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Bacterial Catabolism of Phthalates With Estrogenic Activity Used as Plasticisers in the Manufacture of Plastic Products

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ABSTRACT

Phthalic acid esters (PAEs), the pervasive and ubiquitous endocrine-disrupting chemicals of environmental concern, generated annually on a million-ton scale, are primarily employed as plasticisers in the production of a variety of plastic products and as additives in a large number of commercial supplies. The increased awareness of various adverse effects on the ecosystem and human health including reproductive and developmental disorders has led to a striking increase in research interest aimed at managing these man-made oestrogenic chemicals. In these circumstances, microbial metabolism appeared as the major realistic process to neutralise the toxic burdens of PAEs in an ecologically accepted manner. Among a wide variety of microbial species capable of degrading/transforming PAEs reported so far, bacteria-mediated degradation has been studied most extensively. The main purpose of this review is to provide current knowledge of metabolic imprints of microbial degradation/transformation of PAEs, a co-contaminant of plastic pollution. In addition, this communication illustrates the recent advancement of the structure–functional aspects of the key metabolic enzyme phthalate hydrolase, their inducible regulation of gene expression and evolutionary relatedness, besides prioritising future research needs to facilitate the development of new insights into the bioremediation of PAE in the environment.

1 | Introduction

Human activities have caused extensive environmental pollution, releasing harmful pollutants into the air, water bodies and terrestrial surroundings, ever since the Industrial Revolution, which marked the transition from an agrarian and handicraft economy to one dominated by the scientific and technological development that began in the mid-18th century. A large fraction of these substances are potentially toxic, mutagenic and/or carcinogenic, and can harm human, animal and plant life by accumulating these chemicals through the food chain (Gupta and Singh 2019). Among various pollutants, plastic pollution stands out as a pervasive global issue, impacting diverse ecosystems. Despite international efforts, like the Basel Convention and EU recycling goals, plastic pollution continues to rise, exacerbated by its slow degradation rates and insufficient remediation programmes (MacLeod et al. 2021). The extent of plastic pollution since the Industrial Revolution in 1950 can be perceived from the worldwide making of plastic till recent times showing a continuous escalation in its production (Figure 1A). The severity of pollution in the new millennium can be realised from the extent of plastic production which accounts for more than 65% of the total plastic ever manufactured.

Plastic pollution is accompanied by contaminants, like plasticisers, which are relatively low-molecular-weight (LMW) substances, added to different polymeric materials in a range of

Suman Basu and Mousumi Bhattacharyya contributed equally.

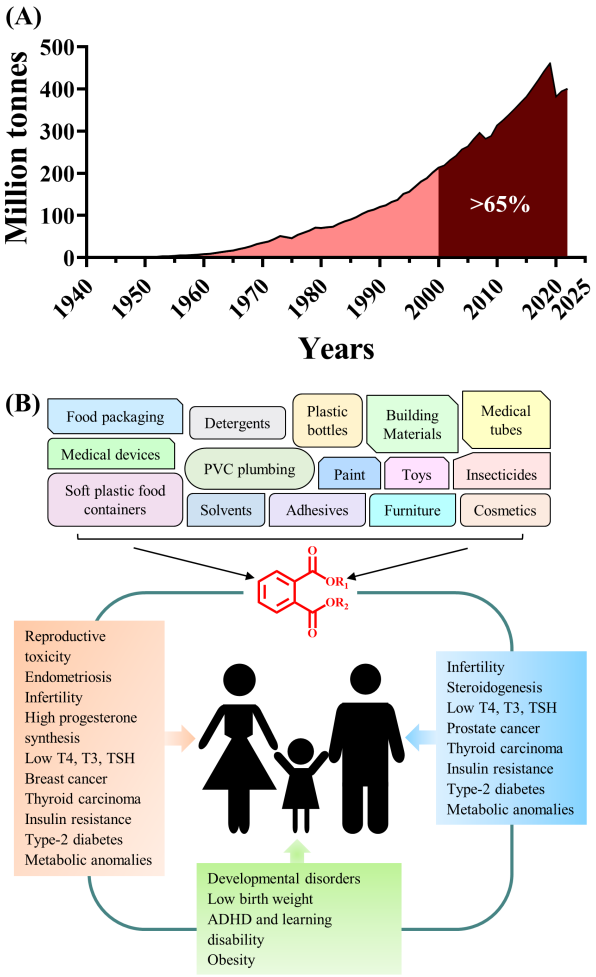

FIGURE 1 | Plastic production, an indirect estimate of the extent of the usage of plasticiser and adverse health effects of plasticiser phthalic acid ester. (A) The estimated annual global plastic production since 1950 (https://ourworldindata.org/plastic-pollution; https://www.statista.com/statistics/282732/global-production-of-plastics-since-1950/; https://theroundup.org/plastic-waste-statistics/). (B) Effects of phthalic acid ester in humans (Giuliani et al. 2020).

0.01%–40.52% (*w*/*w*) (Kim et al. 2020) to enhance their quality and meet the demands of the end product's application. Phthalates are the most widely used plasticisers in various consumer goods for their ability to improve durability, glossiness, longevity and flexibility (Kim et al. 2020; Zhang, Zhang et al. 2018; Ren et al. 2018). Phthalic acid esters (PAEs) or phthalate esters, popularly known as phthalates are clear liquids made by combining phthalic anhydride with alcohols through a process called esterification. The annual production of PAEs accounts for over 70% of the global plasticiser market, with phthalate esters ranging from six to eight million tons (Nahurira et al. 2017; Ren et al. 2018). In Western Europe, out of nearly one million tons of phthalates that are manufactured annually, almost 900,000 tons are utilised to plasticise PVC (Shanmugam et al. 2023). Their physicochemical properties vary based on a variety of side-chain alcohol groups accountable for ranges of volatility and water solubility (Rusyn, Peters, and Cunningham 2006). The high-molecular-weight (HMW) PAEs like di-*n*-octyl phthalate (DnOP), di(2-ethylhexyl) phthalate (DEHP) and benzyl butyl phthalate (BBP) are used in the large production volume furniture-finishing and construction materials, while LMW PAEs such as dimethyl phthalate (DMP), diethyl phthalate (DEP) and dibutyl phthalate (DBP) are commonly used in adhesives, plastic vessel, diluents, lubricants, coatings and varnishes (Sahoo and Kumar 2023). PAEs used in various plastic materials and other consumer products are shown in Figure 1B.

