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Bioremediation of Endocrine Disrupting Chemicals- Advancements and Challenges

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A R T I C L E I N F O

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A B S T R A C T

Endocrine Disrupting Chemicals (EDCs), major group of recalcitrant compounds, poses a serious threat to the health and future of millions of human beings, and other flora and fauna for years to come. A close analysis of various xenobiotics undermines the fact that EDC is structurally diverse chemical compounds generated as a part of anthropogenic advancements as well as part of their degradation. Regardless of such structural diversity, EDC is common in their ultimate drastic effect of impeding the proper functioning of the endocrinal system, basic physiologic systems, resulting in deregulated growth, malformations, and cancerous outcomes in animals as well as humans. The current review outlines an overview of various EDCs, their toxic effects on the ecosystem and its inhabitants. Conventional remediation methods such as physico-chemical methods and enzymatic approaches have been put into action as some form of mitigation measures. However, the last decade has seen the hunt for newer technologies and methodologies at an accelerated pace. Genetically engineered microbial degradation, gene editing strategies, metabolic and protein engineering, and *in-silico* predictive approaches - modern day's additions to our armamentarium in combating the EDCs are addressed. These additions have greater acceptance socially with lesser dissonance owing to reduced toxic by-products, lower health trepidations, better degradation, and ultimately the prevention of bioaccumulation. The positive impact of such new approaches on controlling the menace of EDCs has been outlaid. This review will shed light on sources of EDCs, their impact, significance, and the different remediation and bioremediation approaches, with a special emphasis on the recent trends and perspectives in using sustainable approaches for bioremediation of EDCs. Strict regulations to prevent the release of estrogenic chemicals to the ecosystem, adoption of combinatorial methods to remove EDC and prevalent use of bioremediation techniques should be followed in all future endeavors to combat EDC pollution. Moreover, the proper development, growth and functioning of future living forms relies on their non-exposure to EDCs, thus remediation of such chemicals present even in nano-concentrations should be addressed gravely.

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1. Introduction

As the world royally strides through the 21st century boasting of humongous advancements in science and technology, we are not immune to the problems that come along. Globalization, urbanization, industrial revolution, privatization, and booming economies have been badly hit by the COVID-19 pandemic displaying the vulnerability of the human race to even a teeny tiny virus (Sharifi and Khavarian-Garmsir, 2020; Harris and Moss, 2020; Gupta et al., 2021). The ever increasing release of toxic chemicals as byproducts of various developmental activities is monumental in bringing on this alarm worldwide (Khan et al., 2015; Huang et al., 2017; Cervantes-Ramírez et al., 2018; Bank et al., 2019; Curtis et al., 2019; Alava, 2020; Miller et al., 2020). One such debated group is the Endocrine disrupting chemicals (EDCs) which have now taken the center stage. Their deleterious impact on the well-being of life on our planet as they do not vitiate easily and have a long-lasting residual effect is disconcerting. They also have the propensity to transform into more toxic products principally after treatment or disinfection which has brought this topic from total obscurity to become an international concern (Mnif et al., 2011; De Coster and Van Larebeke, 2012; Nohynek et al., 2013; Kabir et al., 2015; Lauretta et al., 2019; Leusch et al., 2019; La Merrill et al., 2019).

In 2002, World Health Organization's (WHO)International Programme on Chemical Safety (IPCS) defined EDC as an 'exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) population'(IPCS WHO, 2002). This was in fact a modification of the earlier definition proposed by the European Workshop on, 'the impact of endocrine disruptors on human health and wildlife' held in Weighbridge, UK, and moreover replaced the definition laid by the U.S. Environmental Protection Agency (EC 1996; Nowak et al., 2019). European Food Safety Agency (EFSA) had a consensus with the IPCS's definition of EDCs. But it modified another important terminology, the Endocrine active substances (EASs) which the agency had earlier defined in 2010 as a substance having the inherent ability to interact or interfere with one or more components of the endocrine system resulting in a biological effect, but need not necessarily cause adverse effects (EFSA, 2013). There are over 800 EDCs and EASs which are a cause of emerging concern owing to their substantially long-lasting potential to alter the cellular, epigenetic, and molecular functions of the different components of the endocrine system of both man and animals. Their effects akin to hormones may be additive or antagonistic to the coordination function of the endocrine system on different organ systems from head to toe (Bergman et al., 2013; Lauretta et al., 2019; Nowak et al., 2019; Patel et al., 2020; Lopez-Rodriguez et al., 2021).

Initially, artificial biotechnology measures to degrade pollutants, with again tremendous negative impacts, like the production of toxic products and metabolites more damaging to the environment were available and increasing exponentially (Iwasaki et al., 2010; Maroga Mboula et al., 2013; Da Silva et al., 2014; Armijos-Alcocer et al., 2017; Garg et al., 2019; Zhou et al., 2020). Nevertheless, their routine use was discouraged except for the environmentally friendly techniques and was soon replaced by bioremediation. Such efforts traditionally aimed at eliminating or breaking down the multifarious persistent organic pollutants (POP) including the EDCs by biological means to less detrimental products or reinstating the equilibrium in the environment by using it wisely at different polluted sites (Azubuike et al., 2016; Zouboulis et al., 2019; Gholami et al., 2019; Gao et al., 2020). However, the existing technologies though popular are facing much criticism owing to the failure to completely clear out despite the time invested, owing to the reduced bioavailability, low efficiency, and deficiency of good assays to evaluate the effectiveness of the procedures in addition to the obvious limitation that they cannot be used for non-biodegradable EDCs. Hence newer technologies and advanced bio-remedial methods are being researched and explored with very few of them hitting the bull's eye (Zhang et al., 2016; Wang et al., 2019; Liu et al., 2019; Hernández-Abreu et al., 2020; Menchén et al., 2020; Singh et al., 2021a; Roccuzzo et al., 2021).

Advanced bioremediation measures to reinstate and renew the balance in various ecological niches by getting rid of EDCs through interdisciplinary interactions and the latest advances in applications of genomics, metagenomics, whole-genome sequencing, proteomics, transcriptomics, metabolomics, computation and bioinformatics, and other novel fields. The use of genetically engineered microbes (GEMs) also known as genetically modified organisms (GMOs) or genetically modified microorganisms, computational approaches i.e. the *in-silico* predictive mechanisms, metabolic or protein engineering to target enzymes are proving to be valuable extenuation strategies (Vilchez-Vargas et al., 2010; Azubuike et al., 2016; Dangi et al., 2019; Liu et al., 2019; Singh et al., 2021a). Metabolic engineering by using DNA recombinant technology or genome editing tools like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) to modify the existing metabolic pathways to alter enzymes and create synthetic communities in a superlative manner for efficacious bioremediation (Dangi et al., 2019; Sharma and Shukla, 2020). Likewise, another option is protein engineering where enzymes are played with to enhance their stability and efficiency for degrading particular substrates or increase the capacity for distinct settings (Deshmukh et al., 2016; Mousavi et al., 2021). Furthermore, technology innovation and artificial intelligence are coming up in a big way; newer computational approaches to bioremediation are expanding their horizons. Predictive bioremediation includes pathway biodegradation prediction systems, molecular docking, molecular dynamic simulation, *in-silico* toxicity analysis expert systems like the Quantitative structure-biodegradation relationship modeling, the Quantitative Structure-Activity Relationship (QSAR)modeling, expert system, programs of machine learning, artificial neural network and genetic algorithm (Pagadala et al., 2017; Acharya et al., 2019; Singh et al., 2021b). The recent years have seen increasing evidence on the role of novel tools comprising of biosurfactants, biofilm producing bacteria and nanotechnology on bioremediation of EDCs (Jim'enez-Penalver et al., 2020; Mohsin et al., 2021; Mallikarjunaiah S et al., 2020). In this context, an updated narrative review on the EDCs, their sources, mechanism of action, conventional and newer bioremediation techniques, is quintessential. This review hopes to do justice to all these aspects and give a bird's eye view of EDCs sources, significance and impact on health in general, while elaborating on bioremediation strategies and novel perspectives and sustainable alternative technologies especially in last five years. This review follows how the earlier physic-chemical, microbial, conventional *in-situ*, and *ex-situ* bioremediation techniques have been ousted and newer technologies have taken the front seat as the tools with the maximum potential to neutralize the EDCs.

2. Overview on EDCs-Types, sources and mechanism of action

Indeed, it has never been easy to classify EDCs as there are diverse factors involved. The different types of EDCs may be demarcated based either on their chemical features, sources of origin, adversative health effects, exposure sources, mechanism of action or any such other commonalities shared (Fig. 1) (Haq and Raj, 2018; Leusch et al., 2019; Patel et al., 2020; Wojcieszynska et al., 2020; Buoso et al., 2020; Lopez-Rodriguez et al., 2021). In addition to knowledge of the mechanisms, source, and types of EDCs, the testing and classification of EDCs should be based on well-regulated and clearly defined international universal standards (Kubickova et al., 2021). An internationally accepted listing based on specific characterizations though long overdue is still on the horizon and so far has never made it to tables. A feasible consensus needs to be made at the earliest by the regulatory bodies and standards need to be put forth very strictly to be adhered globally for a safer tomorrow.

