-based methods, articles were excluded that a) were conference abstracts or comments; b) did not deal with compounds with disruptive action; or c) did not use microorganisms, fungi, or their enzymes for the removal of EDCs.

Recent review papers have been published on EDCs, addressing topics such as occurrence, health effects, and remediation techniques, while others deal with the elimination and bioremediation of a wide group of pollutants or a single family of EDCs (Narayanan et al., 2022; Surana et al., 2022; Tarafdar et al., 2022; Zhang et al., 2013). Ismanto et al. have elaborated an interesting work about EDCs in environmental matrices and their remediation, including a section dedicated to bioremediation technologies (Ismanto et al., 2022). In other recent work, Roccuzo et al. have published a formal in-depth meta-analysis with models and statistical tests to investigate how various variables (e.g., exposure time, type of organism and complexity of contamination) could influence biodegradation, based on the literature (Roccuzo et al., 2021). However, as far as we know, no work focuses in detail on bioremediation as an alternative for the elimination of multiclass EDCs in conventional WTPPs.

This review has been organized into several sections and sub-sections that focus on distinct aspects related to EDCs. First, the primary families of EDCs are defined and the harmful effects of EDCs on biota and human health are summarized. Next, the physicochemical characteristics of these compounds are discussed to better understand their behavior, mobility, bioavailability, and persistence in ecosystems (terrestrial and aquatic). Finally, the main methods used to eliminate EDCs in natural environments and WWTPs is discussed, as well as the principal microorganisms that are used for their elimination.

3. Presence of EDCs in ecosystems, sources and pathways

EDCs encompass a wide variety of compounds that are highly heterogeneous in terms of their molecular structure. These can be classified in several ways according to varying criteria: origin (natural or synthetic), main uses (pesticides, products used in industries, PCPs, etc.), presence of common functional groups, harmful effects on the organism, etc. But the most common classification of these compounds is based on their use, since it allows us to better understand how we are exposed to them in our day to day (Kabir et al., 2015).

Despite the considerable diversity of compounds with potential hormonal activity, emphasis will be placed on those with greater relevance at the biological level (both in humans and in biota) as well as those that have a greater presence and persistence in the terrestrial and marine environments, because of their continual release into the environment. The compounds present in everyday products and drugs are of particular relevance, as well as those found in food packaging (Hashim et al., 2017).

Figure 3

Among the most notable classes of EDCs in the environment are bisphenols used in the manufacturing of plastics, nonylphenols (NPs) used as emulsifying agents, parabens, triclosan and triclocarban used as antimicrobial agents, benzophenones used as UV-filters, and phthalates used in plastics. Other relevant classes include those found in certain pharmaceutical products used as hormonal substitutes, such as natural and synthetic estrogens, and those found in some agricultural pesticides (Gavrilescu et al., 2015; Zhang et al., 2016). However, more and more compounds with endocrine disrupting activity are being discovered and added to the list of EDCs. Figure 3 summarizes the main families of EDCs and their uses.

The distribution and fate of pollutants throughout the environment depend on the properties of the compartments (pH, ions, surfactants, etc.) with which they interact, as well as on the specific properties of the contaminant (polarity, volatility, persistence, and adsorption). The fate of EDCs also depends on their use (PCPs, plastics synthesis, etc.) and the way in which they are disposed of (Geissen et al., 2015). The parameters used to determine their mobility and bioavailability in the environment are the organic carbon-water partition coefficient, K_{oc}; the ratio between the concentrations of a certain substance in a biphasic mixture formed by two immiscible solvents in equilibrium (n-octanol and water), K_{ow}; and Henry's law constant, H_c. (Birkett and Lester, 2003; Campbell et al., 2006; Sarmah et al., 2008). It is important to know the mobility of EDCs since many of them, such as pharmaceuticals present in wastewater, are excreted from the body without undergoing significant modifications in their molecular structure; therefore they maintain their biological activity and can alter physiology of the biota when they reach ecosystems via water (Boxall et al., 2004). There are also factors inherent to soil that affect the mobility of EDCs, such as the quantity, spatial conformation and polarity of organic matter, the presence of inorganic ions (minerals), or the presence of organic matter/mineral complexes (Ren et al., 2018).

The main sources of EDCs in terrestrial environments include the use of pesticides in crops, irrigation with contaminated water, the use of compost obtained from activated sludge in WWTPs, aerosol deposits and industrial and household wastes (Barrios-Estrada et al., 2018) (Figure 4). Most soils are often contaminated by a wide variety of substances apart from EDCs such as surfactants, heavy metals, and other persistent organic pollutants. The presence of these pollutants has been shown to affect the stability of EDCs in the soil, their adsorption to soil organic matter (humic acids, biopolymers such as proteins and polysaccharides), and mobility. For example, the presence of surfactants and detergents increase the mobility of EDCs by enhancing their solubility. Thus they can be easily carried away by water and transported to other ecosystems (Godheja et al., 2016). The EDCs present in aquatic ecosystems come mainly from industrial and municipal wastewater, because conventional water treatment processes are not effective in eliminating those (Barrios-Estrada et al., 2018). The problem posed by these compounds in these environments is their mobility and resistance to degradation. On the one hand, they can travel to remote places and enter groundwater and surface water networks, reaching amounts from ng L^{-1} to µg L^{-1} (Kirchhof and de Gannes, 2013). EDCs can also make their way into drinking water networks, this becoming another route of exposure for the human population (Barrios-Estrada et al., 2018).

Figure 4

4. Effects and mode of action of EDCs on organisms and human health

The endocrine system is responsible for controlling a wide variety of biological processes (such as reproduction, metabolism, development, etc.) through hormones secreted at very low concentrations by the endocrine glands that travel through the bloodstream and act as messengers. Depending on their solubility, they interact with distinct types of receptors: in general terms, the fat-soluble hormones interact with intracellular receptors located in the cell nucleus, and the water-soluble ones with membrane receptors (Lintelmann et al., 2003).

It is difficult to predict the effects of EDCs based on their structure alone, given that even though they do not share the same molecular structure with hormones, they do have some properties in common such as a molecular mass of less than one thousand Daltons (Diamanti-Kandrakis et al., 2009). However, the scientific literature has demonstrated that the presence of phenolic rings (as in the case of alkylphenols, bisphenols and derivatives) gives them an ability to mimic steroid hormones, being able to interact with intracellular and extracellular receptors of thyroid hormones, sex hormones (estrogens and androgens), insulin, and cortisol, either acting as agonists (activating the response) or antagonists (inhibiting the receptor and the associated physiological response) (Diamanti-Kandrakis et al., 2009).

The mechanisms by which EDCs alter the hormonal homeostasis of individuals depend on the concentration of the compound in the body, and they can have different effects due to the phenomenon of non-monotonic dose response. For EDCs it is common that the response may be higher at low doses than at high doses. These results in unpredictable responses, vastly different from the typical dose-response patterns in which, as the dose increases, the effect increases (Vandenberg et al., 2012). Since EDCs are fat-soluble, they can accumulate in adipose tissue (and other matrices such as nails, hair, serum, breast milk, placenta, etc.), as well as traverse biological membranes to interact with the intracellular hormone receptor (Schug et al., 2011). It has been shown that they are also capable of interacting with hormonal receptors present in the plasma membrane depending on the concentration at which they are present within the organism (Jiménez-Díaz et al., 2011; Martín-Pozo et al., 2020; Rodríguez-Gómez et al., 2014; Vandenberg et al., 2012).

The possible synergistic interaction between several EDCs that lead to the appearance of various diseases in humans has also been demonstrated. EDCs have been related to an increased incidence of cancer, fertility problems in men and women (decreased quality of gametes, endometriosis, precocious puberty, alteration of the menstrual cycle), diabetes, obesity, cardiovascular problems, neurodegenerative diseases (Parkinson and Alzheimer), congenital defects (cryptorchidism), or alteration of the immune system, among others. All these alterations and pathologies are the consequence of an alteration of the homeostasis of the hormones of the individuals (Bilal and Iqbal, 2019; Darbre, 2021; Nowak et al., 2018; Schug et al., 2011).

Despite being present in minimal amounts in the environment (on the order of μg L^{-1}), the effects of EDCs on biota can manifest at lower thresholds than those present in the environment (on the order of ng L^{-1}). Articles have been published highlighting the fact that many organisms such as fish, amphibians, mammals, and other vertebrates, as well as some invertebrates (Echinoderms and Mollusks) are susceptible to damaging effects when exposed to EDCs. A decrease in fertility and progeny survival, an increase in mortality rate, as well as other effects derived from the ability of EDCs to mimic their sex hormones have been observed (Diamanti-Kandarakis et al., 2009). Table 1 summarizes the major impacts of EDCs on living organisms and human health.

Table 1

In addition, since most endocrine disruptors are fat soluble they can accumulate in living beings and lead to the phenomenon of biomagnification in ecosystems. This could affect human populations if EDCs are present in species that we usually feed on (fish, meat products, etc.) (Xue et al., 2017).

5. Proposed microorganisms for degradation of EDCS: Bioremediation

Given the awareness of the damage caused by endocrine disruptors both in fauna and in humans, competent organizations such as the US and EU Environmental Protection Agency through the REACH regulation (Registration, Evaluation and Authorization of Chemicals) (EU REACH, 2022) as well as the European Water Framework Directive (founded by the European Parliament), have established regulations that set emission limits to reduce their accumulation in ecosystems. International initiatives include agreements and decisions made at the Rotterdam Convention of the United Nations Environment Program, and the Stockholm Convention (Darbre, 2021). For instance, BPA has been restricted for consumer use since March 2018, and in paper products since January 2020. BPA can be used in food packaging but cannot exceed 0.05 mg kg^{-1} in the food. This has led to the substitution of BPA by other equally harmful bisphenols, and now the authorities have found that 34 other bisphenols must be restricted under EU REACH legislation. Phthalates, for example, are classified as toxic to reproduction, and in particular diethyl hexyl phthalate (DEHP), dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), and benzyl butyl phthalate (BBP) have been restricted in several everyday products including electrical and electronic equipment, swimming aids, or coated fabrics, among others, since 2020 (EU REACH, 2022).

Initially the removal of pollutants with possible hormonal effects was based on purely physical-chemical methods. They included the use of filtration membranes, advanced oxidation processes such as Fenton reactions, ozonation and photo-oxidation, along with other slow and costly processes, with drawbacks such as the formation of reactive oxygen species (ROS) and other potentially harmful substances, or the generation of products with greater hormonal activity with respect to the parental compounds (Ben et al., 2017; Oller et al., 2011; Li et al., 2007; Westerhoff, 2003; Stackelberg et al., 2007; Vieno et al., 2006). The removal ability and effectiveness of EDCs from wastewater is highly dependent on the physical and chemical properties of the compounds. Conventional WWTP water treatment techniques are ineffective in degrading EDCs, so more advanced techniques have been introduced over time with higher efficiency. However, these techniques are still insufficient for complete EDC removal (Table 2).

Table 2

A more sustainable and recent alternative that has proven to be effective is based on bioremediation techniques. Bioremediation consists of the use of microorganisms or their enzymes in order to eliminate or transform pollutants into less toxic substances for the environment and its biota (Sharma et al., 2018). The technique can be carried out in different ways depending on the interaction between the microorganisms, or parts of the microorganism, with the contaminant. Biotransformation, bioadsorption, and bioaccumulation are some of the principal bioremediation techniques (Juwarkar, et al., 2010). The success of the latter two requires specific conditions in the environment and depends on the physicochemical properties of the compounds to be eliminated (Wang and Wang, 2016). Biotransformation has been shown to be the most popular and effective method to remove EDCs since it has fewer limitations regarding bioaccumulation and bioadsorption; it also offers multiple advantages such as simplicity, low cost, speed and high selectivity. However, in processes where the microorganism is used as a whole, bioadsorption processes significantly affect the bioavailability of the compound for the microorganism and, consequently, the degradation rate of the compound (Lang et al., 2009).

