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Role of Carboxylesterases in Xenobiotic Metabolism and Detoxification: Insights for Cheminformatics Approaches

Sakshi Chaudhary[1,*], Neetu Saharan[1]

Abstract

Xenobiotics, which include a wide range of environmental pollutants, food additives, drugs, and carcinogens, are foreign chemical entities that enter the human body and may accumulate, leading to toxic effects. Phase I and phase II metabolic responses are among the detoxification procedures that are necessary to lessen these negative consequences. This review highlights the pivotal role of carboxylesterases (CES), enzymes involved in the hydrolysis of ester, amide, and thioester bonds in xenobiotics, in the metabolism and detoxification of these substances. We discuss the structural and functional properties of CES, their tissue distribution, and the implications of their activity in drug metabolism and environmental toxin clearance. In the context of cheminformatics, we explore how computational models can assist in predicting CES activity, understanding substrate specificity, and designing drug molecules or inhibitors that modulate CES activity. The information presented here provides valuable insights into both pharmacological applications and environmental health assessments.

Keywords: Carboxylesterases, xenobiotics, detoxification, phase I and II metabolism, cheminformatics, drug metabolism, enzyme modulation

INTRODUCTION

Xenobiotics refer to chemical agents foreign to the normal metabolic pathways of an organism. Ingestion, inhalation, and skin absorption are some of the ways that these substances—which include pesticides, food additives, hydrocarbons, environmental contaminants, and medications—enter the body. The body's natural defense mechanisms, including detoxification, aim to render these substances less toxic and facilitate their excretion.

The metabolism of xenobiotics involves a series of biochemical processes that modify these substances to increase their water solubility, thus enabling their elimination. Usually, this procedure consists of phase I and phase II processes, in which phase I uses oxidation, reduction, or hydrolysis to introduce or unwind new functional groups. Phase II involves the conjugation of these metabolites to hydrophilic groups, enhancing their solubility for easier excretion.

***Author for Correspondence**
Sakshi Chaudhary
E-mail: chaudharysakshi5000@gmail.com

[1]Assistant Professor, Department of Biotechnology, Dr. K.N. Modi Institute of Pharmaceutical Education and Research, Modinagar, Ghaziabad, Uttar Pradesh, India

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Carboxylesterases (CES), members of the serine hydrolase superfamily, play a crucial role in the detoxification of xenobiotics, especially in the hydrolysis of ester and amide linkages. These enzymes are found in many different organs, including the brain, gastrointestinal system, and liver. They catalyze the hydrolysis of ester and amide bonds, producing less toxic metabolites that are easier to excrete. The roles of CES in drug metabolism and environmental toxin detoxification make them vital in both pharmacology and environmental health.

Xenobiotic Metabolism and Carboxylesterase Activity

Xenobiotics are primarily metabolized in the liver, which acts as the central hub for biotransformation. The metabolic process is divided into three phases (Table 1):

- *Phase I* involves the modification of xenobiotics by enzymes like cytochrome P450, which introduces functional groups to increase polarity.
- *Phase II* involves the conjugation of the modified compounds to polar groups such as glucuronic acid, sulfate, or glutathione.
- *Phase III* encompasses the transport of these conjugated metabolites out of the cell for excretion.

Carboxylesterases are involved in Phase I reactions and play a significant role in hydrolyzing ester and amide bonds of xenobiotics. This hydrolysis results in the formation of more water-soluble compounds, which are then conjugated in Phase II for further elimination from the body.

In addition to their detoxification function, CES can activate prodrugs, thus playing a dual role in pharmacological processes. For example, the drug irinotecan, used in cancer treatment, requires CES to hydrolyze it into its active metabolite, SN-38. The specificity of CES towards various substrates, such as drugs, pesticides, and environmental pollutants, is essential for predicting the metabolic fate of these compounds [1–13].