EDCs include natural, synthetic, and metabolic steroid or non-steroid derivatives of estrogen and the like hormones. The most infamous representatives of the group include bisphenol A (BPA), nonylphenol (NP)

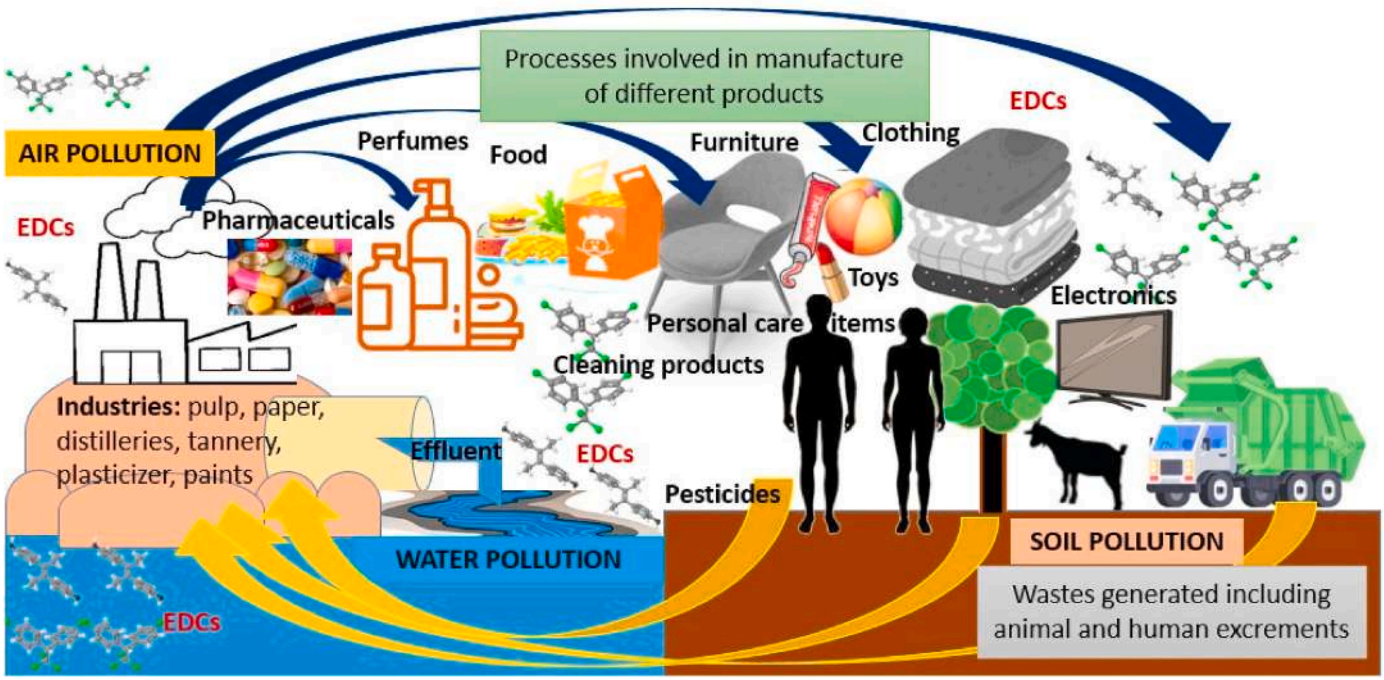


Fig. 1. Different sources of EDCs and its distribution in water, air and on land causing pollution of these natural resources and untoward effects.

together called xenoestrogens, followed by estrone (E1), 17β-estradiol (E2), estriol (E3), 17α-ethinylestradiol (EE2) classically belonging to steroidal estrogens, followed by phthalates, chlorophenols, norethindrone, and triclosan (TCS) (Zhang et al., 2016; Huang et al., 2017; La Merrill et al., 2019; Lopez-Rodriguez et al., 2021). Newer and newer EDCs are being rapidly added to this list.

The categorization of EDCs arbitrarily as belonging to phthalates, bisphenols, parabens, polychlorinated biphenyl (PCBs), Phytoestrogens, Dioxins, dibenzofurans, alkyl phenolic compounds, perfluoroalkyl compounds, pesticides or fungicides, UV filters, pharmaceuticals, flame retardants, mercury, etc. Was done to understand broadly its mechanism of actions (La Merrill et al., 2019; Lopez-Rodriguez et al., 2021). However, the earlier report in 2012 by UNEP and WHO, classified EDCs based on their physico-chemical structure and or sources into 11 types under four categories of persistent and bioaccumulative halogenated compounds, less persistent and bioaccumulative compounds, pesticides, pharmaceuticals, personal care products, and other chemicals. Only the most relevant and specific EDCs are illustrated in the Table .1 (IPCS WHO, 2002; Bergman et al., 2013; Patel et al., 2020; Wojcieszynska et al., 2020; Buoso et al., 2020).

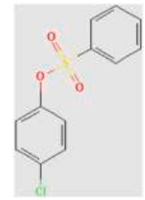
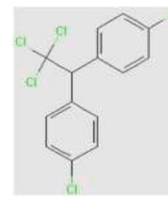
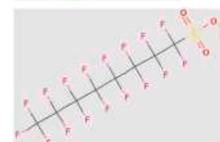
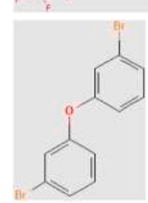
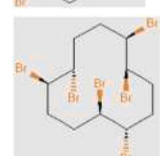
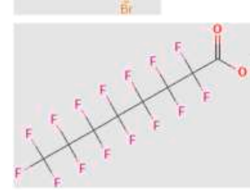
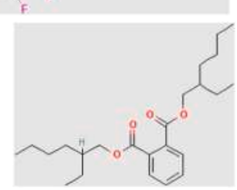
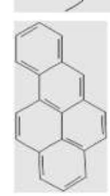
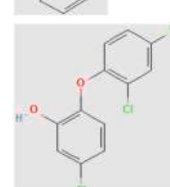
EDCs with its 'hormone like action' may be stimulating or deterring the functioning of the endocrine system, typically undesirably affecting the normal utility of the system. The signaling function is colossally affected by certain precise activities at the molecular level and at the tissue level, whether males or females, changes in the cycle of life, the diurnal rhythm and even the changes in the seasons. All these factors interplay and probably interfere with the normal operations of hormones maintaining the harmony of our internal milieu and thereby having injurious consequences (Boas et al., 2012; Nowak et al., 2019; La Merrill et al., 2019).

The major contrivances of EDCs action may be at the level of the hormone receptors whereby its binding can activate or inhibit the entire signal transduction pathways, or inhibit or stimulate the receptor itself, further it can have downstream interfaces with other components of the signaling pathway, stimulate or inhibit the synthesis of an endogenous hormone, bind to the same transport proteins, thereby reducing the levels of endogenous hormones in circulation (Bergman et al., 2013; Combarnous, 2017; Combarnous and Diep Nguyen, 2019; Lauretta et al., 2019). Their main characteristics include EDC's ability to bind with or activate hormone receptors, antagonize them, alter the expression and release of hormones, alter the signal transduction in responsive cells, induce epigenetic modifications, alter the transport across cell membranes, hormone circulatory levels, and distribution, its clearance and ultimate fate (La Merrill et al., 2019).

The mechanism of action of EDC resembles steroid hormones by either direct genomic transcriptional action of the classical receptors' ligand binding complex or the nongenomic action through the second messenger systems. This non genomic action occurs through complex interactions by the activation of the Mitogen activated Protein kinase (MAPK) pathway or and the Nuclear Factor Kappa Beta (NF-κβ) signal cascade systems thereby acting as transcription factors in the nucleus. However, the non-genomic action of the non-classic receptors namely the ionic channels is the other alternative pathway mediated by the adenyl cyclase enzyme's conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). In addition, EDCs can cause alteration in the histones, methylation of DNA and affect the expression of noncoding RNA (Fig. 2) (Lösel and Wehling, 2003; Bergman et al., 2013; Combarnous, 2017; Combarnous and Diep Nguyen, 2019; Nowak et al., 2019; La Merrill et al., 2019). Thus the ability of EDC to critically affect the cells at DNA level, RNA level, and protein expression level is certain.

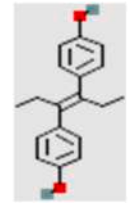
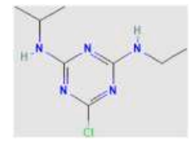
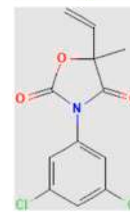
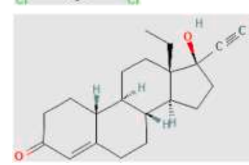
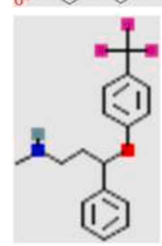
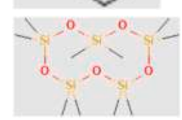
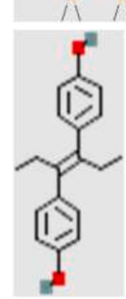
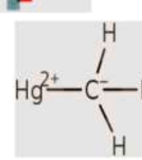
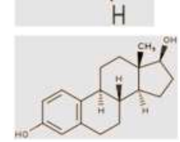
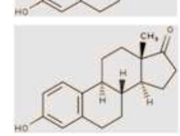
Recent studies show EDCs have a negative effect on bone structure and function. They alter the bone modeling and remodeling, and the release of paracrine hormones. Thereby altering the release of systemic hormones, cytokines, chemokines and growth factors. Their capacity to disrupt stem cell fate, bone marrow mesenchymal stem cell (BMSC) differentiation and bone marrow niche organization is well established (Turan and S. 2021). Malachite green (MG) have been recently included in the exhaustive list of EDCs as a result of its toxicity, mutagenicity, carcinogenicity, and teratogenicity properties. Furthermore, MG has respiratory toxicity and reduces the fertility of both humans and animals. In addition, conventional techniques are ineffective in treating and biodegrading MG. However, they can be degraded by using liquid-solid adsorption method like the Acid Functionalized Maize Cob (Ojediran et al., 2021).

