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Review Article

Transitioning from Oxime to the Next Potential Organophosphorus Poisoning Therapy Using Enzymes

Rauda A. Mohamed,[1,2] Keat K. Ong,[1,3] Noor Azilah M. Kasim,[1,3] Norhana A. Halim,[3] Siti Aminah M. Noor,[3] Victor F. Knight,[1,2] Nurul Najwa Ab. Rahman,[1] and Wan Md Zin W. Yunus[2]

[1]*Centre for Chemical Defence, National Defence University of Malaysia, Kuala Lumpur 57000, Malaysia*
[2]*Centre for Tropicalization, National Defence University of Malaysia, Kuala Lumpur 57000, Malaysia*
[3]*Centre for Defence Foundation Studies, National Defence University of Malaysia, Kuala Lumpur 57000, Malaysia*

Correspondence should be addressed to Wan Md Zin W. Yunus; wanmdzin@upnm.edu.my

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For years, organophosphorus poisoning has been a major concern of health problems throughout the world. An estimated 200,000 acute pesticide poisoning deaths occur each year, many in developing countries. Apart from the agricultural pesticide poisoning, terrorists have used these organophosphorus compounds to attack civilian populations in some countries. Recent misuses of sarin in the Syrian conflict had been reported in 2018. Since the 1950s, the therapy to overcome this health problem is to utilize a reactivator to reactivate the inhibited acetylcholinesterase by these organophosphorus compounds. However, many questions remain unanswered regarding the efficacy and toxicity of this reactivator. Pralidoxime, MMB-4, TMB-4, obidoxime, and HI-6 are the examples of the established oximes, yet they are of insufficient effectiveness in some poisonings and only a limited spectrum of the different nerve agents and pesticides are being covered. Alternatively, an option in the treatment of organophosphorus poisoning that has been explored is through the use of enzyme therapy. Organophosphorus hydrolases are a group of enzymes that look promising for detoxifying organophosphorus compounds and have recently gained much interest. These enzymes have demonstrated remarkable protective and antidotal value against some different organophosphorus compounds *in vivo* in animal models. Apart from that, enzyme treatments have also been applied for decontamination purposes. In this review, the restrictions and obstacles in the therapeutic development of oximes, along with the new strategies to overcome the problems, are discussed. The emerging interest in enzyme treatment with its advantages and disadvantages is described as well.

1. Introduction

Organophosphates (OPs) are a major class of pesticides used in agriculture. Although OP development started early in the 1930s, its prominence as an insecticide and its further recognition to be lethal for humans as a chemical weapon became prominent in the late 1930s and mid-1940s [1]. OPs inhibit the function of acetylcholinesterase (AChE) and other cholinesterases (ChEs), which lead to nerve impulse damaging and finally incapacitating or causing death to the insect. The primary effects of OPs on humans include acute cholinergic toxicity and a delayed polyneuropathy. Both the insecticides and nerve agents' chemical warfare (such as malathion, chlorpyrifos, tabun, sarin, VX, and soman) react in the same way.

Some OP chemical warfare agents and pesticides are shown in Figure 1. The chemical structure of warfare agents consists of a P = O bond, while pesticides consists of a P = S bond. OPs with P = O bonds are direct AChE inhibitors, whereas those with P = S bonding, which are phosphothioates, do not possess anticholinesterase activities before biotransformation and, thus, are nontoxic by themselves [2]. In 1854, Philippe de Clermont, a French chemist, synthesized the first OP compound tetraethyl pyrophosphate

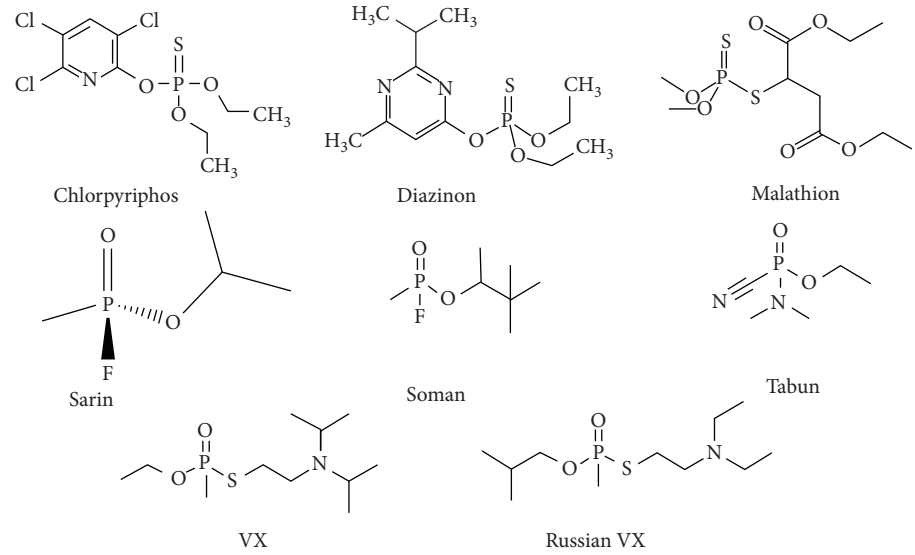

Figure 1: General structure of OP pesticides and chemical warfare agents (structures obtained from https://pubchem.ncbi.nlm.nih.gov/). (a) Chlorpyriphos, (b) diazinon, (c) malathion, (d) sarin, (e) soman, (f) tabun, (g) VX, and (h) Russian VX.