Another classification of bioremediation strategies is based on where the process occurs. In this way, it is possible to distinguish between the *in situ* bioremediation, which acts directly in the contaminated environment, and the *ex situ* bioremediation, which involves moving the contaminated area to another site (Juwarkar et al., 2010).

Depending on how the medium is manipulated, three main bioremediation-based technologies are highlighted: bioaugmentation, biostimulation, and bioventing. Bioaugmentation is a strategy in which microbial communities of fungi and bacteria, or any biological catalyst (enzymes), are used to eliminate contaminants from the environment (Singh et al., 2011). Biostimulation is a practice based on the modification of the contaminated environment in order to promote the growth of existing microorganisms capable of eliminating organic pollutants. Modifications consist of pH adjustments or the addition of nutrients such as phosphorus and nitrogen. In addition, biostimulation can also be promoted by bioaugmentation (Singh et al., 2011). Bioventing is a technology that promotes the natural biodegradation of aerobically degradable pollutants by providing oxygen (aeration) to autochthonous bacteria present in that environment (Hinchee et al., 1996, Hyman and Dupont, 2001).

Bioaugmentation and bioventing are the most commonly used techniques for the elimination of EDCs present in sediments and soils. Bioventing is also used in aquatic environments in order to increase the amount of oxygen in the environment to improve the performance of oxygen-dependent oxidative reactions. Regarding bioremediation processes, either entire microorganisms (colonies, consortia, spores, mycelia) or their parts (enzymes, cell wall) can be used (Gaur et al., 2018).

The most appropriate strategy for the bioremediation of an environment contaminated by EDCs is selected according to several factors: the type of contaminated environment (aquatic or terrestrial), the type of contaminants present in the environment, and the physical-chemical conditions of the environment (Rasheed et al., 2017).

Microorganisms, and specifically bacteria, are the organisms that have the greatest metabolic diversity on the planet. This physiological and metabolic versatility, along with their rapid and effective ability to adapt to the presence of toxic substances that put their survival at risk, makes them excellent candidates for use as a tool to eliminate toxic and recalcitrant organic compounds in contaminated environments (Mohapatra et al., 2021). In general, the elimination and biodegradation of these compounds in extreme environments are usually carried out by gram-negative bacteria since they have multiple sites on their walls where chemisorption (strong binding of molecules to a surface) of EDCs takes place, as opposed to gram positive bacteria (Kim et al., 2010). Their physiological and metabolic versatility as well as their rapid and great capacity to adapt to the presence of toxic substances, makes them excellent candidates for use as a tool to eliminate toxic and recalcitrant organic compounds in contaminated environments (Mohapatra et al., 2021).

In addition, bacteria have a wide variety of enzymes (such as laccases, esterases, oxidoreductases and versatile peroxidases) that, under normal conditions, degrade polymers into simple monomers which they use as a carbon source. Recently it has been shown that these enzymes are also capable of degrading synthetic organic compounds very effectively (Kadri et al., 2017). Apart from bacteria, lignolytic fungi from the soil and the enzymes they produced have also been used to eliminate compounds that present phenolic rings and other xenobiotics (Hashim et al., 2017).

In relation to the use of purified enzymes, these can be free or associated with a matrix (nanoparticles, beds, solid supports, etc.). The immobilization of enzymes on supports has several advantages which include the reuse of the enzyme, prolongation of its useful life, greater thermal stability, and resistance to wide pH ranges. However, the type of support used, as well as the immobilizing method used for the enzyme (covalent bonds, adsorption, electrostatic interactions, etc.) must be considered in order not to alter the efficiency and activity of the enzyme, given that the enzymatic reaction decreases when it is immobilized on a support (Khan and Alzohairy, 2010).

Furthermore, bioremediation based on purified enzymes (produced by the microorganism or from an expression vector) depends not only on the growth of any microorganism in the contaminated environment, but also on the catalytic activity of the enzyme itself secreted by the microorganisms that they synthesize (Ruggaber and Talley, 2006). This limitation is a great problem, especially in nutrient-poor environments (oligotrophic environments) since, under these conditions, microbial growth is extremely limited due to the considerable decrease of the synthesis and production rate of participating enzymes (Gianfreda and Bollag, 2002). Recently, insect engineering (e.g., *Drosophila meganogaster)* has been proposed as an alternative to express functional enzymes and bioremediate environmental contamination (Clark et al., 2022).

5.1. Bacteria-mediated degradation methods

The degradation of EDCs mediated by bacteria can occur in two conditions according to their requirements: in aerobiosis (in presence of oxygen) or in anaerobiosis (in oxygen deficiency or absence) (Wu et al., 2017). Since oxygen is the most common electron acceptor during microbial respiration, a wide variety of microorganisms are capable of degrading contaminants under aerobic conditions. In addition, the degradation of the compounds depends on the enzymes involved in the metabolic pathway to degrade unusual substrates, in which the initial reaction is an oxidative process catalyzed by oxygenases and peroxidases which require the activation and incorporation of oxygen. However, it has also been shown that certain facultative and strict anaerobic bacteria can eliminate EDCs in the absence of oxygen (as in anaerobic digesters). In these oxygen-deficient environments, the microorganisms can use nitrate, manganese iron sulfate and carbonate as electron acceptors, with the consequent reduction of these acceptors, and hence use metabolic routes different from those of those of aerobic microorganisms (Liu et al., 2020; Wu et al., 2017).

Bacteria can degrade a wide variety of synthetic compounds, such as parabens, bisphenols, synthetic hormones, nonylphenol and its derivatives, since they possess a large repertoire of enzymes and genes (oxygenases, peroxidases, lipases, etc.) whose expression is induced in situations of stress (poor availability of nutrients in the environment, presence of toxic substances, etc.) (Budeli et al., 2020).

Many of them can use these compounds as a carbon source and therefore could be used in contaminated soil, water and in WWTPs. The efficiency of the process depends on many factors that can affect the growth and production of key enzymes for the biodegradation of these compounds. However, these limitations can be overcome by purifying enzymes from those strains that are capable of effectively and rapidly degrading EDCs and using them either in their free form or associated with a support or matrix (Bilal et al., 2017).

5.1.1. Degradation of nonylphenol derivatives

Many of the strains that are capable of degrading NP and its derivatives have been isolated from sediments and activated sludge from secondary WWTP treatments (both aerobic and anaerobic treatments) (Chang et al., 2005). Bacteria of the *Sphingomonas* genus, specifically the TTNP3 strain, *Sphingomonas cloacae*, and *Sphingomonas xenophaga*, are capable of degrading NP in aerobiosis (the last two were isolated from WWTP wastewater) (Bhandari et al., 2021). Other bacterial species such as *Stenotrophomonas sp*, *Pseudomonas mandelii*, and *Pseudomonas veronii* are also capable of eliminating NPs (Soares et al., 2003).

Bacteria of the genus *Sphingomonas* are the most effective at eliminating NPs at a rate of 100 mg L^{-1} day^{-1}. Thus, for instance, the *Sphingomonas* TTNP3 strain is capable of degrading them directly in the environment in a very efficient way, using them as a carbon source. In addition, it has been verified that the degradation mediated by this bacterium depends on the length of the alkyl substituent attached to the phenolic ring (Bhandari et al., 2021).

The most accepted explanation of the oxidative fission of NPs involves a hydroxylation of the terminal carbon transforming the molecule to an alcohol. The alcohol is then oxidized to organic acid that will be metabolized by the bacteria through the metabolic pathway of β-oxidation (Vallini et al., 2001). This route is known as ipso type II substitution. Other pathways have also been reported, such as fission of the phenolic ring by elimination of the alkyl substituent (Bhandari et al., 2021).

The products of the ipso type II substitution are hydroquinone (from the phenolic ring) and a carbocation (from the alkyl substituent) that has nine carbon atoms. Eventually, hydroquinone will be metabolized to organic acids. As for the products that derive from the alkyl-type substituents of the parental NP, these are metabolized to give rise to alcohols (nonanol) which are intermediate metabolites of the different strains of *Sphingomonas* (Bhandari et al., 2021).

Nonanols are highly volatile products. Bacteria often use the phenolic ring (hydroquinone) as a source of nutrition for growth and development. All the reactions mentioned above are carried out by monooxygenases. Among them, flavin-dependent monooxygenases, and octylphenol-4-monooxygenase (OpdA) play a key role in the substitution and fission reactions of branched nonylphenol (and derivatives) (Bhandari et al., 2021).

The degradation of NP under anaerobic conditions has also been investigated. This is carried out by genera such as *Pseudomonas*, *Pseudoxanthomonas*, *Thauera*, and *Novosphingobium*, which have been detected in anaerobic digesters of the WWTP. To date, little is still known as to how the degradation occurs. However, although anaerobic degradation is possible, the degradation of NPs under aerobic conditions has been shown to be more efficient (Bhandari et al., 2021).

5.1.2. Degradation of estrogens (natural and synthetic)

The most efficient bacteria for the degradation of synthetic estrogens usually belong to the group of Gram-negative ones, with a degradation efficiency of 44-99% with respect to gram positive ones (30-80%) (Budeli et al., 2020).

The most effective bacteria are of the genus *Achromobacter* (gram -), *Agromyces* (gram +), *Novosphingobium* (gram -), and *Rhodococcus* (gram +) which have the highest estrogen removal efficiencies from the medium (90-99%). The time they must remain in contact with the compound for complete degradation is 48-96 h, and they are capable of completely degrading the estrone (E1) (Adeel et al., 2017). Estradiol (E2) is the most susceptible estrogen to be eliminated by bacteria, since more than 60% of the genera that have been studied can degrade it. For example, all members of the Bacillus genus have been able to completely degrade E2, with a minimum contact time of 96 h for complete degradation (Adeel et al., 2017). Other bacteria, such as *Ochrobactrum* sp. strain FJ1, have also recently been isolated and identified as degraders of E2. Up to 98% removal was observed, which was slightly inhibited by adding an additional carbon source (Zhang et al., 2022). Only bacteria of the genus *Agromyces* and *Rhodococcus* have been able to degrade estriol (E3); *Agromyces* completely eliminated it while *Rhodococcus* could only eliminate 72% of the compounds present in the medium (Bilal et al., 2017).

The aforementioned bacteria are thought to be able to use estrogens as a carbon source when there is a carbon deficit in the medium, thus activating the genes necessary to metabolize them. It has also been shown that using ammonium as a nitrogen source increases the efficiency of estrogen degradation, in addition to being a carbon source. This may be because using ammonium as a source of nitrogen favors tyrosine synthesis by promoting the GS-GOGAT pathway, whose enzymes are involved in the assimilation of inorganic nitrogenous compounds from the environment (Pratush et al., 2020).

5.1.3. Degradation of bisphenols

A great variety of bacterial strains belonging to both the gram-positive (*Streptomyces*, *Bacillus*) and the gram-negative group (*Sphingomonas*, *Pseudomonas*, *Achromobacter*, *Novosphingobium*, *Nitrosomonas*, *Serratia*, *Bordetella*, *Alcaligenes*, *Klebsiella*) which are present in different environments (sediments, soil, and water) are capable of degrading bisphenol A (BPA) and using it as a carbon source to grow (Kang et al., 2005; Mita et al., 2015; Zhang et al., 2013).