CHEMINFORMATICS AND THE ROLE OF CARBOXYLESTERASES

The integration of computational tools and cheminformatics methods can significantly enhance our understanding of CES function in xenobiotic metabolism. By employing molecular docking studies, quantitative structure-activity relationship (QSAR) models, and enzyme-ligand binding simulations, researchers can predict the interactions between CES and various substrates. These computational approaches enable the identification of key active site residues responsible for substrate specificity and the development of inhibitors or modulators of CES activity Xenobiotics must be eliminated from the body, which can be done in one of two ways: either by excreting the medication in its intact, unmetabolized form or by metabolic biotransformation followed by excretion. Although the kidneys do the majority of excretion, other organ systems are also involved. In a similar vein, although the liver is the main location for biotransformation, extrahepatic metabolism occurs in a number of organ systems and impacts numerous medications.

Table 1. Reactions and enzymes involved in Biotransformation process:

Metabolic reactions		
Phase I	***Phase II***	***Phase III***
• Oxidation with cytochrome P450 (most common) • Reduction • Hydrolysis	• Methylation • Glucuronidation (most common) • Acetylation • Sulfation • Conjugation with glutathione • Conjugation with amino acids (glycine, taurine, and glutamic acid)	• ATP-binding cassette (ABC) • Solute carrier (SLC) transporters
Enzymes involved		
Phase I	**Phase II**	**Phase III**
	• Glutathione S-transferases (GSTs), glutamate cysteine ligase (GCL or γ-glutamylcysteine synthetase), uridine 5′-diphospho-glucuronosyltransferase (UDP), UDP-glucuronosyltransferases (UGTs), sulfotransferases, and nicotinamide adenine dinucleotide phosphate-oxidase:quinone oxidoreductase (NQO)	

Drug removal can involve a great deal of complexity because of the numerous organ systems and the range of metabolic changes that occur. While hydrophobic medications undergo biotransformation prior to excretion, hydrophilic pharmaceuticals are usually eliminated immediately by the kidneys. Biotransformation has two functions in this case: it detoxifies the exogenous chemicals and makes them more hydrophilic so that the kidneys can eliminate them [13].

In the large intestine, poorly absorbed xenobiotics are exposed to the gut microbial metabolizing niche after passing through the small intestine. When released into the bloodstream, metabolites are either eliminated by the kidneys or returned to the gut via the biliary duct. Either excretion in the stool or reabsorption in the small intestine are these metabolites' ultimate fates [11].

Carboxylesterase's and their Existence in Human Body

The multigene group of enzymes known as carboxylesterases, or carboxylic-ester hydrolase, is widely distributed throughout the body of mammals and catalyzes the hydrolysis of esters, amides, thioesters, and carbamates. Widely distributed throughout the body, carboxylesterases (CESs) are most abundant in the liver, gastrointestinal tract, brain, and potentially blood. It has long been demonstrated that CES plays a part in detoxicating a range of medications and environmental pollutants [14]. It has been demonstrated that CES in the gut, liver, and other tissues play a major part in the hydrolytic detoxication of several medications. Furthermore, it has been demonstrated that CES are effective hydrolytic catalysts for several physiologically significant substances, including lipid and steroid esters [15]. Over the past ten years, two major carboxylesterases in the human body—CES1 and CES2—have been identified and extensively researched. The metabolism of several endogenous esters, medications containing esters, and environmental toxins depends heavily on these two enzymes [16]. Essential members of the serine hydrolase superfamily, mammalian carboxylesterases (CES, E.C. 3.1.1.1) are found in the lumen of the endoplasmic reticulum in a variety of tissues [17–19]. As their name suggests, CES catalyze the conversion of numerous structurally varied substrates that contain amides or ester into the appropriate carboxylic acid and alcohol. Indeed, CES plays important roles in both endobiotic metabolism and the activation and/or detoxification of xenobiotics by hydrolyzing ester, thioester, amide, and carbamate bonds in a broad range of endo- and xenobiotic substances [19–21]. Although human carboxylesterase 1 (CES1) and human carboxylesterase 2 (CES2) are the two isoenzymes that have been investigated the most in relation to xenobiotic metabolism, three CES have been found in the human body [22–24]. Both CES1 and CES2 are essential for the metabolism of a wide range of ester xenobiotics, including environmental toxicants like pyrethroids and several ester medications including oseltamivir, clopidogrel, irinotecan, and capecitabine [25–29]. Important physiological roles in maintaining lipid homeostasis are played by these two enzymes, which are also known to metabolize endogenous lipids, such as triacylglycerols, cholesteryl esters, and others [30–34].