PAEs are bound non-covalently to plastic matrices. They tend to leach into the environment and thus have been detected ubiquitously (Puri, Gandhi, and Kumar 2023). Phthalate ester concentrations vary widely in air (0.03 ng m^{-3} to 24.19 μg m^{-3}), water (313–4640 ng L^{-1}) and soil (40–348 ng g^{-1}) (Kumari and Pulimi 2023). PAEs are omnipresent pollutants that act as endocrine disruptors, mimicking hormones and causing harmful effects on all life forms (Pan et al. 2024; Mérida et al. 2023; Payne-Sturges, De Saram, and Cory-Slechta 2023; Sahoo and Kumar 2023). They pose risks, such as reproductive toxicity and developmental disorders, among others (Figure 1B) (Arrigo et al. 2023; Diamanti-Kandarakis et al. 2009; Giuliani et al. 2020). Nevertheless, considerable global attention has been warranted primarily for their oestrogenic properties (Macedo et al. 2023; Ahn and Jeung 2023; Wu, Wang et al. 2010). The US Environmental Protection Agency (USEPA) has identified six primary phthalate compounds, DMP, DEP, DBP, DEHP, DnOP and BBP as the major contaminants and imposed restrictions on their usage (Singh et al. 2017). On the other hand, the European authorities proposed regulations to restrict the use of specific phthalates, such as DEHP, BBP, DBP, di-isodecyl phthalate (DIDP) and di-isononyl phthalate (DINP), in consumer products that likely to expose children (Kamrin 2009). Similarly, many Asian and other Western countries proposed restrictions on a few phthalates including DnOP and DEHP. For instance, Japan prohibited the use of DEHP in food-handling gloves and toys (Mutsuga et al. 2002), Australia also put restrictions on the use of certain products that contained more than 1% of DEHP, particularly for children up to 3 years of age (https://www.productsafety.gov.au/bans/dehp-in-childrens-plastic-items). In 2017, China, the largest phthalate manufacturer globally, set regulations on the detection limits of 16 different phthalates in food, food packaging materials and food containers (http://www.chej.org/pvcfactsheets/PVC_Policies_Around_The_World.html).

Given the prolonged natural process of degradation of PAEs, targeted biodegradation processes have emerged as a viable alternative for their elimination (Zhao et al. 2019; Zhang et al. 2020; Wang et al. 2008). Although substantial research exists on microorganism-mediated mineralisation, a comprehensive biomolecular understanding is crucial to explore the catabolic potential and regulation of PAE-degrading catabolic genes in the development of remediation strategies for effective assimilation of various phthalates. With respect to the above perspectives, the present study reviews recent advances both at the biochemical and molecular level to illustrate the structure–function of PAE-degrading catabolic enzymes in the biological management of oestrogenic PAEs of utmost concern.

2 | Phthalates: A Serious Health Threat Targeting Endocrine System

In the last years, scientific literature has ever-increasingly focused on the role of endocrine-disrupting chemicals (EDCs) in human pathophysiology. EDCs are exogenous compounds

that interfere with the synthesis, secretion, transport, metabolism, receptor binding or elimination of endogenous hormones, thereby altering the endocrine and homeostatic systems (Mnif et al. 2011; Kiyama and Wada-Kiyama 2015). Xenoestrogens, structurally similar to oestrogenic hormones (molecular mimicry), can compete with oestrogens and sequester target receptors, disrupting normal hormone functions (Josh et al. 2014; Hamid et al. 2020; Reddy, McCarthy, and Raval 2022). They interfere with natural oestrogenic activities, alter reproductive function and cause neurological disorders. They impair brain development, cognitive function and sexual behaviour and promote metabolic disorders. Xenoestrogens are often recognised as precursors to neurological diseases (Macedo et al. 2023; Ahn and Jeung 2023; Reddy, McCarthy, and Raval 2022).

Phthalate diesters are considered potential EDCs that can penetrate the human body by ingestion, inhalation and dermal absorption and cause damage to various organs and tissues (Arrigo et al. 2023). In spite of their short half-lives in tissues, studies revealed chronic exposure to phthalates can negatively influence the endocrine system as well as the performance of several organs, which imparts long-standing adverse impacts on the reproductive systems in young and adolescents, pregnancy success and child growth and development (Payne-Sturges, De Saram, and Cory-Slechta 2023; Mérida et al. 2023; Eales et al. 2022; Maqbool et al. 2016). Experimental studies in humans also established moderate to robust adverse impacts on neurodevelopment and respiratory systems, besides evidence for various other unfavourable outcomes including low birth weight, endometriosis, decreased testosterone, decreased intelligence, attention-deficit hyperactivity disorder, Type 2 diabetes and breast/uterine cancer (Arrigo et al. 2023; Eales et al. 2022; Zarean et al. 2016).

Studies revealed the oestrogenic potential of individual PAEs in the order: BBP>DBP > diisobutyl phthalate (DiBP) > DEP>DiNP (Harris et al. 1997; Hamid et al. 2020). Studies have confirmed the endocrine disruption abilities of PAEs, while the order of effective concentration (EC_{50}) for toxicity or mortality depends on the test organism and chemical structure. For yeasts, the oestrogenic potential order is BBP (EC_{50}: 2.65 μg L^{-1}) > DBP (EC_{50}: 8.37 μg L^{-1}) > DEP (EC_{50}: 39.13 μg L^{-1}) > DMP (EC_{50}: 55.71 μg L^{-1}). On the other hand, DEHP showed maximum oestrogenic activity and higher toxicity based on the oestrogen receptors (ERα and ERβ) binding in zebrafish (Hamid et al. 2020).

3 | Phthalate Management: Metabolic Imprints

Microbial intrusion is the most efficient and eco-friendly method for the complete assimilation of PAEs, as biodegradation addresses the shortcomings of abiotic or conventional physicochemical techniques at an inexpensive cost and under ambient conditions. Microbial degradation is mainly reported in bacteria and fungi and can occur commonly in three different ways—aerobic, obligate anaerobic or facultative anaerobic conditions (Fang, Liang, and Zhang 2007; Chang, Liao, and Yuan 2005). Indeed, the aerobic degradation of PAEs has been the most widely studied mechanism for more than six decades in a large number of Gram-positive and Gram-negative bacteria compared to only a few reports in fungi (Qiao et al. 2024 and references therein; Puri, Gandhi, and Kumar 2023 and references therein; Naveen et al. 2022). Notably, *Pleurotus ostreatus* and mycelial fungi, such as *Aspergillus parasiticus*, *Fusarium subglutinans* and *Penicillium funiculosum* have been reported as the potent degraders of BBP or DEHP where the extracellular ligninolytic enzymes play important roles in the degradation process (Gao and Wen 2016). Nevertheless, a few studies reported fungal utilisation of DEHP and DBP individually as the sole carbon and energy sources (Ferrer-Parra et al. 2018; González-Márquez et al. , 2019; Ahuactzin-Pérez et al. 2018). On the other hand, the abiotic degradation of PAEs in the environment mainly involves hydrolysis and/or photo-degradation. Aqueous hydrolysis of PAEs is insignificant and their half-lives have been reported to be in the range of 3.2 years for DMP to 2000 years for DEHP (Prasad 2021). While the photolytic half-lives of PAEs in an aquatic environment were estimated to be 2.4–12 years for DEP and DBP and 0.12–1.5 years for DEHP (Staples et al. 1997).

In effect, the biodegradation of PAEs depends upon their structural complexity, interacting microorganisms and several environmental factors. The PAEs with longer and branched alkyl side chains, such as DEHP, DnOP and alkyl aryl phthalate, like BBP are less susceptible to biodegradation than those with shorter alkyl chains, such as DMP, DEP and DBP. Numerous bacterial strains that degrade PAE have been identified to date; however, most of these strains have been found to assimilate low-molecular-weight phthalates (Zhu et al. 2022; Gao and Wen 2016; Ghosh and Sahu 2022; Yang et al. 2018). Table 1 summarises the list of bacterial strains involved in the degradation of HMW PAEs where it appeared that the species of actinobacterial genera were predominantly reported for their assimilation (Kapanen et al. 2007).

