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Review

Characterization of the role of esterases in the biodegradation of organophosphate, carbamate, and pyrethroid pesticides

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ABSTRACT

Ester-containing organophosphate, carbamate, and pyrethroid (OCP) pesticides are used worldwide to minimize the impact of pests and increase agricultural production. The toxicity of these chemicals to humans and other organisms has been widely reported. Chemically, these pesticides share an ester bond in their parent structures. A particular group of hydrolases, known as esterases, can catalyze the first step in ester-bond hydrolysis, and this initial regulatory metabolic reaction accelerates the degradation of OCP pesticides. Esterases can be naturally found in plants, animals, and microorganisms. Previous research on the esterase enzyme mechanisms revealed that the active sites of esterases contain serine residues that catalyze reactions via a nucleophilic attack on the substrates. In this review, we have compiled the previous research on esterases from different sources to determine and summarize the current knowledge of their properties, classifications, structures, mechanisms, and their applications in the removal of pesticides from the environment. This review will enhance the understanding of the scientific community when studying esterases and their applications for the degradation of broad-spectrum ester-containing pesticides.

1. Introduction

Organophosphate, carbamate, and pyrethroid (OCP) pesticides have been used to control pests in agricultural fields for decades. These chemicals have also been widely used as insecticides, herbicides, nerve agents, and mosquito repellents (Gammon et al., 2019; Lin et al., 2020). The organophosphates are also used as flame retardants for various materials such as polyvinylchloride plastics, polyurethane, electronics, textiles, paint, and furniture (Wei et al., 2015; Wang et al., 2018a; Kurt-Karakus et al., 2018). Organophosphate flame retardants do not inhibit carboxylesterase. Each of the three pesticide groups was designed and selected to kill target insect species; however, their non-target effects cannot be ignored. The excessive application of these pesticides has placed strong selective pressures on insects and other living systems, leading to the rapid development of resistance (Latif and Subrahmanyam, 2010a; Chen and Zhan, 2019). Moreover, due to the increasing demand for these pesticides, adverse effects have consequently been reported in humans and other organisms (Birolli et al., 2019). OCP pesticides are less persistent in nature, yet they are unsafe for humans, even when exposed to small concentrations (Muzinic et al., 2018). The reproductive toxicity has previously been established for these groups of pesticides (Martin-Reina et al., 2017). Subsequently, microbial approaches to reduce the concentrations of these pesticides from the environment have received considerable attention (Chen et al., 2011a, 2011b; Gangola et al., 2016; Bhatt et al., 2019a). Individual microbial cells or mixed cultures have been used for the degradation of pesticides from agricultural fields or other environments (Zhan et al., 2020). Single microbial cells degrade pesticides using their metabolic pathways, and mixed microbial cultures can perform the same complex task with combined metabolism. Each member in a mixed culture can reduce the metabolic burden of the monoculture (Bhatt et al., 2021a). Previous studies have reported the pesticide degradation potential of mixed cultures and critical points in the development of microbial consortia (Birolli et al., 2019; Bhatt et al., 2020a).

OCP pesticides are ester-bond-containing and can be degraded by breaking the ester bond through cleavage, hydrolysis, and irreversible inhibition (Mishra et al., 2020; Cycoń and Piotrowska-Seget, 2016) (Fig. 1**a–c**). The mechanism of carboxylesterases can also mediate the

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detoxification of organophosphates, which is based on an irreversible inhibition that does not require hydrolysis of the ester bond (Wheelock et al., 2008; Shimshoni et al., 2019). These pesticides are lipophilic and thus accumulate in fatty tissues. Hydrolysis of ester bonds can increase their water solubility, and hydrolytic cleavage can convert them into alcohols and carboxylic acids (Shimshoni et al., 2019; Brander et al., 2016). Biological methods have been shown to be more effective than chemical methods in remediating OCP and other ester bond-containing pesticides from contaminated environment (Cycoń et al., 2017; Singh, 2014). Biologically, the hydrolysis of ester bonds is possible through reactions catalyzed by esterases, which belong to the hydrolase super-family and encompass a broad group of enzymes (Korczynska et al., 2014; Chen and Zhan, 2019; Tang et al., 2011; Bai et al., 2019). OCP-degrading esterases have been purified from various microbes and found to be suitable for degradation in contaminated environments (Dave et al., 1993; Rai and Padh, 2001; Choi et al., 2004; Naqvi et al., 2009; Kumar et al., 2018). These esterases interact with OCP pesticides, viz., carboxylesterases, phosphotriesterases, and cholinesterases.

The catalytic mechanism of an OCP-degrading esterase is dependent on a specific catalytic triad, consisting of three amino acid residues (serine, histidine, and glutamine or aspartate) within the active site of the esterase enzyme (Zhan et al., 2020; Bhatt et al., 2020b). In the first

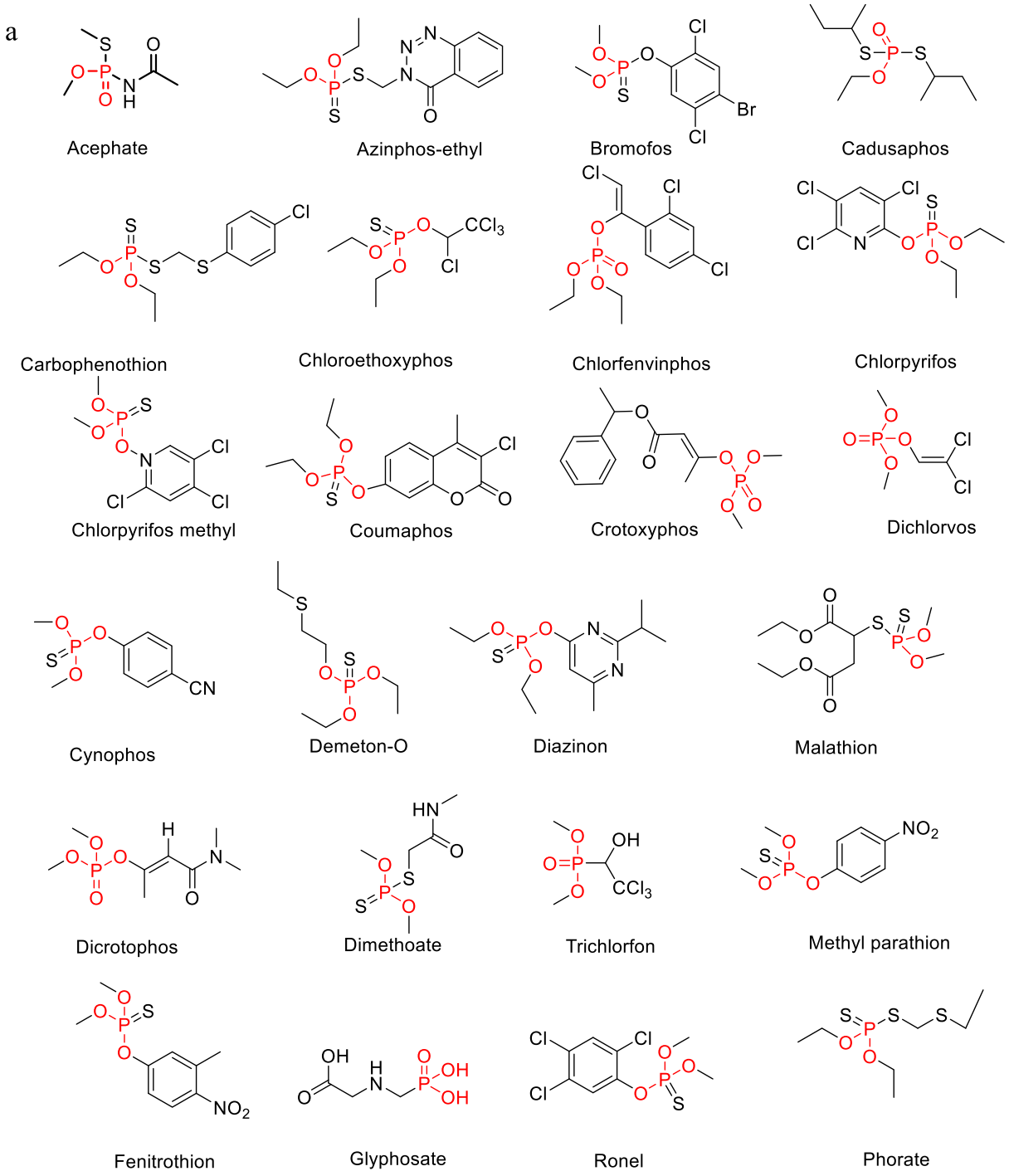

Fig. 1. Molecular structures of the (a) organophosphates, (b) carbamates, and (c) pyrethroids that are used worldwide. The atoms shown in red represent the target sites for esterases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

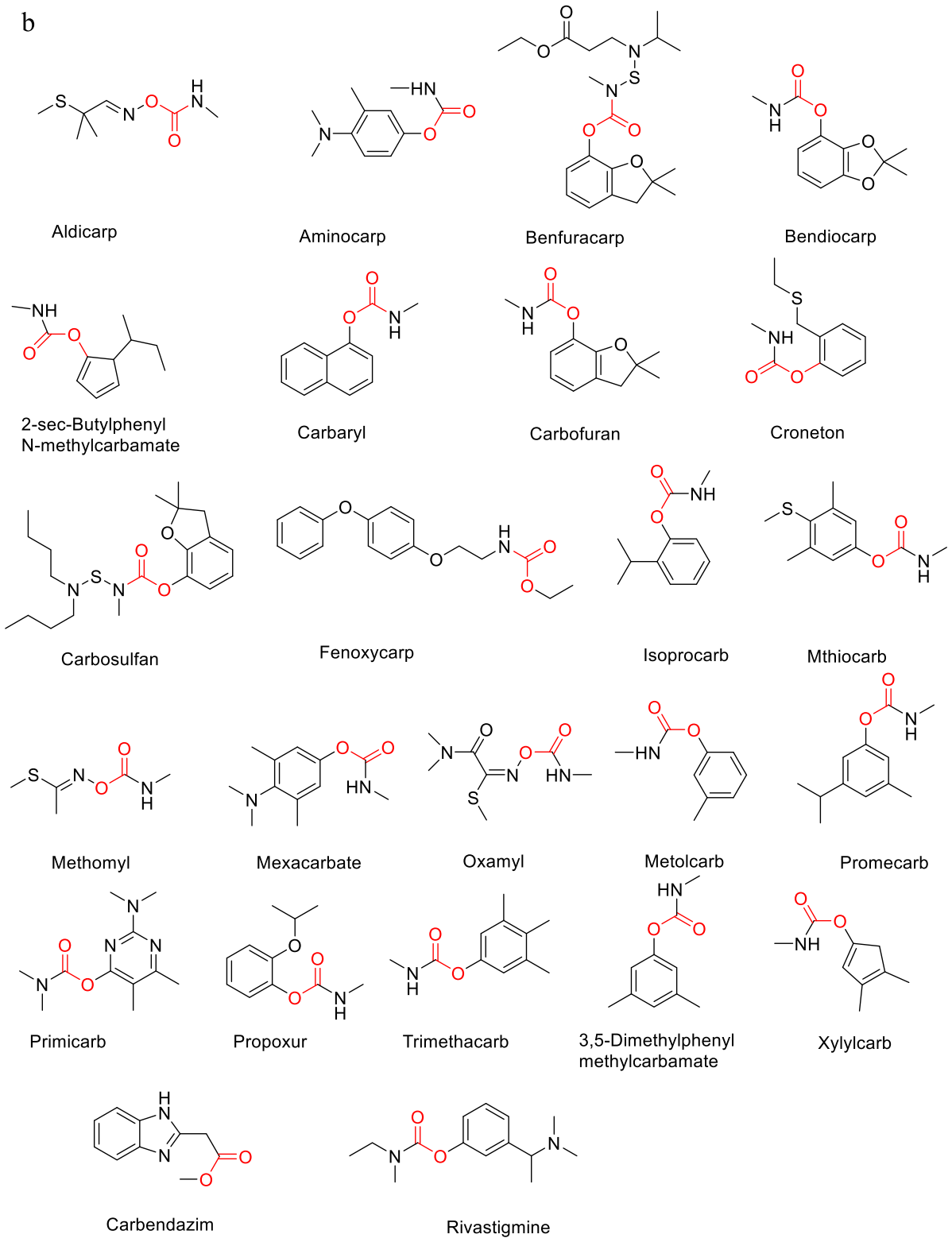

Fig. 1. (*continued*).

reaction, a nucleophilic attack by the base activates the serine oxygen atom on the carbonyl carbon of the substrate and leads to the formation of an acyl esterase intermediate with the release of an alcohol (Fig. 2). Serine contains a hydroxyl group (OH^-) that is activated by the catalytic histidine/aspartate, which takes the electron from the hydroxyl group of serine (Bornscheuer, 2002). The transient tetrahedral intermediate formed by this reaction is stabilized by the peptide nitrogen atom that forms an oxyanion hole. The nucleophilic attack changes the geometry surrounding the carbon from trigonal planar to tetrahedral. This unstable tetrahedral intermediate contains the negative charge on its oxygen atom derived from the carbonyl group. Furthermore, the tetrahedral intermediate collapses with esterase and forms the acyl–esterase complex (Bornscheuer, 2002).