The carboxylesterase enzymes used in the studies reported in the previous studies were obtained mainly from the liver of animals that contained the greatest activity of CES. While hepatic enzymes from animals have provided a convenient source of a model enzyme, differences in substrate specificity have prompted researchers to use the human enzyme directly. To provide a direct supply of the enzyme from human sources, carboxylesterase (human esterase D) has been recently cloned and sequenced, and its specific role in detoxication has begun to be examined.

Numerous research conducted in the last 20 years have shed light on the functions of CES in xenobiotic metabolism and metabolic disorders [30]. Finding CES modulators to control lipid metabolism or boost the efficacy of ester medications has garnered a lot of attention due to the crucial functions that CES plays in both endogenous and xenobiotic metabolism [35–40].

The relevance and latest developments in the identification of CES modulators are discussed in this study, along with the structural and catalytic characteristics of CES, tissue distribution, biological functions, substrate specificities, and inhibitor profiles of the two main CES. Pharmacologists will find it highly useful to investigate the connection between CES and human illnesses or to validate CES's

role in xenobiotic metabolism. Additionally, it will help medicinal chemists create more powerful CES inhibitors or inducers or create optimal pro-drugs that can be activated by a specific CES isoform in the human body.

Function of carboxylesterases in xenobiotic metabolism

Exposure to lipophilic xenobiotics can result in their accumulation in cells and tissues at concentrations that elicit toxic effects. Toxicities may arise from the interaction of these compounds with cellular receptors, signal-transduction pathways, or, if the xenobiotic is chemically reactive, following covalent modification of cellular macromolecules [41] Organisms have adapted several defense strategies to reduce the degree of toxicity following xenobiotic exposures. These include the expression of enzymes that metabolize lipophilic xenobiotics to water-soluble metabolites that can be cleared from the body [42]. Carboxylesterases are broadly distributed in nature and commonly originate in mammalian liver. Many participate in first phase of metabolism of xenobiotics such as toxins or medication; as a result carboxylates are then conjugated by other enzymes to increase solubility and ultimately excreted[43, 58].

Carboxylesterases (E.C. 3.1.1.1; CEs) have been identified in organisms ranging from bacteria to man and are thought to be responsible for the detoxification of xenobiotics CES catalyze the hydrolysis of ester, thioester, and also time to time amide bonds during the process of metabolism of xenobiotics and endogenous chemicals [44]. Generally, formation of more polar readily excreted products by hydrolysis of lipophilic esters to carboxylic acids constitutes a detoxication process. While many animal and nonspecific human carboxylesterases have been reported in the literature, few highly substrate-selective human liver carboxylesterases have been described. In animals, carboxylesterases are widely circulated in different tissues. The large amount of CES in various animal tissues in part compensates for the relatively low specific activity of the enzyme [45].

Detoxication studies with xenobiotics have not yet been entirely examined with the purified human EsD. Most of the EsD data for humans have been inferred from studies utilizing human serum or analogous carboxylesterases isolated from rats or other mammals. Human esterase D (EsD, carboxylesterase, aliesterase, EC 3.1.1.1) is one of several nonspecific esterases identified in human tissue that contribute to the hydrolytic detoxication or metabolism of xenobiotics, drugs, and enviromental chemicals [46]. Like other human esterases (paraoxonase/arylesterase, sterol esterase, and carboxyl ester lipase), the physiological function of EsD is not well understood. EsD is, however, distinguishable from other esterases by its specificity for the hydrolysis of 4-methylumbelliferyl ester. The location of the catalytic amino acid residues at the bottom of a long active site gap seems somewhat counterintuitive for an enzyme that can metabolize substrates having diverse chemical structures. If the sole purpose of CEs is to detoxify xenobiotics, then it might be predicted that the residues responsible for hydrolysis would be much more readily available, perhaps on the outside of the protein [47].