Various potential strains of the genus *Rhodococcus* were reported to degrade a wide array of PAEs (Kurane 1986; Nalli, Cooper, and Nicell 2002; Zhao et al. 2018; Zhang, Zhang et al. 2018). Among the high production volume HMW PAEs, several pure bacterial strains of the genera, such as *Gordonia*, *Nocardia*, *Rhodococcus*, *Bacillus*, *Burkholderia*, *Pseudomonas*, etc. were reported to assimilate DnOP and DEHP completely by utilising them as the sole carbon and energy sources (Wang, Ren et al. 2022; Sarkar, Chowdhury, and Dutta 2013; Zeng et al. 2004; Liu et al. 2021; Hsu et al. 2023; Li et al. 2019; Wang, Gan et al. 2022; Chang et al. 2022; Huang et al. 2019; Feng et al. 2002; Meng et al. 2015; Rashmi et al. 2023; Yuan, Huang, and Chang 2010). Often, the bacterial consortium was reported to assimilate these HMW PAEs more efficiently and at a faster rate (Wu, Wang et al. 2010; Wu, Liang et al. 2010; Wang et al. 2021). Again, in some cases, due to the lack of a defined organisation of operonic genes, one or more intermediates may accumulate in the bacterial degradation of PAEs. In this context, bacterial co-metabolism often appeared as the effective process for the mineralisation of phthalates via metabolic cooperation (Basu et al. 2023; Chatterjee and Dutta 2008; Li et al. 2019; Lu et al. 2020). A large number of studies on the general aspects of the biodegradation of PAEs by bacteria, fungi and algae have been reviewed in the recent past (Gao and Wen 2016; Ghosh and Sahu 2022; Qiao et al. 2024; Kaur et al. 2023; Puri, Gandhi, and Kumar 2023; Tran et al. 2022; Naveen et al. 2022; Mondal et al. 2022). A recent review by Qiao et al. (2024) focussed specifically on the PAE uptake processes in their assimilation in Gram-negative and Gram-positive bacteria. Further, emphases

TABLE 1 | Phthalic acid ester-degrading bacterial strains.

Organism	Phthalic acid esters	References
Actinobacteria		
Mycolicibacterium sp. MBM	DMP, DEP, DBP, DEHP, DnOP, BBP	Bhattacharyya et al. (2023)
Mycolicibacterium phocaicum RL-HY01	DEHP	Ren et al. (2021)
Microbacterium sp. CQ0110Y	DEHP	Chen et al. (2007)
Gordonia sp. GZ-YC7	DEHP	Hu et al. (2022)
Gordonia sp. Dop5	DnOP	Sarkar, Chowdhury, and Dutta (2013)
Gordonia sp. GONU	DMP, DEP, DBP, DEHP, DnOP, BBP	Dhar et al. (2023)
Gordonia alkanivorans YC-RL2	DEHP	Nahurira et al. (2017)
Gordonia sp. Lff	DnOP	Wang, Ren et al. (2022)
Gordonia sp. 5F	DEHP	Huang et al. (2019)
Gordonia hongkongensis RL-LY01	DEHP	Ren et al. (2023)
Gordonia sp. MTCC 4818	BBP, DEHP	Chatterjee, Mallick, and Dutta (2005)
Gordonia terrae RL-JC02	DEHP	Zhang et al. (2020)
Arthrobacter sp. HS-B2	BBP	Yang et al. (2013)
Nocardia asteroides LMB-7	DEHP	Chang et al. (2022)
Nocardia erythropolis	DEHP, DBP	Kurane, Suzuki, and Takahara (1979)
Firmicutes		
Bacillus mojavensis B1811	DEHP, BBP, DPP	Zhang, Zhang et al. (2018)
Bacillus marisflavi RR014	BBP, DMP	Kaur et al. (2021)
Bacillus firmus MP04	DEHP	Rashmi et al. (2023)
Bacillus velezensis NP05	DIBP	Mu et al. (2024)
Bacillus velezensis NP05	DIBP	Mu et al. (2024)
Proteobacteria		
Pseudomonas fluorescens FS1	DEHP	Feng et al. (2002)
Pseudomonas fluorescens B-1	BBP	Xu et al. (2007)
Pseudomonas sp. PS1	DBP	Cheng et al. (2023)
Pseudoxanthomonas sp.	DEHP	Meng et al. (2015)
Hyphomicrobium sp. PD-2	DnOP	Liu et al. (2021)
Acinetobacter sp. HS-B1	BBP	Yang et al. (2013)
Acinetobacter sp. LUNF3	DEP, DBP, BBP	Fan et al. (2023)
Pantoea dispersa BJQ0007	DMP, DBP, DEP, DIBP, DEHP	Xu et al. (2022)
Janthinobacterium sp. E1	DEHP, DMP, DBP	Zhang et al. (2024)
Burkholderia sp. SP4	DEHP	Hsu et al. (2023)
Burkholderia pyrrocinia B1213	DEHP	Li et al. (2019)

Note: The phthalic acid ester-degrading strains were selected based on the utilisation of at least one high-molecular-weight phthalates, namely, DnOP, DEHP or BBP. Abbreviations: BBP, benzyl butyl phthalate; DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DIBP, diisobutyl phthalate; DiNP, diisononyl phthalate; DMP, dimethyl phthalate; DnOP, di-*n*-octyl phthalate; DPP, diphenyl phthalate.

were given on the interactions of PAEs with the components of the bacterial cell envelope leading to cell disruption while proposing membrane protein-assisted transport as the main assimilation strategy in bacteria with an overview of several reported transporters and outer membrane proteins in facilitating the transport of PAEs and its analogues. Moreover, recent developments in the biodegradation of phthalate which appeared as an eco-friendly and sustainable approach for the removal of these

contaminants from key environmental matrices have been addressed (Kaur et al. 2023). Thus, in comparison to the recent published reviews as cited above, the current review aims to offer a comprehensive overview on the bacterial metabolism of PAE degradation with distinctive insights into the PA degrading operons, associated induction-regulation mechanisms and structure–function relationship of various types of phthalate esterases.

Among successful PAE bioremedial studies, *Gordonia* sp. showed over 99% degradation efficiency even at high initial concentrations of DMP, DEP and DBP both under batch shake flasks and continuous stirred tank bioreactor (CSTB) conditions. On the other hand, degradation of the high-molecular-weight PAE, namely, BBP, DEHP and DnOP was much more efficient under CSTB conditions than that under batch shake flasks conditions (Kanaujiya, Sivashanmugam, and Pakshirajan 2022). In a separate study, the biodegradation of DMP and DEP in a two-phase partitioning bioreactor (TPPB) was investigated both under batch mode and fed-batch mode using *Cellulosimicrobium funkei*. Under the batch mode, 93% degradation was achieved within 60 h while under the fed-batch mode of operation, a complete degradation up to 3500 mg/L of phthalates was achieved within 24 h (Kanaujiya and Pakshirajan 2022). In recent reports, various methods for the removal of PAEs from the environment including processes of bioremediation and their performances have been described (Kumari and Pulimi 2023; Kanaujiya et al. 2023; Tran et al. 2022).