The strain of the genus *Arthrobacter* is capable of using BPA as a carbon source in the presence of oxygen in a wide range of pH (5-9) and temperature (20-40ºC). The proposed Bendegradation mechanism consists of the breakdown of the complex, giving rise to hydroquinone and p-hydroxybenzoic acid, which are metabolized by the Krebs Cycle to generate biomass. In the case of the presence of halogenated substituents (chlorine, bromine), dehalogenation is carried out prior to the oxidative process (Ren et al., 2016).

The degradation mediated by the *Sphingomonas* TTNP3 strain (as with NP degradation) also forms hydroquinone and a carbocation (hydroxypropylphenol). The two phenolic rings of the parent compound are separated, and the same products are formed, but in this case the carbocation carries a phenolic ring. Subsequently, hydroquinone is metabolized through the Tricarboxylic Acid Cycle (TAC) (Zhang et al., 2013). Another *Sphingomonas* strain, specifically the MV1 strain, is capable of degrading BPA to p-hydroxybenzoic acid, ultimately metabolized to CO_2 and H_2O. No intermediate metabolites were detected by liquid chromatography (LC) UV-detection analysis (Zhang et al., 2013). Bacteria of the genus *Pseudomonas sp*. are other gram-negative bacteria capable of completely degrading BPA and using it as a source of carbon and energy. An example is *Pseudomonas paucimobilis* FK-4, isolated from sludge from treatment plants of epoxy resin manufacturing, which has been able to degrade 100 mg L^{-1} of BPA to concentrations below the detection limit of the appropriate instrumentation in 12 h (ultra-high performance liquid chromatography, UHPLC) (Zhang et al., 2013).

Achromobacter xyloxidans strain B-116, a bacterium isolated from municipal solid waste compost leachates, can grow and degrade 86% of BPA at an initial concentration of 5 mg L^{-1}, using it as a carbon source. The main *Achromobacter* enzymes that participate in the elimination of BPA are cytochrome P450 monooxygenases (in the presence of NADH), ammonium monooxygenases (AMO) and extracellular laccases (Zhang et al., 2013).

5.1.4. Degradation of parabens

Due to the antimicrobial activity of parabens, prior to the study of the degradation mechanism it is necessary to select resistant strains of bacteria, capable of growing in their presence. Both the bacterias' ability to grow in the medium and their capacity to eliminate the parabens effectively must be ascertained (Juárez-Jiménez et al., 2019). Few microorganisms are capable of degrading parabens. However, the existence of some bacterial species capable of surviving in their presence (resistance) and degrading them has been found. Some examples of them are *Pseudomonas beteli*, *Burkhorderia latens* and *Enterobacter cloacae* that were isolated from wastewater (Juárez-Jiménez et al., 2019; Valkova et al., 2001). Other studies have shown that some bacteria present in contaminated soil containing methylparaben (MPB) and butylparaben (BPB) are capable of using them as a carbon source. These strains (based on 16S rRNA gene analysis) have been found to be very close to *Bacillus safensis* (gram +), which is both capable of growing in a medium containing parabens and effectively degrading the compounds at a rate directly proportional to the amount present in the medium (first order reaction) (Juárez-Jiménez et al., 2019).

5.2. Fungal mediated degradation

Most fungi are multicellular organisms that do not form true tissues (hyphae) and that can be found in many environments, both free and in symbiosis. Additionally there are unicellular ones (yeasts) capable of biodegradation of organic pollutants (Marcelo-Fernández et al., 2017). Within ecosystems, fungi play a particularly key role breaking down dead organic matter through the secretion of a wide variety of extracellular enzymes and acids. These are capable of degrading complex polymers present in the soil (such as cellulose, lignin, chitin, pectins, etc.) into simple monomers that can then be metabolized to form new biomass (Gupta et al., 2017). In addition, mycodegradation can be combined with plant-based adsorbents or other adsorbent materials, succeeding in effectively eliminating EDCs, especially phenolic compounds, in an easy, eco-friendly, simple and inexpensive way (Loffredo et al., 2021). Lignolytic enzymes of fungi of the genera *Trametes*, *Aspergillus*, and *Phanerochaete*, have been found capable of efficiently degrading a wide variety of xenobiotics with possible endocrine action. The main extracellular enzymes involved belong to the group of lignin peroxidases that include laccases, manganese-dependent peroxidases, and versatile peroxidases (Bokade et al., 2021; Hashim et al., 2017).

The lignolytic oxidoreductases of fungi are capable of degrading EDCs present both at high concentrations (experimental laboratory conditions) and at low concentrations (typical of the medium, from ng L^{-1} to mg L^{-1}). In addition, these enzymes have low energy requirements since they do not need the substrates to have a certain redox potential or the presence of co-substrates (Lloret et al., 2012). The most common transformations catalyzed by these oxidoreductases take place through coupled oxidations, which generate polymers or oligomers as products and which have significantly lower endocrine activity with respect to the original compounds (Cabana et al., 2007). The degradation of these compounds is also carried out by oxidative processes (Becker et al., 2017). The mechanisms of action of the main lignolytic enzymes involved in fungal-mediated degradation of EDCs are described below.

5.2.1. Laccases

Laccases are extracellular oxidoreductases that belong to the group of oxidases with multiple copper molecules in their active center. In addition to fungi, it has been proven that they are also synthesized by bacteria, plants and insects, and that their function varies from one species to another (Barrios-Estrada et al., 2018). The laccases that are applied in bioremediation techniques usually come from lignolytic fungi belonging to the two large divisions that constitute the subkingdom Dikarya: *Basidiomycetes* and *Ascomycetes* (Becker et al., 2017). Laccases, and in particular Daiwa laccases purified from *Trametes sp*., are capable of degrading a wide variety of xenobiotics and EDCs that have a phenol in their structure. These include BPA, triclosan, synthetic estrogens, chlorinated pesticides, nonylphenol and derivatives, naproxen, diclofenac, or oxybenzone. The enzymatic oxidation of these compounds is coupled with the reduction of O_2 to H_2O, hence no toxic substances are generated in the reaction (Barrios-Estrada et al., 2018; Bokade et al., 2021; Tanaka et al., 2001).

The major benefits of laccases in the field of bioremediation of EDCs is their low selectivity (ability to degrade of a wide range of compounds), high affinity for the substrate (low K_m), which is why they can eliminate the substrates present in the medium at low concentrations (Bilal et al., 2019). In contaminated media, laccases can be introduced by inoculating the fungus that produces them, as free enzymes (purified from the fungus) or immobilized in a matrix (Barrios-Estrada et al., 2018). The immobilization of the enzyme in a matrix has several advantages from an economic point of view, compared to the use of free enzymes. Immobilization allows them to be reused and retained in the system for a longer time while preserving their catalytic properties. Free enzymes, on the other hand, often cannot be reused after a specific number of reaction cycles because of the inactivation/inhibition of the enzyme (due to elevated temperatures, changes in pH, or the presence of inhibitors) or because of their loss during the process, given their mobility (Ardao et al., 2015; Bilal et al., 2017). When comparing the removal efficiency of NP and BPA using free enzymes versus the use of immobilized enzymes, a significant difference in removal efficiency is observed. For example, for free forms the removal efficiency of NP and BPA was 44% for *T. versicolor laccase* and 54% for *M. thermophila laccase*. In contrast, when the enzymes were immobilized on acrylic beads, elimination percentages up to 97% were achieved for both enzymes after 24 h of treatment (Becker et al., 2017). Immobilization is achieved through various approaches, depending on the nature of the bond between the enzyme and the matrix (covalent bonds, adsorption, entrapment, cross bonds or encapsulation), the goal being for the bond to not affect the catalytic capacity or the efficiency of the enzymatic reaction (Bilal et al., 2017).

Further comparative inquiries have been conducted to determine which fungus produces the laccase that effectively degrades a wide range of EDCs depending on the conditions of temperature, pH, enzyme concentration, and the substrate to be removed (Barrios-Estrada et al., 2018). The most effective laccases in eliminating EDCs such as BPA, nonylphenol and triclosan have been shown to come from *Trametes versicolor*, *Trametes vilosa* and *Coriolopsis polyoma* (Fukuda et al., 2004; Hundt et al., 2000).

5.2.2. Lignin peroxidases

Lignin peroxidases are enzymes that belong to the family of oxidoreductases and are responsible for oxidizing and depolymerizing lignin, using hydrogen peroxide (H_2O_2) as a co-substrate and veratryl alcohol as a mediator (under natural conditions). They contain a heme group (heterocyclic center with an Fe atom inside) as a prosthetic group and cofactor. These enzymes are synthesized by lignolytic fungi of the *Basydiomycota* division such as *Phanerochaete chrysosporium*, *Trametes versicolor* and by bacteria (Sharma et al., 2018). Lignin peroxidases oxidize a wide range of EDCs (with or without phenolic rings in their structure including herbicides, polycyclic aromatic hydrocarbons (PAHs) and other PCPs) as well as xenobiotics (which have a redox potential above 1.4 V), due to their low specificity for the substrate (Bilal et al., 2019; Piontek et al., 2001; Singh et al., 2021). They degrade compounds through initial oxidation followed by subsequent oxidative reactions through the generation of intermediate cationic radicals (Bokade et al., 2021; Sharma et al., 2018). Lignin peroxidases purified from bacteria are more efficient at degrading lignin polymers compared to those synthesized by fungi, as they have higher substrate specificity and thermal stability. They are also effective for eliminating EDCs (Sharma et al., 2018; Singh et al., 2021). These enzymes have been shown to possess greater catalytic activity and greater affinity for the substrate when associated with carbon nanotubes (Bilal et al., 2019).

5.2.3. Manganese peroxidases

These enzymes belong to the group of hydrogen peroxide oxidoreductases which also have a heme group as a prosthetic group. Mn peroxidases have shown the ability of degrading many toxic compounds including EDCs (PAHs, pesticides, bisphenols, and NPs) in the presence of H_2O_2. They are responsible for oxidizing Mn^{2+} ions (part of the composition of wood) to Mn^{3+} through successive reactions. The generated Mn^{3+} ions act as an oxidizing agent for phenolic compounds and many EDCs (Ten Have and Teunissen, 2001; Sharma et al., 2018).

5.3. Applications of bioremediation techniques in contaminated environments

According to Budeli et al. (2020), current wastewater treatment processes in WWTPs are not sufficient for the elimination of all pollutants. Typical proceedings in a WWTP include primary treatments (removal of large waste through physical processes) followed by secondary treatments (activated sludge and anaerobic digesters). Tertiary treatments can also be added to eliminate pathogens from the water, which are usually chlorination or other similar methods. On certain occasions, these physical-chemical processes are intended for the elimination of nutrients such as nitrogen and phosphorus. The aforementioned treatments do not achieve complete elimination of EDCs. Consequently, remaining contaminants in the WWTP effluents, reach aquatic and terrestrial ecosystems as a final destination (Budeli et al., 2020).

Several strategies can be implemented to eliminate EDCs in wastewater treatments, such as the introduction of additional bioreactors with microorganisms capable of degrading them, the introduction of microorganisms in the tanks where secondary treatments take place, or the introduction of additional treatment systems in conjunction with the main ones (Nguyen et al., 2014; Rostro-Alanis et al., 2016; Vieira et al., 2020). Some interesting proposed methods for eliminating EDCs in the environment are described below.

As far as enzymes are concerned, immobilized laccases are good candidates for the elimination of EDCs directly in WWTPs since they can be used both as individual molecules (free system) or associated with a matrix. The use of co-substrates (generally organic acids added to the medium that act as electron shuttles between the enzyme and the substrate) promote degradation by increasing the redox potential of the medium (Nguyen et al., 2014; Rostro-Alanis et al., 2016; Sharma et al., 2022).