Esterified chemicals are found in many pharmaceuticals, illegal narcotics, and environmental toxicants. Pyrethroid insecticides, phthalate esters, chemotherapeutic prodrugs (like irinotecan), and drugs like cocaine and heroin are a few examples. These compounds are cleared (or bioactivated in the case of irinotecan) from the body in part by the action of CEs [48]. There are varieties of toxic compounds which are detoxified by carboxylesterases as given in Table 2.

Some xenobiotic metabolism has been shown in earlier research. Here, we employ pyrethroid insecticides as an example, which are particularly significant due to their widespread usage in public health procedures [48] and agriculture [49]. The restricted use of organophosphate (OP) insecticides will lead to an increase in the use of pyrethroids in agricultural activities. Human exposure to these substances will therefore undoubtedly rise in the near future. Inhibition experiments have previously shown the significance of esterases in the detoxification of pyrethroids. For instance, pyrethroid trans-esterase activity was observed when mice were given OP pesticides prior to dosage. This consequently made the pyrethroid more poisonous in vivo. This outcome gave clear proof of the critical role

hydrolytic metabolism plays in pyrethroid detoxification. In-depth research has been done on how rodent and human hepatic microsomes process pyrethroids. The small intestine, for example, also has relatively high CE concentrations in humans and rats, which may help with pyrethroid metabolism. Few studies have been conducted on these tissues in relation to pyrethroid metabolism. According to findings, these chemicals' bioavailability may be severely restricted by intestinal CEs' metabolism of them. Purified human and rodent CEs' pyrethroid substrate preferences show some intriguing differences. Several type II pyrethroids, which differ from type I compounds by having an alcohol moiety with a cyano functionality, hCE1 hydrolyzed pyrethroids far more quickly than rat Hydrolase A did. Since oxidation is the main metabolic pathway in rat liver, hydrolysis appears to be the predominant metabolic process that clears the type II chemical deltamethrin in human liver [18]. Trans-permethrin and bioresmethrin, on the other hand, were digested by rat and human CEs at comparable rates.

There is evidence of interindividual variance in hepatic hydrolytic activity in the human population. When tested with esterified substrates (para-nitrophenyl valerate, trans-permethrin, and bioresmethrin), individual human liver microsomal samples were found to have different degrees of hydrolytic activity. In contrast, the concentrations of hCE1 protein remained impressively constant (1.3-fold variation, CV percent =9%) when they were present in the same microsomal samples.

As a result, CE activity in human liver microsomes does not seem to be well predicted by the sheer abundance of hCE1 and hCE2. Since many medicinal medications and environmental toxins are processed by these enzymes, it will be crucial to describe the variables that result in changed CE activity in human liver microsomes. However, hCE1 accounts for the majority of the esterolytic activity in human liver microsomes and its average level is almost 50 times higher than hCE2 in the pooled samples of human liver microsomes [23]. Preincubation of human liver microsomes with a particular hCE1 inhibitor can suppress 80% of its hydrolytic activity toward pyrethroid substrates, providing evidence in favour of this.

Additionally, prodrugs that are selectively triggered by CES can be designed using cheminformatics, increasing the effectiveness of medication therapy while reducing side effects. For example, by modifying the structure of drugs to incorporate ester linkages, researchers can develop prodrugs that are activated by CES enzymes, such as CES1 and CES2, which are abundant in liver and gut tissues.

Function of Carboxylesterases in Xenobiotic Detoxification

Carboxylesterases play a critical role in the detoxification of xenobiotics by hydrolyzing ester, amide, and thioester linkages in a variety of substrates. These enzymes are involved in the detoxification of pharmaceuticals, environmental toxins, and even natural compounds like lipid esters and steroid hormones.

Table 2. Some toxic compounds are detoxified by human carboxylesterases.