Table 1
The grouping and classification of EDCs with important examples and their corresponding chemical structures (IPCS WHO, 2002; Bergman et al., 2013; Patel et al., 2020; Wojcieszynska et al., 2020; Buoso et al., 2020).

Group	Classification	Examples of EDC compounds	Chemical structure
PERSISTENT BIO-ACCUMULATIVE HALOGENATED COMPOUNDS	1. Persistent Organic Pollutants (POPs)	Polychlorinated biphenyls (PCBs) {PubChemID[a]: 6636 MF[b]: $C_{12}H_9ClO_3S$, MW[c]: 268.72 g/mol}	
		Dichlorodiphenyltrichloroethane (DDT) {PubChem ID: 3036, MF: $C_{14}H_9Cl_5$, MW: 354.5 g/mol}	
		Perfluorooctanesulfonate (PFOs) {PubChem CID: 74483, MF: $C_8HF_{17}O_3S$, MW: 500.13 g/mol}	
		Polybrominateddiphenyl ethers (PBDEs) like 3,3′-Dibromodiphenyl Ether {PubChem CID: 13283773, MF: $C_{12}H_8Br_2O$, MW: 328 g/mol}	
	2. Other persistent and bio-accumulative chemicals	Hexabromocyclododecane (HBCDD) {PubChem CID: 11763618, MF: $C_{12}H_{18}Br_6$, MW: 641.7 g/mol}	
		Perfluorooctanoic acid (PFOA) {PubChem CID: 9554, MF: $C_8HF_{15}O_2$, MW: 414.07 g/mol}	
	3. Plasticizers & Other Additives in Materials and Goods	Phthalates like Di(2-ethylhexyl) phthalate (DEHP) {PubChem CID: 8343, MF: $C_{24}H_{38}O_4$, MW: 390.6 g/mol}	
	4. Polycyclic Aromatic Chemicals (PACs) including polycyclic aromatic hydrocarbons (PAHs) **LESS PERSISTENT & LESS BIOACCUMULATIVE COMPOUNDS**	Benzo[a]pyrene (BaP) {PubChemCID: 2336, MF: $C_{20}H_{12}$, MW: 252.3 g/mol}	
	5. Halogenated Phenolic Chemicals (HPCs)	Triclosan { PubChem ID:5564, MF: $C_{12}H_7Cl_3O_2$, MW: 289.5 g/mol }	
	6. Non-halogenated Phenolic Chemicals (Non-HPCs)	Bisphenol A (BPA) {PubChemCID: 6623, MF: $C_{15}H_{16}O_2$, MW: 228.29 g/mol}	

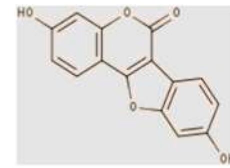
(continued on next page)

Table 1 (*continued*)

Group	Classification	Examples of EDC compounds	Chemical structure
			
PHARMACEUTICALS &PERSONAL CARE PRODUCTS	7. Current-use Pesticides	Atrazine {PubChemCID: 2256, MF: $C_8H_{14}ClN_5$, MW: 215.68 g/mol}	
		Vinclozolin {PubChemCID: 39676, MF: $C_{12}H_9Cl_2NO_3$, MW: 286.11 g/mol}	
	8. Pharmaceuticals, Growth Promoters, & Personal Care Product	Levonorgestrel (synthetic progestagen) {PubChem CID: 13109, MF: $C_{21}H_{28}O_2$, MW: 312.4 g/mol}	
		Selective serotonin reuptake inhibitors (Fluoxetine) {PubChem CID: 3386, MF: $C_{17}H_{18}F_3NO$, MW: 309.33 g/mol}	
		Cyclic methyl siloxanes (D5) {PubChem CID: 10913, MF: $C_{10}H_{30}O_5Si_5$, MW: 370.77 g/mol}	
		Diethylstilbestrol (DES) {PubChem CID: 448537, MF: $C_{18}H_{20}O_2$, MW: 268.3 g/mol}	
	9. Metals & Organometallic Chemicals	Methylmercury {PubChem CID: 6860, MF: CH_3Hgz, MW: 215.63 g/mol}	
	10. Natural Hormones	17β-Estradiol {PubChem CID:5757, MF: $C_{18}H_{24}O_2$, MW: 272.4 g/mol}	
		Estrone {PubChemCID: 5870, MF: $C_{18}H_{22}O_2$ MW: 270.4 g/mol}	
	11. Phytoestrogens		

(*continued on next page*)

Table 1 (*continued*)

Group	Classification	Examples of EDC compounds	Chemical structure
		Coumestrol {PubChemCID: 5281707, MF: $C_{15}H_8O_5$, MW: 268.22 g/mol}	

[a] PubChem CID:Compound ID number.
[b] MF- Molecular formula.
[c] MW- Molecular weight.

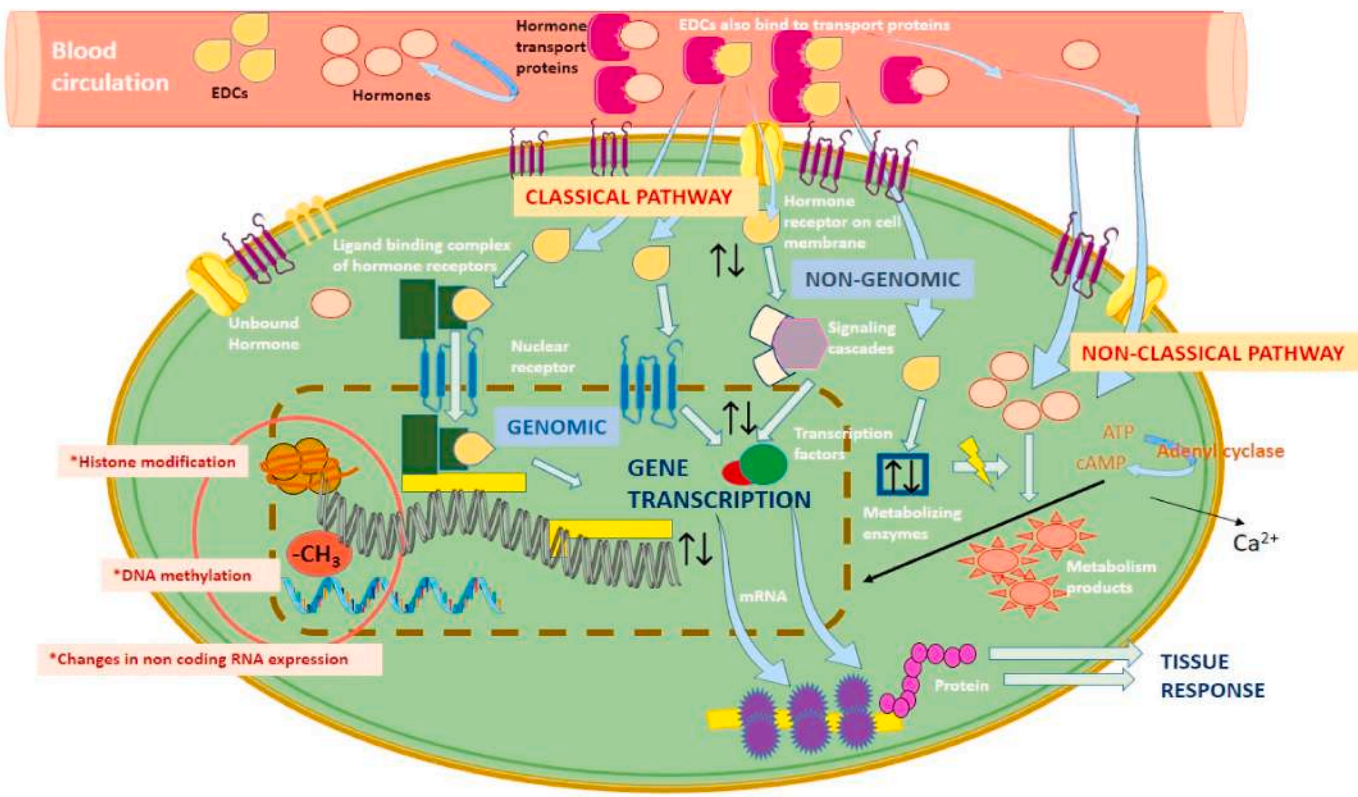


Fig. 2. The general mechanism of action of different EDCs involves three pathways.

