

MEDICAL ASPECTS OF ESTERASES: A MINI REVIEW

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ABSTRACT

Nowadays, esterases represent high growth potential in the World Industrial Enzymes Market. The industrial applications of esterases provide an immense contribution to the eco-friendly approaches towards nature as also in the food, textile industries as additives in detergents, agrochemical (herbicides, insecticides) industries, and bioremediation. The current review is focused mainly on different medical aspects of esterases because they find implications in treatment of cancer, cardiovascular diseases and neuropathy. The role of esterase has been observed in the treatment of hereditary angioedema (HAE). The arylesterase (ARE) has been found to show antioxidant activity in plasma cells and its low activity resulted in multiple myelomas accounting for 1% of neoplastic diseases and 13% of hematological malignancies in U. S. A. Lung cancer is one of the most lethal forms of cancers and reports have indicated that tumors of the lung, colon and liver had high esterase expressions and therefore could be exploited for selective drug conversion using an ester prodrug strategy. Human serum paraoxonase (PON1) and arylesterase (ARE) are lipophilic antioxidant enzymes. Hypercholesterolaemia has been found to be associated with reduced PON1 enzyme activities and patients are under increased oxidative stress. Esterases from animal and plant origins have been used as effective drugs and as detection probes for toxic compounds using chiral technology.

Keywords: Neuropathy, Neuropathy target esterase (NTE), Hereditary angioedema, Gene therapy, Organophosphates

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INTRODUCTION

Esterases belong to the family of lipolytic hydrolases and catalyze the hydrolysis and the formation of ester bonds [1]. Esterases catalyze esterification, transesterification and interesterification reactions [2]. These enzymes affect the rates of reversible reactions depending on the thermodynamics that means in an organic phase esterase favors ester formation and in the aqueous phase carry out ester hydrolysis [3]. Esterases differ from lipases mainly on the basis of substrate specificity and interfacial activation [4]. Esterases hydrolyze short chain carboxylic acids (less than C-12) while lipases hydrolyze insoluble long chain (greater than C-12) triglycerides [5-7]. These are attractive biocatalysts as they do not require cofactors [8]. The Enzyme Commission number assigned to esterase is E. C 3.1.1. x, where x depends on the substrate [9]. Esterases play a major role in the degradation of natural materials and industrial pollutants, viz., cereal wastes, plastics and other toxic chemicals. A newly isolated gene Car EW from *Bacillus* sp. K91 was shown to be responsible for the catalytic hydrolysis and detoxification of di isobutyl phthalate (DiBP) to phthalic acid (PTH) that can be completely mineralized [10]. Esterase is useful in the synthesis of optically pure compounds, perfumes and antioxidants [11]. The EstB28 was the first esterase to be characterized from the wine-associated lactic acid bacterium, *Oenococcus oeni* [12] and esters are

quantitatively significant constituents of wine [13]. A novel extracellular esterase from *Salimicrobium* sp. LY19 has exhibited thermo-stable, alkali-stable, halo-tolerant and organic solvent-tolerant properties that could be exploited in industrial organic synthesis reactions [14]. As applications of esterases are found in various fields and due to growing interest in this enzyme, various aspects of esterases have been reported mainly in the avenues of distribution, quantitation, production, targeted synthesis, purification and molecular biology. Esterases are less explored enzymes and this is the first review exploring recent highly valuable research and application in medicine.

Source and production of esterase

Esterases are widely distributed in animals, plants and microorganisms but microbial sources are considered as prominent for esterase production. The microbial sources include bacteria, fungi, yeasts and actinomycetes. Samples such as cheese surface [15], oil contaminated area of city garbage or marine squid have been used for microbial esterase production [16]. The biochemical properties of some of the microbial esterases are given in table 1. Different sources yield different esterases such as carboxyl esterase, choline esterase, acetyl xylan esterase, aryl esterase, phosphotri-esterase, phenolic esterase, pig liver esterase, acetylcholine esterase and tannin esterase [11].