S.N.	Toxic compounds	Carboxylesterase source	Reference
1.	Herbicides	Human liver, skin, plasma	[50, 49]
2.	Pyrethroid	Adult rat	[51, 50]
3.	Cocaine	Purified from human liver	[52]
4.	Nicotinic acid esterase	Human plasma	[53]
5.	Procaine	Purified from human liver, intestinal mucosa	[54]
6.	Aspirin	Purified from human liver, intestinal mucosa	[54]
7.	Clofibrate	Purified from human liver, intestinal mucosa	[54]
8.	Meperidine	Human liver	[55]
9.	Acrylates	Mouse nasal mucosa	[56]
10.	Vantin	Purified from human liver, intestinal mucosa	[57]

The hydrolysis of pyrethroid insecticides, commonly used in agriculture, provides a clear example of CES's role in xenobiotic metabolism. The liver and small intestine are primary sites of pyrethroid metabolism, where CES enzymes hydrolyze these lipophilic compounds to more water-soluble products, facilitating their excretion [58, 59].

Through their role in the hydrolysis of xenobiotics, CES not only mitigate the toxicity of these compounds but also contribute to maintaining physiological balance by regulating lipid metabolism and modulating drug activity.

CONCLUSION

Carboxylesterases are vital enzymes that aid in xenobiotic metabolism and detoxification. Their ability to hydrolyze ester and amide bonds in a variety of substrates, including environmental pollutants, pharmaceuticals, and natural compounds, positions them as key players in both drug metabolism and environmental health. The integration of cheminformatics approaches can aid in predicting CES-substrate interactions, optimizing drug design, and understanding the metabolic pathways of xenobiotics. As we continue to explore CES modulators and their roles in human diseases, these insights can lead to the development of more effective therapies and environmental interventions.

REFERENCES

1. Joseph P. Transcriptomics in toxicology. Food Chem Toxicol. 2017;109(Pt 1):650–662. doi:10.1016/j.fct.2017.07.031.
2. Mansuy D. Le métabolisme des xénobiotiques: effets bénéfiques, effets néfastes. Biol Aujourdhui. 2013;207(1):33–37. doi:10.1051/jbio/2013003.
3. Patterson AD, Gonzalez FJ, Idle JR. Xenobiotic metabolism: a view through the metabolometer. Chem Res Toxicol. 2010;23(5):851–860. doi:10.1021/tx100020p.
4. Detoxification and Substance Abuse Treatment Treatment Improvement Protocol (TIP) Series. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2006.
5. Kreitinger JM, Beamer CA, Shepherd DM. Environmental immunology: lessons learned from exposure to a select panel of immunotoxicants. J Immunol. 2016;196(8):3217–3225. doi:10.4049/jimmunol.1502149.
6. Croom E. Metabolism of xenobiotics of human environments. Prog Mol Biol Transl Sci. 2012;112:31–88. doi:10.1016/B978-0-12-415813-9.00003-9.
7. Godin SJ, Scollon EJ, Hughes MF, Potter PM, DeVito MJ, Ross MK. Species differences in the in vitro metabolism of deltamethrin and esfenvalerate: differential oxidative and hydrolytic metabolism by humans and rats. Drug Metab Dispos. 2006;34(10):1764–1771. doi:10.1124/dmd.106.010058.
8. Sterri SH, Fonnum F. The role of carboxylesterases in therapeutic intervention of nerve gases poisoning. In: Gupta RC, editor. Handbook of Toxicology of Chemical Warfare Agents. 2nd ed. San Diego: Academic Press; 2015.
9. Yan B. Carboxylesterases. In: Wexler P, editor. Encyclopedia of Toxicology. 3rd ed. Oxford: Elsevier; 2014. p. 695–698.
10. Bachmann K. Drug metabolism. In: Pharmacology. Philadelphia: Elsevier; 2009. p. 131–173.
11. Koppel N, Maini Rekdal V, Balskus EP. Chemical transformation of xenobiotics by the human gut microbiota. Science. 2017;356(6344). doi:10.1126/science.aag2770.
12. Abdelsalam NA, Ramadan AT, ElRakaiby MT, Aziz RK. Toxicomicrobiomics: the human microbiome vs. pharmaceutical, dietary, and environmental xenobiotics. Front Pharmacol. 2020;11:390. doi:10.3389/fphar.2020.00390.
13. Clarke G, Sandhu KV, Griffin BT, Dinan TG, Cryan JF, Hyland NP. Gut reactions: breaking down xenobiotic–microbiome interactions. Pharmacol Rev. 2019;71(2):198–224. doi:10.1124/pr.118.015768.
14. Wang D, Zou L, Jin Q, Hou J, Ge G, Yang L. Human carboxylesterases: a comprehensive review. Acta Pharm Sin B. 2018;8(5):699–712. doi:10.1016/j.apsb.2018.05.005.