The use of laccases as the sole enzyme is less efficient compared to the use of the 3 lignolytic enzymes (laccases, Mn peroxidases, and lignin peroxidases), since it has been shown that, in conjunction, these are capable of synergistically degrading the different types of EDCs (as they degrade lignin under natural conditions) present in wastewater (Vieira et al., 2020).

Other techniques based on the use of enzymes are the biological filtration membranes and the packed bed reactor. Filtration membranes consist of the immobilization of the enzymes for bioremediation to a membrane whose pore size is less than 10kDa. The contaminated water or matrix passes through this membrane where the retention and degradation of the analytes by these enzymes take place (Barrios-Estrada et al., 2018). The packed bed system or reactor consists of a cylindrical support filled with diverse materials associated with enzymes (usually from lingolytic fungi) to degrade the EDCs immobilized in a matrix (Barrios-Estrada et al., 2018).

Two-stage systems (Two System Stage, TSS) are modified enzymatic membrane reactors in which the process takes place in two physically separated stages. An interesting proposal as an alternative to this configuration is the use of versatile peroxidases from lignolytic fungi in the presence of Mn^{2+} ions (Singh et al., 2021). Complex EDC polymers are broken, and the resulting monomers are oxidized by the action of the produced Mn^{3+} ions (oxidant). Since the half-life of Mn^{3+} is noticeably short, an organic dicarboxylic acid (such as malonate or oxalate) is needed for the formation of a stable Mn^{3+}-complex (Taboada-Puig et al., 2015). The two-stage system method was fourteen times more efficient with respect to enzymatic membrane reactors since problems such as inactivation of membrane-associated enzymes, possible clogging and the uptime of the process are avoided. It resulted in a reduced enzyme inactivation, while the rate of degradation of enzymes was increased. In TSS the bioreactors where the complexes are formed are physically separated from those which catalyze the reactions and the oxidation of the compounds. Through this strategy, EDCs have been efficiently eliminated from waters both at experimental concentrations (1.3-8.8 mg L^{-1}) and environmental concentrations (1.2-6.1 mg L^{-1}) (Taboada-Puig et al., 2015).

A remarkable application regarding the use of complete microorganisms was proposed with the fungus *T. versicolor*. It was capable of degrading a mixture of EDCs in the bioreactors by means of its lignolytic enzymes, completely removing them in just 4 days (up to 21 mg L^{-1}). In addition, it has been proven that it was capable of degrading EDCs in the absence of nutrients in the medium using them as a carbon source. This means a reduction in the associated cost, eliminating the need to add nutrients or co-substrates for it to grow (Pezzella et al., 2017).

The use of consortiums of microorganisms in secondary or separate treatment tanks has also been proposed, targeting EDCs that have not been eliminated in previous treatments (primary, secondary and tertiary). This technique offers the great benefit of taking advantage of mutualistic, co-metabolic and synergistic interactions between bacteria in microbial communities to improve the efficiency of EDC elimination. In this method, greater reaction efficiency can be further achieved by applying bioventing and biostimulation techniques (Liu et al., 2020). Another recent study has isolated and studied the groups of fungi and bacteria naturally present in sewage sludge, capable of degrading BPA and diclofenac by up to 80%. These findings highlight the importance of characterizing the native mycobiome that could be used in EDC biotransformation technologies (Conejo-Saucedo et al., 2020).

6. Conclusions and future perspectives

Bioremediation processes are a promising and sustainable strategy for removing EDCs. The major benefit that bioremediation offers is to the environment. Compared to physicochemical methods, bioremediation processes are ecofriendly, less intrusive, and less harmful to ecosystems. Microorganisms and fungi can use EDCs as a carbon source under aerobic conditions, which means that they end up transforming them into CO_2 and H_2O. It can also be a very cost-effective technology, as treatment using bioremediation as the main tool is usually less expensive than using conventional treatment methods. And most importantly, it can effectively eliminate EDCs entirely. Despite the benefits raised above, however, they have some limitations, and certain important aspects of the methods must be considered for practical purposes. Biodegradation products should not be more persistent or toxic than the initial ones, which is a potential outcome; it may be complicated to extrapolate pilot and laboratory studies to large-scale mass operations; and these methods can be time consuming, since processes involving microorganisms can be slow.

Synthetic biology and bioengineering open new perspectives and expand the possibilities of bioremediation. Future biotechnology-based techniques may include enzyme design, molecular modeling, cloning and genome editing. Thorough examination of strains capable of growing in contaminated media has enabled the identification of the genes that codify for the enzymes involved in the EDCs metabolization pathway. These genes can be inserted, cloned, and expressed in cloning vectors to obtain a large amount of enzymes for bioremediation processes. In addition, the use of genetic engineering techniques allows for improving the resistance of enzymes in more extreme environments (salinity, temperature and pH), such as polluted wastewater, particularly when their efficiency is significantly reduced in the presence of other substances. These advancements also entail the parallel development of machine learning algorithms and protocols, a significant increase in computational power for investigation in this direction. We must not forget the essential contribution of predictive mathematical models, allowing us to know the potential degradation pathways of a determined EDC. These tools together will help scientists choose the best bioremediation approach.

As for new trends, interest is growing in the creation of efficient enzymes that can be applied to EDC remediation. There are several advantages with respect to the use of extracellular enzymes purified from bacteria and fungi in the wastewater treatment process; they offer fast treatment, are easy to maintain and operate, and do not require substrate or sludge output, as is the case with microorganisms. However, they are not yet applied in WWTPs. This method has not progressed beyond the laboratory phase, despite satisfactory results. The combination of the most efficient bacterial and fungal enzymes (peroxidases, laccases, and bacterial enzymes) in supports has proven to be one of the most efficient methods to eliminate EDCs in bioremediation processes.

More research is crucial for the advancement of the effective application of bioremediation. First, further the identification of microbial strains capable of using EDCs as a carbon and energy source would be particularly helpful. The ideal bacteria should be capable of completely degrading the contaminants through their incorporation into the metabolic pathways for the generation of biomass without generating metabolites or toxic by-products. Second, endocrine activity studies should not cease, as many synthetic substances with potential endocrine disrupting action have not yet been catalogued. The parent EDC should be evaluated, as well as the degradation pathways and potential endocrine activity of the generated metabolites. Third, it is necessary to study in more depth the relationships between distinct species of microorganisms, such as their synergy or co-metabolism, as well as other interactions in which bacteria couple their metabolism and their reactions. A better understanding of these interactions would, for example, potentially increase the performance of the degradation processes of EDCs, generate products much less toxic with respect to parental compounds, or even innocuous final products.

Finally, further research is necessary especially on new strategies, which must be evaluated to compare results with conventional treatment methods. The improvement and updating of current bioremediation technologies thanks to genetic and molecular engineering techniques is particularly promising, potentially leading to the adoption of even greener and more effective methods, highly efficient in the elimination of EDCs and with lower impact on the environment.

Declaration of competing interest

The authors declare no competing interests

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Figure Captions

Figure 1. Number of publications with the search terms “endocrine disruptors” AND “bioremediation” (retrieved on 04/09/2022).

Figure 2. Subject area of the documents used for the elaboration of the bibliographic work. Results from the search terms “endocrine disruptors” AND “bioremediation” (retrieved on 04/09/2022).

Figure 3. Structure and uses of the main types of EDCs present in the environment. *Own elaboration.*

Figure 4. Contamination sources and paths of EDCs into terrestrial and aquatic ecosystems. *Own elaboration. Created with BioRender.com*

Strategies based on the use of microorganisms for the elimination of pollutants with endocrine-disrupting activity in the environment

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ABSTRACT

The continuous contamination of the environment by a high variety of pollutants is an alarming problem worldwide that requires prompt, effective and sustainable solutions. Among these pollutants, endocrine disrupting chemicals (EDCs) are of special concern due to their persistence and toxicity, interfering with the hormonal homeostasis of humans and wildlife. In addition, conventional physical-chemical treatments are not efficient enough to completely remove EDCs. This review aimed at compiling all the available information about the bioremediation processes capable of transforming EDCs into more environmentally friendly chemicals, focusing on microorganisms, enzymes and fungi. The review outlines the principal sources of EDCs, the problems associated with their presence in the environment, their harmful effects on wildlife, as well as providing an overview of bioremediation as an alternative and efficient strategy for their elimination. The proposed mechanisms to minimize the persistence of EDCs based on the use of microorganisms are described, as well as their potential implementation in wastewater treatment plants. Although the use of bioremediation processes is relatively unexplored, research has shown that microbial communities, enzymes, or fungi are a promising alternative thanks to their ability to efficiently transform EDCs into non-hazardous end products. Aerobic bacteria belonging to the genus *Sphingomonas*, *Achromobacter* or *Pseudomonas*, among others, have proven to be highly effective in the removal of EDCs, such as nonylphenols, bisphenols, and parabens.

Keywords: Endocrine disrupting chemicals (EDCs); Xenobiotics; Degradation; Wastewater treatment plant (WWTP); Bioremediation; Microorganisms

Abbreviations: AMO, ammonium monooxygenases; BBP, benzyl butyl phthalate; BPA, bisphenol A; BPB, butylparaben; DBP, dibutyl phthalate; DEHP, diethyl hexyl phthalate; DIBP, diisobutyl phthalate; E1, estrone; E2, estradiol; E3, estriol; EE2, 17α-ethynylestradiol; EDCs, endocrine disrupting chemicals; EPB, ethylparaben; H_c, Henry's law constant; IFN-γ, interferon gamma; K_{oc}, organic carbon-water partition coefficient; K_{ow}, octanol-water partition coefficient; LC, liquid chromatography; MPB, methylparaben; NP, nonylphenol; OpdA, octylphenol-4-monooxygenase; PAH, polycyclic aromatic hydrocarbon; PCPs, personal care products; REACH, Registration, Evaluation and Authorization of Chemicals; ROS, reactive oxygen species; TAC, tricarboxylic acid cycle; TNF-α, tumor necrosis factor; TSS, two system stage; UHPLC, ultra-high performance liquid chromatography; WWTP, wastewater treatment plant.

1. Introduction

During the last decades, the presence of micropollutants in the environment has increased considerably worldwide as a consequence of growing anthropogenic activity and industrialization (chemical industry, plastics manufacturing, pesticide synthesis and use, the manufacturing and use of pharmaceutical and personal care products, PCPs) (Mohapatra et al., 2021). The main sources of pollutants in natural environments are from industrial effluents, wastewater treatment plants (WWTPs), leaching processes in agricultural soils, as well as via accidental discharges into aquifers and oceans (Barrios-Estrada et al., 2018).

Emerging pollutants are defined as unregulated chemical substances that are suspected of affecting the environment or whose effects are unknown at very low concentrations, usually in the range of μg L^{-1} to ng L^{-1} (Deblonde et al., 2011). Furthermore, many of these compounds are persistent and ubiquitous in the environment (Combalbert and Hernandez-Raquet, 2010; García-Fernández et al., 2022; Hashim et al., 2017). Persistence of pollutants in ecosystems is a direct consequence of their resistance to degradation due to their physical-chemical properties, making them more bioavailable to living beings (Petrie et al., 2015). In addition, some of these pollutants are xenobiotics and micropollutants capable of altering the normal physiology of organisms (metabolism, reproduction, and behavior) since they have the potential to simulate endogenous hormones and stimulate or inhibit their responses in the body. These specific substances are commonly known as endocrine disrupting chemicals (EDCs) (Kidd et al., 2012).