(TEPP) and described it as a phosphor ester [3]. Compounds containing P-F bonds were successfully synthesized in 1932, by Willy Lange at the University of Berlin.

AChE plays an important role in the hydrolysis of the neurotransmitter acetylcholine (ACh), which is found in both peripheral and central nervous systems [4] (Figure 2). The inhibition of AChE is initiated by phosphorylating the serine hydroxyl group on the enzyme. Phosphorylated serine causes the accumulation of acetylcholine, hence over stimulating the nicotinic and muscarinic receptors. The reactivation of inhibited AChE via nucleophilic attack is when the phosphylated group from the OP-AChE adducts is transferred to oxygen from the reactivator. Consequently, the AChE is activated. The mechanism of oxime reactivation is shown in Figure 3. Since the 1950s to date, oximes such as pralidoxime (2-PAM), MMB-4, TMB-4, obidoxime, and HI-6 have been commercialized and successfully treated many cases of OP intoxications [5–9]. However, due to the limitations of oximes, such as unequal effectiveness of their treatment of intoxication by different OPs, aging, and the ability to penetrate the blood-brain barrier (BBB), the development of oximes to overcome these issues have been carried out extensively.

The development is mainly to focus on the reactivation towards a broader spectrum of OP nerve agents and pesticides, with, more recently, the focus been on the ability to reactivate the AChE in the central nervous system (CNS). Since the chemical structure of OPs determines the reactivation potential, the diversity of chemical structure of OPs is the main issue for reactivation to occur. Nevertheless, there are several commercialized antidotes that have been approved for its broad substrate specificity. For example, methoxime shows to be a good reactivator in case of cyclosarin, sarin, and VX intoxication. For military purpose, HI-6 is preferred since it is able to reactivate almost all nerve agent-inhibited AChE except tabun [10]. Contrarily, HI-6 is unable to reactivate pesticide-inhibited AChE if civilian importance is considered [10, 11].

Treatment of OP poisoning is more efficient when the oxime is enabled to reactivate both central and peripheral nervous system AChE. Most of the oximes have low penetration through the blood-brain barrier which is due to the charged molecules resulting in low diffusion ability. Apart from utilizing uncharged oximes which has been found to solve this problem, an interesting alternative is to develop a sugar-oxime conjugate.

To further benefit the treatment of OP poisoning, other adjunctive treatment modalities have been explored. Cohen and Warringa had first proposed the application of enzymes as the alternative approach for the treatment of OP intoxication [12]. Enzymes are biocatalysts that can inactivate OPs in the bloodstream or hydrolyze them into safer metabolites before they can reach AChE at the physiological sites. The application of enzymes can be divided into stoichiometric scavengers, catalytic scavengers, and various types of OP-hydrolytic enzymes. There are several advantages and disadvantages of enzyme application in OP poisoning, regarding the time of administration, doses, routes of administration, ease of storage, and distribution to exposed individuals which will be discussed further in this review.

1.1. Oxime Development Based on Its Chemical Structures and Its Application in Different Countries. A fundamental comprehension of the specific toxicity of different OPs is a must to develop effective therapies and also in the assessment of the existing antidote restrictions and its medication regimens. Chemical structure of substituents on P atom of an OP, in addition to the structure of the leaving group, determines the critical ability of the reactivator to reactivates the inhibited AChE. Due to the rigorous production of these OP compounds along with the poisoning issues, for years, oximes have been well established as an antidote for OP intoxication. Starting as early as the 1950s, oximes have been explored (Figure 4). The first oxime was discovered by UK

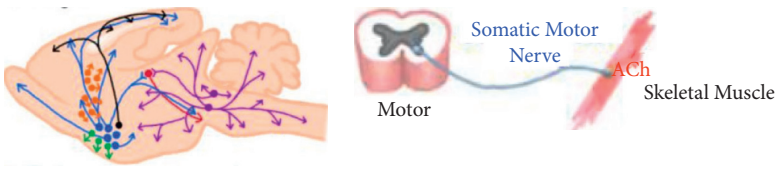

Figure 2: (a) ACh in central nervous systems shown as orange and green cell clusters, limbic structures in blue, and cholinergic projection represented by the black pathway; (b) ACh in the peripheral nervous system (picture adapted from https://nba.uth.tmc.edu/neuroscience/m/s1/chapter11.html).