3.1 | Hydrolytic Pathway and Metabolism of Phthalic Acid

Bacterial assimilation of phthalates involves a series of steps that start with de-esterification (esterase-mediated hydrolysis of ester bonds) to produce phthalic acid (PA) via corresponding phthalate monoester and with the simultaneous release of side-chain alcohol. The hydrolysed product PA is further metabolised via the multi-component phthalic acid dioxygenases: phthalate 4,5-dioxygenase, which is primarily found in Gram-negative bacteria and phthalate 3,4-dioxygenase, which is mostly prevalent in Gram-positive bacteria, followed by a phthalate dihydrodiol dehydrogenase and a decarboxylase to furnish protocatechuic acid (PCA) (Vamsee-Krishna and Phale 2008). It is important to mention here that certain amino acids of the α-subunit of phthalate 3,4-dioxygenase interact with specific parts of the substrate facilitating its regiospecific 3,4-dihydroxylation. Again, PCA is metabolised by the *ortho*-cleavage dioxygenase pathway (found in both actinobacteria and proteobacteria) or the *meta*-cleavage dioxygenase pathway, found only in proteobacteria leading to TCA cycle intermediates (Basu et al. 2023). A general scheme illustrating hydrolytic metabolism of PAEs and the metabolic pathways in the assimilation of hydrolysed product PA are summarised in Figure 2A. Although fairly less attention has been paid to the anaerobic degradation of phthalates, in the recent past, the potential of denitrifying bacteria, such as *Thauera* and *Aromatoleum* species and sulphate-reducing bacterium *Desulfosarcina cetonia* were reported (Ebenau-Jehle et al. 2017; Junghare, Spiteller, and Schink 2016). Insight into the anaerobic degradation pathway of PAEs revealed that in denitrifying bacteria, succinyl-CoA-dependent coenzyme A (CoA) transferase initiates the activation of PA to form phthaloyl-CoA as the first intermediate, which is acted upon by a decarboxylase to form benzoyl-CoA followed by dearomatisation via class I benzoyl-CoA reductases (ATP-independent) to produce cyclohexa-1,5-diene-1-carboxyl-CoA (Figure 2A) (Boll et al. 2014; Buckel et al. 2014). Later, the degradation of these intermediates occurs via the benzoyl-CoA degradation pathway followed by sequential β-oxidation-like catabolism accompanied by hydrolytic ring cleavage to form three acetyl-CoA and CO_2 (Fuchs, Boll, and Heider 2011). Nevertheless, phthalate metabolism under anaerobic conditions is slower and known as a rate-limiting step (Gao and Wen 2016).

3.2 | Hydrolytic Pathway and Metabolism of Side Chain Alcohols

Bacteria possess specific enzymes or sets of specific enzymes for the complete metabolism of the side chain alcohol group derived from the hydrolysis of phthalate esters (Figure 2B). The enzymatic pathways involved in the metabolism of both short-chain and long-chain alcohols vary depending on the length of the alcohol chain and bacterial species involved in the processes. The bacterial metabolism of long-chain alcohols, such as those containing four or more carbon atoms involves the action of NAD^+-dependent fatty alcohol/aldehyde dehydrogenases to furnish fatty acids via fatty aldehyde. Interestingly, recent reports revealed the involvement of $NAD(P)^+$-independent dehydrogenases in the metabolism of PAE-hydrolysed side-chain alcohols (1-butanol, 1-octanol and 2-ethyl hexanol) in actinobacterial species, in contrast to typical involvement of $NAD(P)^+$-dependent alcohol and aldehyde dehydrogenases (Bhattacharyya et al. 2023; Basu et al. 2023; Dhar et al. 2023).

Next, the fatty acids that have even/odd number of carbon atoms in their aliphatic chain are metabolised to acetyl-CoA/propionyl-CoA (which is eventually converted to succinyl-CoA by a group of specific enzymes) via the β-oxidation pathway providing energy to bacteria (Voet and Voet 2010). While the branched fatty acyl-CoA obtained from branched side-chain alcohol by the action of dehydrogenases undergoes a combination of β-oxidation and α-oxidation in the assimilation process (Voet and Voet 2010). On the other hand, short-chain alcohols, like methanol and ethanol can be metabolised through more than one pathway as revealed from various studies (Dorokhov et al. 2015; Trotsenko 1983; Huang, Shu, and Lin 2024).

Apart from alkanols, the metabolism of other side-chain alcohols, such as cyclohexanol, phenol and benzyl alcohol that are obtained respectively from the enzymatic hydrolysis of large production volume PAEs, dicyclohexyl phthalate, diphenyl phthalate and benzyl butyl phthalate require a separate set of enzymes (Figure 2B). Conventionally, cyclohexanol is oxidatively metabolised to adipic acid through a combination of dehydrogenase, monooxygenase and lactone hydrolase. Then, the metabolite adipic acid enters the β-oxidation pathway for the complete assimilation of cyclohexanol (Donoghue and Trudgill 1975). In contrast, the anaerobic metabolism of cyclohexanol is facilitated mainly by a combination of hydratase, dehydrogenase and hydrolase (Wang et al. 2013). While phenol is transformed into a central intermediate catechol via phenol monooxygenase (Figure 2B) (Hasan and Jabeen 2015).