According to the official definition of the US Environmental Protection Agency, an endocrine disruptor is *“an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes”* (Kavlock et al., 1996). EDCs are a group of compounds with diverse molecular structures. Despite this, they share common characteristics, such as their high rate of persistence in the environment. They are generally highly resistant to degradation (both oxidative and UV), to elevated temperatures (high thermal stability) and to a wide ranges of pH (extreme pHs). As a result, these compounds tend to accumulate in the environment, posing a risk to the health of animals and humans (Hashim et al., 2017). Some of these substances have low solubility in water and a fat-soluble nature, and they tend to accumulate within biological tissues, particularly in adipose tissue. Thus they become inaccessible to the organs in charge of detoxifying (mainly the liver) and eliminating them (the kidneys) and, therefore, have a tendency to bioaccumulate (Gómez-Regalado et al., 2021; Kidd et al., 2012). Bioaccumulation has another consequence at the environmental and ecosystem level since it leads to the phenomenon of biomagnification, the increasing concentration of a contaminant in organism tissues at successive levels of the trophic chain (Martín et al., 2020).

The negative impact, high persistence and ubiquity of EDCs in the natural environment are a matter of great concern today. Efforts are being made to reduce their presence, but their elimination is a major challenge that requires innovative and more sustainable strategies. Conventional WWTPs are inefficient at completely removing EDCs which are consequently prevalent in wastewater effluents and the marine waters they’re ultimately discharged into (Azizi et al, 2022; Ben et al., 2017; Liu et al., 2009; Surana et al., 2022). Such technologies are typically based on physical, chemical, electrochemical and biological processes, highly related to the EDCs properties (Azizi et al, 2022). In this context, the scientific community has proposed several mechanisms for better eliminating EDCs from either from industrial effluents and urban waste, or contaminated environments. Advanced oxidation techniques have been proposed, applied directly in the treatment of industrial and urban wastewater, to enhance the removal efficacy of these micropollutants. Although these processes are effective, both the high associated cost and the volume of generated waste that is potentially harmful to the environment make it difficult to put into practice on a large scale (Ben et al., 2017; Liu et al., 2009).

The use of microorganisms or fungi as tools for EDCs elimination is therefore an interesting, sustainable and eco-friendly alternative. The idea is to use microorganisms capable of efficiently degrading EDCs, thanks to their enzymatic mechanisms, to improve the effectiveness of conventional activated sludge systems (Roccuzo et al., 2021).

The aim of the present review article is to give an overview of the bioremediation of EDCs using bacterial communities, fungi, and their enzymes. The first part is devoted to general aspects of EDCs (main sources, physicochemical characteristics and factors that influence their elimination). Then the bioremediation mechanisms of EDCs proposed by the scientific community are reported on and discussed. Finally, practical considerations and selected application approaches in WTPPs are suggested, with emphasis placed on the advantages of using microorganisms in conventional techniques.

2. Methods for literature search

In this review, different databases (Scopus, Web of Science (WoS), PubMed, CAS Finder) have been consulted for the search of information. The scientific articles that have been selected for the elaboration of this bibliographic work have been obtained by using the search keywords ("Endocrine Disruptor" OR "EDC" OR "WWTP EDC" OR "Emerging Contaminants") AND ("Bioremediation" OR "Micropollutants Bioremediation" OR "Bacterial degradation" OR "Removal enzymes" OR "Microorganism degradation"). In addition, the reference list of these articles was reviewed to identify other potential published studies on the topic.

Figure 1

As shown in Figure 1, the available information and published reports focused on bioremediation are relatively scarce (a total of 413 documents have been reported since 2001 – data from Scopus). Consequently, the selected articles that provided useful information for the present review were mainly limited to a 10-year period. Given the scarcity of available scientific reports on EDC bioremediation processes, certain works from previous years (up to 15 years ago) were also included, providing relevant contextual information.

A large part of the selected articles belongs to environmental sciences, although journals from other areas have also been consulted (Figure 2). From the bibliographic reviews on EDCs, an attempt has been made to obtain and synthesize the maximum information available on the mechanism of action of endocrine disruptors in humans and in ecosystems (at the molecular, cellular, physiological, and metabolic levels), their physicochemical properties and their behavior in the environment (mobility, persistence, and bioavailability).

Figure 2

A more specific search was made for experimental articles on bioremediation methods. These lay the groundwork for the development of new methods based on the use of microorganisms or their enzymes as tools for the removal of EDCs from WWTPs and environments contaminated by these compounds, but also to better understand the degradation reactions of these compounds at the molecular (biochemical) level. For the search of the proposed degradation-bioremediation-based methods, articles were excluded that a) were conference abstracts or comments; b) did not deal with compounds with disruptive action; or c) did not use microorganisms, fungi, or their enzymes for the removal of EDCs.

Recent review papers have been published on EDCs, addressing topics such as occurrence, health effects, and remediation techniques, while others deal with the elimination and bioremediation of a wide group of pollutants or a single family of EDCs (Narayanan et al., 2022; Surana et al., 2022; Tarafdar et al., 2022; Zhang et al., 2013). Ismanto et al. have elaborated an interesting work about EDCs in environmental matrices and their remediation, including a section dedicated to bioremediation technologies (Ismanto et al., 2022). In other recent work, Roccuzo et al. have published a formal in-depth meta-analysis with models and statistical tests to investigate how various variables (e.g., exposure time, type of organism and complexity of contamination) could influence biodegradation, based on the literature (Roccuzo et al., 2021). However, as far as we know, no work focuses in detail on bioremediation as an alternative for the elimination of multiclass EDCs in conventional WTPPs.

This review has been organized into several sections and sub-sections that focus on distinct aspects related to EDCs. First, the primary families of EDCs are defined and the harmful effects of EDCs on biota and human health are summarized. Next, the physicochemical characteristics of these compounds are discussed to better understand their behavior, mobility, bioavailability, and persistence in ecosystems (terrestrial and aquatic). Finally, the main methods used to eliminate EDCs in natural environments and WWTPs is discussed, as well as the principal microorganisms that are used for their elimination.

3. Presence of EDCs in ecosystems, sources and pathways

EDCs encompass a wide variety of compounds that are highly heterogeneous in terms of their molecular structure. These can be classified in several ways according to varying criteria: origin (natural or synthetic), main uses (pesticides, products used in industries, PCPs, etc.), presence of common functional groups, harmful effects on the organism, etc. But the most common classification of these compounds is based on their use, since it allows us to better understand how we are exposed to them in our day to day (Kabir et al., 2015).

Despite the considerable diversity of compounds with potential hormonal activity, emphasis will be placed on those with greater relevance at the biological level (both in humans and in biota) as well as those that have a greater presence and persistence in the terrestrial and marine environments, because of their continual release into the environment. The compounds present in everyday products and drugs are of particular relevance, as well as those found in food packaging (Hashim et al., 2017).

Figure 3

Among the most notable classes of EDCs in the environment are bisphenols used in the manufacturing of plastics, nonylphenols (NPs) used as emulsifying agents, parabens, triclosan and triclocarban used as antimicrobial agents, benzophenones used as UV-filters, and phthalates used in plastics. Other relevant classes include those found in certain pharmaceutical products used as hormonal substitutes, such as natural and synthetic estrogens, and those found in some agricultural pesticides (Gavrilescu et al., 2015; Zhang et al., 2016). However, more and more compounds with endocrine disrupting activity are being discovered and added to the list of EDCs. Figure 3 summarizes the main families of EDCs and their uses.

The distribution and fate of pollutants throughout the environment depend on the properties of the compartments (pH, ions, surfactants, etc.) with which they interact, as well as on the specific properties of the contaminant (polarity, volatility, persistence, and adsorption). The fate of EDCs also depends on their use (PCPs, plastics synthesis, etc.) and the way in which they are disposed of (Geissen et al., 2015). The parameters used to determine their mobility and bioavailability in the environment are the organic carbon-water partition coefficient, K_{oc}; the ratio between the concentrations of a certain substance in a biphasic mixture formed by two immiscible solvents in equilibrium (n-octanol and water), K_{ow}; and Henry's law constant, H_c. (Birkett and Lester, 2003; Campbell et al., 2006; Sarmah et al., 2008). It is important to know the mobility of EDCs since many of them, such as pharmaceuticals present in wastewater, are excreted from the body without undergoing significant modifications in their molecular structure; therefore they maintain their biological activity and can alter physiology of the biota when they reach ecosystems via water (Boxall et al., 2004). There are also factors inherent to soil that affect the mobility of EDCs, such as the quantity, spatial conformation and polarity of organic matter, the presence of inorganic ions (minerals), or the presence of organic matter/mineral complexes (Ren et al., 2018).

The main sources of EDCs in terrestrial environments include the use of pesticides in crops, irrigation with contaminated water, the use of compost obtained from activated sludge in WWTPs, aerosol deposits and industrial and household wastes (Barrios-Estrada et al., 2018) (Figure 4). Most soils are often contaminated by a wide variety of substances apart from EDCs such as surfactants, heavy metals, and other persistent organic pollutants. The presence of these pollutants has been shown to affect the stability of EDCs in the soil, their adsorption to soil organic matter (humic acids, biopolymers such as proteins and polysaccharides), and mobility. For example, the presence of surfactants and detergents increase the mobility of EDCs by enhancing their solubility. Thus they can be easily carried away by water and transported to other ecosystems (Godheja et al., 2016). The EDCs present in aquatic ecosystems come mainly from industrial and municipal wastewater, because conventional water treatment processes are not effective in eliminating those (Barrios-Estrada et al., 2018). The problem posed by these compounds in these environments is their mobility and resistance to degradation. On the one hand, they can travel to remote places and enter groundwater and surface water networks, reaching amounts from ng L^{-1} to µg L^{-1} (Kirchhof and de Gannes, 2013). EDCs can also make their way into drinking water networks, this becoming another route of exposure for the human population (Barrios-Estrada et al., 2018).

Figure 4

4. Effects and mode of action of EDCs on organisms and human health

The endocrine system is responsible for controlling a wide variety of biological processes (such as reproduction, metabolism, development, etc.) through hormones secreted at very low concentrations by the endocrine glands that travel through the bloodstream and act as messengers. Depending on their solubility, they interact with distinct types of receptors: in general terms, the fat-soluble hormones interact with intracellular receptors located in the cell nucleus, and the water-soluble ones with membrane receptors (Lintelmann et al., 2003).

It is difficult to predict the effects of EDCs based on their structure alone, given that even though they do not share the same molecular structure with hormones, they do have some properties in common such as a molecular mass of less than one thousand Daltons (Diamanti-Kandrakis et al., 2009). However, the scientific literature has demonstrated that the presence of phenolic rings (as in the case of alkylphenols, bisphenols and derivatives) gives them an ability to mimic steroid hormones, being able to interact with intracellular and extracellular receptors of thyroid hormones, sex hormones (estrogens and androgens), insulin, and cortisol, either acting as agonists (activating the response) or antagonists (inhibiting the receptor and the associated physiological response) (Diamanti-Kandrakis et al., 2009).

The mechanisms by which EDCs alter the hormonal homeostasis of individuals depend on the concentration of the compound in the body, and they can have different effects due to the phenomenon of non-monotonic dose response. For EDCs it is common that the response may be higher at low doses than at high doses. These results in unpredictable responses, vastly different from the typical dose-response patterns in which, as the dose increases, the effect increases (Vandenberg et al., 2012). Since EDCs are fat-soluble, they can accumulate in adipose tissue (and other matrices such as nails, hair, serum, breast milk, placenta, etc.), as well as traverse biological membranes to interact with the intracellular hormone receptor (Schug et al., 2011). It has been shown that they are also capable of interacting with hormonal receptors present in the plasma membrane depending on the concentration at which they are present within the organism (Jiménez-Díaz et al., 2011; Martín-Pozo et al., 2020; Rodríguez-Gómez et al., 2014; Vandenberg et al., 2012).