Table 1: Biochemical properties of different esterases from different microbial sources

Microbial source	Esterase type	Optimum pH	Optimum temp (°C)	Molecular weight	Reference
<i>Bacillus pseudofirmus</i>	EstOF4	8.5	50	64	[17]
<i>Bacillus pumilus</i>	Acetyl xylan esterase	8.0	55	40	[18]
Recombinant	Pyrethroid hydrolyzing	6.5	Upto 45	36.7	[19]
<i>Escherichia coli</i>	Enzyme				
<i>Aspergillus awamori</i>	Acetylcysteine	7.0	Upto 40	31	[20]
Metagenome	Pyrethroid hydrolyzing	7.0	40	31	[21]
<i>Bacillus subtilis</i> NRRL 365	Carboxyl esterase I			36	[5]
<i>Bacillus subtilis</i> NRRL 365	Carboxyl esterase II			105	[5]
<i>Rhodospiridium toruloides</i>	Cephalosporin Esterase	6.0	25	80	[22]
<i>Aureobasidium pullulans</i>	Feruloyl esterase	6.7	60-65		[23]
<i>Thermoanaerobacterium</i> sp. Strain JW/SL-YS485	Acetyl xylan esterase I	7.0	80	195	[24]
<i>Pseudomonas stutzeri</i> Strain A1501	Esterase	9.0	50	-	[25]

For example, pancreatic cholesterol esterase catalyzes the hydrolysis of cholesterol esters into their component sterols and fatty acids, also, the reaction catalyzed is shown in (fig. 1) [26]. Cholesterol esterase is an important enzyme and functions to control the bioavailability of cholesterol from dietary cholesterol esters, transport of free cholesterol to the enterocyte and absorption of free cholesterol [27].

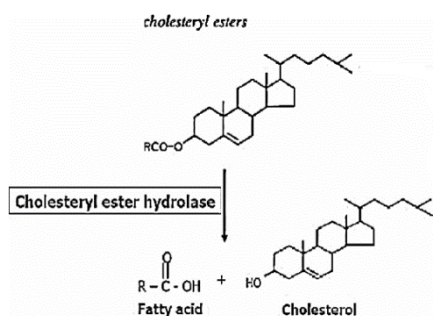


Fig. 1: The reaction is showing hydrolytic cleavage of cholesterol ester by cholesterol esterase (cholesteryl ester hydrolase) [27]

Esterases from an extremophilic origin, in particular, are most robust biocatalysts because they can function under the harsh conditions of industrial processes owing to their inherent thermostability and resistance towards organic solvents, which combined with their high chemo-, regio- and enantioselectivity make them very attractive biocatalysts for a variety of industrial applications [28]. In most cases, such substrates contain the required inducer. On the other hand, phosphotriesterase from *Pseudomonas montelli* [29], which is regulated by phosphate and carbon sources, thermostable intracellular esterase from *Bacillus* sp. and tributyrin-induced esterase in *Lactobacillus casei* [30] differ from the enzymes produced by *Aspergillus* sp. or *Sporotrichum* sp. Esterases are produced in many ways and there is often no need for high purity [31]. However, the wide spectrum of application and the growing demand for esterase can be satisfied by the development of suitable production strategies.

Medical applications of esterases

Application in chiral drug synthesis

Esterases are mainly used in the synthesis of optically pure compounds and fine chemicals of interest in the pharmaceuticals such as antibiotics and anti-inflammatory drugs [28]. In pharmaceutical industries, esterase produced chiral drugs such as anti-inflammatory drugs which have been used as pain killing agents [32]. An esterase from *Trichosporon brassicae* has been used extensively for the production of optically pure (S)- and/or (R)-ketoprofen [2-(3-benzoylphenyl) propionic acid] (fig. 2), which is very effective in the reduction of inflammation and relief of pain resulting from arthritis, sunburn, menstruation and fever [33]. Stereospecific conversions have been reported in the production of pharmaceutical intermediates with respect to taxol semi-syntheses, viz., thromboxane-A₂-antagonist, acetylcholine esterase inhibitors, anti-cholesterol drugs [34]. An esterase from *Pseudomonas stutzeri* strain A1501 has been characterized with unique stereospecific properties to be useful in industrial chiral synthesis [25].