3. Effects of EDCs on ecology and human health

3.1. Ecological concerns associated with EDC

The negative impact our expansion has brought upon the environment is visible as macro-pollutants and invisible as micro-pollutants, only to be manifested years later. The harmful effect of EDC on the ecosystem and its inhabitants is evident in analyzing different members of the food chain. The inhibitory role on amino acid synthesis or photosynthetic ability is some effects of EDC such as herbicides, and plasticizers such as bisphenol A on plants (Kim et al., 2018). Moreover, Polychlorinated biphenyls and dioxins in the form of fertilizers are found to bioaccumulate in plants subsequently in herbivores that consume those (Antolin Rodriguez et al. 2016; Di Guardo et al., 2020; Han et al., 2022). Such bioaccumulation and associated biomagnification in different fishes and wildlife is also reported (Godfray et al., 2019). The high incidence of EDC in drinking water and aquatic systems is a true indication of the extent of its transmissibility to various living forms (Gonsioroski et al., 2020; Wee and Aris, 2019; Pironti et al., 2021).

As noted in the fish and mammals EDC critically affect the development of gonads, induce sexual malformations, and change the onset of puberty (Delbes et al., 2022). Exposure to EDC during their development cause impairment of gonads, gamete development, and function of egg and sperms of bivalve molluscs (Luckenbach et al., 2009). Exposure to chemicals such as vinclozolin and dicofol causes impaired embryonic development of planktonic crustaceans such as *Daphnia* (Haeba et al., 2008). EDC such as 4-tert-Octylphenol (4-tOP) and triclosan (TCS) represent highly prevalent pollutants in the air, water, and soil ecosystem and they are found to cause imbalances in algae, fish, and daphnids (Olaniyan and Okoh, 2020). Toxicity studies with persistent organic pollutants (POPs) and endocrine-disrupting chemicals (EDCs) on *Caenorhabditis elegans* indicate that they could cause oxidative stress, apoptosis, and disruption of insulin/IGF-1 signaling pathway (Chen et al., 2019). The persistence and progression of EDC in the ecosystem are found to aggravate by increasing temperature globally on climate change as well they are also found to contribute to the development of non-communicable diseases such as diabetes (Kumar et al., 2020).

3.2. Human health concerns associated with EDC

Exposure to EDCs seems to be strongly associated with dysfunction of reproductive and developing systems when observed over the background of known influences and the changes in current human health trends warrant concern and the need for high research priority in understanding these mechanisms (Diamanti-Kandarakis et al., 2009; Kiess et al., 2021). The difficulty in analyzing human studies is to really comprehend the impact of EDCs on health. Though often conducted using various experimental designs and exposure conditions at different time intervals, it is difficult to predict the propensity to develop the disease later in adult life and follow them up. Despite finding difficulties in establishing a direct causal association to EDCs, exposure to them has been attributed to numerous adverse health outcomes and subsequent involvement of various systems (Fig. 3).

In the male reproductive system, primarily, there are two effects that have been most commonly attributed to EDCs; they are deranged reproductive function which manifests as a decline in semen quality, and infertility (Maffini et al., 2006). EDC causes disrupted fetal development which manifests as urogenital abnormalities such as cryptorchidism and hypospadias (Skakkebæk et al., 2001; Kumar et al., 2020). Nevertheless, evidence on the temporal trends of both the above-mentioned effects is poorly explained by existing studies and several meta-analyses. Studies had done yet have always been retrospective and the direct causal association of EDCs remains speculative. Available human and experimental animal studies show that a number of chemicals can derange the development of the male reproductive tract via endocrine mechanisms. Moreover, several disorders of the female reproductive system such as ovulatory dysfunction (PCOS), disorders of lactation and other breast diseases (Fenton, 2006; Kawa et al., 2021) endometriosis, and uterine leiomyomas have been associated with EDCs (McLachlan et al., 2006; Newbold et al., 2007). Premature thelarche has also been reported following exposure to phthalates (Li et al., 2006) and sexual precocity related to DDT exposure (Diamanti-Kandarakis et al., 2009) have also been recorded although both these data need to be replicated. A neuroendocrine mechanism was proposed as a result of experiments conducted on rodents. The interrelation of sexual precocity and ovulatory disorders with EDCs can be indirectly attributed to IUGR at birth and metabolic syndrome in adolescence (Ibáñez and de Zegher, 2006).

A substantial increase in the incidence of breast cancer among women in the industrialized world, observed during the span of the last 50 years has been attributed the exposure to hormonally active EDCs especially xenoestrogens (Davis et al., 1993; Akhbarizadeh et al., 2021). The incidence of rare vaginal cancers was also seen in daughters of mothers who received DES (Diethylstilbestrol); this may be an unprecedented response to in utero exposure of high dosage of DES or due to the compound itself activating various pathways. Other EDCs may not contribute to this but may lead to reproductive changes as mentioned above (Swan, 2000). Significant correlations have been made between prostate cancer and pesticides like organochlorines and thiophosphates, among which many of them are acetylcholine esterase inhibitors and also have the ability to inhibit major p450 enzymes. These enzymes are responsible for the metabolism of many steroid hormones like estradiol, estrone, and testosterone, thereby disrupting the normal hormonal balance and may lead to the development of prostate cancer (Alavanja et al., 2003; Mahajan et al., 2006). EDCs have been reported to disrupt the link between developmental programming and reproductive maturation as pointed out by the interrelationship between carcinoma *in situ in* the fetal testis to the development of testicular cancer in adulthood. This is a representation of the links between incidence of adult disease and fetal environment, although a definite correlation has not yet been established (Bay et al., 2006; Sharpe, 2006).

In addition, reduced circulating levels of thyroid hormones has been attributed to a large number of industrial chemicals, which can act through various mechanisms such as hormone synthesis, release, transport of thyroid hormones in the blood, their metabolism, and clearance (Brucker-Davis, 1998; Howdeshell, 2002). EDCs can also have neurobiological and neurotoxic effects along with endocrine effects on other neuroendocrine systems, especially neuroendocrine cells found in the brain (Diamanti-Kandarakis et al., 2009). The rise in the incidence of such complex diseases with multifactorial causality equals the heightened use of industrial chemicals which suggests that EDCs may be linked to this modern era epidemic (Baillie-Hamilton, 2002). However, owing to poor evidence regarding the same, further research is needed to elucidate all possible interactions between a wide spectrum of industrial chemicals and metabolic deregulation.

4. Physico-chemical strategies in remediation of EDCs

Over the past couple of decades, our acceptance of different

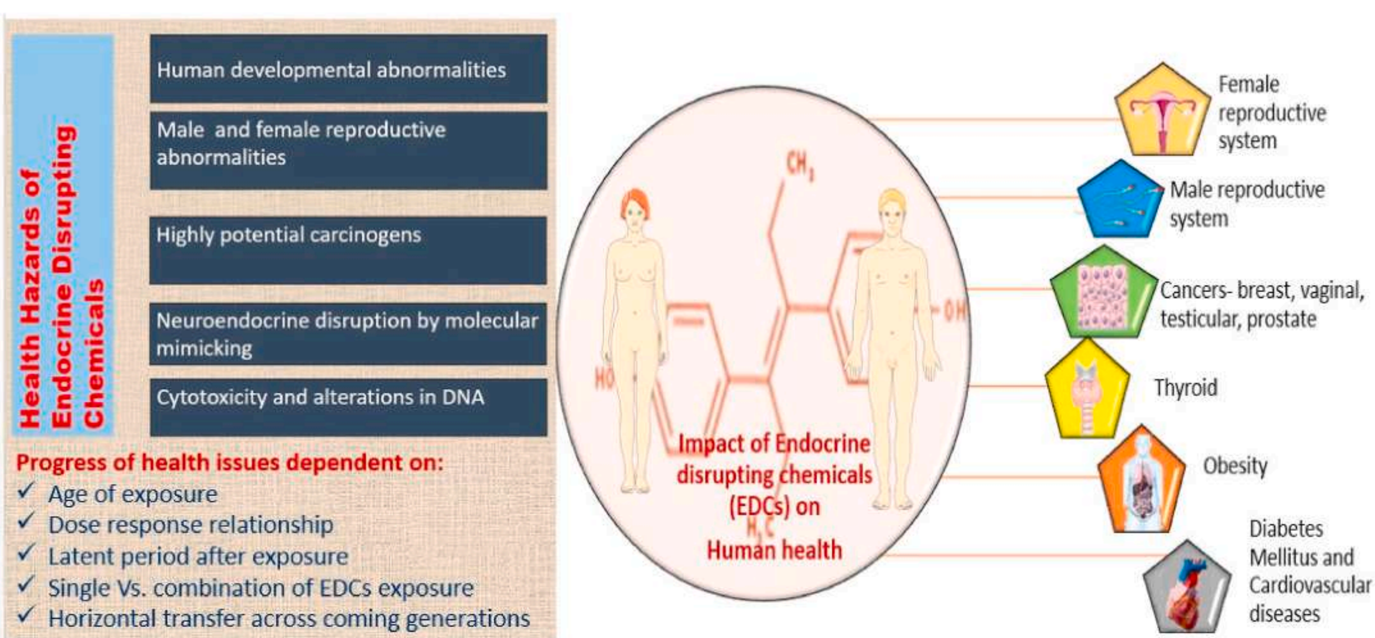


Fig. 3. The impact of EDCs on human health, the hazards and the factors depending on which the progress of health issue occur.

chemicals to be an endocrine disruptors or have the potential is increasing owing to solid data from research, toxicity analysis, and mounting evidence following risk assessments on their impact on the environment (Bergman et al., 2013; Patel et al., 2020; Buoso et al., 2020). As more EDCs are being added and are ubiquitous in nature, there is a proportional enlargement of non-regulated pollutants; hence its mitigation strategies need to be looked carefully in greater depth and with more understanding starting from the conventional. The early measures of removal of EDCs ranged from crude processes such as excavations and landfilling, incineration, to complex oxidation processes photodegradation, dechlorination, and electrocatalytic processes. The various physico-chemical ecofriendly approaches are detailed below.