The possible synergistic interaction between several EDCs that lead to the appearance of various diseases in humans has also been demonstrated. EDCs have been related to an increased incidence of cancer, fertility problems in men and women (decreased quality of gametes, endometriosis, precocious puberty, alteration of the menstrual cycle), diabetes, obesity, cardiovascular problems, neurodegenerative diseases (Parkinson and Alzheimer), congenital defects (cryptorchidism), or alteration of the immune system, among others. All these alterations and pathologies are the consequence of an alteration of the homeostasis of the hormones of the individuals (Bilal and Iqbal, 2019; Darbre, 2021; Nowak et al., 2018; Schug et al., 2011).

Despite being present in minimal amounts in the environment (on the order of µg L^{-1}), the effects of EDCs on biota can manifest at lower thresholds than those present in the environment (on the order of ng L^{-1}). Articles have been published highlighting the fact that many organisms such as fish, amphibians, mammals, and other vertebrates, as well as some invertebrates (Echinoderms and Mollusks) are susceptible to damaging effects when exposed to EDCs. A decrease in fertility and progeny survival, an increase in mortality rate, as well as other effects derived from the ability of EDCs to mimic their sex hormones have been observed (Diamanti-Kandarakis et al., 2009). Table 1 summarizes the major impacts of EDCs on living organisms and human health.

Table 1

In addition, since most endocrine disruptors are fat soluble they can accumulate in living beings and lead to the phenomenon of biomagnification in ecosystems. This could affect human populations if EDCs are present in species that we usually feed on (fish, meat products, etc.) (Xue et al., 2017).

5. Proposed microorganisms for degradation of EDCS: Bioremediation

Given the awareness of the damage caused by endocrine disruptors both in fauna and in humans, competent organizations such as the US and EU Environmental Protection Agency through the REACH regulation (Registration, Evaluation and Authorization of Chemicals) (EU REACH, 2022) as well as the European Water Framework Directive (founded by the European Parliament), have established regulations that set emission limits to reduce their accumulation in ecosystems. International initiatives include agreements and decisions made at the Rotterdam Convention of the United Nations Environment Program, and the Stockholm Convention (Darbre, 2021). For instance, BPA has been restricted for consumer use since March 2018, and in paper products since January 2020. BPA can be used in food packaging but cannot exceed 0.05 mg kg^{-1} in the food. This has led to the substitution of BPA by other equally harmful bisphenols, and now the authorities have found that 34 other bisphenols must be restricted under EU REACH legislation. Phthalates, for example, are classified as toxic to reproduction, and in particular diethyl hexyl phthalate (DEHP), dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), and benzyl butyl phthalate (BBP) have been restricted in several everyday products including electrical and electronic equipment, swimming aids, or coated fabrics, among others, since 2020 (EU REACH, 2022).

Initially the removal of pollutants with possible hormonal effects was based on purely physical-chemical methods. They included the use of filtration membranes, advanced oxidation processes such as Fenton reactions, ozonation and photo-oxidation, along with other slow and costly processes, with drawbacks such as the formation of reactive oxygen species (ROS) and other potentially harmful substances, or the generation of products with greater hormonal activity with respect to the parental compounds (Ben et al., 2017; Oller et al., 2011; Li et al., 2007; Westerhoff, 2003; Stackelberg et al., 2007; Vieno et al., 2006). The removal ability and effectiveness of EDCs from wastewater is highly dependent on the physical and chemical properties of the compounds. Conventional WWTP water treatment techniques are ineffective in degrading EDCs, so more advanced techniques have been introduced over time with higher efficiency. However, these techniques are still insufficient for complete EDC removal (Table 2).

Table 2

A more sustainable and recent alternative that has proven to be effective is based on bioremediation techniques. Bioremediation consists of the use of microorganisms or their enzymes in order to eliminate or transform pollutants into less toxic substances for the environment and its biota (Sharma et al., 2018). The technique can be carried out in different ways depending on the interaction between the microorganisms, or parts of the microorganism, with the contaminant. Biotransformation, bioadsorption, and bioaccumulation are some of the principal bioremediation techniques (Juwarkar, et al., 2010). The success of the latter two requires specific conditions in the environment and depends on the physicochemical properties of the compounds to be eliminated (Wang and Wang, 2016). Biotransformation has been shown to be the most popular and effective method to remove EDCs since it has fewer limitations regarding bioaccumulation and bioadsorption; it also offers multiple advantages such as simplicity, low cost, speed and high selectivity. However, in processes where the microorganism is used as a whole, bioadsorption processes significantly affect the bioavailability of the compound for the microorganism and, consequently, the degradation rate of the compound (Lang et al., 2009).

Another classification of bioremediation strategies is based on where the process occurs. In this way, it is possible to distinguish between the *in situ* bioremediation, which acts directly in the contaminated environment, and the *ex situ* bioremediation, which involves moving the contaminated area to another site (Juwarkar et al., 2010).

Depending on how the medium is manipulated, three main bioremediation-based technologies are highlighted: bioaugmentation, biostimulation, and bioventing. Bioaugmentation is a strategy in which microbial communities of fungi and bacteria, or any biological catalyst (enzymes), are used to eliminate contaminants from the environment (Singh et al., 2011). Biostimulation is a practice based on the modification of the contaminated environment in order to promote the growth of existing microorganisms capable of eliminating organic pollutants. Modifications consist of pH adjustments or the addition of nutrients such as phosphorus and nitrogen. In addition, biostimulation can also be promoted by bioaugmentation (Singh et al., 2011). Bioventing is a technology that promotes the natural biodegradation of aerobically degradable pollutants by providing oxygen (aeration) to autochthonous bacteria present in that environment (Hinchee et al., 1996, Hyman and Dupont, 2001).

Bioaugmentation and bioventing are the most commonly used techniques for the elimination of EDCs present in sediments and soils. Bioventing is also used in aquatic environments in order to increase the amount of oxygen in the environment to improve the performance of oxygen-dependent oxidative reactions. Regarding bioremediation processes, either entire microorganisms (colonies, consortia, spores, mycelia) or their parts (enzymes, cell wall) can be used (Gaur et al., 2018).

The most appropriate strategy for the bioremediation of an environment contaminated by EDCs is selected according to several factors: the type of contaminated environment (aquatic or terrestrial), the type of contaminants present in the environment, and the physical-chemical conditions of the environment (Rasheed et al., 2017).

Microorganisms, and specifically bacteria, are the organisms that have the greatest metabolic diversity on the planet. This physiological and metabolic versatility, along with their rapid and effective ability to adapt to the presence of toxic substances that put their survival at risk, makes them excellent candidates for use as a tool to eliminate toxic and recalcitrant organic compounds in contaminated environments (Mohapatra et al., 2021). In general, the elimination and biodegradation of these compounds in extreme environments are usually carried out by gram-negative bacteria since they have multiple sites on their walls where chemisorption (strong binding of molecules to a surface) of EDCs takes place, as opposed to gram positive bacteria (Kim et al., 2010). Their physiological and metabolic versatility as well as their rapid and great capacity to adapt to the presence of toxic substances, makes them excellent candidates for use as a tool to eliminate toxic and recalcitrant organic compounds in contaminated environments (Mohapatra et al., 2021).

In addition, bacteria have a wide variety of enzymes (such as laccases, esterases, oxidoreductases and versatile peroxidases) that, under normal conditions, degrade polymers into simple monomers which they use as a carbon source. Recently it has been shown that these enzymes are also capable of degrading synthetic organic compounds very effectively (Kadri et al., 2017). Apart from bacteria, lignolytic fungi from the soil and the enzymes they produced have also been used to eliminate compounds that present phenolic rings and other xenobiotics (Hashim et al., 2017).

In relation to the use of purified enzymes, these can be free or associated with a matrix (nanoparticles, beds, solid supports, etc.). The immobilization of enzymes on supports has several advantages which include the reuse of the enzyme, prolongation of its useful life, greater thermal stability, and resistance to wide pH ranges. However, the type of support used, as well as the immobilizing method used for the enzyme (covalent bonds, adsorption, electrostatic interactions, etc.) must be considered in order not to alter the efficiency and activity of the enzyme, given that the enzymatic reaction decreases when it is immobilized on a support (Khan and Alzohairy, 2010).

Furthermore, bioremediation based on purified enzymes (produced by the microorganism or from an expression vector) depends not only on the growth of any microorganism in the contaminated environment, but also on the catalytic activity of the enzyme itself secreted by the microorganisms that they synthesize (Ruggaber and Talley, 2006). This limitation is a great problem, especially in nutrient-poor environments (oligotrophic environments) since, under these conditions, microbial growth is extremely limited due to the considerable decrease of the synthesis and production rate of participating enzymes (Gianfreda and Bollag, 2002). Recently, insect engineering (e.g., *Drosophila meganogaster)* has been proposed as an alternative to express functional enzymes and bioremediate environmental contamination (Clark et al., 2022).

5.1. Bacteria-mediated degradation methods

The degradation of EDCs mediated by bacteria can occur in two conditions according to their requirements: in aerobiosis (in presence of oxygen) or in anaerobiosis (in oxygen deficiency or absence) (Wu et al., 2017). Since oxygen is the most common electron acceptor during microbial respiration, a wide variety of microorganisms are capable of degrading contaminants under aerobic conditions. In addition, the degradation of the compounds depends on the enzymes involved in the metabolic pathway to degrade unusual substrates, in which the initial reaction is an oxidative process catalyzed by oxygenases and peroxidases which require the activation and incorporation of oxygen. However, it has also been shown that certain facultative and strict anaerobic bacteria can eliminate EDCs in the absence of oxygen (as in anaerobic digesters). In these oxygen-deficient environments, the microorganisms can use nitrate, manganese iron sulfate and carbonate as electron acceptors, with the consequent reduction of these acceptors, and hence use metabolic routes different from those of those of aerobic microorganisms (Liu et al., 2020; Wu et al., 2017).

Bacteria can degrade a wide variety of synthetic compounds, such as parabens, bisphenols, synthetic hormones, nonylphenol and its derivatives, since they possess a large repertoire of enzymes and genes (oxygenases, peroxidases, lipases, etc.) whose expression is induced in situations of stress (poor availability of nutrients in the environment, presence of toxic substances, etc.) (Budeli et al., 2020).

Many of them can use these compounds as a carbon source and therefore could be used in contaminated soil, water and in WWTPs. The efficiency of the process depends on many factors that can affect the growth and production of key enzymes for the biodegradation of these compounds. However, these limitations can be overcome by purifying enzymes from those strains that are capable of effectively and rapidly degrading EDCs and using them either in their free form or associated with a support or matrix (Bilal et al., 2017).

5.1.1. Degradation of nonylphenol derivatives

Many of the strains that are capable of degrading NP and its derivatives have been isolated from sediments and activated sludge from secondary WWTP treatments (both aerobic and anaerobic treatments) (Chang et al., 2005). Bacteria of the *Sphingomonas* genus, specifically the TTNP3 strain, *Sphingomonas cloacae*, and *Sphingomonas xenophaga*, are capable of degrading NP in aerobiosis (the last two were isolated from WWTP wastewater) (Bhandari et al., 2021). Other bacterial species such as *Stenotrophomonas sp*, *Pseudomonas mandelii*, and *Pseudomonas veronii* are also capable of eliminating NPs (Soares et al., 2003).

Bacteria of the genus *Sphingomonas* are the most effective at eliminating NPs at a rate of 100 mg L^{-1} day^{-1}. Thus, for instance, the *Sphingomonas* TTNP3 strain is capable of degrading them directly in the environment in a very efficient way, using them as a carbon source. In addition, it has been verified that the degradation mediated by this bacterium depends on the length of the alkyl substituent attached to the phenolic ring (Bhandari et al., 2021).