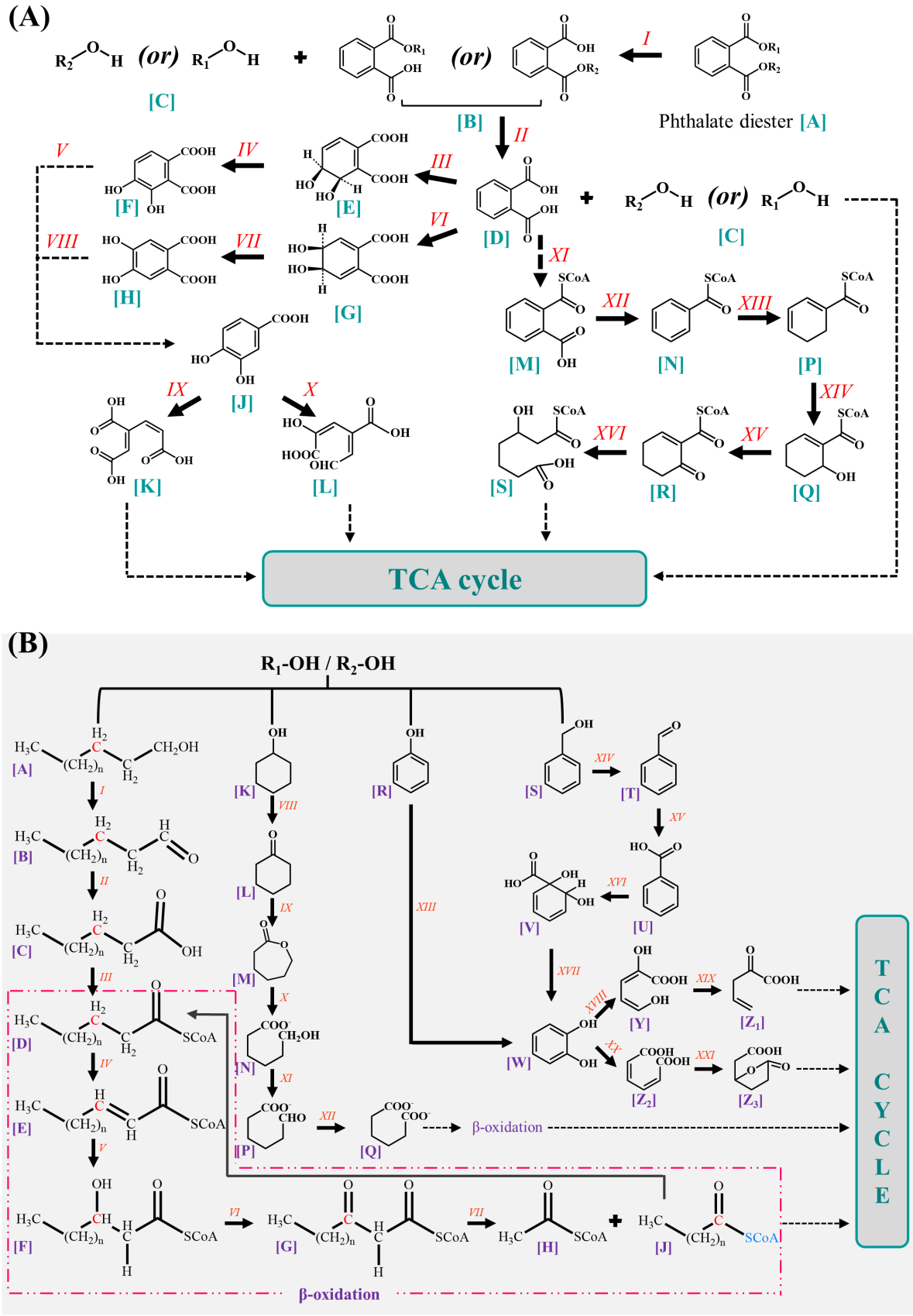

FIGURE 2 | Legend on next page.

Alternatively, anaerobic phenol degradation produces 4-hydroxybenzoate either directly through carboxylase or indirectly through synthase and carboxylase via the production of phenylphosphate. The resultant 4-hydroxybenzoate eventually enters into an anaerobic benzoate pathway which ultimately leads to the release of acetyl-CoA (Dalal, Pandey,

FIGURE 2 | (A) Conventional microbial degradation pathways of phthalic acid ester (Wei et al. 2021; Stanislauskienė et al. 2011; Dhar et al. 2023). Substrate and metabolic intermediates: A, phthalate diester; B, phthalate monoester; C, side-chain alcohol; D, phthalic acid; E, cis-3,4-dihydroxy-3,4-dihydrophthalate; F, 3,4-dihydroxyphthalate; G, cis-4,5-dihydroxy-4,5-dihydrophthalate; H, 4,5-dihydroxyphthalate; J, protocatechuic acid; K, β-carboxy-cis,cis-muconic acid; L, 2-hydroxy-4-carboxymuconic semialdehyde; M, phthaloyl-CoA; N, benzoyl-CoA; P, cyclohex-1,5-diene-1-carboxyl-CoA; Q, 6-hydroxycyclohex-1-ene-1-carboxyl-CoA; R, 6-oxocyclohex-1-ene-1-carboxyl-CoA; S, 3-hydroxypimelyl-CoA. Enzymes: I, esterase; II, esterase; III, phthalate 3,4-dioxygenase; IV, cis-3,4-dihydroxy-3,4-dihydrophthalate dehydrogenase; V, 3,4-dihydroxyphthalate-2-decarboxylase; VI, phthalate 4,5-dioxygenase; VII, cis-4,5-dihydroxy-4,5-dihydrophthalate dehydrogenase; VIII, 4,5-dihydroxyphthalate-2-decarboxylase; IX, protocatechuate 3,4-dioxygenase; X, protocatechuate 4,5-dioxygenase; XI, phthalate-CoA transferase; XII, phthaloyl-CoA decarboxylase; XIII, benzoyl-CoA reductase; XIV, cyclohex-1,5-diene-1-carboxyl-CoA hydratase; XV, 6-hydroxycyclohex-1-ene-1-carboxyl-CoA dehydrogenase; XVI, 6-oxo-cyclohex-1-ene-1-carboxyl-CoA hydrolase. (B) Metabolism of common side-chain alcohols (alkanol, cyclohexanol, phenol and benzyl alcohol) derived from phthalic acid ester hydrolysis (Voet and Voet 2010; Donoghue and Trudgill 1975; Basu et al. 2023). Side-chain alcohols and their pathway intermediates: A, alkanol; B, alkanal; C, alkanoic acid; D, fatty acyl-CoA; E, trans-Δ2-enoyl-CoA; F, 3-L-hydroxyacyl-CoA; G, β-ketoacyl-CoA; H, acetyl-CoA; J, fatty acyl-CoA (two C atoms shorter); K, cyclohexanol; L, cyclohexanone; M, 1-oxa-2-oxocycloheptane; N, 6-hydroxyhexanoate; P, 6-oxohexanoate; Q, adipate; R, phenol; S, benzyl alcohol; T, benzaldehyde; U, benzoic acid; V, cis-1,6-dihydroxy-2,4-cyclohexadiene-1-carboxylic acid; W, catechol; Y, 2-hydroxy muconic semialdehyde; Z1, 2-oxopent-4-enoate; Z2, muconic acid; Z3, muconolactone. Enzymes: I, NAD(P)+-dependent alcohol dehydrogenase; II, NAD(P)+-dependent aldehyde dehydrogenase; III, acyl-CoA synthetase; IV, acyl-CoA dehydrogenase; V, enoyl-CoA hydratase; VI, 3-L-hydroxyacyl-CoA dehydrogenase; VII, β-ketoacyl-CoA thiolase; VIII, cyclohexanol dehydrogenase; IX, cyclohexanone 1,2-monooxygenase; X, 1-oxa-2-oxocycloheptane lactonase; XI, 6-hydroxyhexanoate dehydrogenase; XII, 6-oxohexanoate dehydrogenase; XIII, phenol hydroxylase; XIV, NAD(P)+-dependent alcohol dehydrogenase; XV, NAD(P)+-dependent aldehyde dehydrogenase; XVI, benzoate 1,2-dioxygenase; XVII, 1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate dehydrogenase; XVIII, catechol 2,3-dioxygenase; XIX, hydroxymuconic semialdehyde hydrolase; XX, catechol 1,2-dioxygenase; XXI, muconate lactonase.

and Dubey 2012; Li et al. 2022). While the BBP hydrolysed product benzyl alcohol is metabolised to benzaldehyde by a NAD^+-dependent dehydrogenase followed by its conversion to benzoic acid via the involvement of a NAD^+-dependent dehydrogenase (Basu et al. 2023). The intermediate benzoic acid is further metabolised to catechol which is the key central intermediate generated during both phenol and benzyl alcohol biodegradation by various microbial strains. Catechol is degraded either via *meta*-cleavage pathway by catechol 2,3-dioxygenase or *ortho*-cleavage pathway by catechol 1,2-dioxygenase in the production of 2-hydroxymuconic semialdehyde or *cis,cis*-muconate, both of which are further metabolised and enter the tricarboxylic acid cycle (Figure 2B) (Hasan and Jabeen 2015).