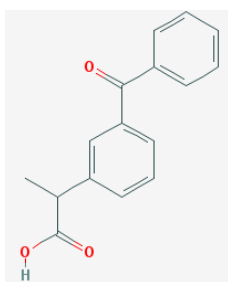


Fig. 2: The structure of Ketoprofen-pain-killer and anti-inflammatory drug [35]

Application in neuropathy

Neuropathy is a disease affecting nerves, which may impair sensation, movement, gland or organ function. NTE is a membrane-bound protein found in neurons of vertebrates and plays a central role in both chemically induced and spontaneously occurring neurological diseases [36]. During screening of neurotoxicity of potential organophosphorous neurotoxicants (paraoxon, malaoxon, chlorpyrifos-oxon, dichlorovos, and trichlorfon) on neuroblastoma cell lines (human SHSY5Y and murine NB41A3), it was demonstrated that acute and delayed neurotoxicity is consequence of differential inhibition of target esterases acetylcholinesterase (AChE) and NTE by organophosphorous compounds [37]. The role of NTE in neurodegeneration was experimentally proved in NTE knockout mice generated by cre-loxP site-specific recombination and had revealed that NTE absence resulted in hippocampal and thalamic neuronal vacuolation and extensive membrane deformities [38]. Studies in mammalian cell line and yeasts have revealed that loss of NTE phospholipase activity and accumulation of phosphatidylcholine due to organophosphorous induced delayed neuropathy (OPIDN) resulted in endoplasmic reticulum malfunction and hindrance in axonal transport [39]. This is explained in the pathway (fig. 3) which describes that phosphatidylcholine (PtdCho) at the cytoplasmic face of the endoplasmic reticulum membrane is deacylated by NTE to form soluble products, free fatty acids (FFA) and glycerophosphocholine (GroPCho) but inhibition of NTE by organophosphates resulted in OPIDN [40]. Recently, the role of NTE was reviewed in metabolism and pathophysiology, NTE mediated production of glycerophosphocholine which is an abundant renal medullary organic osmolyte protects renal medullary cells from the high interstitial concentrations of NaCl and urea [41]. The role of NTE has been recognized to control the cytotoxic accumulation of lysophospholipid in mammalian membranes and to maintain lipid bilayer fluidity. The fluorescence recovery after pattern photobleaching (FRAPP) was used to study the effect of the hydrolysis of 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine (p-lysoPC) by the catalytic domain of NTE on different supported bilayer membranes (sBLMs) formulations and it was concluded that there was a significant decrease in the fluidity of sBLMsm reconstituted on silica [42].

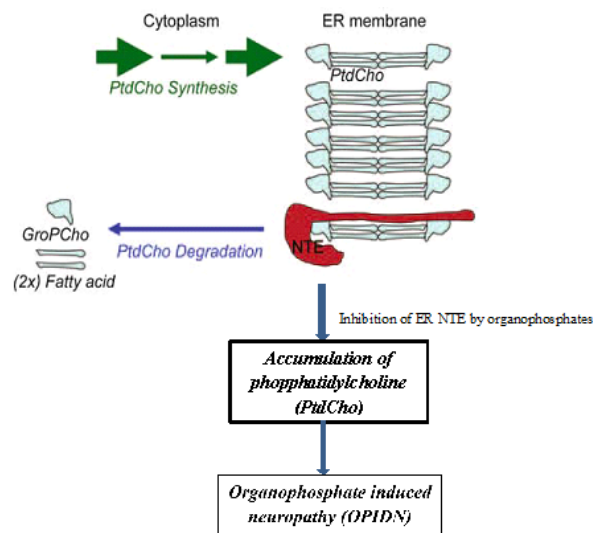


Fig. 3: This diagram shows a relationship between NTE and OPIDN [40]