The most accepted explanation of the oxidative fission of NPs involves a hydroxylation of the terminal carbon transforming the molecule to an alcohol. The alcohol is then oxidized to organic acid that will be metabolized by the bacteria through the metabolic pathway of β-oxidation (Vallini et al., 2001). This route is known as ipso type II substitution. Other pathways have also been reported, such as fission of the phenolic ring by elimination of the alkyl substituent (Bhandari et al., 2021).

The products of the ipso type II substitution are hydroquinone (from the phenolic ring) and a carbocation (from the alkyl substituent) that has nine carbon atoms. Eventually, hydroquinone will be metabolized to organic acids. As for the products that derive from the alkyl-type substituents of the parental NP, these are metabolized to give rise to alcohols (nonanol) which are intermediate metabolites of the different strains of *Sphingomonas* (Bhandari et al., 2021).

Nonanols are highly volatile products. Bacteria often use the phenolic ring (hydroquinone) as a source of nutrition for growth and development. All the reactions mentioned above are carried out by monooxygenases. Among them, flavin-dependent monooxygenases, and octylphenol-4-monooxygenase (OpdA) play a key role in the substitution and fission reactions of branched nonylphenol (and derivatives) (Bhandari et al., 2021).

The degradation of NP under anaerobic conditions has also been investigated. This is carried out by genera such as *Pseudomonas*, *Pseudoxanthomonas*, *Thauera*, and *Novosphingobium*, which have been detected in anaerobic digesters of the WWTP. To date, little is still known as to how the degradation occurs. However, although anaerobic degradation is possible, the degradation of NPs under aerobic conditions has been shown to be more efficient (Bhandari et al., 2021).

5.1.2. Degradation of estrogens (natural and synthetic)

The most efficient bacteria for the degradation of synthetic estrogens usually belong to the group of Gram-negative ones, with a degradation efficiency of 44-99% with respect to gram positive ones (30-80%) (Budeli et al., 2020).

The most effective bacteria are of the genus *Achromobacter* (gram -), *Agromyces* (gram +), *Novosphingobium* (gram -), and *Rhodococcus* (gram +) which have the highest estrogen removal efficiencies from the medium (90-99%). The time they must remain in contact with the compound for complete degradation is 48-96 h, and they are capable of completely degrading the estrone (E1) (Adeel et al., 2017). Estradiol (E2) is the most susceptible estrogen to be eliminated by bacteria, since more than 60% of the genera that have been studied can degrade it. For example, all members of the Bacillus genus have been able to completely degrade E2, with a minimum contact time of 96 h for complete degradation (Adeel et al., 2017). Other bacteria, such as *Ochrobactrum* sp. strain FJ1, have also recently been isolated and identified as degraders of E2. Up to 98% removal was observed, which was slightly inhibited by adding an additional carbon source (Zhang et al., 2022). Only bacteria of the genus *Agromyces* and *Rhodococcus* have been able to degrade estriol (E3); *Agromyces* completely eliminated it while *Rhodococcus* could only eliminate 72% of the compounds present in the medium (Bilal et al., 2017).

The aforementioned bacteria are thought to be able to use estrogens as a carbon source when there is a carbon deficit in the medium, thus activating the genes necessary to metabolize them. It has also been shown that using ammonium as a nitrogen source increases the efficiency of estrogen degradation, in addition to being a carbon source. This may be because using ammonium as a source of nitrogen favors tyrosine synthesis by promoting the GS-GOGAT pathway, whose enzymes are involved in the assimilation of inorganic nitrogenous compounds from the environment (Pratush et al., 2020).

5.1.3. Degradation of bisphenols

A great variety of bacterial strains belonging to both the gram-positive (*Streptomyces*, *Bacillus*) and the gram-negative group (*Sphingomonas*, *Pseudomonas*, *Achromobacter*, *Novosphingobium*, *Nitrosomonas*, *Serratia*, *Bordetella*, *Alcaligenes*, *Klebsiella*) which are present in different environments (sediments, soil, and water) are capable of degrading bisphenol A (BPA) and using it as a carbon source to grow (Kang et al., 2005; Mita et al., 2015; Zhang et al., 2013).

The strain of the genus *Arthrobacter* is capable of using BPA as a carbon source in the presence of oxygen in a wide range of pH (5-9) and temperature (20-40ºC). The proposed Bendegradation mechanism consists of the breakdown of the complex, giving rise to hydroquinone and p-hydroxybenzoic acid, which are metabolized by the Krebs Cycle to generate biomass. In the case of the presence of halogenated substituents (chlorine, bromine), dehalogenation is carried out prior to the oxidative process (Ren et al., 2016).

The degradation mediated by the *Sphingomonas* TTNP3 strain (as with NP degradation) also forms hydroquinone and a carbocation (hydroxypropylphenol). The two phenolic rings of the parent compound are separated, and the same products are formed, but in this case the carbocation carries a phenolic ring. Subsequently, hydroquinone is metabolized through the Tricarboxylic Acid Cycle (TAC) (Zhang et al., 2013). Another *Sphingomonas* strain, specifically the MV1 strain, is capable of degrading BPA to p-hydroxybenzoic acid, ultimately metabolized to CO_2 and H_2O. No intermediate metabolites were detected by liquid chromatography (LC) UV-detection analysis (Zhang et al., 2013). Bacteria of the genus *Pseudomonas sp*. are other gram-negative bacteria capable of completely degrading BPA and using it as a source of carbon and energy. An example is *Pseudomonas paucimobilis* FK-4, isolated from sludge from treatment plants of epoxy resin manufacturing, which has been able to degrade 100 mg L^{-1} of BPA to concentrations below the detection limit of the appropriate instrumentation in 12 h (ultra-high performance liquid chromatography, UHPLC) (Zhang et al., 2013).

Achromobacter xyloxidans strain B-116, a bacterium isolated from municipal solid waste compost leachates, can grow and degrade 86% of BPA at an initial concentration of 5 mg L^{-1}, using it as a carbon source. The main *Achromobacter* enzymes that participate in the elimination of BPA are cytochrome P450 monooxygenases (in the presence of NADH), ammonium monooxygenases (AMO) and extracellular laccases (Zhang et al., 2013).

5.1.4. Degradation of parabens

Due to the antimicrobial activity of parabens, prior to the study of the degradation mechanism it is necessary to select resistant strains of bacteria, capable of growing in their presence. Both the bacterias' ability to grow in the medium and their capacity to eliminate the parabens effectively must be ascertained (Juárez-Jiménez et al., 2019). Few microorganisms are capable of degrading parabens. However, the existence of some bacterial species capable of surviving in their presence (resistance) and degrading them has been found. Some examples of them are *Pseudomonas beteli*, *Burkhorderia latens* and *Enterobacter cloacae* that were isolated from wastewater (Juárez-Jiménez et al., 2019; Valkova et al., 2001). Other studies have shown that some bacteria present in contaminated soil containing methylparaben (MPB) and butylparaben (BPB) are capable of using them as a carbon source. These strains (based on 16S rRNA gene analysis) have been found to be very close to *Bacillus safensis* (gram +), which is both capable of growing in a medium containing parabens and effectively degrading the compounds at a rate directly proportional to the amount present in the medium (first order reaction) (Juárez-Jiménez et al., 2019).

5.2. Fungal mediated degradation

Most fungi are multicellular organisms that do not form true tissues (hyphae) and that can be found in many environments, both free and in symbiosis. Additionally there are unicellular ones (yeasts) capable of biodegradation of organic pollutants (Marcelo-Fernández et al., 2017). Within ecosystems, fungi play a particularly key role breaking down dead organic matter through the secretion of a wide variety of extracellular enzymes and acids. These are capable of degrading complex polymers present in the soil (such as cellulose, lignin, chitin, pectins, etc.) into simple monomers that can then be metabolized to form new biomass (Gupta et al., 2017). In addition, mycodegradation can be combined with plant-based adsorbents or other adsorbent materials, succeeding in effectively eliminating EDCs, especially phenolic compounds, in an easy, eco-friendly, simple and inexpensive way (Loffredo et al., 2021). Lignolytic enzymes of fungi of the genera *Trametes*, *Aspergillus*, and *Phanerochaete*, have been found capable of efficiently degrading a wide variety of xenobiotics with possible endocrine action. The main extracellular enzymes involved belong to the group of lignin peroxidases that include laccases, manganese-dependent peroxidases, and versatile peroxidases (Bokade et al., 2021; Hashim et al., 2017).

The lignolytic oxidoreductases of fungi are capable of degrading EDCs present both at high concentrations (experimental laboratory conditions) and at low concentrations (typical of the medium, from ng L^{-1} to mg L^{-1}). In addition, these enzymes have low energy requirements since they do not need the substrates to have a certain redox potential or the presence of co-substrates (Lloret et al., 2012). The most common transformations catalyzed by these oxidoreductases take place through coupled oxidations, which generate polymers or oligomers as products and which have significantly lower endocrine activity with respect to the original compounds (Cabana et al., 2007). The degradation of these compounds is also carried out by oxidative processes (Becker et al., 2017). The mechanisms of action of the main lignolytic enzymes involved in fungal-mediated degradation of EDCs are described below.

5.2.1. Laccases

Laccases are extracellular oxidoreductases that belong to the group of oxidases with multiple copper molecules in their active center. In addition to fungi, it has been proven that they are also synthesized by bacteria, plants and insects, and that their function varies from one species to another (Barrios-Estrada et al., 2018). The laccases that are applied in bioremediation techniques usually come from lignolytic fungi belonging to the two large divisions that constitute the subkingdom Dikarya: *Basidiomycetes* and *Ascomycetes* (Becker et al., 2017). Laccases, and in particular Daiwa laccases purified from *Trametes sp*., are capable of degrading a wide variety of xenobiotics and EDCs that have a phenol in their structure. These include BPA, triclosan, synthetic estrogens, chlorinated pesticides, nonylphenol and derivatives, naproxen, diclofenac, or oxybenzone. The enzymatic oxidation of these compounds is coupled with the reduction of O_2 to H_2O, hence no toxic substances are generated in the reaction (Barrios-Estrada et al., 2018; Bokade et al., 2021; Tanaka et al., 2001).

The major benefits of laccases in the field of bioremediation of EDCs is their low selectivity (ability to degrade of a wide range of compounds), high affinity for the substrate (low K_m), which is why they can eliminate the substrates present in the medium at low concentrations (Bilal et al., 2019). In contaminated media, laccases can be introduced by inoculating the fungus that produces them, as free enzymes (purified from the fungus) or immobilized in a matrix (Barrios-Estrada et al., 2018). The immobilization of the enzyme in a matrix has several advantages from an economic point of view, compared to the use of free enzymes. Immobilization allows them to be reused and retained in the system for a longer time while preserving their catalytic properties. Free enzymes, on the other hand, often cannot be reused after a specific number of reaction cycles because of the inactivation/inhibition of the enzyme (due to elevated temperatures, changes in pH, or the presence of inhibitors) or because of their loss during the process, given their mobility (Ardao et al., 2015; Bilal et al., 2017). When comparing the removal efficiency of NP and BPA using free enzymes versus the use of immobilized enzymes, a significant difference in removal efficiency is observed. For example, for free forms the removal efficiency of NP and BPA was 44% for *T. versicolor laccase* and 54% for *M. thermophila laccase*. In contrast, when the enzymes were immobilized on acrylic beads, elimination percentages up to 97% were achieved for both enzymes after 24 h of treatment (Becker et al., 2017). Immobilization is achieved through various approaches, depending on the nature of the bond between the enzyme and the matrix (covalent bonds, adsorption, entrapment, cross bonds or encapsulation), the goal being for the bond to not affect the catalytic capacity or the efficiency of the enzymatic reaction (Bilal et al., 2017).