The acylation reaction leads to the formation of a covalent bond

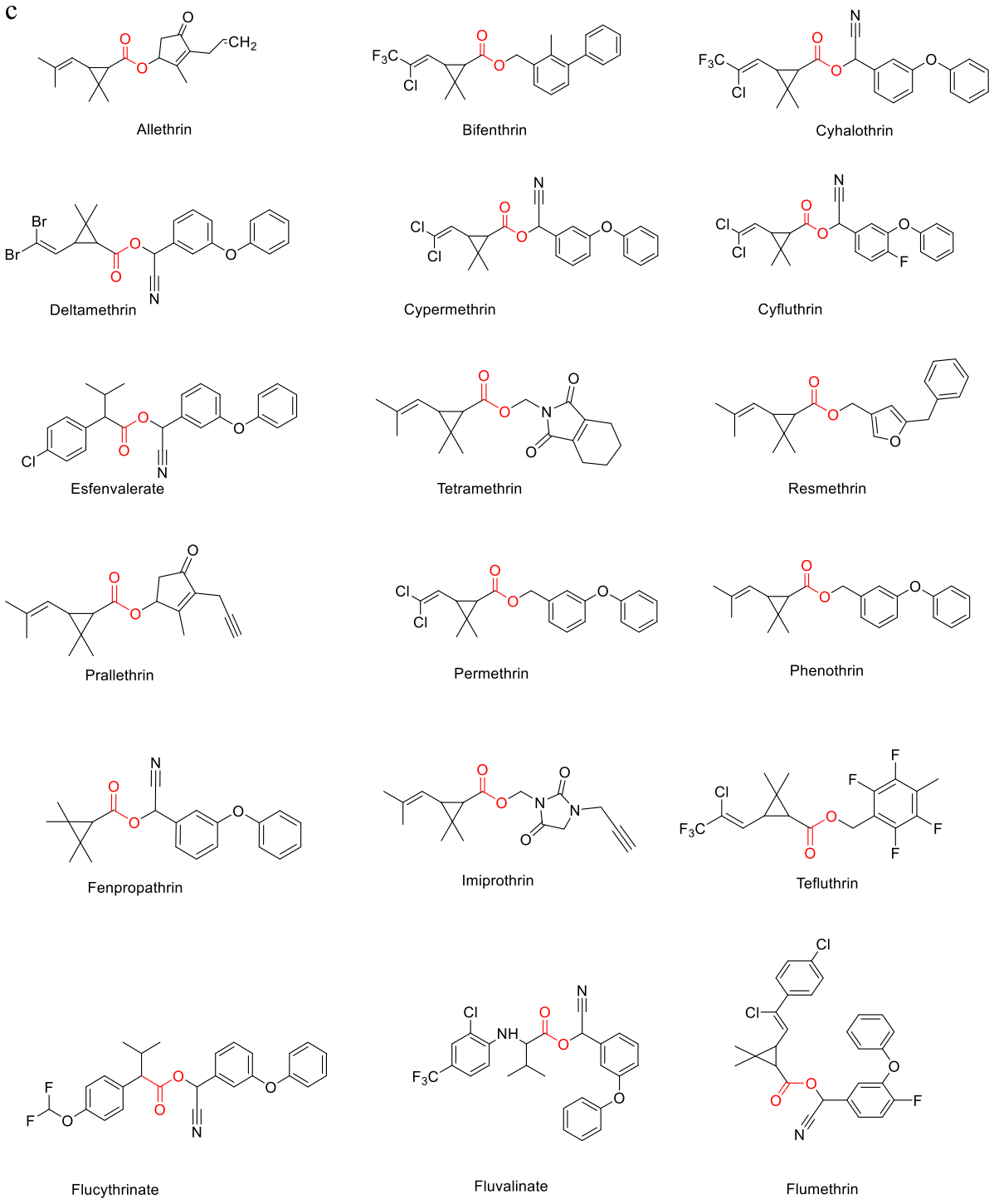

Fig. 1. (*continued*).

between the esterase and pesticides. The second step is a diacylation reaction, in which a water molecule acts as a nucleophile (OH^-) and attacks the acylated intermediate, leading to the formation of carboxylic acid (Wang et al., 2018b). In this reaction step, a proton is transferred from the histidine to the leaving group, and the acid group of the pesticide covalently binds with the serine. Furthermore, in the next reaction, histidine activates the water molecule that acts as a nucleophile and donates the proton to the serine and releases the acyl part of the pesticide (Wang et al., 2018b; Rauwerdink and Kazlauskas, 2015).

Histidine is present in the active site of serine hydrolases and can act as an acid and/or base during the catalytic mechanism of esterases. In OCP degradation, histidine acts as an acid and releases alcohol (R–OH) (Huang et al., 2021). The water molecule binds to the acyl–esterase intermediate complex. The active site histidine acts as a base to deprotonate the water so that it can attack the carbonyl carbon of the acyl–esterase complex and form a second tetrahedral intermediate. After completion of this reformation of carbon–oxygen, esterases will be released for the next reaction. This role of catalytic histidine as a base is universal to most α and β hydrolase enzymes. It has been observed that the same core catalytic machinery catalyzes 17 various reactions in α and β hydrolase (Rauwerdink and Kazlauskas, 2015).

After decades of successful application of OCP pesticide degradation,

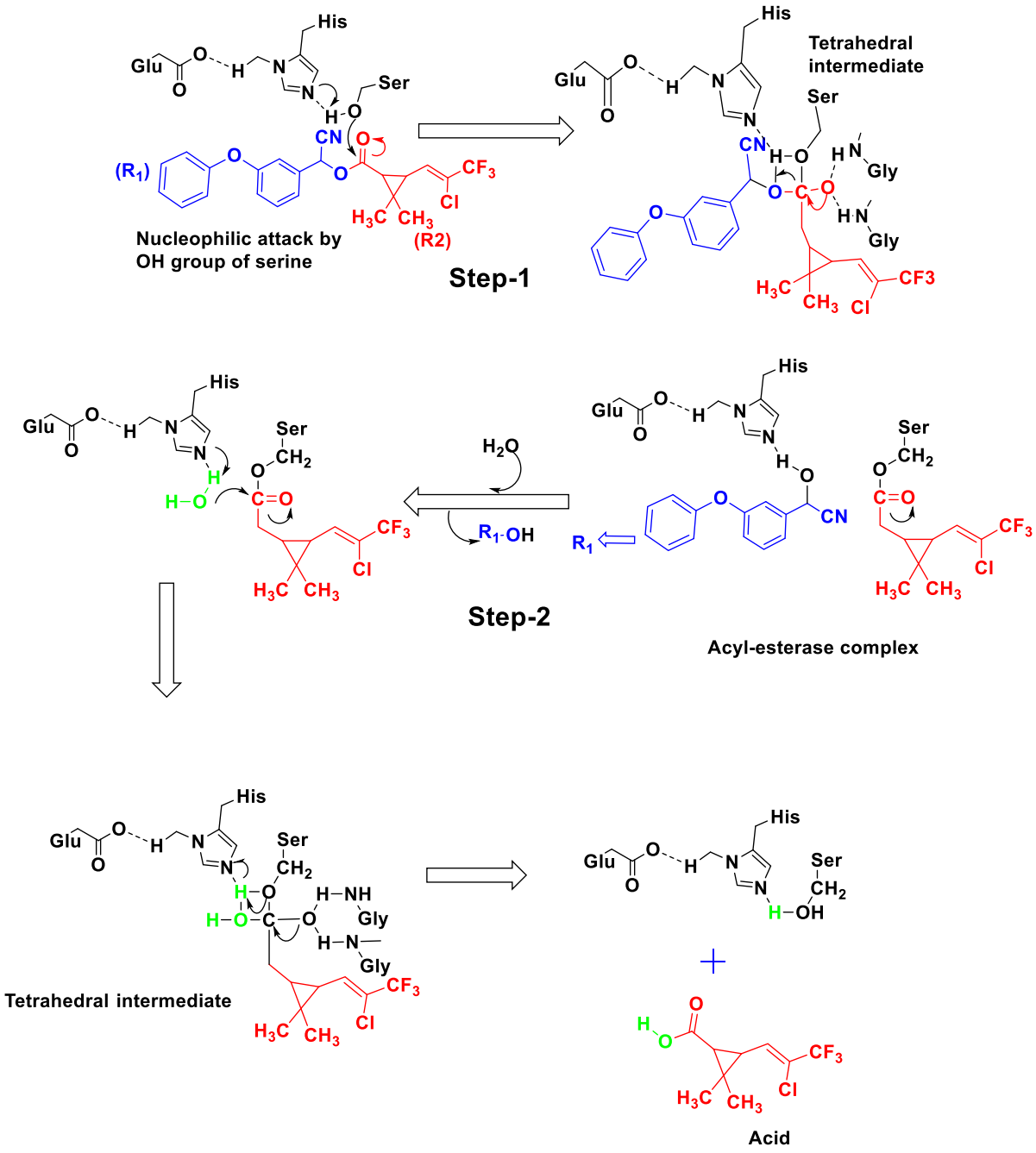

Fig. 2. Detailed catalytic mechanisms of an esterase using the active site amino acid with the ester pesticide (cyhalothrin). Serine (Ser), Histidine (His), Glutamine (Glu), and Glycine (Gly) are participating in two-step catalysis reactions. The hydroxyl group (OH^-) of serine is acting as a nucleophile to attack the ester bond of cyhalothrin. R_1 and R_2 of cyhalothrin are highlighted in blue and red, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increased knowledge regarding esterases from plants, animals and microbes has further shed light on how esterases can be directly used in the bioremediation of OCP group pesticides. Biotechnological techniques, such as heterologous gene expression, enzyme immobilization, and metagenomics as well as other omics technologies have also greatly improved our understanding of the real performance of esterases for the large-scale treatment of OCP pesticides (Rai and Padh, 2001; Rodríguez et al., 2020). However, limited information is available regarding the phylogenetic analysis of esterases, and their role in the degradation of OCP pesticides is still insufficient, so we retrieved and compiled information from various sources to create a better understanding. Here, we discuss OCP pesticides' degrading esterases that have been reported in plants, animals, and microbes, along with their roles and mechanisms in pesticide degradation. We also list different types of authentic literature on esterases that act on the ester bonds of OCP pesticides.

2. The biochemical properties of esterases acting on OCP pesticides

Pesticide-degrading esterases have been investigated for their biochemical properties, such as optimal pH, temperature, inhibitors, molecular weight, and enzyme kinetic parameters (Sharma et al., 2018; Bhatt, 2019; Gangola et al., 2018; Bhatt et al., 2020c; Pandey et al., 2010; Crow et al., 2007; Stok et al., 2004; Wu et al., 2006; Zhai et al.,

2012). The presence of the pyrethroid-degrading esterase was reported in *Bacillus subtilis* with a lower esterase K_m (Michaelis–Menten constant) for the cypermethrin, suggesting that the esterase preferentially used this pesticide during degradation (Gangola et al., 2018). In a similar study, enzyme kinetics and molecular docking analyses were performed to understand the degradation of allethrin with *Pseudomonas nitroreducens* CW7. The results confirmed that allethrin degradation is mediated by bacterial esterases (Bhatt et al., 2020c). In another study, the pyrethroid-degrading esterase was investigated in *Rhodopseudomonas palustris* PSB-S. pH and temperature were optimized as 6.0 and 35 °C for the enzyme Est3385, respectively, which has a molecular mass of 33.94 kDa (Bhatt et al., 2020a; Bai et al., 2019).