4.1. Chemisorption by activated carbon

It is a process commonly used for the removal of organic waste and carbon by utilizing activated carbon either in its powdered or granular format. It is specifically effective in treating EDCs in wastewater. This adsorptive technology though has been grasped; it is extremely dependent on the optimal pH, optimal temperature, adsorbent's dose, and presence of any interfering substance. It is not suitable for large-scale applications (Haq and Raj, 2018; Gao et al., 2020). Several interactive forces are involved in the adsorption mechanism, which includes hydrogen bonding, pore filling, hydrophobic interactions and π-π interactions. These processes can result in energy and economy compromises through pyrolysis and additional activation steps by gases or chemical agents. It has been noted that this process is efficacious in removing EDCs. Eg. Acetaminophen, Caffeine, Erythromycin-H_2O Sulfamethoxazole, Fluoxetine, Pentoxifylline, Meprobamate, Dilantin. However, its efficacy is affected when the natural organic matter get attached to its binding site and block its pores (Snyder et al., 2007). Metal-organic frameworks have attracted attention as a novel porous material, particularly for the adsorption of EDCs from aqueous solutions. When compared to traditional adsorbents, several controllable characteristics such as customizable porosity, hierarchical organization, huge surface area and pore volume, superior adsorption and recyclability capabilities provide a new perspective. The use of appropriate metal clusters, surface modifiers, and organic linkers can justify their selectivity for the removal of various EDCs (Aris et al., 2020).

4.2. Membrane technologies

Most water pollutants are removed using membranes which are permeable and made up of thin material layers. It works based on the mesh size of the membrane which aids in the elimination of microbes and salt from the water. It selectively filters and removes the pollutants which are bigger than the pore size and allows the small-sized contaminants and water molecules to pass through (Katibi et al., 2021).

These technologies involve either a pressure-based or electricity-based separation with microfiltration, ultrafiltration, nanofiltration, and reverse osmosis utilizing the pressure. Microfiltration and ultrafiltration used in membrane bioreactors in water treatments do not have any barrier effect on EDCs removal in general. However, due to 100% particle retention, which promotes the EDCs removal through adsorption to sludge flocs, a high rate of EDC removal may be predicted when compared to typical purification methods (Wintgens et al., 2004). Both Nanofiltration and reverse osmosis are efficient in EDCs separation, chiefly for phytoestrogens, PAH, xenoestrogens, synthetic hormones, etc. However, for low molecular weight substances reverse osmosis is preferred (Haq and Raj, 2018).

4.3. Advanced oxidation processes

Initial oxidation processes used oxidants are used to convert EDCs to less toxic forms by a redox reaction. This technique uses chemicals like dichlorine (Cl_2), Chlorine dioxide (ClO_2), Hydrogen peroxide (H_2O_2), and processes like ozonisation. This was useful with estrogens remediation. Here too optimal technical conditions, pH, high costs. Moreover, researchers noted numerous remnants being persistent even after a chemical oxidative process; hence it is not in favor anymore. However, newer modifications i.e. the photocatalytic technology boast of high degradation and mineralization abilities by using sunlight as the energy source. Here no to fewer toxic byproducts are left over after the process. Generally, semiconductor materials are used like titanium dioxide (TiO_2) and zinc oxide (ZnO). There are a lot of nanocomposites being tried out as photocatalysts (Haq and Raj, 2018; Gao et al., 2020; Wang et al., 2020).

5. Microbial degradation of EDC

The search for the best management processes which are able to better neutralize the hazardous chemicals lead to the discovery of biodegradation processes, especially those involving microorganisms (Sotelo et al., 2012; Hazra et al., 2014; Rovani et al., 2014; Donati et al., 2019; Hernández-Abreu et al., 2020; Eltoukhy et al., 2020; Zhang et al., 2021). The skyrocketing costs, non-biocompatibility, large-scale reagent requisition, and formation of resultant secondary toxic products limits the value of the conventional approaches (Dangi et al., 2019). Bioremediation is the process where microbes are employed to breakdown hazardous chemicals completely or reduce them to less toxic products. The use of microbes came to the forefront because of their attractive properties of being eco-friendly, lower costs involved, fewer space constraints, and equipment demands (Gao et al., 2020; Pang et al., 2020; Singh et al., 2021a). Thereby, they conveniently degrade EDCs faster by using them as an energy source, and altering it into less toxic and benign byproducts while avoiding in entirety, the use of chemicals and conserving natural resources. In order to better escalate the efficiency and shrink the long process, nutrient sources, and biological catalysts, are added (Cajthaml, 2015; Zhang et al., 2016; Patel et al., 2020; Wojcieszynska et al., 2020; Roccuzzo et al., 2021).

The most sought organisms include bacteria, fungi, and microalgae as noted in Table 2 (Jaiswal and Shukla, 2020; Kalra et al., 2021; Tran et al., 2021). The remediation processes may be undertaken aerobically or anaerobically in bacteria. The bacteria commonly used are *Achromobacter*sp., *Alcaligenes* sp.,*Burkholderia*sp.,*Comamonas*sp., *Dehalococcoides*sp., *Pseudomonas* sp., *Ralstonia*sp., *Rhodococcus*sp., and *Sphingomonas*sp. While fungi used includes *Pleurotusostreatus*, *Fusarium* sp., *Phanerochaetechrysosporium, Trametes versicolor, Aspergillus* sp., *Fomitopsis palustris, Pythium ultimum, Stereumhirsutum, Candida aquatextoris,* etc. (Cruz-Morató et al., 2014; Cajthaml, 2015; Zhang et al., 2016; Dangi et al., 2019; Mohammadi et al., 2021).

The mechanisms involved in the breakdown of EDCs by these bacteria are biodegradation and biotransformation with the help of enzymes like hydrogenases, dehydrogenases, dioxygenases, hydroxylases, transferases, and laccases. This is similar to microalgae where they too cause the EDCs to undergo biotransformation with help of laccases, manganese peroxidases and cytochrome P-450. On the other hand, in fungi only biotransformation is similar to bacteria and microalgae, while the other mechanisms like bioadsorption and bioaccumulation of EDCs are done by the help of enzymes peroxidases, cytochrome P-450, and *glutathione s-transferases* (Wojcieszynska et al., 2020). A meta-analysis reported that there is an effect of EDC class, the members within the EDC group, and dissimilar organism class on the exposure time. In addition, the complexity of the EDC affected the bioremediation while organism class did not have a significant effect. Moreover, the delivery mechanism of the organism and the carrier material greatly influenced biodegradation (Roccuzzo et al., 2021).

6. Traditional approaches in bioremediation of EDCs

Microbes may occupy the areas polluted by EDCs indigenously or are artificially introduced to that zone to minimize the drastic effect of these

Table 2
An overview of microbial degradation of EDC.

Name of organism	Treated pollutant	Mechanism	Reference
Bacteria			
Pseudomonas aeruginosa, Pseudomonas lutoi	bisphenol	Enzyme mediated	Al-Hashimi, (2018)
Mycobacterium sp. DBP42, *Halomonas* sp. ATBC28 (marine isolates)	dibutyl phthalate (DBP) and bis(2-ethyl hexyl) phthalate (DEHP), acetyl tributyl citrate (ATBC)	Esterases and enzymes involved in the β-oxidation pathway	Wright et al. (2020)
Pseudomonas putida strain YC-AE1	Bisphenol A	Enzyme mediated	Eltoukhy et al. (2020)
Fungi			
Diaporthe longicolla	bisphenol	Laccase mediated	Baluyot et al. (2022)
White rot fungi	bisphenol A, bisphenol S, and nonylphenol from wastewater	Ligninolytic enzymes such as laccase, manganese peroxidase, lignin peroxidase, and versatile peroxidase	Grelska and Noszczyńska, (2020)
Trametes versicolor	EDCs, such as phenols, parabens and phthalate	Lignolytic enzymes	Pezzella et al. (2017)
Yeasts such as Candida rugopelliculosa RRKY5, Galactomyces candidum RRK17 and G. candidum RRK22	estrogenic alkylphenols	Enzyme mediated	Rajendran et al. (2016)
Algae			
Green algae Nannochloris sp.	17β-estradiol (E2), 17α-ethinylestradiol (EE2), and salicylic acid (SAL)	Bioadsorption and bioaccumulation	Bai and Acharya, (2019)
Green algae, Chlorococcum sp. *or Scenedesmus* sp	Endosulphan	Biosorption, coupled with their biotransformation	Sethunathan et al. (2004)

harmful compounds either through in-*situ* or *ex-situ methods* (Chaudhary and Kim, 2019; Singh et al., 2021a). As evident by the name *in-situ* bioremediation are measures done directly at the location site without any diggings or transfer, while in *ex-situ*, off-site remedial methods are undertaken whereby the EDC contaminated soil or water are transported to another locality for processing outside the original area of contamination (Fig. 4). *In-situ* measures aid in detoxifying dyes, solvents which are chlorinated, heavy metals, and polluted sites with hydrocarbons (Chandra and Kumar 2017; Chaudhary and Kim, 2019; Singh et al., 2021a).