Further comparative inquiries have been conducted to determine which fungus produces the laccase that effectively degrades a wide range of EDCs depending on the conditions of temperature, pH, enzyme concentration, and the substrate to be removed (Barrios-Estrada et al., 2018). The most effective laccases in eliminating EDCs such as BPA, nonylphenol and triclosan have been shown to come from *Trametes versicolor*, *Trametes vilosa* and *Coriolopsis polyoma* (Fukuda et al., 2004; Hundt et al., 2000).

5.2.2. Lignin peroxidases

Lignin peroxidases are enzymes that belong to the family of oxidoreductases and are responsible for oxidizing and depolymerizing lignin, using hydrogen peroxide (H_2O_2) as a co-substrate and veratryl alcohol as a mediator (under natural conditions). They contain a heme group (heterocyclic center with an Fe atom inside) as a prosthetic group and cofactor. These enzymes are synthesized by lignolytic fungi of the *Basydiomycota* division such as *Phanerochaete chrysosporium*, *Trametes versicolor* and by bacteria (Sharma et al., 2018). Lignin peroxidases oxidize a wide range of EDCs (with or without phenolic rings in their structure including herbicides, polycyclic aromatic hydrocarbons (PAHs) and other PCPs) as well as xenobiotics (which have a redox potential above 1.4 V), due to their low specificity for the substrate (Bilal et al., 2019; Piontek et al., 2001; Singh et al., 2021). They degrade compounds through initial oxidation followed by subsequent oxidative reactions through the generation of intermediate cationic radicals (Bokade et al., 2021; Sharma et al., 2018). Lignin peroxidases purified from bacteria are more efficient at degrading lignin polymers compared to those synthesized by fungi, as they have higher substrate specificity and thermal stability. They are also effective for eliminating EDCs (Sharma et al., 2018; Singh et al., 2021). These enzymes have been shown to possess greater catalytic activity and greater affinity for the substrate when associated with carbon nanotubes (Bilal et al., 2019).

5.2.3. Manganese peroxidases

These enzymes belong to the group of hydrogen peroxide oxidoreductases which also have a heme group as a prosthetic group. Mn peroxidases have shown the ability of degrading many toxic compounds including EDCs (PAHs, pesticides, bisphenols, and NPs) in the presence of H_2O_2. They are responsible for oxidizing Mn^{2+} ions (part of the composition of wood) to Mn^{3+} through successive reactions. The generated Mn^{3+} ions act as an oxidizing agent for phenolic compounds and many EDCs (Ten Have and Teunissen, 2001; Sharma et al., 2018).

5.3. Applications of bioremediation techniques in contaminated environments

According to Budeli et al. (2020), current wastewater treatment processes in WWTPs are not sufficient for the elimination of all pollutants. Typical proceedings in a WWTP include primary treatments (removal of large waste through physical processes) followed by secondary treatments (activated sludge and anaerobic digesters). Tertiary treatments can also be added to eliminate pathogens from the water, which are usually chlorination or other similar methods. On certain occasions, these physical-chemical processes are intended for the elimination of nutrients such as nitrogen and phosphorus. The aforementioned treatments do not achieve complete elimination of EDCs. Consequently, remaining contaminants in the WWTP effluents, reach aquatic and terrestrial ecosystems as a final destination (Budeli et al., 2020).

Several strategies can be implemented to eliminate EDCs in wastewater treatments, such as the introduction of additional bioreactors with microorganisms capable of degrading them, the introduction of microorganisms in the tanks where secondary treatments take place, or the introduction of additional treatment systems in conjunction with the main ones (Nguyen et al., 2014; Rostro-Alanis et al., 2016; Vieira et al., 2020). Some interesting proposed methods for eliminating EDCs in the environment are described below.

As far as enzymes are concerned, immobilized laccases are good candidates for the elimination of EDCs directly in WWTPs since they can be used both as individual molecules (free system) or associated with a matrix. The use of co-substrates (generally organic acids added to the medium that act as electron shuttles between the enzyme and the substrate) promote degradation by increasing the redox potential of the medium (Nguyen et al., 2014; Rostro-Alanis et al., 2016; Sharma et al., 2022).

The use of laccases as the sole enzyme is less efficient compared to the use of the 3 lignolytic enzymes (laccases, Mn peroxidases, and lignin peroxidases), since it has been shown that, in conjunction, these are capable of synergistically degrading the different types of EDCs (as they degrade lignin under natural conditions) present in wastewater (Vieira et al., 2020).

Other techniques based on the use of enzymes are the biological filtration membranes and the packed bed reactor. Filtration membranes consist of the immobilization of the enzymes for bioremediation to a membrane whose pore size is less than 10kDa. The contaminated water or matrix passes through this membrane where the retention and degradation of the analytes by these enzymes take place (Barrios-Estrada et al., 2018). The packed bed system or reactor consists of a cylindrical support filled with diverse materials associated with enzymes (usually from lingolytic fungi) to degrade the EDCs immobilized in a matrix (Barrios-Estrada et al., 2018).

Two-stage systems (Two System Stage, TSS) are modified enzymatic membrane reactors in which the process takes place in two physically separated stages. An interesting proposal as an alternative to this configuration is the use of versatile peroxidases from lignolytic fungi in the presence of Mn^{2+} ions (Singh et al., 2021). Complex EDC polymers are broken, and the resulting monomers are oxidized by the action of the produced Mn^{3+} ions (oxidant). Since the half-life of Mn^{3+} is noticeably short, an organic dicarboxylic acid (such as malonate or oxalate) is needed for the formation of a stable Mn^{3+}-complex (Taboada-Puig et al., 2015). The two-stage system method was fourteen times more efficient with respect to enzymatic membrane reactors since problems such as inactivation of membrane-associated enzymes, possible clogging and the uptime of the process are avoided. It resulted in a reduced enzyme inactivation, while the rate of degradation of enzymes was increased. In TSS the bioreactors where the complexes are formed are physically separated from those which catalyze the reactions and the oxidation of the compounds. Through this strategy, EDCs have been efficiently eliminated from waters both at experimental concentrations (1.3-8.8 mg L^{-1}) and environmental concentrations (1.2-6.1 mg L^{-1}) (Taboada-Puig et al., 2015).

A remarkable application regarding the use of complete microorganisms was proposed with the fungus *T. versicolor*. It was capable of degrading a mixture of EDCs in the bioreactors by means of its lignolytic enzymes, completely removing them in just 4 days (up to 21 mg L^{-1}). In addition, it has been proven that it was capable of degrading EDCs in the absence of nutrients in the medium using them as a carbon source. This means a reduction in the associated cost, eliminating the need to add nutrients or co-substrates for it to grow (Pezzella et al., 2017).

The use of consortiums of microorganisms in secondary or separate treatment tanks has also been proposed, targeting EDCs that have not been eliminated in previous treatments (primary, secondary and tertiary). This technique offers the great benefit of taking advantage of mutualistic, co-metabolic and synergistic interactions between bacteria in microbial communities to improve the efficiency of EDC elimination. In this method, greater reaction efficiency can be further achieved by applying bioventing and biostimulation techniques (Liu et al., 2020). Another recent study has isolated and studied the groups of fungi and bacteria naturally present in sewage sludge, capable of degrading BPA and diclofenac by up to 80%. These findings highlight the importance of characterizing the native mycobiome that could be used in EDC biotransformation technologies (Conejo-Saucedo et al., 2020).

6. Conclusions and future perspectives

Bioremediation processes are a promising and sustainable strategy for removing EDCs. The major benefit that bioremediation offers is to the environment. Compared to physicochemical methods, bioremediation processes are ecofriendly, less intrusive, and less harmful to ecosystems. Microorganisms and fungi can use EDCs as a carbon source under aerobic conditions, which means that they end up transforming them into CO_2 and H_2O. It can also be a very cost-effective technology, as treatment using bioremediation as the main tool is usually less expensive than using conventional treatment methods. And most importantly, it can effectively eliminate EDCs entirely. Despite the benefits raised above, however, they have some limitations, and certain important aspects of the methods must be considered for practical purposes. Biodegradation products should not be more persistent or toxic than the initial ones, which is a potential outcome; it may be complicated to extrapolate pilot and laboratory studies to large-scale mass operations; and these methods can be time consuming, since processes involving microorganisms can be slow.

Synthetic biology and bioengineering open new perspectives and expand the possibilities of bioremediation. Future biotechnology-based techniques may include enzyme design, molecular modeling, cloning and genome editing. Thorough examination of strains capable of growing in contaminated media has enabled the identification of the genes that codify for the enzymes involved in the EDCs metabolization pathway. These genes can be inserted, cloned, and expressed in cloning vectors to obtain a large amount of enzymes for bioremediation processes. In addition, the use of genetic engineering techniques allows for improving the resistance of enzymes in more extreme environments (salinity, temperature and pH), such as polluted wastewater, particularly when their efficiency is significantly reduced in the presence of other substances. These advancements also entail the parallel development of machine learning algorithms and protocols, a significant increase in computational power for investigation in this direction. We must not forget the essential contribution of predictive mathematical models, allowing us to know the potential degradation pathways of a determined EDC. These tools together will help scientists choose the best bioremediation approach.

As for new trends, interest is growing in the creation of efficient enzymes that can be applied to EDC remediation. There are several advantages with respect to the use of extracellular enzymes purified from bacteria and fungi in the wastewater treatment process; they offer fast treatment, are easy to maintain and operate, and do not require substrate or sludge output, as is the case with microorganisms. However, they are not yet applied in WWTPs. This method has not progressed beyond the laboratory phase, despite satisfactory results. The combination of the most efficient bacterial and fungal enzymes (peroxidases, laccases, and bacterial enzymes) in supports has proven to be one of the most efficient methods to eliminate EDCs in bioremediation processes.

More research is crucial for the advancement of the effective application of bioremediation. First, further the identification of microbial strains capable of using EDCs as a carbon and energy source would be particularly helpful. The ideal bacteria should be capable of completely degrading the contaminants through their incorporation into the metabolic pathways for the generation of biomass without generating metabolites or toxic by-products. Second, endocrine activity studies should not cease, as many synthetic substances with potential endocrine disrupting action have not yet been catalogued. The parent EDC should be evaluated, as well as the degradation pathways and potential endocrine activity of the generated metabolites. Third, it is necessary to study in more depth the relationships between distinct species of microorganisms, such as their synergy or co-metabolism, as well as other interactions in which bacteria couple their metabolism and their reactions. A better understanding of these interactions would, for example, potentially increase the performance of the degradation processes of EDCs, generate products much less toxic with respect to parental compounds, or even innocuous final products.

Finally, further research is necessary especially on new strategies, which must be evaluated to compare results with conventional treatment methods. The improvement and updating of current bioremediation technologies thanks to genetic and molecular engineering techniques is particularly promising, potentially leading to the adoption of even greener and more effective methods, highly efficient in the elimination of EDCs and with lower impact on the environment.

Declaration of competing interest

The authors declare no competing interests

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Figure Captions

Figure 1. Number of publications with the search terms "endocrine disruptors" AND "bioremediation" (retrieved on 04/09/2022).

Figure 2. Subject area of the documents used for the elaboration of the bibliographic work. Results from the search terms "endocrine disruptors" AND "bioremediation" (retrieved on 04/09/2022).

Figure 3. Structure and uses of the main types of EDCs present in the environment. *Own elaboration.*

Figure 4. Contamination sources and paths of EDCs into terrestrial and aquatic ecosystems. *Own elaboration. Created with BioRender.com*