The distribution of the carbamate-degrading gene *cehA* and *mcd* was investigated in soil. Oxamyl degradation was studied in 16 different soil samples in Greece. The q-PCR-based study determined the expression pattern of *cehA* and *mcd* in different soil types. The *cehA* gene positively correlated with pH, whereas *cehA* and pH negatively correlated with oxamyl degradation (Rousidou et al., 2017). In the same study, the expression of *cehA* and *mcd* genes were found to be enhanced with carbofuran treatment (Rousidou et al., 2017). The carbamate hydrolase (mcbA) isolated from *Pseudomonas* sp. XWY-1 was able to hydrolyze carbamate pesticides such as carbaryl, carbofuran, isoprocarb, fenobucarb, propoxur, and aldicarb. The active site of mcbA contains the histidine that is crucial for the catalysis (Zhu et al., 2018).

Biochemical characterizations of the carbendazim-degrading esterase have been reported for *Nocardioides* sp. strain SG-4G. This enzyme contains a 242 amino acid long serine hydrolase and exhibits K_{cat} and K_m values of 160/min and 6.1 μM, respectively, against the pesticide methyl-1*H*-benzimidazol-2-ylcarbamate (Gangola et al., 2018). Carbaryl-degrading esterase (CehA) of *Rhizobium* sp. AC100 (80 kDa) was investigated and the optimized conditions were found to be 30 °C and pH 7 (Hashimoto et al., 2002). Similarly, the biochemical properties of esterases in the degradation of phenmedipham, carbaryl, methyl carbamate, and carbendazim are characterized and listed in Table 1. In a study of carbamate hydrolase, CehA was investigated in *Sphingobium* sp. CFD-1. The amino acid sequences among the CehA presented more than 99% similarity (Jiang et al., 2021). The CehA from a different organism showed conserved amino acids. Enzymatic analysis suggested that catalytic activity (K_{cat}/K_m) of CehA was higher against carbaryl than carbofuran and oxamyl. A point-mutation-based study was conducted to determine the different substrate preferences of the carbamate hydrolase in the environment (Jiang et al., 2021).

Organophosphates degraded by the esterases, such as organophosphate hydrolase, phosphotriesterase, methyl parathion hydrolase, are also reported and characterized on the basis of their biochemical properties. For instance, the phosphotriesterase of *Pseudomonas monteilii* C11 has a molecular weight 19.6 kDa, and can degrade organophosphates most efficiently at a temperature of 37 °C and pH 6.5 (Horne et al., 2002). For the esterase of *P. diminuta* MG, the optimized biochemical parameters are a temperature of 37 °C, pH 8.0, and molecular weight of 34.41 kDa (McDaniel et al., 1988; Harper et al., 1988). The pH, temperature, and substrate concentration affect the organophosphate hydrolase activity (Harper et al., 1988).

The activities of the esterases on the esters in the pesticides, were compared using thirteen different esterases in wheat, by isoelectric focusing (pH 4–8) against α-naphthyl acetate (Hatfield and Potter, 2012). *Dendrolimus superans* (Lepidoptera), with a molecular weight of 84.78 kDa, contains carboxylesterase, α-naphthyl acetate, and β-naphthyl acetate, and has been used for carboxylesterase bioassays (Cummins et al., 2001). The bacterium *Ochrobactrum anthropi* strain, YZ-1, of activated sludge was studied in the laboratory to determine its carboxylesterase activity. The purified enzyme (PytZ) contained an open reading frame of 609 bp. The optimal temperature and pH for the PytZ were 35 °C and 7.5, respectively. The enzyme was stable at a wide range of pH and temperatures without any cofactors (Zhai et al., 2012). A thermophilic esterase from *B. acidocaldarius,* with a molecular mass of 34 kDa, was found to be monomeric in nature and, based on its substrate specificity and inhibitors, considered to be a B-type esterase (Zou et al., 2014). A high substrate concentration can result in substrate inhibition, which decreases the catalytic rate of esterase and can also inhibit microbial growth rate. In enzyme kinetics, substrate inhibition of growth might be competitive or noncompetitive. Various chemicals such as bisbenzene sulfonamides, benzil, isatin, 1,2-Bis (1*H*-indol-3yl) ethane 1, 2 dione, hyrtiosin B, 1-phenyl 2-pytidinyl ethane 1,2 dione, trifluoroketones, loperamide, and 27 hydroxycholesterols are all considered inhibitors for carboxylesterases (Manco et al., 1998). Para-nitrophenyl ester was the best substrate for the bioassays with K_m and K_{cat} values of 11 ± 2 μmol and 6610 ± 880 /s, respectively. The optimum temperature and pH for this esterase were 70 °C and 7.1, respectively (Zou et al., 2014).

Biochemically tested esterases from calf retina had an optimum pH between 7.5 and 8.0. Substrates *p*-nitrophenol, α-naphthol, *o*-nitrophenol, and tyrosine had the same V_{max} but different K_m values; however, their activities were inhibited by divalent cations and molybdate. Competitive inhibition was obtained with low fluoride concentrations and non-competitive inhibition at high (≥ 20 mM) fluoride concentrations (Lam and Li, 1973). Ferulic acid esterase, with a molecular weight of 31 kDa, was purified and characterized from *Lactobacillus johnsonii,* and its optimal activity was noted at a pH 7.8 and 20 °C. The K_m values for ethyl ferulate (20–60 μM) were higher than those for chlorogenic acid (10–50 μM), demonstrating that the ferulic acid esterase has better catalytic activities and affinities (Kin et al., 2009; Li et al., 2019). The biochemical properties of different esterases suggest that they have different optimal working conditions (e.g., pH, temperature, pesticide concentration, microbial strains, and surrounding physicochemical environment). These parameters are helpful for understanding the functional environments for esterases during ester pesticide degradation. Most of the reported pesticide-degrading esterases acted on substrates at pH 7.0 and temperatures of approximately 30 °C. The optimized degradation conditions are different for various categories of esterases (Cycoń and Piotrowska-Seget, 2016; Wheelock et al., 2008).

3. Catalytic mechanism and classification of esterases acting on OCP pesticides

In recent years, increasing attention has been paid to the application of esterases in the biodegradation of OCP pesticides. Research has focused on the isolation and purification of esterases from plants, animals, and microorganisms; however, there is limited information available about the classification of these esterase enzymes. Esterase classification has only been reported in limited papers and requires more detailed work. The traditional classification was based on enzyme–substrate reactions, whereas the recent classifications are based on biochemistry, structural biology, and omics-based approaches (Punta et al., 2012), the combination of which provides an effective system to classify the esterases and their importance in the degradation of OCP pesticides.

Acetylcholinesterase belongs to the serine hydrolase family of enzymes. The esterases are distinct from other members of the serine family of hydrolases due to the absence of interfacial activation (Mizoi et al., 2020). Pesticide degrading esterases obey Michaelis Menten kinetics, whereas other serine hydrolases need a lower substrate concentration before achieving higher activity. In other serine hydrolases, a hydrophobic domain covers the active site of the hydrolase, due to the interfacial activation (Khan et al., 2017). At the minimum substrate concentration, the active site is accessible, whereas, at higher concentrations, it is not accessible (Rauwerdink and Kazlauskas, 2015). Esterases can also be distinguished from other serine hydrolases on the basis of a pH dependent electrostatic signature, due to which, esterase showed the optimum activity at pH 6–7, whereas other serine hydrolases have shown it at pH 8. Serine hydrolases have diverse folds and enzymatic functions; however, they have common active sites. The catalytic

Table 1
Esterase enzyme reported for OCP pesticides' degradation and its biochemical characterization (MW = molecular weight, Temp = temperature).

Enzymes	Enzyme class	Pesticides/other substrates	Biochemical properties	Sources	References
Phosphotriesterase (HocA)	3.1.8.1	Organophosphate	Temp = 37 °C, pI = 6.5, MW = 19.6 kDa	*Pseudomonas monteilii* C11	(Horne et al., 2002)
Phosphotriesterase (OPD)	3.1.8.1	Organophosphate	Temp = 37 °C, pH = 8.0, MW = 34.41 kDa	*Pseudomonas diminuta* MG,	(McDaniel et al., 1988)
Organophosphate hydrolase (OPD)	3.1.8.1	Organophosphate	No data	*Flavobacterium* sp.	(Harper et al., 1988; Gudla et al., 2019)
Organophosphorous hydrolase (OPH)	3.1.8.1	Chlorpyrifos, diazinon	No data	*Cronobacter muytjensii* GH10	(El-Sayed et al., 2018)
Organophosphorous hydrolase (OPH)	3.1.8.1	Chlorpyrifos, diazinon	No data	*Pseudomonas aeruginosa* GH2NO8	(El-Sayed et al., 2018)
Organophosphorous hydrolase (OPH)	3.1.8.1	Chlorpyrifos, diazinon	No data	*Achromobacter xylosoxidans* GH9OP	(El-Sayed et al., 2018; Gao et al., 2012)
Methyl parathion hydrolase (MPH)	3.1.8.1	Methyl parathion	Temp = 30 °C, pH = 8.0, MW = 36.5 kDa	*Plesiomonas* sp. M6	(Fu et al., 2004)
Methyl parathion hydrolase	3.1.8.1	Methyl parathion	Zn^{2+} containing enzyme	*Pseudomonas* sp. WBC-3	(Dong et al., 2005)
Organophosphate pesticide hydrolase	3.1.8.1	Methyl parathion	Temp = 37 °C, pH = 7.0	*Pseudaminobacter* sp. mp-1	(Zhang et al., 2005, 2014)
Methyl parathion hydrolase	3.1.8.1	Methyl parathion	pH = 7–8, Temp = 30 °C	*Plesiomonas* sp. M6	(Cui et al., 2001)
Carbaryl hydrolase (CehA)	3.1.1.1	Carbaryl	Temp = 30 °C, pH = 7.0, MW = 80 kDa	*Rhizobium* sp. AC100	(Hashimoto et al., 2002)
Phenmedipham hydrolase	3.1.1.1	Phenmedipham	Temp = 30 °C, pH = 6.8, MW = 55 kDa	*Arthrobacter oxydans* P52	(Pohlenz et al., 1992)
Carbaryl hydrolase (CahA)	3.1.1.1	Carbaryl	MW = 52 kDa	*Arthrobacter* sp. RC100	(Naqvi et al., 2009; Hashimoto et al., 2006)
CehA	3.1.1.1	Carbamate	Temp = 30 °C, K_m = 880, K_{cat} = 0.7	*Sphingobium* sp. CFD1	(Jiang et al., 2021)
Carbamate hydrolase	3.1.1.1	Carbamate	Temp = 40 °C, pH = 7.0, K_{cat} = 2.12	*Pseudomonas* sp. XWY-1	(Zhu et al., 2018)
Carbofuran hydrolase	3.1.1.1	Methyl carbamate	No data	*Achromobacter* sp. WM111	(Naqvi et al., 2009)
Carbendazim hydrolase	3.1.1.1	Carbendazim	K_m = 6.1, k_{cat} = 170 min^{-1}, MW = 26.327 kDa	*Nocardioides* sp. SG-4G, *Mycobacterium* sp. SD4	(Gangola et al., 2018; Lei et al., 2017a, 2017b)
Carboxylesterase (EstPS)	3.1.1.1	Cypermethrin; fenpropathrin; fenvalerate; bifenthrin	Temp = 60 °C, pH = 8.0, MW = 68 kDa	*Pseudomonas synxantha* PS1	(Zhang et al., 2017)
Pyrethroid hydrolase	3.1.1.88	Lambda- cyhalothrin, *β*-cypermethrin, deltamethrin, permethrin	pH = 7.5, Temp = 35 °C, K_m = 2.34 mM L^{-1}, V_{max} = 56.33 = nM min^{-1}, no cofactor required	*Ochrobactrum anthropi* YZ-1	(Zhai et al., 2012; Ruan et al., 2013)
Esterase (Est3385)	3.1.1.88	Fenpropathrin	pH = 6.0, Temp = 35 °C, K_m = 0.734 and V_{max} = 0.918	*Rhodopseudomonas palustris* PSB-S	(Luo et al., 2018, 2019)
Permethrinase (hydrolase)	3.1.1.88	*Trans*-permethrin, *cis*-permethrin, racemic-permethrin, β-naphthyl acetate	MW = 61 kDa	*Bacillus cereus*	(Maloney et al., 1993)
Carboxylesterase	3.1.1.1	Cypermethrin	pH = 7.0, Temp = 37 °C, MW = 22 kDa	*Methylobacterium* sp. A-1	(Diegelmann et al., 2015)
Thermostable pyrethroid hydrolase (Sys 410)	3.1.1.88	Cyhalothrin, cypermethrin, sumicidin, deltamethrin, *p*-nitrophenyl acetate, *p*-nitrophenyl butyrate	pH = 6.5, Temp = 55 °C, MW = 30.8 kDa	Soil samples, unclutured microbes	(Fan et al., 2012)
Carboxylesterase	3.1.1.1	Cypermethrin, fenvalerate, permethrin, *p*-nitrophenyl acetate	pI = 5.8, MW = 60 kDa, k_{cat} = 0.12	Mouse liver microsomes	(Stok et al., 2004)
Carboxylesterase	3.1.1.1	Pyrethroids	pH = 9, Temp = 80–90 °C	*Sulfolobus tokodaii*	(Wu et al., 2006; Wei et al., 2013)
Esterase (EstP)	3.1.1.88	Cypermethrin, permethrin, envalerate, malathion, deltamethrin	pH = 7.0, Temp = 30 °C	*Klebsiella* sp. ZD112	(Wu et al., 2006)
Esterase (Est5S)	3.1.1.1	*p*-Nitrophenol butyrate, chlorpyrifos	pH = 7.0, Temp = 40 °C, MW = 40 kDa	Uncultured cow rumen bacteria	(Kambiranda et al., 2009)
α-esterase	3.1.1.1	Malathion	pH = 7, Temp = 30 °C	*Bactrocera dorsalis* (Hendel)	(Li et al., 2017; Wang et al., 2016a)
Cold adapted esterase (Est684)	3.1.1.1	Cyhalothrin; cypermethrin; fenvalerate	Temp = 18 °C, pH = 7.0, MW = 24.97 kDa	Mao-tofu metagenome	(Fan et al., 2017)
Pyrethroid hydrolase (PytH)	3.1.1.88	Permethrin; fenpropathrin; cypermethrin; cyhalothrin; fenvalerate; deltamethrin; bifenthrin	Temp = 50 °C, pH = 7.5, MW = 31 kDa	*Sphingobium* sp. JZ-1	(Wang et al., 2009)
Pyrethroid hydrolase	3.1.1.88	Fenpropthrin, deltamethrin, fenvalerate, cypermethrin, permethrin, cyhalothrin	No data	*Sphingobium faniae* sp. nov.	(Guo et al., 2009)
Pye3	3.1.1.88	Cypermethrin; permethrin; fenvalerate; deltamethrin	Temp = 40 °C, pH = 7.0, MW = 31.5 kDa	Metagenome of vegetable soil	(Li et al., 2008)
Esterase	3.1.1.88	Allethrin; cyphenothrin; permethrin; tetramethrin; cypermethrin; chlorempenthri n; bifenthrin;	Temp = 37 °C, pH = 7.0, K_m = 0.954	Wastewater sludge	(Bhatt et al., 2020c)