Application in anti-tumour and cancer treatment

Various lethal forms of cancer have been recognized and lung cancer is one of them. Recent chemotherapeutic strategies against lung cancer lack broad specificity and efficiency. A biocompatible and biodegradable poly (ethylene glycol)-b-poly (D, L-26 lactic acid) (PEG-b-PLA) micelle-delivered β -lap-dC3 and 28-dC6 prodrugs nanotherapeutics were converted to β -lapachone (β -lap) using

porcine liver esterase (PLE). The β -lapachone produg showed antitumor efficacy and long-term survival using cytotoxicity assays on A549 and H596 lung cancer cells [43]. In a neural stem cells (NSCs)-derived enzyme/prodrug therapy (NDEPT), anti-tumor effect of NSCs expressing carboxylesterase (CE) was proved to treat primary lung cancer or metastatic lung cancer in the brain [44]. Neural stem cells (NSCs) expressing rabbit carboxylesterase (F3. CE) could inhibit the growth of A549 human non-small cell lung adenocarcinoma cells *in vitro* and *in vivo* and thus delivering therapeutic genes to brain tumors has been considered as an effective treatment for lung cancer brain metastases [45].

Application in biosensor fabrication

In the fabrication of a cholesterol based biosensor, cholesterol esterase in conjunction with cholesterol oxidase and peroxidase was immobilized onto polyaniline films and has been used as sensing elements in estimation of cholesterol concentration and resulted in improved shelf-life of biosensor electrodes [46]. The estimation of metabolites such as glucose, urea, lactate, and cholesterol in the blood sample is important in clinical diagnostics and prevention of a number of clinical disorders such as hypertension, arteriosclerosis, cerebral thrombosis and coronary heart diseases [47, 48].

Recently, highly sensitive fluorogenic esterase probes derived from the far-red fluorophore 7-hydroxy-9H-(1, 3 dichloro-9, 9-dimethylacridin-2-one) (DDAO) have been used to detect low picogram amounts of PLE activity in mycobacterial lysates during different stages of tuberculosis infection [49]. *Mycobacterium tuberculosis* esterases have the distinct role in pathogenesis [50] and this has been difficult to characterize them because most form inclusion bodies in heterologous hosts [51]. In a recent report, esterase has been used with ferrocene capped gold nanoparticle for cholesterol detection in blood samples [52].

HAE treatment

HAE is an autosomal dominant disease, characterized by episodes of painful excess fluid build-up, typically affecting the bowels, face and upper airway, body trunk, genitalia, and extremities [53]. HAE is caused by a deficiency in C1 esterase inhibitor (C1-INH) with no differences in prevalence based on gender or race [53]. Management of HAE may include treatment for acute attacks, or short-or long-term prophylaxis for prevention of HAE attacks [54]. In the case of a patient with HAE that included hypovolemic shock, ascites, severe sepsis from nosocomial pneumonia, renal and respiratory failure

was given a trial of daily intravenous infusion of Human plasma-derived C1 esterase inhibitor (pdC1-INH) concentrate, his clinical status was found to be improved, particularly renal function [55]. Thus, human plasma-derived C1 esterase inhibitor (pdC1-INH) is indicated for the treatment of both HAE attacks and prevention of HAE episodes in patients undergoing medical treatment.

Application in gene therapy

Gene therapy involves replacing a defective gene in the body with a healthy one. This can be done by removing cells from the body using genetic engineering techniques to change defective sequences in the DNA, then reinserting the cells instead of using drugs or surgery. A replacement therapy has also been designed for raising serum levels of PON1 paraoxonase/arylesterase enzymes by using a gene delivery vector for hydrolytic destruction of organophosphate before it can enter the brain and cause toxicity [56].

Application in treatment of hypercholesterolemia

Hypercholesterolemia is characterized by very high levels of cholesterol in the blood and it is an established risk factor for atherosclerosis and coronary heart disease (CHD) [57] in humans. In a report while studying the action of cholesterol esterase it was found that cholesterol esterase targeted inhibitors could be useful therapeutics for limiting cholesterol absorption [58].