15. Hatfield MJ, Umans RA, Hyatt JL, Edwards CC, Wierdl M, Tsurkan L, et al. Carboxylesterases: general detoxifying enzymes. Chem Biol Interact. 2016;259(Pt B):327–331. doi:10.1016/j.cbi.2016.02.011.
16. Sanghani SP, Sanghani PC, Schiel MA, Bosron WF. Human carboxylesterases: an update on CES1, CES2 and CES3. Protein Pept Lett. 2009;16:1207–1214. doi:10.2174/092986609789071324.
17. Satoh T, Hosokawa M. Structure, function and regulation of carboxylesterases. Chem Biol Interact. 2006;162:195–211. doi:10.1016/j.cbi.2006.07.001.
18. Satoh T, Hosokawa M. The mammalian carboxylesterases: from molecules to functions. Annu Rev Pharmacol Toxicol. 1998;38:257–288. doi:10.1146/annurev.pharmtox.38.1.257.
19. Ross MK, Crow JA. Human carboxylesterases and their role in xenobiotic and endobiotic metabolism. J Biochem Mol Toxicol. 2007;21(4):187–196. doi:10.1002/jbt.20178.
20. Hosokawa M. Structure and catalytic properties of carboxylesterase isozymes involved in metabolic activation of prodrugs. Molecules. 2008;13:412–431. doi:10.3390/molecules13020412.
21. Imai T. Human carboxylesterase isozymes: catalytic properties and rational drug design. Drug Metab Pharmacokinet. 2006;21:173–185. doi:10.2133/dmpk.21.173.
22. Redinbo MR, Potter PM. Mammalian carboxylesterases: from drug targets to protein therapeutics. Drug Discov Today. 2005;10:313–325. doi:10.1016/S1359-6446(05)03383-0.
23. Satoh T, Taylor P, Bosron WF, Sanghani SP, Hosokawa M, La Du BN. Current progress on esterases: from molecular structure to function. Drug Metab Dispos. 2002;30:488–493. doi:10.1124/dmd.30.5.488.
24. Potter PM, Wolverton JS, Morton CL, Wierdl M, Danks MK. Cellular localization domains of a rabbit and a human carboxylesterase: influence on irinotecan (CPT-11) metabolism by the rabbit enzyme. Cancer Res. 1998;58:3627–3632.
25. Zhu HJ, Wang X, Gawronski BE, Brinda BJ, Angiolillo DJ, Markowitz JS. Carboxylesterase 1 as a determinant of clopidogrel metabolism and activation. J Pharmacol Exp Ther. 2013;344:665–672. doi:10.1124/jpet.112.201640.
26. Zhu HJ, Markowitz JS. Activation of the antiviral prodrug oseltamivir is impaired by two newly identified carboxylesterase 1 variants. Drug Metab Dispos. 2009;37(2):264–267. doi:10.1124/dmd.108.024943.
27. Nishi K, Huang H, Kamita SG, Kim IH, Morisseau C, Hammock BD. Characterization of pyrethroid hydrolysis by the human liver carboxylesterases CES1 and CES2. Arch Biochem Biophys. 2006;445(1):115–123. doi:10.1016/j.abb.2005.11.005.
28. Imai T, Ohura K. The role of intestinal carboxylesterase in the oral absorption of prodrugs. Curr Drug Metab. 2010;11(9):793–805. doi:10.2174/138920010794328904.
29. Lian J, Nelson R, Lehner R. Carboxylesterases in lipid metabolism: from mouse to human. Protein Cell. 2018;9(2):178–195. doi:10.1007/s13238-017-0437-z.
30. Alam M, Ho S, Vance DE, Lehner R. Heterologous expression, purification, and characterization of human triacylglycerol hydrolase. Protein Expr Purif. 2002;24(1):33–42. doi:10.1006/prep.2001.1553.
31. Ruby MA, Massart J, Hunerdosse DM, Schönke M, Correia JC, Louie SM, et al. Human carboxylesterase 2 reverses obesity-induced diacylglycerol accumulation and glucose intolerance. Cell Rep. 2017;18(3):636–646. doi:10.1016/j.celrep.2016.12.070.
32. Crow JA, Herring KL, Xie S, Borazjani A, Potter PM, Ross MK. Inhibition of carboxylesterase activity of THP-1 monocytes/macrophages and recombinant human carboxylesterase 1 by oxysterols and fatty acids. Biochim Biophys Acta. 2010;1801(1):31–41. doi:10.1016/j.bbalip.2009.09.002.
33. Alam M, Vance DE, Lehner R. Structure-function analysis of human triacylglycerol hydrolase by site-directed mutagenesis: identification of the catalytic triad and a glycosylation site. Biochemistry. 2002;41(21):6679–6687. doi:10.1021/bi0255625.
34. Wang DD, Zou LW, Jin Q, Hou J, Ge GB, Yang L. Recent progress in the discovery of natural inhibitors against human carboxylesterases. Fitoterapia. 2017;117:84–95. doi:10.1016/j.fitote.2017.01.010.