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Table 1 (*continued*)

Enzymes	Enzyme class	Pesticides/other substrates	Biochemical properties	Sources	References
PytH	3.1.1.88	Permethrin; fenpropathrin; cypermethrin; fenvalerate; deltamethrin; cyhalothrin; bifenthrin	No data	*Sphingobium faniae* JZ-2	(Xu et al., 2020)

mechanism for most of the serine hydrolases are similar (Baxter et al., 2004).

The same core catalytic machinery of esterases catalyzes different reactions. The α/β hydrolase, containing the catalytic triad Ser-His-Asp, also has the same protein fold and core catalytic machinery that catalyzes the 17 contrasting reactions. The common hydrolyzed reactions

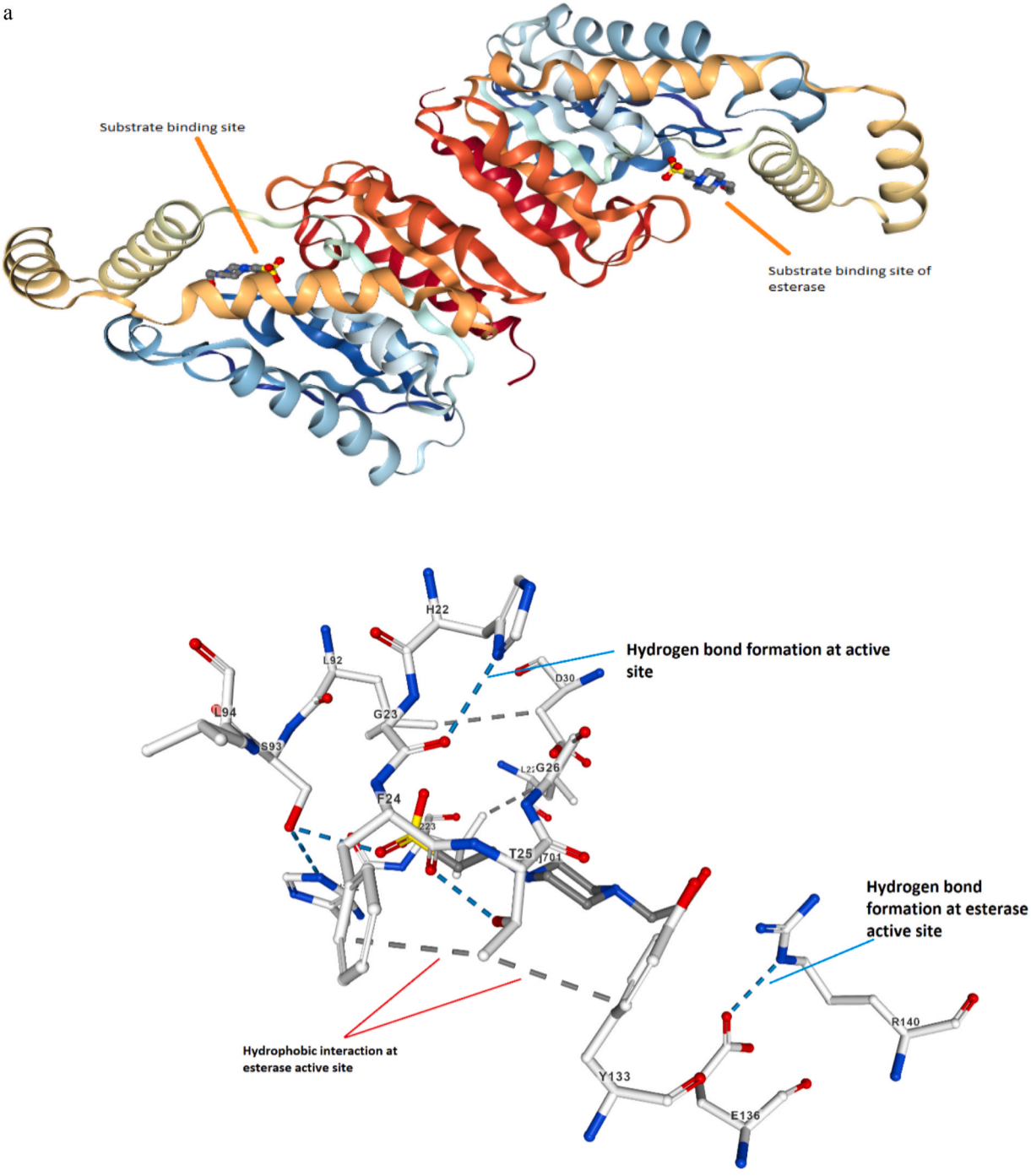

Fig. 3. Carboxylesterase structure and function. (a) A 3D view of the carboxylesterase from *Bacillus stearothermophilus*; carboxylesterase represents the α/β helix in the two subunits and the ligand binding sites on the active sites of the enzyme (Cuff et al., 2004). (b) The protein feature view of the carboxylesterase from *B. stearothermophilus* (PDB, ID-1R1D). (c) The detailed amino acid sequence of Chain-A of carboxylesterase.
The sequences were retrieved from the protein data bank (http://www.rcsb.org/).

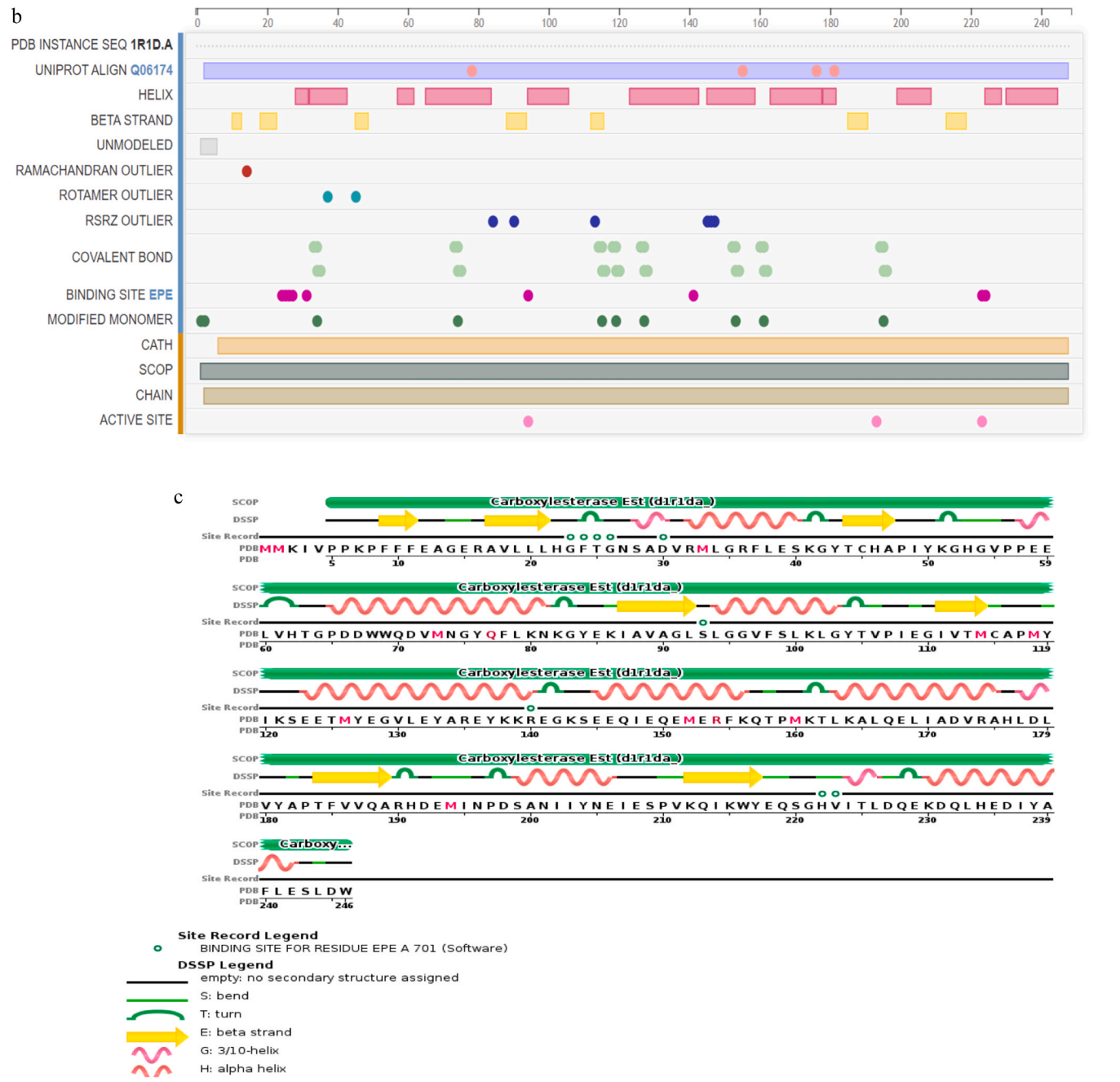

Fig. 3. (*continued*).

involve C–O, C–N, and C–C bonds (Liu et al., 2007). All α/β hydrolase fold enzymes consist of cap or lid domains and catalytic domains. The oxyanion hole is formed by the hydrogen bonds in esterases. The histidine atoms play an important role in the formation of hydrogen bonds, which makes the initial interaction between the active site catalytic triad and OCP group pesticides (Cuff et al., 2004; Udatha et al., 2011) (Fig. 3**a–c**). The lid or cap domain forms the rest of the pesticide binding site (Bhatt et al., 2020b; Baxter et al., 2004). The retrieved sequences of the esterases are helpful for categorizing them into separate groups based on their amino acid sequences (Aldridge, 1993).