3.3 | Alternate Pathways of PAE Metabolism

A few studies elucidated that phthalates with longer alkyl side chains may undergo cytochrome P450-mediated hydroxylation of the alkyl group followed by dehydrogenation and finally, β-oxidation resulting in shortening of the length of the long side chain structured phthalates, which then underwent de-esterification step (Amir et al. 2005; Liang et al. 2008). Alternatively, transesterification may take place by cutting out and replacing the long alkyl chains with shorter ones and then initiating de-esterification yielding PA (Jackson, Labeda, and Becker 1996; Cartwright et al. 2000; Lee et al. 2007; Liang et al. 2008). Nevertheless, the complete biodegradation pathways differ in terms of structurally different PAEs and metabolically distinct organisms, which are occasionally found to produce atypical intermediates (Chen et al. 2007; Ahuactzin-Pérez et al. 2018; Tang et al. 2016).

3.4 | Molecular Advances in PAE Metabolism

Despite a large number of bacterial strains that are capable of degrading one or multiple phthalate diesters (Table 1), only a limited number of studies showed purification and characterisation of phthalate esterases. Among others, the specific activity of the diesterase (GoEst15) from *Gordonia* sp. strain 5F was determined to be 69.8 ± 1.8 U/mg towards *p*-nitrophenyl butyrate (Huang et al. 2019) while that of the diesterase (DphN1) from *Acinetobacter* sp. LUNF3 showed 1.81, 2.72 and 2.07 U/mg protein against DEP, BBP and DBP, respectively (Fan et al. 2023). On the other hand, the catalytic efficiency of the di-mono esterase (EstM2) towards several phthalate mono- and diesters was found in the range of 15–90 $mM^{-1}\,s^{-1}$ (Sarkar et al. 2020). The purified monoesterase (MehpH) enzyme from *Rhodococcus* sp. EG-5 showed a specific activity of 26 μmol/min/mg protein (Iwata et al. 2016) while that of the monoesterase (MphG1) from *Gordonia* sp. YC-JH1 exhibited the specific activity of 3.14 U/mg protein towards a monoalkyl phthalate (Fan et al. 2018).

Besides biochemical investigations, whole genome sequence information is quite important to experimentally validate sequence data by other molecular analyses to understand the nature of phthalate esterases and other catabolic genes involved in the complete assimilation of PAEs. Nonetheless, several studies revealed that microbial phthalate-degrading genes are inducible rather than constitutive (Basu et al. 2023; Bhattacharyya et al. 2023; Dhar et al. 2023; Ferrer-Parra et al. 2018; Ríos González, González Márquez, and Sánchez 2019; González-Márquez et al. 2019). In recent reports, whole genome sequence data were effectively used in combination with the results of proteome/transcriptome and RT-PCR analyses, revealing the inducible regulation of multiple catabolic genes and operons involved in the assimilation of DOP, DEHP and BBP in actinobacterial strains (Dhar et al. 2023; Bhattacharyya et al. 2023; Basu et al. 2023). Both proteogenomic and metabolomics approaches were also exploited for the molecular characterisation of the DEHP catabolic pathway in *Mycobacterium* sp. DBP42 (Wright et al. 2020). In another study, the genome data of *Rhodococcus* sp. strain HS-D2, isolated from river sediment, revealed the

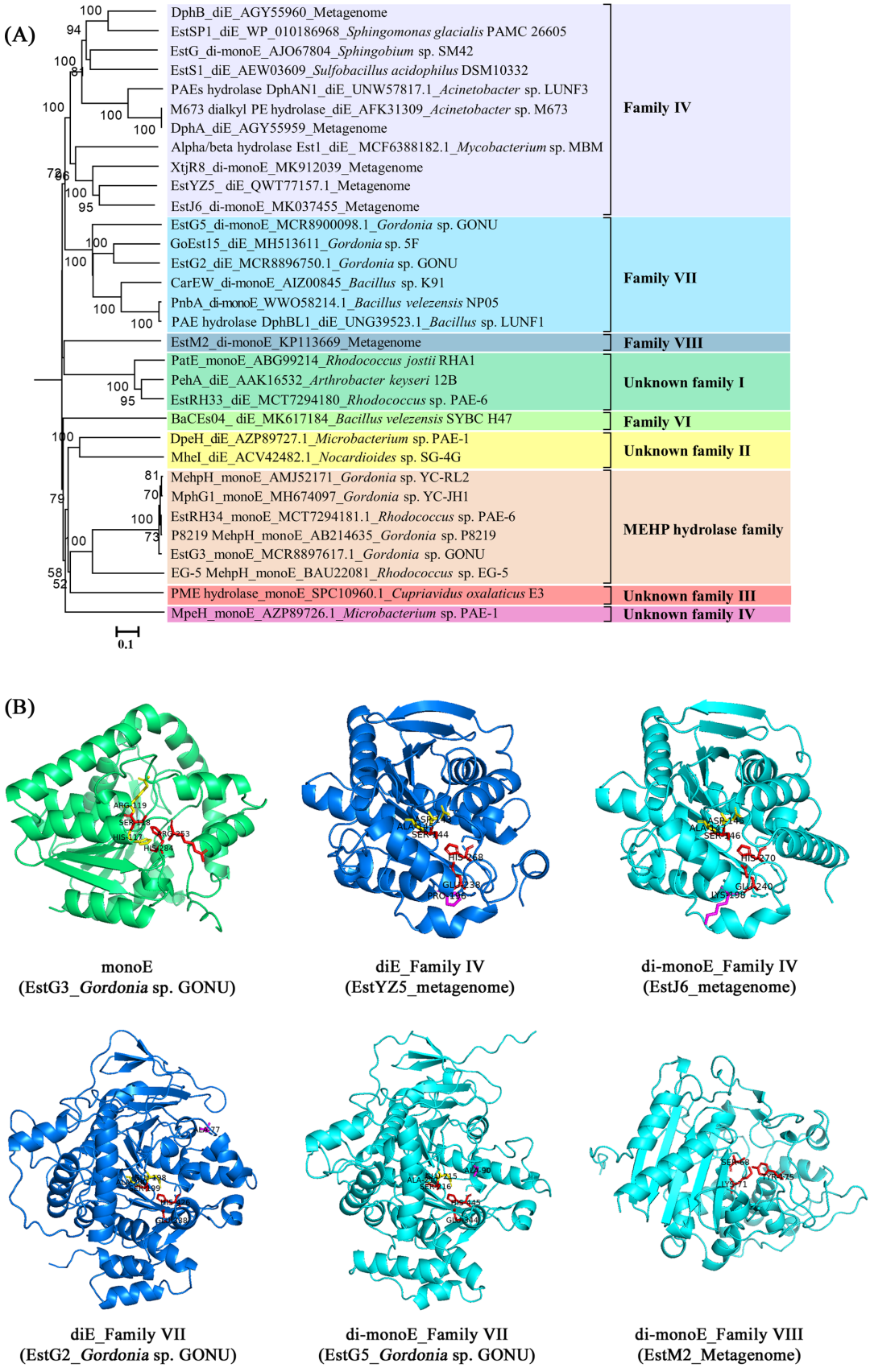

FIGURE 3 | Legend on next page.

presence of MEHP hydrolase and PAE hydrolase as catabolic esterases (Zhang, Chen et al. 2018). Recently, metagenomic sequencing was employed to reveal potential microbes and genes involved in the degradation of DEHP in aerobic and anaerobic soil samples, suggesting members of *Actinomycetales* as one of the potent degraders (Zhu et al. 2020).