Application in diagnostics

Multiple myelomas is a cancer of the plasma cells and it accounts for 1% of neoplastic diseases and 13% of hematological malignancies in U. S. A. In multiple myeloma patients, it was reported that activity of arylesterase was significantly lower as compared to controls and patients suffered from high oxidative stress [59]. A thermostable bacterial cocaine esterase was identified to degrade cocaine in rodents and provide protection against convulsant and lethal effects of cocaine, thus preventing adverse effects of cocaine on the central nervous system [60]. The role of esterases has also been identified in implementing malaria control strategies, where they help in insecticide bendiocarp resistance in *Anopheles gambiae Tanguieta* [61]. The presence of leukocyte esterase in the synovial fluid has recently been proposed as a marker for periprosthetic joint infection [62].

Other applications of esterases

Nowadays, esterases represent high growth potential in the World Industrial Enzymes Market.

Table 2: Applications of different esterases in various fields

Esterase type	Application	Reference
i. Acetylcholinesterase	Development of new drugs for schistosomiasis biomarker for detection of organophosphates in a marine environment, assessment of poison due to pesticides and heavy metals.	[64] [65] [66]
ii. Arylesterase	Flavor development in food and alcoholic beverages.	[67]
iii. Carboxylesterases	Helpful in degradation of ethylene glycol di benzoate ester, lowering toxicity of malathion, hydrolysis of aspirin and organophosphorus insecticides, determining metabolic resistances to pyrethroid insecticides, D-acetylthioisobutyric acid, synthesis of racemates of esters of 1,2-isopropylidenglycerol.	[68-74]
iv. Cephalosporin acetyesterase	Applicable in the detection of acetyl groups from cephalosporin derivatives.	[31]
v. Cholesterol esterase and pseudocholinesterase	Degradation of poly (ether-urethane), prerequisite for working on sodium pump in various tissues.	[75, 76]
vi. Cinnamoyl ester hydrolase	Plant cell wall degradation	[77]
vii. Erythromycin esterase	Development of clinical medicine in human, poultry and fish.	[78]
viii. Ferulic acid esterase	Release of the ferulic acid.	[79]
ix. Feruloyl esterase	Synthesis of pentyl ferulate ester used in cosmetics and perfumes industries, decolorization of paper mill effluent.	[80, 81]
x. Methyl jasmonate esterase	Hydrolysis of methyl esters of abscisic acid, indole-3-acetic acid and fatty acids.	[82]
xi. Phosphotriesterase	Hydrolysis of products of coumaphos and coroxon.	[83]

They have many applications in the food industry (modification of fats to develop organoleptic and nutritional qualities) and the paper industry (removal of pitch from paper pulp), as additives in detergents, synthesis of biopolymers, biodiesel production, cosmetic (flavor and fragrance compounds) and agrochemical (herbicides, insecticides) industries, and bioremediation and waste treatment [28]. In particular, carboxylesterases play an important role in the detoxification of xenobiotics and many agrochemicals and insecticides [63]. Some of the applications of different esterases have been given in table 2.

CONCLUSION

Esterases are being used from diagnostics to the treatment of cancer, neurodegeneration diseases as well as other chronic diseases such as hereditary angioedema and hypercholesterolemia. The demand for these enzymes in medicine is now greatly increasing due to their role in the production of β -lap prodrug nanotherapeutics for the treatment of neural stem cell cancer, chiral drug synthesis and gene therapy. This is the only review on medical aspects of esterases despite the fact that these enzymes are extensively exploited in medicine. Microbial esterases have been better exploited in microbial fermentations using recombinant and protein engineering techniques but esterases from animal and plant origins are also used as effective drugs. Esterases are very potent eco-friendly enzymes as they also have immense application in detoxification of xenobiotic and bioremediation but their role in medicine is very important. There is a very less literature available for esterases as compared to lipases and thus, a great need to explore these enzymes and the future scope of research in this field is highly valuable.

CONFLICT OF INTERESTS

Declared none

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