Aldridge first gave the classification of the esterases (Bhatt et al., 2019b). Furthermore, according to the International Union of Biochemistry, hydrolases (ENZYME Class 3) are divided into a broad range of categories, among which group I (EC 3.1) consists of esterase enzymes that are able to catalyze esterification and transesterification reactions. As per their substrate specificities, esterases are further classified into several subclasses, among which, the major subclasses include carboxylic-ester hydrolases (EC 3.1.1), thioester hydrolases (EC 3.1.2), phosphoric-monoester hydrolases (EC 3.1.3), phosphoric-diester hydrolases (EC 3.1.4), triphosphoric-monoester hydrolases (EC 3.1.5), sulfuric-ester hydrolases (EC 3.1.6), diphosphoric monoesterases (EC 3.1.7), and phosphoric-triester hydrolases (EC 3.1.8). Nucleases were previously categorized under EC 3.1.4, but are now placed under the new sub-subclasses, such as exonucleases (EC 3.1.11–16) and endonucleases (EC 3.1.21–31) (Table S1). Recently, the nomenclature committee of the International Union of Biochemistry and Molecular Biology (NC-IUMB) further revised the classification of hydrolases (McDonald, 2019).

Carboxylic-ester hydrolases (3.1.1) (CEHs) represent an important group of esterases and can be further classified into multiple sub-classes

with a wide variety of substrate specificities. All CEHs have conserved amino acid sequences (a catalytic triad), indicating that their basic modes of action are highly similar. We have summarized the modes of action for 96 subclasses of the CEHs (Table S2). Importantly, CEHs from different subclasses, as well as other types of hydrolases that can act on ester bonds (EC 3.1), have been reported to function as OCP hydrolases

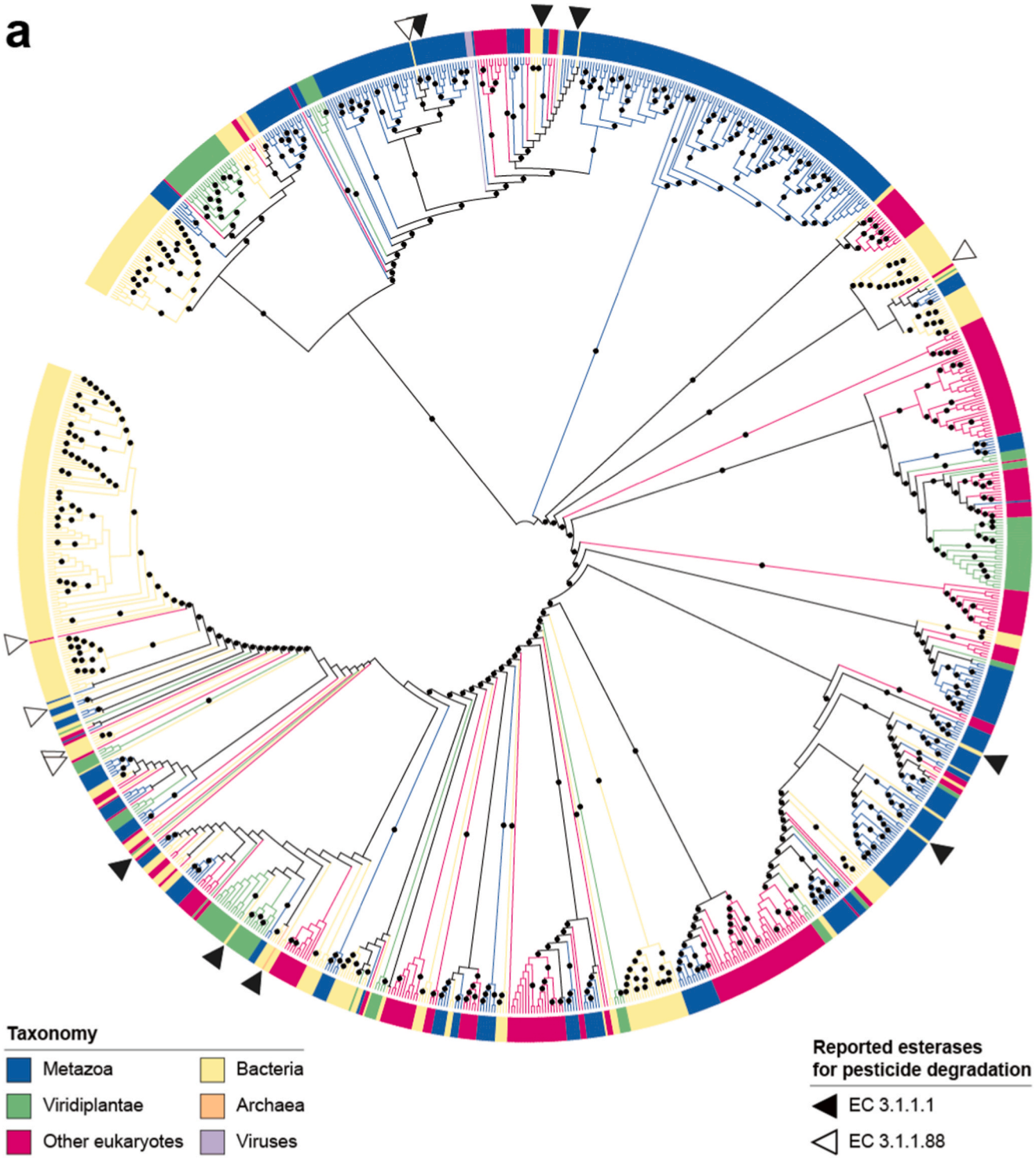

Fig. 4. Phylogenetic analyses reveal complicated relationships between pesticide-degrading esterases and other esterases. (a) The largest cluster resulting from the MCL analysis contains 14 of the 20 reported pesticide-degrading carboxylic ester hydrolases. (b) The third largest cluster resulting from the MCL analysis contains seven of the 10 reported pesticide-degrading phosphotriesterases. The trees were constructed using the Graph Splitting approach, which has been recently shown to have a better performance in the phylogenetic analysis of highly diverged sequences than methods based on multiple-sequence alignment. The reliabilities of branches were evaluated using the Edge Perturbation method with 1000 replicates, and branches with support greater than 90% are highlighted by black dots. Branches are also colored by the taxonomic groups to which each esterase sequence belongs. Previously reported esterases with functions in the degradation of ester-containing pesticides are indicated by black triangles in the outer most circle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

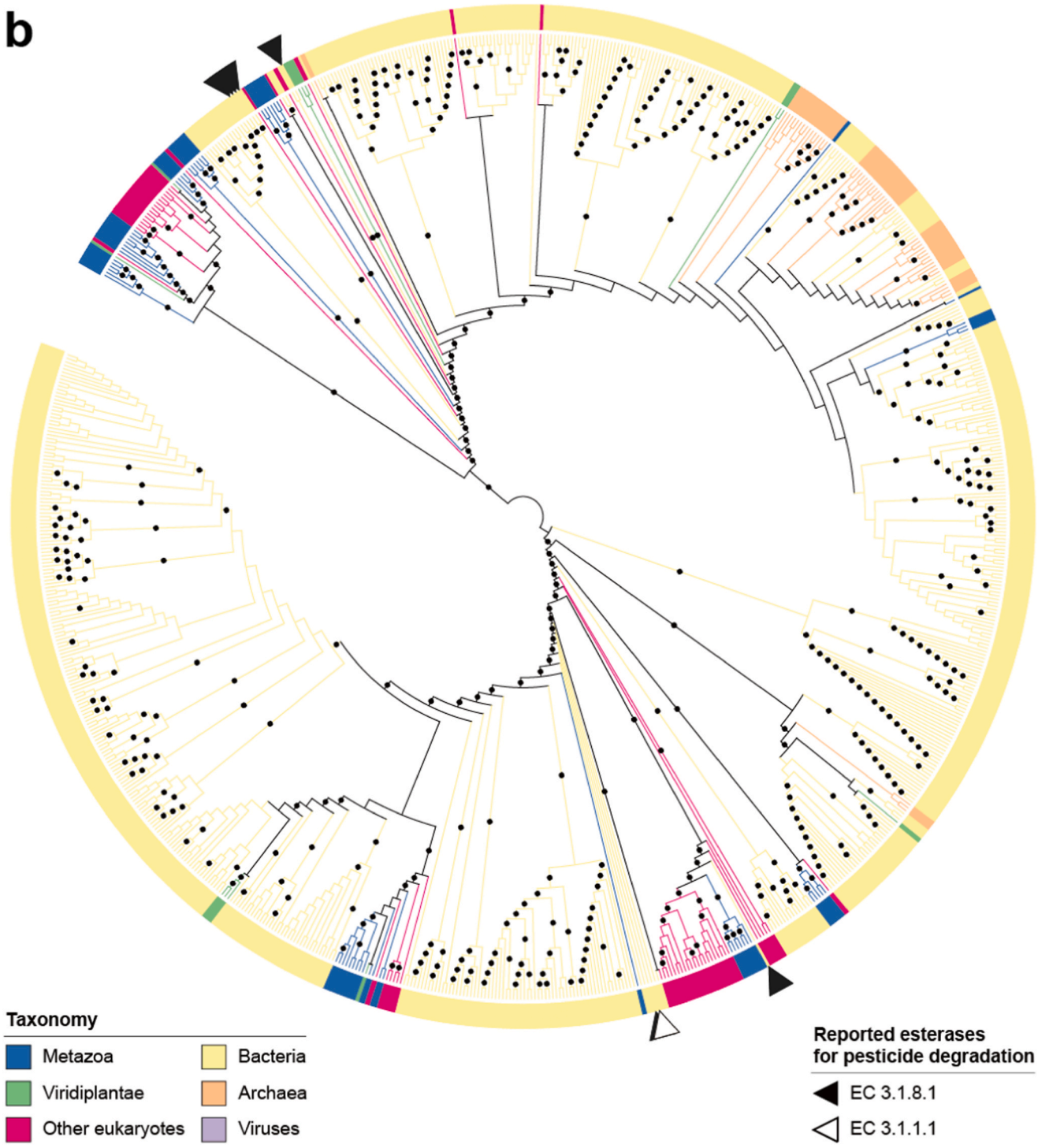

Fig. 4. (*continued*).

(Sharma et al., 2018; Bhatt et al., 2020c; Punta et al., 2012; Han et al., 2012; Kuipers et al., 2010).

To further illustrate this point, we have examined the relationships between the reported esterases for pesticide degradation and other esterases. To that end, we retrieved, from the Swiss-Prot database, a total of 20,799 protein sequences corresponding to the class EC 3.1, and also collected, from the literature, 30 previously reported esterases involved in OCP biodegradation (Table 1). all-against-all sequence comparisons of the above-mentioned esterases were conducted using BLASTP, followed by a similarity-based sequence clustering using the Markov Clustering algorithm, MCL, with a low inflation value (I=1.2), which favors coarse-grained clustering. This clustering analysis resulted in 348 clusters that share no or very low levels of sequence similarity between each other and differ greatly in their domain compositions.

The 30 reported esterases for pesticide degradation were distributed in eight different clusters, indicating that they have highly diverse origins. Importantly, 14 of the 20 CEHs were classified in the largest cluster with 1030 sequences, whereas seven out of 10 phosphotriesterases were found in the third-largest cluster, with 823 sequences. We then carried out phylogenetic analyses of each cluster, respectively, to further investigate their evolutionary histories. Both phylogenies in Fig. 4**a** and **b** showed that the reported esterases for pesticide degradation were

scattered in a number of separate, well-supported clades that contain both eukaryotic and prokaryotic sequences. The results again suggest that the esterases with functions in the biodegradation of ester-containing pesticides may have evolved multiple times from different ancestral esterases or due to other mechanisms, such as horizontal gene transfer (Raymond et al., 1998).