35. Dominguez E, Galmozzi A, Chang JW, Hsu KL, Pawlak J, Li W, et al. Integrated phenotypic and activity-based profiling links Ces3 to obesity and diabetes. Nat Chem Biol. 2014;10(2):113–121. doi:10.1038/nchembio.1429.
36. Crow JA, Middleton BL, Borazjani A, Hatfield MJ, Potter PM, Ross MK. Inhibition of carboxylesterase 1 is associated with cholesteryl ester retention in human THP-1 monocyte/macrophages. Biochim Biophys Acta. 2008;1781(11):643–654. doi:10.1016/j.bbalip.2008.07.005.
37. Yoon KJP, Hyatt JL, Morton CL, Lee RE, Potter PM, Danks MK. Characterization of inhibitors of specific carboxylesterases: development of carboxylesterase inhibitors for translational application. Mol Cancer Ther. 2004;3(8):903–909.
38. Xu Y, Zhang C, He W, Liu D. Regulations of xenobiotics and endobiotics on carboxylesterases: a comprehensive review. Eur J Drug Metab Pharmacokinet. 2016;41(4):321–330. doi:10.1007/s13318-016-0326-5.
39. Hicks LD, Hyatt JL, Stoddard S, Tsurkan L, Edwards CC, Wadkins RM, et al. Improved, selective, human intestinal carboxylesterase inhibitors designed to modulate 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (irinotecan; CPT-11) toxicity. J Med Chem. 2009;52(12):3742–3752. doi:10.1021/jm9001296.
40. Aranda J, Cerqueira NM, Fernandes PA, Roca M, Tuñon I, Ramos MJ. The catalytic mechanism of carboxylesterases: a computational study. Biochemistry. 2014;53(36):5820–5829. doi:10.1021/bi500934j.
41. Liebler DC, Guengerich FP. Elucidating mechanisms of drug-induced toxicity. Nat Rev Drug Discov. 2005;4(5):410–420. doi:10.1038/nrd1720.
42. Chambers JP, Hartgraves SL, Murphy MR, Wayner MJ, Kumar N, Valdes JJ. Effects of three reputed carboxylesterase inhibitors upon rat serum esterase activity. Neurosci Biobehav Rev. 1991;15(1):85–88. doi:10.1016/S0149-7634(05)80096-X.
43. Cashman JR, Perotti BY, Berkman CE, Lin J. Pharmacokinetics and molecular detoxication. Environ Health Perspect. 1996;104(Suppl 1):23–40. doi:10.1289/ehp.96104s123.
44. Jones RD, Taylor AM, Tong EY, Repa JJ. Carboxylesterases are uniquely expressed among tissues and regulated by nuclear hormone receptors in the mouse. Drug Metab Dispos. 2013;41(1):40–49. doi:10.1124/dmd.112.048397.
45. Ross MK, Crow JA. Human carboxylesterases and their role in xenobiotic and endobiotic metabolism. J Biochem Mol Toxicol. 2007;21(4):187–196. doi:10.1002/jbt.20178.
46. Tsujita T, Okuda H. The synthesis of fatty acid ethyl ester by carboxylester lipase. Eur J Biochem. 1994;224(1):57–62. doi:10.1111/j.1432-1033.1994.tb19994.x.
47. Shibata Y, Takahashi H, Chiba M, Ishii Y. Prediction of hepatic clearance and availability by cryopreserved human hepatocytes: an application of serum incubation method. Drug Metab Dispos. 2002;30(8):892–896. doi:10.1124/dmd.30.8.892.
48. Hodgson E, Levi PE. Pesticides: an important but underused model for the environmental health sciences. Environ Health Perspect. 1996;104(Suppl 1):97–106. doi:10.1289/ehp.96104s197.
49. Spitzen J, Koelewijn T, Mukabana WR, Takken W. Effect of insecticide-treated bed nets on house-entry by malaria mosquitoes: the flight response recorded in a semi-field study in Kenya. Acta Trop. 2017;172:180–185. doi:10.1016/j.actatropica.2017.05.008.
50. Clark NW, Scott RC, Blain PG, Williams FM. Fate of fluazifop butyl in rat and human skin in vitro. Arch Toxicol. 1993;67(1):44–48. doi:10.1007/BF02072034.
51. Cantalamessa F. Acute toxicity of two pyrethroids, permethrin and cypermethrin, in neonatal and adult rats. Arch Toxicol. 1993;67(7):510–513. doi:10.1007/BF01969923.
52. Casida JE, Ueda K, Gaughan LC, Jao LT, Soderlund DM. Structure-biodegradability relationships in pyrethroid insecticides. Arch Environ Contam Toxicol. 1975;3(4):491–500. doi:10.1007/BF02220819.
53. Brzezinski MR, Abraham TL, Stone CL, Dean RA, Bosron WF. Purification and characterization of a human liver cocaine carboxylesterase that catalyzes the production of benzoylecgonine and the formation of cocaethylene from alcohol and cocaine. Biochem Pharmacol. 1994;48(9):1747–1755. doi:10.1016/0006-2952(94)90461-8.