FIGURE 3 | (A) Phylogenetic relationship of reported phthalate hydrolases (Bhattacharyya et al. 2022; Dhar et al. 2023; Sarkar et al. 2020; Basu et al. 2023; Fan, Guo et al. 2023; Fan, Li et al. 2023; Krishnani, Oakeshott, and Pandey 2023; Mu et al. 2024; Cheng et al. 2023). The selected phthalate hydrolases employed for phylogenetic analysis are indicated by their functional type (diE, monoE and di-monoE) and family affiliation. Numbers at the nodes indicate the levels of bootstrap support based on neighbour joining analysis of 100 resampled data sets. Bootstrap values below 50% are not shown. The scale bar represents 0.1 substitutions per amino acid position. The GenBank accession numbers of the sequences are indicated within parentheses. The multiple sequence alignment was performed using ClustalX2 and the phylogenetic tree was constructed using the neighbour joining algorithm as implemented in Tree Explorer 2.12. Abbreviated terms, diE, monoE and di-monoE represent diesterase, monoesterase and diesterase-monoesterase, respectively. (B) Structural prediction by AlphaFold analysis of selected phthalate hydrolases showing catalytic triad residues (marked in red). In the case of catalytic serine belonging to the pentapeptide GXSXG motif, the serine-neighbouring residues (X) are marked in yellow. The upper panel from left to right: Monoesterase (EstG3) belonging to the MEHP hydrolase family, family IV diesterase (EstYz5) and family IV diesterase-monoesterase (EstJ6). Structurally, EstYz5 and EstJ6 are quite conserved. The only apparent difference near the catalytic pocket region is a nonpolar proline (Pro196) in EstYz5 in comparison to a basic lysine (Lys198) in aligned EstJ6, where the residues are marked in magenta. The lower panel from left to right: Family VII diesterase (EstG2), family VII diesterase-monoesterase (EstG5) and family VIII diesterase-monoesterase (EstM2). Again, structurally, EstG2 and EstG5 are quite conserved. The only apparent positional difference of the nonpolar alanine residues, Ala77 and Ala90 (marked in magenta), which are distal and proximal to the catalytic center of EstG2 and EstG5, respectively.

4 | Structure-Functional Perspective of Phthalate Hydrolases

The key enzyme, esterase or hydrolase that initiates the PAE-degradation pathways are categorised in the superfamily of hydrolases (Huang et al. 2019, 2020; Xu et al. 2020; Bhattacharyya et al. 2022). The phthalate esterases display structural variations and are either monomeric, dimeric or hexameric showing efficient enzymatic activity in pH ranges of 7–10 and temperature ranges of 30°C–70°C (Huang et al. 2019, 2020; Sarkar et al. 2020; Lu et al. 2020).

The majority of the reported PAE metabolic operons are inducible where PAE or its metabolite activates the gene expression systems (Phale et al. 2007; Vamsee-Krishna and Phale 2008; Basu et al. 2016; Wang, Gan et al. 2022; Dhar et al. 2023; Bhattacharyya et al. 2023). Esterases often reside in distinct operons, and their expression is under distinct inducer-specific regulations. Thus, it is imperative that neither all PAEs can upregulate a specific esterase, nor one particular upregulated esterase can metabolise (hydrolyse) all PAEs (Dhar et al. 2023; Basu et al. 2023; Bhattacharyya et al. 2023). In a recent study, phthalate diesterase-monoesterase (EstG5) and phthalate diesterase (EstG2) in *Gordonia* sp. GONU were reported to express only in the presence of a specific inducer and exclusively involved in the conversion of DnOP and DEHP respectively (Dhar et al. 2023). It was observed that strain GONU can hydrolyse DnOP to PA using a diesterase-monoesterase (EstG5) while for the hydrolysis of its isomer DEHP, a combination of a diesterase (EstG2) and a monoesterase (EstG3) is needed resulting in the sequential formation of MEHP and PA.

Available molecular information of 32 functionally characterised phthalate hydrolases revealed that the majority of the hydrolases showed distinct substrate specificity and are categorised as monoesterase, diesterase and diesterase-monoesterase, capable of hydrolysing phthalate monoester, phthalate diester and both phthalate monoester and diester, respectively. Figure 3A revealed the phylogenetic affiliation of phthalate hydrolases with respect to the superfamily of esterases classifying the phthalate monoesterases belonging to MEHP [mono(2-ethylhexyl) phthalate] hydrolase family, phthalate diesterase belonging to family IV, VI and VII, while phthalate diesterase-monoesterase belonging to family IV, VII and family VIII (beta-lactamase family of enzymes) (Bhattacharyya et al. 2022; Dhar et al. 2023; Sarkar et al. 2020; Basu et al. 2023; Fan et al. 2023; Fan et al. 2023; Krishnani, Oakeshott, and Pandey 2023; Mu et al. 2024; Cheng et al. 2023). However, there are a few reported phthalate hydrolases that do not belong to any of the known families of esterases. Among all the classified phthalate esterases, one of the catalytic triad residues, serine, is present in the conserved pentapeptide motif (GXSXG). In the catalytic mechanism for MEHP hydrolases (monoesterases), apart from the catalytic triad residues, the presence of basic amino acids (H and R) in the pentapeptide motif GHSRG could neutralise the negative charge of the carboxylate anion of the monoester substrate leading to catalysis, which otherwise would inhibit nucleophilic attack (Maruyama et al. 2005). On the other hand, in different families of diesterase and diesterase-monoesterase, characteristic acidic residues are present in place of the basic residues of the pentapeptide motif of MEHP hydrolases.