At the same time, esterases can be classified using a superfamily-based approach, which defines superfamilies on the basis of structural and sequence similarity. The database 3DM (ABHD) has proven to be suitable for the recruitment of esterases, as per their similarity after their amino acid alignments, this approach is helpful to understand the rational modifications in proteins. The 3DM information system collects, combines, and integrates multiple different types of data. It can automatically build an entire molecular class-specific information system (MCSIS) (Udatha et al., 2011; Aldridge, 1993). Another classification of pesticide-degrading esterases is based on the mode of interaction between enzymes and organophosphate molecules (diethyl-*p*-nitrophenyl phosphate or paradox) and categorizes esterases into three types, namely Est-A, Est-B, and Est-C. Est-A esterases hydrolyse organophosphates, Est-B esterases are inhibited by organophosphates, and Est-C esterases do not interact with the organophosphates. It was observed that Est-A esterases hydrolyse organophosphates more rapidly than do Est-B esterases (Kin et al., 2009; Romano et al., 2015; Chang et al., 2004).

4. Heterologous expression of esterases acting on OCP pesticides

Reliable, rapid, and informative assays such as genomic, metagenomic, and protein-engineering-based methods are prerequisites for the screening of new esterases (Romano et al., 2015). Recent developments in high-throughput sequencing technologies have allowed whole genomes of the microorganisms to be determined effectively, which enables genomewide identification of esterases. Furthermore, the metagenomic approach can reveal the enormous reservoir of metabolic diversity in the entire microbiota. Therefore, it can help to identify the enzymes that are directly responsible for the catalysis of pesticides, and these can subsequently be cloned from the metagenomic library for further examination (Ferrer et al., 2015). Enzymatic screening of the metagenome library is advantageous to mine the new enzymes' activities and discover the novel amino acid sequences not reported earlier, and it has been shown to be helpful for the discovery of carboxylesterases (Popovic et al., 2017). Biochemical and structural analyses of these enzymes have uncovered different molecular mechanisms and adaptations in extreme environmental conditions (Ferrer et al., 2016). Protein engineering tools are also helpful in the discovery of the esterase and enhancement in their catalytic activity (Lutz and Iamurri, 1685).

Rapid advancements in recombinant DNA (rDNA) technology have facilitated the extraction and cloning of the genes that encode for esterases from microorganisms, plants, and animals to facilitate their study and expression in suitable microbial systems for large-scale applications. rDNA technology is advantageous for producing OCP-degrading enzymes on a large scale. These enzymes can be produced heterogeneously in microbes. Direct application of these enzymes to contaminated sites could be an effective method to remove OCP pesticides. Esterases that can degrade different groups of pesticides have been identified heterogeneously in bacterial systems (Bhatt et al., 2020c; Bhatt et al., 2019b). The use potent esterases for the large-scale removal of environmental contaminants is a promising approach; however, ethical concerns about the use of rDNA have also been raised in the last decades (Thompson, 2020). These genetically engineered microbes may affect the indigenous environmental microbial communities. For instance, a transferred gene can alter the natural state of organisms through transgene expression.

Recombinant esterases can also be used as tools to detect traces of OCP in the environment, and the esterases of animals and plants expressed in suitable expression systems can be used as molecular probes (Reiter et al., 2000; Panda and Gowrishankar, 2005; Rosano and Ceccarelli, 2014; Liu et al., 2017). Previously, researchers have expressed esterase genes in bacterial genera with strong promoters. *Escherichia coli* is used commonly in laboratories for the heterologous expression of esterases, as it is easy to handle (Rai and Padh, 2001; Naqvi et al., 2009). Microbes other than *E. coli* can also be used for heterologous esterase production, such as *S. cerevisiae*, *Pichia pastoris*, and other yeasts (Jain et al., 2019). For the discovery of new esterases, a number of liquid and solid assays have been developed.

The esterase assays based on the substrate specificity, (meta-) genomic approaches, protein engineering, and the development of molecular probes are useful for discovery of new esterases (Jain et al., 2019). For instance, a novel esterase gene (*estI*) of *Lactobacillus casei* CL96 was amplified using polymerase chain reaction (PCR) and expressed in different microbial systems (*Escherichia coli*, *Methylobacterium extorquens*, and *P. pastoris*) with strong promoters. The activity of the esterase was monitored with *p*-nitrophenyl caprylate (Choi et al., 2004). The discovery of novel esterases for the degradation of OCP pesticides will be useful for exploring the mechanism and application used to clean the contaminated environment.

The carboxylesterase gene of *Alicyclobacillus tengchongensis*, which encodes 513 amino acids with a molecular weight of 57.82 kDa, was cloned and expressed in *E. coli* BL21. The amino acid sequence of this enzyme showed a high similarity with serine hydrolases and its active site contains serine, glutamine, and histidine (Ser204, Glu325, and His415). The optimum activity of the purified enzyme was obtained with β-naphthyl acetate at pH 7.0 and 60 °C. It was found that one unit of the enzyme hydrolyzed 50% of the 5 mg malathion in 25 min and 89% after 100 min. These results show that this enzyme could be utilized for malathion detoxification in contaminated environments (Xie et al., 2013).

Heterologous gene expression is useful for transferring the desired genes in microbial strains, plants, and animals, and the stability of the synthesized proteins in microbial systems can be enhanced by post-translational modifications (Bhatt et al., 2020b). For instance, heterologous expression, posttranslational modification, and genetic engineering of the *opd* gene was conducted on *Flavobacterium* sp. ATCC 27551 and *P. diminuta* (Harper et al., 1988). The esterase, Est5s, from the rumen bacteria of a cow was explored using metagenomic approaches and expressed in yeast (*Pichia pastoris*) to demonstrate its hydrolytic activity against organophosphates. Random mutagenesis in *Pichia pastoris* showed high catalytic mechanisms in response to the pyrethroids (Liu et al., 2017). The *est5S* gene has been cloned and expressed with yeast for the large-scale production of recombinant esterases. The nucleotide length of the recombinant Est5s esterase gene was 1098 bp, and that codes for 366 amino acids, with a molecular mass of 40 kDa. High level heterologous expression was observed with *Pichia pastoris* (4.0 gm/L) at an optimal temperature of 40 °C, at pH 7.0. The enzyme Est5s, was able to degrade chlorpyrifos (100 mg/L) and other organophosphates, such as cadusafos (CS), coumaphos (CM), diazinon (DZ) fonofos, ethoprophos (EP), fenamiphos (FM), methyl parathion (MPT), and parathion (PT), by up to 68%, 60%, 80%, 40%, 45%, 60%, 95%, and 100%, respectively (Wei et al., 2013).

Organophosphate hydrolase can be used as a biosensor for residual pesticide detection. It acts on a wide variety of chemical bonds such as P–F, P–O, P–S, and P–CN, and performs the reaction via electrochemical, optical, magnetoelastic, and surface plasmon resonance methods (Jain et al., 2019). Parathion hydrolase was used for the hydrolysis of the triester linkage of the organophosphate pesticides. For instance, the *opd* gene of *Flavobacterium balustinum*, which encodes a parathion hydrolase, was cloned and expressed in *E. coli* strain BL21. This enzyme needs posttranslational modifications, and the process was investigated with expression patterns. The outer membrane protein OmpF is expressed in the periplasmic space of *E. coli,* and correlated with *opd* gene expression. The histidine-tagged parathion hydrolase of *Flavobacterium balustinum* was used to study the posttranslational modification in *E. coli*. Phosphate

metabolism is linked with parathion hydrolase production in *E. coli*. Parathion hydrolase is an immature protein with a 29 amino acid signal sequence, which works efficiently after posttranslational modification. Terminal signal sequence and regulatory proteins accelerate the secretion of parathion hydrolase. Parathion hydrolase showed 100% similarity with the OmpF protein. These findings suggest that parathion hydrolase and phosphate metabolism might be linked to each other (Siddavattam et al., 2006). The carboxylesterase coding gene, *CaE B1*, was associated with insecticide resistance in mosquitoes and was expressed in *E. coli*. Western blotting, a proteinase accessibility assay, and immunofluorescence microscopy were used to determine the expression patterns of CaE B1 on the surface of *E. coli* cells (Zhang et al., 2004). Green fluorescent protein (GFP) fusion assays were also used to study the organophosphate detoxifying hydrolase gene (Brander et al., 2016; Kang et al., 2002; Lee et al., 2016). To increase the production of the organophosphate hydrolase coding *oph* gene during the experiment, anti-GFP and anti-OPH (two copies) were used, and higher yields were obtained in the western blot analysis as compared to the one copy fusion, whereas lower yields were noted with the two copies of OPH without the GFP (Wu et al., 2001).

Carbamate-degrading genes from the microbiome of the bovine rumen microbes were characterized by metagenomics. Cloning and sequencing revealed that the novel carboxyl ester hydrolase belongs to the lipolytic family IV of the esterases (Ufarté et al., 2017). The heterologous expression of the carbamate hydrolase from *Achromobacter* WM111 was studied in *E. coli*, and the purified enzyme was found to be able to hydrolyze carbamates more efficiently (Naqvi et al., 2009). Heterologous gene expression is important for the degradation of the

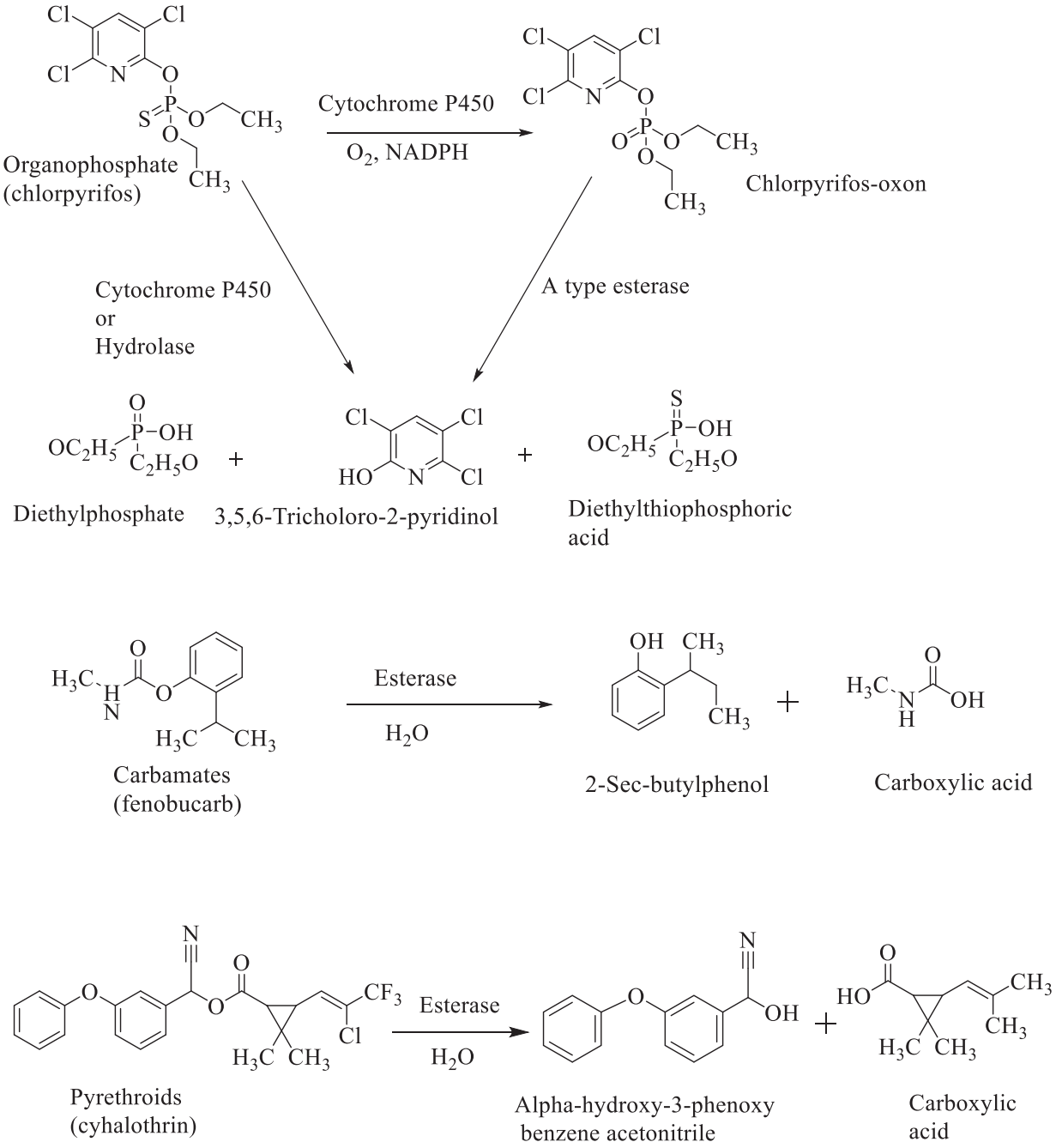

Fig. 5. The biochemical mechanisms of cytochrome P50 and esterases in the degradation of organophosphates, carbamates and pyrethroids (Mishra et al., 2020; Bhatt et al., 2020b; Testai et al., 2010).