6.1. *In-situ bioremediation measures*

6.1.1. *Natural attenuation*

This is a relatively an inexpensive and less arduous way by which the contaminants are naturally reduced with help of physical, chemical, and biological transformation which results in stabilization of the contaminants. However, it is time-consuming and in some cases, unintended leaching may occur (Azubuike et al., 2016; Donati et al., 2019; Chaudhary and Kim, 2019; Janssen and Stucki, 2020).

6.1.2. *Enhanced attenuation*

6.1.2.1. Bioventing and bioslurping. It is the process of instilling air in a regulated manner to the microbes inherent in the contaminated area, thereby promoting the growth of indigenous microbes. This process is further enhanced by supplying nutrients and other substrates needed for the microbe. In addition, the delivery of high flow rate ensures the clearing of volatile and non-volatile materials through physical and biological means respectively (Chaudhary and Kim, 2019). Additionally, Bioslurping is a combination of bioventing along with the use of vacuum and vapour extractors with the aim of providing oxygen and there by enhancing the degradation process. It creates a straw-like effect or a 'slurp' of liquids which can then be processed by bioslurping, for the removal of volatile to semi-volatile compounds and light non-aqueous phase liquids (LNAPLs). However, it is noted that factors like excessive soil moisture, and saturated lenses in soil affect the technique negatively (Azubuike et al., 2016). Bioventing technique are used to reduce BETX (benzene, toluene, ethylbenzene and xylenes) complex compounds and petroleum hydrocarbon (Bijalwan A. and Bijalwan V. 2016).

6.1.2.2. Biosparging. Similarly, to bioventing, in biosparging there is a

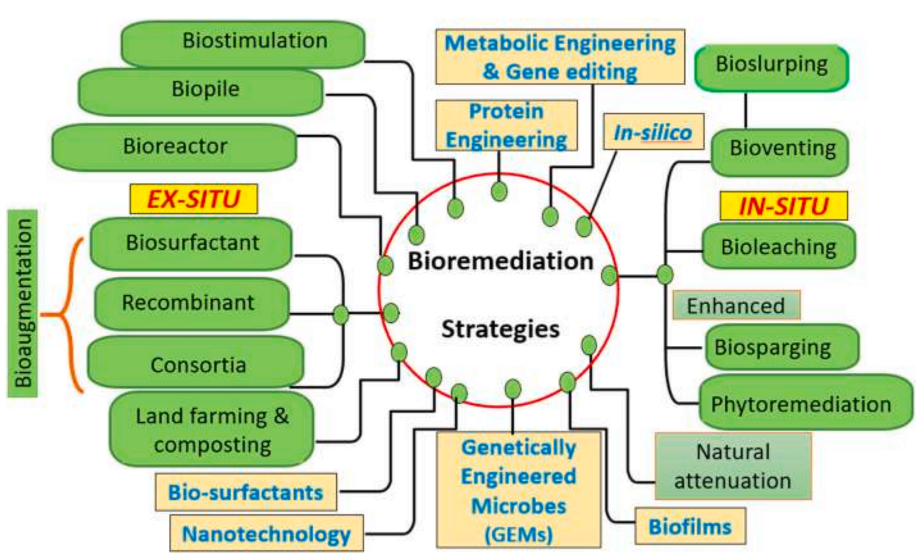


Fig. 4. The various conventional and novel bioremediation strategies employed in EDCs degradation.

drive for volatile compounds from saturated to unsaturated zones (Chaudhary and Kim, 2019). It is used to treat aquifers contaminated with diesel and kerosene (Sharma et al., 2021).

6.1.2.3. Bioleaching. It is a highly used technique in mining to separate metal from mineral ores. Similarly, the microbes which are acidophilic are used to decrease the metal impurities in residues which further makes it easy to remediate the EDCs in that sediment (Fonti et al., 2016).

6.2. Ex-situ bioremediation measures

6.2.1. Bioaugmentation

Besides the addition of a microbe to the contaminated site, extra growth potentiating factors are supplied to enrich the process of bioremediation. The use of co-metabolism wherein biosurfactants producing microbes like *Pseudomonas*, *Acinetobacter, Rhodococcus*, *Micrococcus*, and *Bacillus*, or using a recombinant pool of microbes or the usage of a consortium of different microbes each acting as a separate catalyst can really augment and improve the turnover time of remediation process. It is used for the partial removal of polychlorinated biphenyl, 2, 4-6-trichlorophenol and Atrazine. Eg: 2, 4-6- trichloro phenol is removed by adding *Alcalgenes eutrophus* TCP strain (Phale PS et al. 2019). However, there is a restriction on the use of non-indigenous microbes and the entire process is very dependent on the environmental factors (Chaudhary and Kim, 2019; Joe et al., 2019; Singh et al., 2021a).

6.2.2. Biopile

This process involves piling contaminated soil with EDCs and providing the appropriate temperature, moisture, nutrients, and oxygen to promote the microbiological action. It is an effective technique to treat large volumes of soil in a limited space. However, operations cost management and electricity supply are the major limitations (Azubuike et al., 2016; Chaudhary and Kim, 2019; Singh et al., 2021a). Acidic petroleum sludge can be treated with biopile technique thereby reducing the volume of the sludge (Naeem U and Qazi MA 2020).

6.2.3. Biostimulation

The process of bioremediation is enhanced by supplying nutrients, especially nitrogen, phosphorous, moisture, oxygen, optimal pH, and temperature in the area contaminated with EDCs. This may be expedited by the use of surfactants, spray foams, etc. The main highlight is that this process favors the multiplication of indigenous microbes, allows better bioavailability for contaminants, and improves the nutrition of the soil. However, issues of algal blooming, toxic surfactants increase may be faced (Chaudhary and Kim, 2019; Singh et al., 2021a). Biostimulation techniques are used to reduce BETX (benzene, toluene, ethylbenzene and xylenes) complex compounds, oil spils and petroleum hydrocarbons (Simpanen S et al., 2016, Nikolopoulou M, and Kalogerakis N 2010).

6.2.4. Bioreactor

The bioprocess occurs in a sealed-off reactor under controlled conditions i.e. optimum pH, temperature, constant agitation, and oxygen along with the degrading microbe and waste being efficiently removed. This is suitable for numerous applications both aerobic and anaerobic in controlled laboratory settings and for conduct of novel studies (Chaudhary and Kim, 2019; Singh et al., 2021a). It is useful for the effective removal of endocrine disruptive chemicals including compounds with nitrates, herbicides, pesticides, and organic and inorganic contaminants from the water. Thus being used in municipal and industrial waste-water treatment, ground and drinking water abatement, and odor control (Cicek, 2003).

6.2.5. Phytoremediation

Plants such as *Brassica juncea* L., *Salix alba* L., *Populus deltoides* L., *Helianthus annuus* L., etc are used to remove volatile contaminants in soil and water. Phytoremediation is an eco-friendly technique to detoxify the soil, but the chance of toxic products being left behind in the soil also does occur (Azubuike et al., 2016; Chaudhary and Kim, 2019; Singh et al., 2021a). Peroxidase enzyme produced by the plant root promotes detoxification by removal of phenol and chlorophenol (Singh AK et al. 2021). Petroleum hydrocarbons, chlorinated solvents, pesticides, metals, radionuclides, explosives, excess nutrients, atrazine, polychlorinated biphenyl, and hydrophobic organics like pentacholro phenol are removed using this bioremediation technique (Tabei K and Sakakibara Y 2006).

6.2.6. Land farming

Land farming comprises periodic tilling of land to provide better aeration and growth supporting conditions to indigenous microbes involved in decontaminating soil (Azubuike et al., 2016; Chaudhary and Kim, 2019).

6.2.7. Composting

Composting involves the microbial conversion of plant-based material of contaminated soil to organic soil amendments with simultaneous removal of xenobiotics. It is an environment-friendly technique, though it requires a big space and frequent aeration (Azubuike et al., 2016; Chaudhary and Kim, 2019). It is useful for the removal of petroleum hydrocarbons (Yaohui Xu and Mang Lu 2010).

7. Newer trends and sustainable alternative technologies

The conservative approaches had many drawbacks which included lengthy processing time and cost, whereas some methods required space, constant aeration, and mixing, others presented a multitude of issues including toxic waste dissemination, leaching and incomplete degradation of EDCs (Azubuike et al., 2016; Chaudhary and Kim, 2019; Singh et al., 2021a).This forced us to delve into and think harder to come out with ground-breaking approaches to bridge the gap despite the fact that the already existing techniques did try to address the issue of EDCs at hand. Newer approaches targeting EDCs but within the specific time frames, space, and other constraints were pursued. Using technological advancements in science to our advantage and viable substitutes, ranging from modifying existing enzymes, using gene editing tools like CRISPR and genetic engineering, metabolic and protein engineering and last but not the least using prediction strategies to either delay or prevent the formation of toxic substances (Fig. 5) (Liu et al., 2019; Chaudhary and Kim, 2019; Janssen and Stucki, 2020; Sakshi and Haritash, 2020; Bhatt et al., 2021; Singh et al., 2021b; Tran et al., 2021).