Not all unconventional phthalate esterases belong to a single unknown family. Based on structural variance at the sequence level and evolutionary distances, four different unknown families can be proposed. The members of the unknown family I (PatE, PehA and EstRH33) showed a high degree of sequence similarity where PatE is reported as a monoesterase (Hara et al. 2007), while PehA and EstRH33 are reported as phthalate diesterases (Eaton 2001; Basu et al. 2023). Unlike classified phthalate diesterases and MEHP hydrolase family proteins, they do not have a characteristic pentapeptide motif. In addition, DpeH and MheI, biochemically characterised as diesterases, comprising a catalytic triad Asp-Ser-His, belong to unknown family II (Bhattacharyya et al. 2022). However, in this unknown family, the pentapeptide motif GHSG/YG does not comply with the GD/ESAG pentapeptide motif of typical family IV and family VII diesterases. Apart from the above, MpeH and PME hydrolase are both phthalate monoesterases, which showed distant evolutionary relatedness to the MEHP hydrolase family and do not exhibit the characteristic features of the MEHP hydrolase family proteins at the sequence level. The conventional GHSRG pentapeptide motifs of MEHP hydrolase were substituted by GHSGG and GISVG respectively in MpeH and PME hydrolases, designated as a member of unknown families III and IV. Nevertheless, the discovery of a large number of phthalate hydrolases of diverse structural nature is anticipated in the future due to continued interest in the metabolism of oestrogenic PAEs, which, with time, will enrich

the unknown families of phthalate hydrolases leading to their structure–functional characterisation.

Again, esterases belonging to different families were found to have distinct 3D structural conformations with the conserved α/β hydrolase fold. To date, among phthalate hydrolases, only the crystal structure of a typical monoalkyl phthalate hydrolase (MehpH) belonging to the MEHP hydrolase family was analysed revealing two major domains: an α-helical lid domain and an α/β hydrolase core (Chen et al. 2023). The catalytic triad, essential for substrate hydrolysis, is located at the bottleneck of the substrate entrance tunnel. To evaluate the structural features of phthalate esterases, Figure 3B depicts the 3D structure of phthalate monoesterase (EstG3) from *Gordonia* sp. GONU belonging to the family MEHP hydrolase, generated using the program AlphaFold (Jumper et al. 2021), correlates quite well with the crystal structure of MehpH. For information, EstG3 showed 99.66% identity with MehpH at the sequence level (Dhar et al. 2023). On the other hand, both phthalate diesterase and phthalate diesterase-monoesterase are distributed in family IV and family VII esterases. Figure 3B also depicts the 3D structures of phthalate diesterase-monoesterase (EstJ6) and phthalate diesterase (EstYZ5) belonging to family IV esterase, biochemically characterised from metagenomic samples (Qiu et al. 2020; Yan et al. 2021) and phthalate diesterase-monoesterase (EstG5) and phthalate diesterase (EstG2) belonging to family VII esterase, biochemically characterised from *Gordonia* sp. GONU (Dhar et al. 2023). Again, the AlphaFold-assisted 3D structure of family VIII esterase (EstM2), biochemically characterised as diesterase-monoesterase and obtained from a metagenomic sample is presented in Figure 3B showing the catalytic triad residues. All the 3D structures of esterases belonging to family IV, family VII, family VIII and MEHP family are structurally distinct. Apart from very small visible differences (Figure 3B), both the diesterase and diesterase-monoesterase belonging to family IV showed near-perfect alignment and the same is true for the diesterase and diesterase-monoesterase belonging to family VII. Thus, besides additional functional validation of esterases towards a variety of phthalate diesters and phthalate monoesters, a careful structural investigation is necessary to observe potential structural differences in these family-specific esterases executing either diesterase activity or diesterase plus monoesterase activities. Complementary investigations are also warranted to understand the exact catalytic mechanism of diesterase-monoesterase performing both diesterase and monoesterase activities.

5 | Conclusion and Future Direction

The rise in environmental pollution awareness has prompted research on strategies to clean up various pollutants including extensively discharged phthalates in the environment. Among different approaches, microbial degradation offers more effective and economical solutions for phthalate removal and presents an affordable and environmentally friendly option for degrading phthalates under natural conditions (Singha and Shukla 2023; Ren et al. 2023; Tran et al. 2022; Xu et al. 2024; Annamalai and Vasudevan 2020; Kirchhoff 2003). In microbial degradation, a combination of diverse microbial consortia would be a better strategy since this would allow participation of a variety of resident organisms capable of utilising different substrates/intermediates, consequently increasing the rate of degradation. Alternatively, genetically modified microbial variants that can produce more catabolic enzymes can enhance biodegrading ability. Further, a combination of PAE catabolic enzymes or microorganisms with nanoparticles may enhance their activity (Ayilara and Babalola 2023). Moreover, investigation of the variety of non-cultivated microorganisms from PAE-contaminated environmental niches holds promise for discovering novel biocatalysts.

Nevertheless, effective bioremediation strategies require a deeper understanding of the metabolic capability of potential microbes and that of site-specific microbial communities, besides environmental adaptability. Despite having a large number of studies on microbial degradation of PAEs and annotation of many esterases/hydrolases and catabolic genes in the genome sequences of PAE-degrading organisms, there is still limited information on the regulation of genes and operons responsible for the metabolism of PAEs and precise evaluation of substrate specificity of esterases at the biochemical and molecular levels. To advance the field of bioremediation, it is essential to have a better understanding of the metabolic potential of individual microorganisms or consortia, and besides biochemical information, knowledge of genomic, transcriptomic and proteomic profiles can effectively help in developing fruitful strategies with the exploration of possible solutions in the bioremediation of pollutants like PAEs available in different environmental matrices, industrial waste effluents and polluted land. Again, combining omics data with genetically engineered tools can provide a directed microbial remediation process (Bala et al. 2022). Further, the inducible catabolic operon may be exploited for the development of bacterial whole-cell bioreporters (Deb et al. 2018) to detect PAEs in contaminated environments and can also evaluate the extent of their removal before and after the process of bioremediation.

Among various genes/enzymes involved in the phthalate metabolism, phthalate esterase/hydrolase is least studied at the molecular level, which will help to understand the structure-function relationship of this important enzyme catalysing diesterase, monoesterase or diesterase-monoesterase (dual) reaction. Again, with the discovery of new phthalate esterases, the phylogenetically affiliated families of phthalate esterases are either reclassified with extended families or are classified into different unknown families deserving additional research to unveil the functional and evolutionary perspectives of all extant phthalate hydrolases. Moreover, sustainable solutions are highly needed on the deadly impacts of the toxicity of PAEs, a co-contaminant of various plastic products that are being extensively released into the environment. In this context, the green plastic additives, often bio-based and specifically designed to maintain a balance in enhancing the performance or characteristics of polymers while reducing their environmental impact due to biodegradation are used as a viable alternative where epoxidised vegetable oils were frequently studied as the bio-based plasticisers (Wang et al. 2024). Lastly, public awareness and media responsibility are essential to draw the attention of government, non-government organisations and scientific communities for strict regulation and to work/strategise for zero discharge/emission of phthalates, developing

safer alternatives (green plasticiser) and proper remediation strategy to restore contaminated environments to ensure the health of current and future generations and that of other life forms on this planet.

Author Contributions

Rinita Dhar: writing – original draft, conceptualization, software, formal analysis, investigation. **Suman Basu:** writing – original draft, investigation, conceptualization. **Mousumi Bhattacharyya:** writing – original draft, investigation, conceptualization. **Debarun Acharya:** formal analysis, software. **Tapan K. Dutta:** conceptualization, supervision, writing – review and editing, project administration, resources, investigation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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