54. Durrer A, Walther B, Racciatti A, Boss G, Testa B. Structure-metabolism relationships in the hydrolysis of nicotinate esters by rat liver and brain subcellular fractions. Pharm Res. 1991;8(7):832–839. doi:10.1023/A:1015839109449.
55. Inoue M, Morikawa M, Tsuboi M, Ito Y, Sugiura M. Comparative study of human intestinal and hepatic esterases as related to enzymatic properties and hydrolyzing activity for ester-type drugs. Jpn J Pharmacol. 1980;30(4):529–535. doi:10.1254/jjp.30.529.
56. Luttrell WE, Castle MC. Species differences in the hydrolysis of meperidine and its inhibition by organophosphate compounds. Toxicol Sci. 1988;11(1):323–332. doi:10.1093/toxsci/11.1.323.
57. Stott WT, McKenna MJ. Hydrolysis of several glycol ether acetates and acrylate esters by nasal mucosal carboxylesterase in vitro. Fundam Appl Toxicol. 1985;5(2):399–404. doi:10.1016/0272-0590(85)90088-0.
58. Potter PM, Wadkins RM. Carboxylesterases—detoxifying enzymes and targets for drug therapy. Curr Med Chem. 2006;13(9):1045–1054. doi:10.2174/092986706776360969.
59. Wikipedia contributors. (2024). Carboxylesterase. Wikipedia. Available from: https://en.wikipedia.org/wiki/Carboxylesterase