7.1. Enzymatic approaches and protein engineering

Microbial enzymes are capable of breaking down the harmful contents in the soil or water. Hence, either the entire microbe per se or only the isolated enzyme may be used for bioremediation of EDCs. The use of extracellular enzymes alone provides stability, specificity, mobility, biodegradability, ease of storage, and handling. Unlike the entire microbe which demands explicit conditions, nutrients, and balance. In normal situations and settings, the production of the enzyme may be low. Nonetheless, enzyme use as a standalone tool for speeding up bioremediation measures is noteworthy (Ravichandran and Sridhar, 2016; Wang et al., 2018; Chowdhary et al., 2019; Lee et al., 2019; Wojcieszynska et al., 2020; Mousavi et al., 2021; Singh et al., 2021a). The use of metabolomics, proteomics, and genetic engineering has been able to help with upgrading its abilities (Jaiswal et al., 2019; Sakshi and Haritash, 2020; Méndez García and García de Llasera, 2021; Singh et al., 2021a). The classical enzymes harnessed for their prowess in bioremediation, to name a few, are the peroxidases (lignin, laccase, manganese, and versatile peroxidases), oxygenases (mono- or di-), hydrolases (esterase, lipase, aminohydrolase, nitrilase, cutinase, and organophosphorus hydrolase), phosphodiesterases, halogenases, transferases, and

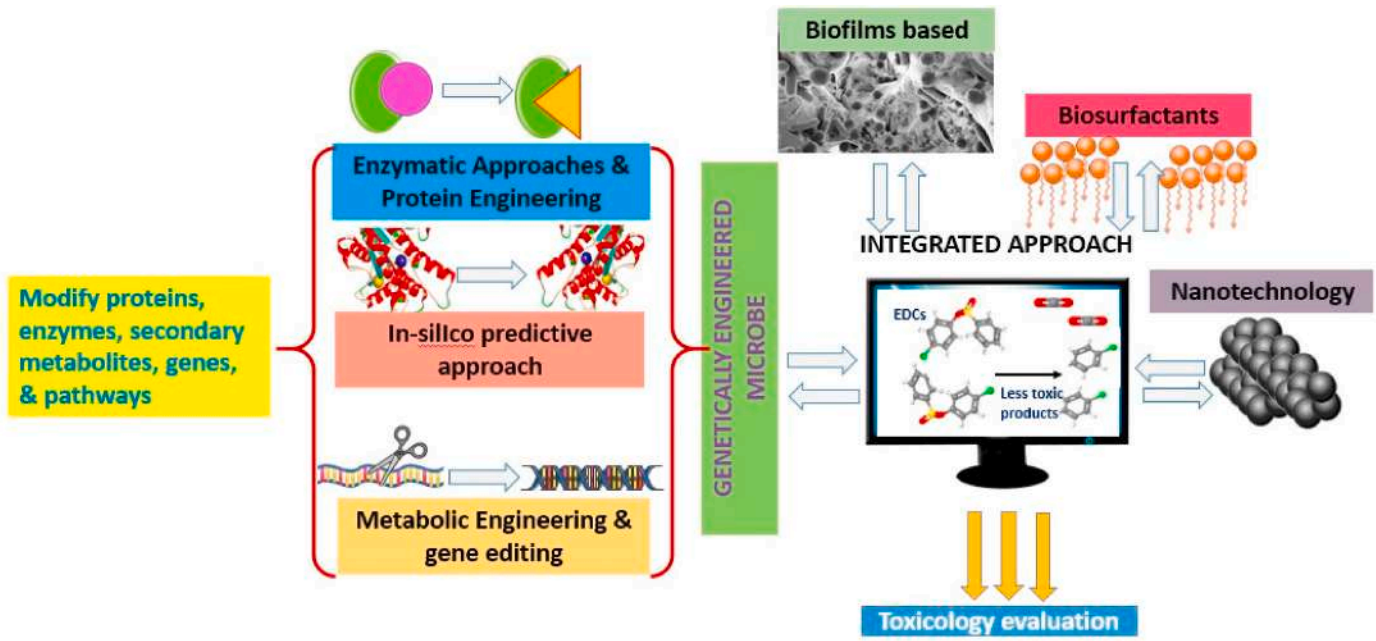


Fig. 5. The novel approaches involving enzymatic, protein engineering, in-silico predictive metabolic and gene editing for bioremediation of EDCs.

oxidoreductases (Bansal and Kanwar, 2013; Cajthaml, 2015; Eibes et al., 2015; Mousavi et al., 2021). Protein engineering has proved beneficial in improving the enzymatic approach further. The existing proteins are modified to gain better and novel spectrum including improving catalytic activities, stability, regulatory control and localization. Enzyme chimera may help to get the best of different structures and generate more potential enzymes with more scope for engineering further to get better enzymes for degrading EDCs (Li et al., 2020). Falade et al. investigated a number of ligninolytic enzymes such as laccase, peroxidase, etc. in EDC removal from wastewater (Falade et al., 2018).

7.2. Metabolic engineering and gene editing

Metabolic engineering in bioremediation is performed to constructively alter the microbe's metabolic pathway for ultimately detoxifying the various EDCs. The description and categorization of the various metabolites produced by microbes under stress will aid in choosing the best approach. These metabolites intensify interactions and thereby improve processes by providing better stability, bioavailability, and additional properties like biofilm formation. The tweaking of the existing pathways improved the yield and increased the amendment of the EDCs to safe options by better enzyme action and increasing the bioavailability for neutralization of the toxic component. It also improved the range of degradation of various EDC substrates and allowed for new functions absent in the original naïve microbe. Introduction of novel gene clusters, performing regulatory engineering, knock-out and knock-in of genes and stimulating precursors for early response and action are some of the possible of metabolic engineering (Cuperlovic-Culf, 2018; Dangi et al., 2019). The application of computational biology has greatly aided in improving the targeting of novel molecules. It may be either a reference-based reconstruction or de-novo synthesis followed by experimental validation and finally field testing (Dangi et al., 2019).

The main gene editing tools with the bio-remedial application include Zinc finger nucleases, Transcriptional activator like effector nucleases and Clustered regularly interspaced short palindromic repeats- *C*RISPR *a*ssociated (CRISPR-Cas) systems. They act like molecular scissors causing double stranded breaks in gene of interest followed by different repair mechanisms ultimately creating microbes with better bioremediation potential. However, the major disadvantages include mutations and accidental dissemination of the modified microbe (Canver et al., 2018; Jaiswal et al., 2019; Li et al., 2020; Tran et al., 2021).

7.3. Genetically engineered microbes

Although there is a daily exponential surge in the generation of EDCs, the existing bacteria are known to aid in bio-remedial activities either *in-situ* or *ex-situ* have the major limitation of being slow and the entire restoration is a time-consuming process (Liu et al., 2019; Janssen and Stucki, 2020; Tran et al., 2021). Therefore, the design and development of novel microbial scavengers is a feasible eco-friendly trend. It has been based on the different omics technologies, engineering whereby a modification of the enzymes, new pathway generation, better control over various bio parameters, and biosensing capabilities are targeted (Liu et al., 2019).

The entire process of generating a new GMO is long and complex. Initially, the microbes are screened for favorable traits which improve the naïve microbe hence the first step is identification, this is followed by evaluation of the traits and these modifications are undertaken by recombinant DNA technology or other methods of genetic engineering. The new microbe has improved degrading activities and is now re-evaluated for the traits. Different toxicological tools were used for the detection of the quantity of the products. Finally, the microbe is ready for field testing at the application level (Donati et al., 2019; Liu et al., 2019).

The use of metagenomics in using the whole genome sequences and designing modified microbes is being looked into. Its ability to predict the causes changes in sequence would bring about is noteworthy. However, this field is rapidly evolving with new concepts, field testing, and newer genetically modified organisms being researched widely (Singh et al., 2021b). GEMs are superior scavengers with stable properties like catabolism, metabolism, and degradation enzyme activities (Liu et al., 2019; Chaudhary and Kim, 2019; Janssen and Stucki, 2020; Singh et al., 2021a). However, the ability of tinkering with genes have prompted adoption of stringent laws and regulations internationally. Australia, France, Germany, Algeria, Madagascar, Turkey, Bhutan, Peru, Venezuela, Belize are few countries to have banned all GMOs usage in their respective countries (Sharma P et al., 2022; Prakash D et al., 2011; Countries That Ban Gmos 2022).

7.4. In-silico predictive approaches

Mankind has taken giant leaps in computational technology, the great benefit of this omnipresent technology has, is that it is rapidly adapting and bringing change which may be used to our advantage in diverse aspects of bioremediation. The capabilities of software to predict a target based on its chemical properties or predict its likelihood of getting degraded before it is even produced or once after production how to degrade it best. This robust system may be exploited and novel bioremediation strategies may be defined. The different algorithms and tools available online may suit multifarious applications starting from the prediction of novel chemical compounds, their toxicity, the pathways involved in their degradation, biotransformation, and validation of different models (Pavan et al., 2006; Leusch et al., 2019; Zhou et al., 2020; Singh et al., 2021b).

There are ligand-based and structure-based methods. The expert systems QSARmodel belongs to the former and is one of the simplest prediction tools which uses binary signs for a given character and is among the least expensive technique. It uses molecular descriptors which uses the molecule as a whole and further characterization based on dimensions and characteristics including molecular weight, atoms, bonds, rings, and geometry to be classified as either as one dimensional or two dimensional or three dimensional or four dimensional. The major drawback is that is very experimental in nature and that erroneous data initially may lead to a complete failure of a generation of products of expectation (Schneider et al., 2019; Celino-Brady et al., 2021; Goya--Jorge et al., 2021).