OCP pesticides. Mining esterase-coding genes from organisms that are efficient in pesticide degradation is a viable strategy for the rapid removal of toxic pesticides.

OCP-degrading esterases are important for the bioremediation of these group pesticides from the contaminated environments. They are hydrolases that share some common features among microbial strains. The catalytic triad and biochemical features of these enzymes advocate their importance regarding bioremediation. Previous researchers identified and characterized novel esterases using genomic, metagenomic, and proteomic approaches. These data suggested the application of esterases as a promising candidate for the remediation of OCP pesticides. Purified sequenced esterases can be applied in various industrial and environmental applications. Future research on their inhibitors, cofactors, and substrates could explore the depth of their biochemistry and applications for cleaning the environment (Rodríguez et al., 2020).

5. Applications of esterases acting on OCP pesticides

OCP pesticides affect both target and non-target species. Hydrolysis, oxidation, and photolysis are the principal modes of degradation for man-made compounds (Romano et al., 2015), and these processes are facilitated by microorganisms and by chemical and physical processes. Microbial degradation is the natural conversion of toxic xenobiotics into non-toxic products, and microbial enzymes are the cause of all pesticide conversion processes (Bhatt et al., 2021b; Zhang et al., 2021). Microbes produce several types of esterases that detoxify ester-containing pesticides and other compounds with similar (Chen and Zhan, 2019; Bhatt et al., 2020c) (Fig. 5).

Bioremediation of toxic pollutants using enzymes is more efficient when compared to other chemical methods, as the enzymes are produced by potentially degrading microbes (Smith et al., 2016; Tang et al., 2009). During bioremediation, intracellular and extracellular enzymes participate in catabolic reactions. Esterases belong to the hydrolase family, which has several subfamilies, and is possibly the largest in enzymology. Esterases are considered regulatory enzymes as they catalyze the first step in many OCP pesticide degradation (Bhatt et al., 2020c; Diegelmann et al., 2015; Han et al., 2012). They also have broad substrate specificity, with flexible active sites and strong affinities for various substrates (Diegelmann et al., 2015; Han et al., 2012).

The organophosphates and pyrethroids are mineralized through the hydrolysis of phosphoester and carboxylester bonds, respectively (Pandey et al., 2010; Liu et al., 2015; Yang et al., 2018; Chen et al., 2014; Singh et al., 2012a, 2012b). Organophosphate pesticides contain phosphorous groups as phosphonate and phosphate esters. These chemical bonds are cleaved due to the enzymatic actions mediated by esterases. The active site of the enzyme plays a crucial role in the degradation of these pesticides. There are sequential reactions in the microbial degradation of ester-containing pesticides, include hydrolysis, oxidation, alkylation, and dealkylation (Singh and Walker, 2006). Hydrolase enzymes are frequently reported to contribute to the hydrolysis of organophosphates, carbamates, and pyrethroids, due to their cleavage of the ester linkage. There have been esterases isolated from mutant target species (*Lucilia cuprina*) that have developed pesticide resistance (Newcomb et al., 1997). A large number of aliphatic and aromatic esters are hydrolyzed by carboxyl esterases (Chen et al., 2013, 2015; Xiao et al., 2015; Zhan et al., 2018a).

Most of the esterase properties reported have been from mammalian and insect cells, and there have been limited investigations into microbial cells (Iwamura et al., 2012; Kakugawa et al., 2015). Microbial cells (bacteria and fungi) produce extracellular and intracellular esterases (Yoshida et al., 2016; Felux et al., 2015; Liang et al., 2005). Contrasting molecular weight esterases have been found in *B. subtilis* (Meghji et al., 1990). Different types of esterases have been reported in microbial species, such as *Pseudomonas* sp., *Bacillus* sp., and *Saccharomyces* sp. Esterases of *B. subtilis* NRRL 365 that were inhibited by mercuric chloride, were similar to *Saccharomyces cerevisiae*, *B. subtilis* spores, *Pseudomonas* sp., and *P. cepacia*. Esterases from *B. subtilis* NRRL365, were reported as nonspecific carboxylesterases (Meghji et al., 1990; Gai et al., 2012). In insects, esterases showed resistance towards ester-containing pesticides, due to mutations. Esterases are also important in other medical areas, due to their involvement in breaking down vectors and pest controlling chemicals (Xiao et al., 2015; Akbar et al., 2015; Chen et al., 2011c; Li et al., 2009; Nauen, 2007). Metagenomic approaches have been used by researchers for the identification of the potential degrading esterase from the environment (Ferrer et al., 2015). Furthermore, these degradation-specific genes/proteins could be used as molecular markers for identification of the degradation-specific potential microbial strains.

5.1. The role of esterases in the degradation of organophosphates

Organophosphates contain a phosphorous atom and a characteristic phosphoryl bond (P=O) or thiophosphoryl bond (P=S). These groups of chemicals are esters of phosphoric acids that have a variety atoms in combination with them, such as oxygen, carbon, sulfur, or nitrogen (Fig. 1**a**) (Gupta, 2006). Organophosphate-degrading hydrolases have been reported in mammalian cells, due to the surrounding exposure in the environment (Sogorb and Vilanova, 2002). Esterases help to protect cells from the toxic effects of organophosphates (Bai et al., 2019; Rauwerdink and Kazlauskas, 2015).

Table 1 lists the esterases, with respect to their organophosphate pesticide degradation. Organophosphate catalyzing esterases are divided into two categories (i) organophosphate inhibitory esterases (B-esterases) and (ii) organophosphate hydrolyzing esterases (A-esterases) (Walker, 1993). Organophosphate hydrolase, phosphotriesterases, and methyl parathion hydrolase are the main detoxifying enzymes for organophosphates (Kumar et al., 2018; Cui et al., 2001). Insect resistance is mediated using the hydrolases that can hydrolyze the organophosphates and neutralize their effects. In a study on cotton bollworm, it was found that *Helicoverpa armigera* (Hubner) damages cotton and other summer crops in Australia and is widely managed with insecticides. It was noticed that *H. armigera* has a long history of insecticide resistance against organophosphates. The insecticide resistance in *H. armigera* mediated via the esterases belongs to the hydrolase group of the enzymes (Latif and Subrahmanyam, 2010b; Gunning et al., 1996; Yuan et al., 2015).

Organophosphate pesticides with esters or thiols are derived from phosphoric, phosphonic, or phosphoramidic acids. Organophosphates exhibit toxicological effects via non-reversible phosphorylation of the esterases in the central nervous system and inhibit acetylcholinesterase. Inhibition of acetylcholinesterase causes overstimulation of the nicotinic acid and muscarinic acetylcholine receptors. Organophosphates are mainly detoxified through hydrolysis and oxidation mechanisms by esterases (Sogorb and Vilanova, 2002). Heterologously expressed esterases have been reported to degrade organophosphorus more rapidly, as compared to the normal esterases.

A metagenomics approach was utilized to extract cow rumen bacterial esterases by expressing them in a yeast system (*Pichia pastoris*). The expressed esterase enzyme gene was 1098 bp and encoded 366 amino acids, with a molecular weight of 40 kDa (Ferrer et al., 2015). A study was conducted on a *Helicoverpa armigera* strain (MonoR), by collecting 15 generations from fields that showed high levels of resistance to monocrotophos (Ferrer et al., 2015). It was concluded that the esterases played a major role in the organophosphate resistance (Han et al., 2012).

A twenty-one-fold higher resistance was observed against the organophosphate insecticide malathion, in the fruit fly *Bactrocera dorsalis*. A study with the triphenylphosphate (TPP) carboxylesterase inhibitor in a synergism bioassay revealed the presence of carboxylesterase in the resistance mechanisms of *B. dorsalis*. Furthermore, an esterase coding gene, BdCaE2, was found to be involved in the resistance towards malathion (Wang et al., 2016b). The

organophosphate hydrolase presents in living cells, and its expression can be upregulated or downregulated in the presence of this group of pesticides. As the main applications of the pesticides are to control insect pests, there have been various esterases that were isolated and characterized from insect cells.

5.2. Role of esterases in carbamate degradation

Insecticidal carbamate compounds are derived from carbamic acid, which exhibits a wide range of biocide activities. Unlike organophosphates, carbamates are not structurally complex, but their toxicity is similar to that of organophosphates (Fig. 1**b**). The only difference is that the phosphorylation of the serine is non-reversible, whereas carbamylation of the same serine residue is less stable. Previously, it was confirmed that carboxylesterase detoxifies carbamates by hydrolyzing ester bonds (Sogorb and Vilanova, 2002; Negi et al., 2014; Yang et al., 2011; Miyamoto et al., 1969). Carbamate biodegradation pathways have been reported by various researchers (Lin et al., 2020; Yang et al., 2011).

The enzymes belonging to P450 monooxygenases, glutathione S-transferases, carbamate hydrolases, and carboxylesterases mainly contribute to the detoxification of carbamates (Ndiath, 2019; Russell et al., 2011). Carbamate resistance in *H. armigera* has been reported in cotton fields and linked to the carbamate-hydrolyzing esterase (Bai et al., 2019; Gunning et al., 1996). Phenylcarbamate hydrolase, which is able to degrade phenylcarbamate, was purified from the bacterium *Arthrobacter oxydans* P52. The discovered enzyme is a monomer with a molecular weight of 55 kDa. The gene (41 kb) encoding phenylcarbamate degradation was located in the plasmid (pHP52) of the *A. oxydans* P52. The partial amino acid sequence was documented after cloning and expression in *E. coli* (Pohlenz et al., 1992). The *N*-methylcarbamate hydrolase enzyme from *Pseudomonas* strain CRL-OK, which hydrolyses the carbamate linkage of carbaryl, was identified and purified (Mulbry and Eaton, 1991).

Engineered *Pseudomonas putida* is able to degrade carbamate pesticides (Gong et al., 2018). Methyl-carbamate-degrading hydrolase was isolated and purified from *Achromobacter* WM111 and it was found to catalyze the hydrolysis of carbaryl, α-naphthyl acetate, and phosphotriester. The enzyme was found to be resistant to solvents and thermal denaturation (Naqvi et al., 2009). The carbaryl hydrolase genes *cehA* and *cahA* were detected with *Rhizobium* and *Arthrobacter*, respectively (Rousidou et al., 2017). The *CehA* gene was also reported in *Pseudomonas* and *Novosphingobium* (Nguyen et al., 2014; Rousidou et al., 2016). The *CehA* and *mcd* genes were mainly encoded for the carbamate hydrolase enzyme. The oxamyl degradation role of the carbamate hydrolase genes *cehA* and *mcd* has previously been documented (Rousidou et al., 2016). Carbofuran-degrading hydrolase, CehA, has been reported from the *Sphingobium* sp., strain CDS-1 (Yan et al., 2018). Recently, AmeH, a carbamate C–N hydrolase, was investigated in the degradation of the methomyl in *Aminobacter aminovorans* MDW-2 (Jiang et al., 2021). It was concluded that the carbamate group of pesticides is mainly degraded by hydrolases. The application of such enzymes to contaminated sites might be beneficial to decontaminate carbamates in the environments.

5.3. Role of esterases in pyrethroid degradation

Synthetic pyrethroids were developed from the natural pyrethrum insecticide to improve the specificity and activity (Fig. 1**c**). Esterases play important roles in pyrethroid degradation by cleaving the ester bond (Bhatt et al., 2020d). Based on the structure, pyrethroids are divided into two categories, as Type I and Type II (Bhatt et al., 2020b). Type II pyrethroids contain an α-cyano group that is not present in Type I (Bhatt et al., 2020e). Pyrethroids are neurotoxic and bind with Na^+ channels to cause prolonged openings (Chen and Zhan, 2019). Pyrethroid pesticides are also degraded by esterases, as documented for the carbamates and organophosphates. Pyrethroid hydrolase is able to split into esters, acid, and alcohol, with water (Hu et al., 2019). Esterases of insect, animals, plants, and bacteria can easily hydrolyze pyrethroids from the target sites.

Insect esterases are responsible for the resistance toward pyrethroids. Esterases of *Spodoptera littoralis* larval homogenates were tested against α-naphthyl acetate, β-naphthyl acetate, and *p*-nitrophenyl acetate (Shankarganesh et al., 2012). These esterases are responsible for the *S. littoralis* resistant strains. Insect esterases are highly polymorphic enzymes and have broad substrate specificity. Esterases are responsible for various forms of insect resistance (*Culex* and *Anopheles* mosquitoes). Increased esterase activity against fenitrothion and deltamethrin has been found in the Guatemalan *A. albimanus* (Brogdon and Barber, 1990). Esterases of milkweed bugs, houseflies, mealworms, cabbage loopers, and mouse livers hydrolyzed (+) *trans* and (+) *cis* forms of resmethrin and tetramethrin; however, were unable to hydrolyze the S-bioallethrin. The *trans*-isomer was rapidly cleaved by the milkweed bug, looper, and mouse esterases.

Pyrethroid-degrading esterases were less active in insects as compared to mouse liver (Meghji et al., 1990). *H. armigera* (Hubner) is resistant to pyrethroids and three modes of pyrethroid resistance mechanisms have been reported for this pest: (i) nerve insensitivity; (ii) reduced pyrethroid penetration through the cuticle; and (iii) piperonyl butoxide synergid factors (Latif and Subrahmanyam, 2010b; Gunning et al., 1996; Yuan et al., 2015). Hydrolysis of the pyrethroid esters is a major detoxification route that enhances insect resistance. Resistant Australian *H. armigera* showed approximately 50-fold higher esterase activity, as compared to susceptible insects. Pyrethroid esfenvalerate resistance is correlated with α-naphthyl acetate. Three esfenvalerate metabolites, 3-phenoxybenzaldehyde, 3-phenoxybenzyl alcohol, and 3-phenoxybenzoic acid, were found during the degradation (Bai et al., 2019; Gunning et al., 1996).

The *Marietta* strain of the German adult male cockroach exhibited five-times higher resistance to cypermethrin as compared to the susceptible *Orlando* strain. Decreased cypermethrin resistance was observed after S,S,S-tributylphosphorotrithioate pre-treatment, which confirms the role of the esterases in insect resistance. Microbial esterases of the *Marietta* strain rapidly metabolized cypermethrin (15.4 ± 1.1 pmol/h/mg) when compared to the *Orlando* strain (12.5 ± 0.2 pmol/h/mg). The activity of the purified esterases from the microsomal cells was confirmed by using the α-naphthyl acetate as a substrate, at the rate of 25.5 μmol/min/mg of the microsomal esterase *Marietta* (MErar). Male cockroaches of the Marietta strain showed five-fold resistance to cypermethrin compared to the susceptible Orlando strain. Cypermethrin metabolization by MErar, at a rate of 3461 pmol/min/mg protein, showed 225-fold increased activity compared to the microsomal cells. The molecular weight of MErar was calculated to be 57 kDa by SDS-PAGE and 64 kDa by gel filtration chromatography, indicating that it is a monomer esterase. MErar inhibition by paraoxon and phenyl methyl sulfonyl fluoride indicated it to be a B-type serine esterase. In the normal condition (susceptible Orlando strains), cypermethrin metabolization was lower compared with the resistant strain (Valles and Strong, 2001). To know the effects of the permethrin on the α-esterase in *Aedes aegypti*, mosquitoes were collected from the different zones of the Baja California Peninsula. Ten groups of 90 *Aedes aegypti* females were used in the study, and permethrin exposure resulted in elevated levels of α-esterase (Flores et al., 2005).

Mechanisms of the pyrethroid resistance that were reported in *H. armigera* included enhanced metabolism, nerve insensitivity, and low penetration. Increased esterase activity has also been reported in *Helicoverpa zea*, *Spodoptera frugiperda*, *Agrotis ipsilon*, *Trichoplusia ni*, and *Blattella germanica* (Latif and Subrahmanyam, 2010a). Increased midgut esterase activity was found in the pyrethroid resistant strain of *H. armigera*, whereas no esterase activity was found in the susceptible strains of *H. armigera*. We can use the higher catalytic potential of midgut esterase for large-scale applications via heterologous gene

expression (Flores et al., 2005). The strains of *H. armigera* from Nagpur and Delhi exhibited 2.24- and 1.73-fold higher esterase activity, as confirmed using the native PAGE. The synergists piperonyl butoxide and dihydrodillapiole act as inhibitors for the esterase enzyme. The effect of a *Bacillus thuringiensis* (Bt)-based product (Vectobar) on esterases and phosphatases of the *Aedes aegypti* mosquito larvae has also been studied. A significant reduction in total protein (34%) as well as the activities of acetylcholinesterase and alkaline phosphatase was observed in larvae due to Vectobar. This study concluded that the Bt product Vectobar reduced the esterase activity, which inflicted high mortality on *A. aegypti* larvae (Koodalingam et al., 2012). Pesticide resistance has been reported in *Spodoptera litura* (Fabricius) due to the enhanced levels of esterases, oxidases, and glutathione S-transferases. Dihydrodillapiole reduced *S. litura* resistance against the profenofos, ƛ-cyhalothrin, and cypermethrin.

Esterase activity was determined in *H. armigera* using a multiple plate assay technique that revealed a high degree of resistance towards the deltamethrin. Several Bt-based formulations affected the differential expressions of the esterases and phosphatases in the fourth instar larvae of *A. aegypti* (Montella et al., 2012). Acetylcholinesterase possesses a high catalytic activity, as it facilitates the termination of nerve impulses in insects, by catalyzing neurotransmitters (Montella et al., 2012). The four most important types of insect resistance mechanisms have been reported: point mutations in targeted genes, overexpression or mutations in the genes coding the enzymes, cuticle formation, and behavioral changes (Montella et al., 2012; Ranson et al., 2011; Whalon et al., 2008).

Increased levels of esterase and cytochrome P450 were reported in the presence of the lambda-cyhalothrin in *Aphis glycines* Matsumura. The results indicated a high resistance against chlorpyrifos (11.66-fold), acephate (8.20-fold), cypermethrin (53.24-fold), esfenvalerate (13.83-fold), cyfluthrin (9.64-fold), carbofuran (14.60-fold), methomyl (9.32-fold), and bifenthrin (4.81-fold). These results demonstrated that esterase and cytochrome P450 monooxygenase played critical roles in the development of the resistance against the lambda-cyhalothrin (Xi et al., 2015). Deltamethrin inhibited the permeability of the carboxylesterase 1 in the living cells, and thus confirmed the interaction between the xenobiotics and carboxylesterase1 (Lei et al., 2017b).

Molecular cloning, purification, and biochemical characterizations of the novel pyrethroid hydrolyzing carboxylesterase gene from *Ochrobactrum anthropi* YZ-1 has been documented (Zhai et al., 2012). A novel pyrethroid hydrolase was purified from the cell free extract of *Sphingobium* sp. JZ-2 (Guo et al., 2009). Fenpropathrin served as the preferred substrate for the pyrethroid hydrolase as compared to the other pyrethroids, such as cypermethrin, permethrin, cyhalothrin, bifenthrin, fenvalerate, and deltamethrin (Li et al., 2017). Esterase pytZ was successfully cloned from the genomic library of *O. anthropi* YZ-1, which had an open reading frame of 606 bp and 39–59% homology with other carboxylesterases (Zhai et al., 2012).

A novel carboxylesterase (EstSt7) coding gene was reported in *Sulfolobus tokodaii*. EstST7 showed higher enzyme activity levels at 80 °C over 30 min and had a half-life ($t_{1/2}$) of 180 min at 90 °C. EstSt7 exhibited esterase activity against the substrate *p*-nitrophenyl esters and *p*-nitrophenyl butyrate, and for all pyrethroids (Kambiranda et al., 2009). EstSt7 also hydrolyzed a wide range of synthetic pyrethroids, such as cypermethrin, cyhalothrin, permethrin, fenpropathrin, deltamethrin, and bifenthrin. Based on sequence similarities and phylogenetic analysis, EstSt7 was confirmed as a novel pyrethroid-degrading esterase family of enzymes (Shankarganesh et al., 2012; Wei et al., 2019).

Previously, it has been confirmed that carboxylesterase hydrolyses the ester bond to detoxify the pyrethroids (Miyamoto et al., 1969; Brogdon and Barber, 1990; Liang et al., 2005), and the biodegradation pathway of the pyrethroids has been reported by various researchers (Bhatt et al., 2020c; Chen et al., 2013, 2012, 2011d; Xiao et al., 2015; Zhan et al., 2018b; Pankaj et al., 2016a, 2016b; Lin et al., 2011). P450 monooxygenases, glutathione S-transferases, phosphotriesterases, and carboxylesterases are the main enzymes that detoxify pyrethroid isomers in their environment (Russell et al., 2011). A cold adaptive pyrethroid hydrolase was screened by using a metagenomic approach that showed high esterase activity (Fan et al., 2017). Esterase and laccase in *B. subtilis* facilitate the biodegradation and detoxification of cypermethrin (Bhatt et al., 2020c). Recently carboxylesterase EstA was purified from *Bacillus cereus* BCC01 (Shankarganesh et al., 2012).

Esterases exhibit stereo-selectivity in pyrethroid degradation (Birolli et al., 2018). High enantioselectivity is an important functional property of esterases as biocatalysts (Bhatt et al., 2020c). A structural analysis of esterases suggested that the enantiomer can be stabilized by the π-interaction between the methyl group of the chiral carbon of the pesticide and the aromatic pocket amino acid of the esterase (Ngo et al., 2019). The enantioselectivity is also determined by the reaction kinetics, in which the geometric features of the atoms and groups of the active sites have a different impact on the k_{cat} and K_m for the contrasting substrate (Zhang et al., 2014). The position of the lid or the cap in many esterases affects the enantiomeric forms of the substrate. In the esterases, the cap or lid domains shield the catalytic triad that contributes to the substrate binding (Raymond et al., 1998). Both affinity and stereoselectivity play roles in the substrate binding of the esterases (Pavlova et al., 2009).

6. Conclusions and future prospective

Enzymes are key tools in the biological processing of OCP degradation pathways. Esterases belong to the largest hydrolase family and have been repeatedly reported to be involved in the degradation of OCP pesticides. Owing to the adaptations in the groups of xenobiotics, resistant esterases have evolved in organisms. Mainly, resistance in insect systems has resulted in esterases being less susceptible to pesticides, as resistant esterases play a role in the hydrolysis of ester-containing pesticides. Improvements in genetic engineering techniques have allowed for the rapid use of heterologous gene expression analysis, through which, researchers have cloned and expressed potential esterases from plants and animals into microbial systems.

Heterologous gene expression has shown how esterases are used on a large-scale for the degradation of various pesticides. These steps could be beneficial for understanding pesticide degradation in the environment and the possession of huge application potentials. Due to the universal nature of the esterases in pesticide-degrading microbes, marker genes can be developed from the conserved regions of their genomes, which can be used for large-scale metagenomic studies. These applications will be useful for the identification and characterization of microorganisms that cannot be isolated using culture-dependent approaches. Therefore, metagenomics and other high-throughput sequencing based methods can help fill the gaps among various techniques and thus facilitate the characterization of esterases from various living organisms. In addition, a better understanding of the directed evolution and molecular interactions will enable a more efficient selection of suitable esterases for OCP remediation, leading to a much broader application of esterases in pesticide removal.

The discovered esterases can be used for bioremediation applications for OCP pesticides. By immobilization, esterases can be applied directly to decontaminate OCP pesticides from the environment, having a wide range of substrate specificity. An esterase-based biosensor could be useful for the detection of OCP contamination. The application of esterase in contaminated sites could be more efficient for bioremediation of OCP pesticides than direct use of microbial strains, which would take longer to produce pesticide-degrading enzymes. To apply the esterases efficiently on contaminated sites, future studies are needed to improve their stability in contaminated environments. The combination of *in vitro* and *in silico* tools provides a promising path for developing effective esterase-based remediation of OCP pesticides in the environment.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

All the authors declare that they have no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2020.125026.

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