Structure-based or target-based molecular docking studies and dynamics simulations are useful in envisaging targets for bioremediation. They sample the space confirmation of the ligand in the binding point of a target. The protein-ligand complex interactions are screened by visualization and suggestions for targets are made accordingly and ultimately they are evaluated by scoring. They rely on bioinformatics tools and algorithms to achieve this optimization. Akin to ligand-based methods this too has the potential for errors; also the whole parameters may be biased especially with relation to ligand binding interactions. Comprehensive databases with large amount of data need to be built reliably (Srinivasan et al., 2019; Schneider et al., 2019; Singh et al., 2021b). The different simulation programs include Abalone, Assisted Model Building with Energy Refinement (AMBER), CHARMM, Desmond, GROMACS are offline and developed based on force field (FF). Similarly open, free, academic and commercial software with a clearly defined algorithms like Glide (QPLD algorithm), AutoDock (Lamarckian Genetic Algorithm), Vina (Energy Scoring Function), UCSF Dock (Geometric Matching Algorithm), SwissDock, GOLD (genetic algorithm), etc. are molecular docking programs with application in prediction of targets for bioremediation (McRobb et al., 2014; Vuorinen et al., 2015; Du et al., 2017; Chen et al., 2018; Sun et al., 2019; Singh et al., 2021b).

Another upcoming field using computational biology systems is the different bioremediation predictive pathways (PPs). The complex EDCs can be broken down into the simpler or the simplest molecule with the help of this strategy and their biodegradation worked out. SMILES are the chemical descriptor used and data is uploaded for analysis. There may be biochemically based and non-biochemically based PPs. The major limitation of non-biochemical-based prediction is that they rely on statistical probabilities and in real life that may not hold true, especially with regards to the structural modifications. However, biochemically based PPs work on the principle of information rules for biotransformation. The various prediction pathways for bioremediation include BIOWIN, CATABOL, CRAFT, EAWAG-BBD Pathway Prediction System, enviPath, from Metabolite to Metabolite (FMM), Metarouter, OASIS, PathPred, Zeneth, etc. The major limitations faced include high costs, resources, and inadequate databases, difficulty in the validation and field testing (Vuorinen et al., 2015; Sun et al., 2019; Celino-Brady et al., 2021; Singh et al., 2021b).

7.5. Biosurfactants

Surfactants are chemical compounds which cause a reduction of surface tension and has diverse applications in agriculture, industry including detergent, cosmetics, remediation, and neutralization of pollutants. They may be anionic, cationic, zwitterionic, or nonionic surfactants. They can further sub-classified as synthetic surfactants and biological or biosurfactant (Ng YJ et al., 2022).

Biosurfactants are of particular interest in bioremediation, since they are non-toxic, biodegradable, and biocompatible (Onaizi SA. 2022). They are sub-categorised as glycolipids, fatty acids, phospholipids, polymers, and lipopeptide groups. They help mainly in bioremediation of contaminated soil and water, due to their foaming ability, specific activity, and high selectivity under a wide range of pH, temperature, and salinity (Malkapuram ST et al. 2021) Biosurfactants like rhamnolipids are used for the removal of Bisphenol A (BPA) from wastewater. However, their action is dependent on several parameters like the concentration of BPA in the wastewater, the reaction time, temperature, and salinity of the water (Ng YJ et al., 2022).

7.6. Biofilm based approaches

Biofilms are a community of microbial cells which are attached to the substrate surface by extracellular polymeric substrates (EPS). They are highly complex, heterogeneous, and three dimensional structures which occur on the surfaces like soil, sediments, and water (Sandhya M et al., 2022). The matrix of biofilm contains lipids, exopolysaccharides, proteins, e-DNA, metabolites, particulate materials, and cell-lysis products. The different stages of their development begin with reversible adhesion to a surface, followed by irreversible adhesion, EPS production, microcolony formation, maturation, and finally dispersal of the mature biofilm (Balan B et al., 2021).

Its wide adaptability, biomass, excellent capability to absorb, immobilize, are being harnessed to undertake complete degradation of the toxic pollutants. The genetically modified *Bacillus subtilis* strain, (N4/pHTnha-ami) which produces biofilm having the potency to biodegrade organonitriles completely from wastewater (Balu S et al., 2020). EDCs which can also be detoxified include the hydrocarbons (4-chlorophenol (4-CP), 2, 4- Dicholophenol (2, 4-DCP), 17α-ethinylestradiol (EE2), bisphenol A, pesticides, and heavy metals (Catania V et al., 2020).

7.7. Nanotechnology

Nanomaterials are the building blocks of Nanotechnology, with sizes ranging between 1 and 100 nm (Kuhan et al.2022). They include nanoparticles, nanotubes, nanofilms, etc. They have wide scale usage in medical, pharmaceutical, food and agriculture, environmental, electronic, material engineering, and other industrial processing technologies. Their properties like high surface area, pore size, optical, catalytical, and magnetic properties, antimicrobial activity, and surface chemistry make them ideal candidates for multiple applications especially in remediation of EDCs by water treatment as adsorbents, sensors for water quality monitoring, and disinfection, and for preparation of high-quality nanomembranes. Thereby, making these nanoparticles more flexible, highly efficient, high performance, and low maintenance (Kuhan R et al., 2022; Bhateria R and Singh R 2022). Nanotechnology has a very malleable and effective degradation potential, which is now exploited for removal of EDCs especially from water (Imparato et al., 2022). ZnO, is a commonly used nanoparticle for the degradation of EDCs. In addition nanostructured catalytic membranes, nanosorbents, etc. are highly efficient for the removal of EDCs like BPA (Bisphenol A), Phenol, 2, 4-DCP, 4-CP (4-chlorophenol), and ReOH (resorcinol).

Contemporary research heralds the advent of nanocatalysts. They have the ability to co-exist with other substances but require stricter conditions like high accuracy and sensitivity of the catalyst, optimum initial pollutant concentration, pH values, and the dosage of photocatalysts (González-González RB et al. 2022). These unique features of good specificity, adsorption capacity, raised surface region to volume percentage, ability to enter and penetrate easily, and heightened reactivity help to eliminate toxic materials more easily, and these features make them an ideal candidate for concentration of bioremediation efforts. (Thangavelu L, Veeraragavan GR. 2022).

8. Future perspectives

Older conventional bioremediation techniques though cost-effective are slow, laborious, inefficient and protracted. Hence, novel techniques and approaches developed in biotechnology, must be effectively used in the bioremediation of EDCs like predictive molecular modeling, protein engineering, cloning and genome editing (CRISPR) (Singh et al., 2021a; Ali SS et al. 2021; Granja-Travez et al., 2020; Kumar et al., 2020). These newer methods will aid in detecting how biological systems respond to pollutants, and thereby pave safer and cleaner ways for novel bioremediation of EDCs. Furthermore, the advancement and technological feats we are encompassing need to be responsibly used for mitigation of EDCs in the environment. In the recent years, the role of computational biology or bioinformatics in simplifying predictive bioremediation is being largely studied. The in-silico approaches' ability to predict the chemical property of the compounds, degradation pathways, prediction for novel xenobiotics etc. Will be game changing. The different biodegradation databases/tools/model systems developed like the PathPred, CATALOGIC, BNICE, enviPath, EPI, BIOWIN, MetaRouter, EAWAG-BBDD etc. Will aid researchers in choosing best approach to biodegratio; (Singh et al., 2021b; Ahmad et al., 2020; Bilal M et al., 2020; Mishra B et al., 2021). Nevertheless, a multipronged approach safely choosing a combination of conventional, newer approaches need be tried in the field and their results be evaluated. Reconstruction of the known pathways and synthesis of novel pathways may be our way to a better future. Newer methods of toxicological analysis and predictions need to be availed prior to release of compounds in for regular use. The road ahead is clearly visible despite the bumps and turns. Primary studies comparing and contrasting the existing techniques and newer methodologies of bioremediation need be undertaken. The use of high through put systems, evolving omics including genomics, metagenomics, transcriptomics, metatranscriptomics, metabolomics, fluxomics, proteomics, etc. and the large information databases need to be thoroughly evaluated for the purpose of finding a strategy suitable for degrading most EDCs.

9. Conclusion

A wide range of EDCs is being secreted and dumped into the environment by various industrial manufacturing and processing units. The deleterious effects of these toxic products on health of fauna and flora has been disregarded and their remediation measures being downplayed, thereby remaining a challenge globally. For sustainable development, one needs to evolve, integrate, and empower the existing conventional bioremediation strategies and adopt greener technologies (Singh et al., 2021a). Additionally, the changes in awareness and public policies, governmental restrictions and regulations are needed to increase the comprehension of EDCs and assess their impact in the environment, thereby; limiting their unnecessary usage and increasing search for safer alternatives. The recent fast paced evolution of omics technologies, computational biology, biosurfactants, biofilm forming microbes and genetically modified microbes holds great promise for the future of bioremediation of EDCs (González-González RB et al. 2022; Sandhya M et al., 2022; Ng YJ et al., 2022; Sharma P et al., 2022). Empowering clinical research and promoting interdisciplinary collaborations of individuals belonging to dissimilar scientific backgrounds may lead on to development of novel and sustainable greener options as the ultimate bioremediation strategy.

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Declaration of competing interest

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

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