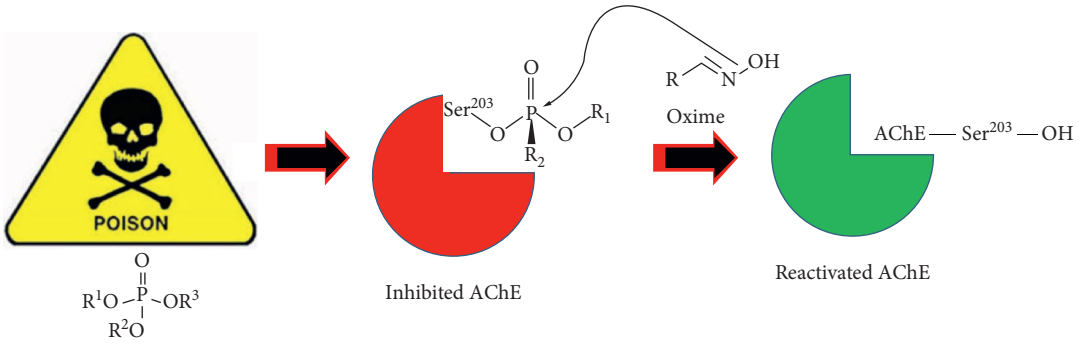

Figure 3: General mechanism of nucleophilic attack from the oxime reactivator towards OP.

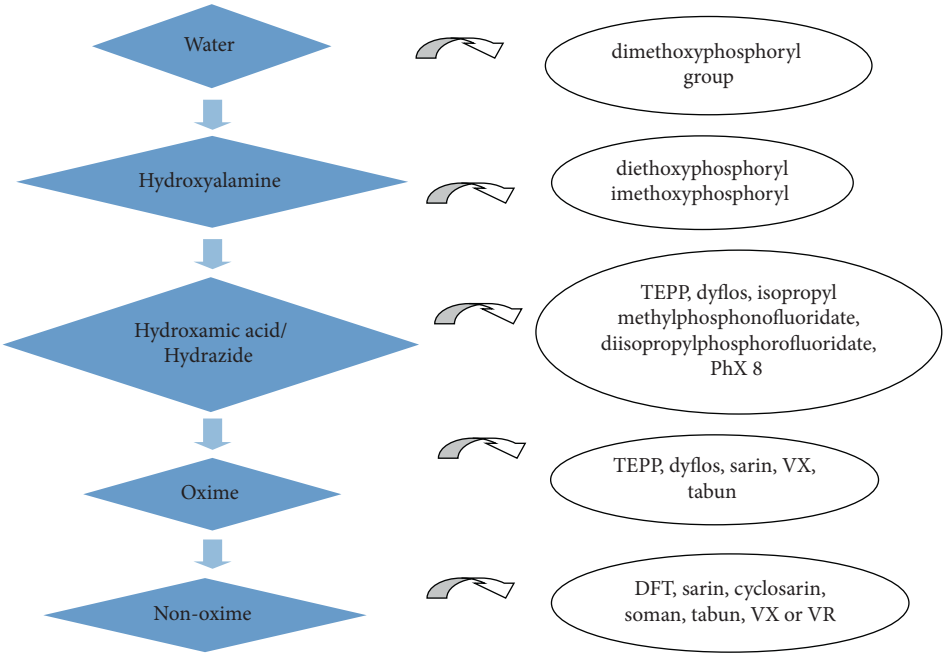

Figure 4: The development of OP-inhibited AChE reactivators and some of the inhibitors tested in the reactivation test.

and US research groups, in 1955 [13, 14], who initiated these studies which spearheaded the development of oximes to the present day. They reported that these compounds of a new series are effective antidotes for ChE inhibited by sarin, TEPP, or dyflos in both the rat brain and red cell. The effectiveness of these compounds was reported as superior compared to hydroxamic acids, mostly towards sarin-inhibited ChE. Water, hydroxylamine, and hydroxamic acids were the earlier reactivators tested prior to oximes [15].

As previously mentioned, the initial effort was targeting the charged mono- and bispyridinium oximes. AChE comprises two important sites: the esteric and anionic sites. OP is attracted to the esteric site and, thus, binds to the hydroxy component of the enzyme, resulting in the

inhibition of the enzyme. Conversely, oxime is attracted to the anionic site of the enzyme, and due to its oximate ion nucleophilicity, phosphate and serine residue that is covalently bonded is attacked by oxime. The OP then leaves the site and regenerates the enzyme.

The first commercialized oxime 2-PAM is monopyridinium oxime. Strong binding of the positively charged pyridinium towards the enzyme active site and the precise orientation of the oxime group for the phosphyl moiety disruption are the two factors contributing to the effectiveness of the charged oxime [16]. This oxime efficiently reactivates sarin or VX-inhibited AChE [6, 17–21]. 2-PAM iodide given with atropine and diazepam had been used to treat victims during the Tokyo sarin attack in 1995, and its clinical report was very encouraging [22]. Nevertheless, 2-PAM was not successful in the reactivation of the tabun-inhibited or soman-inhibited enzyme [23, 24]. Thus, many efforts on the development of novel reactivators to treat tabun and soman poisoning have been carried out. To date, K203 has been nominated as the best treatment for tabun-inhibited AChE [25, 26], and this reactivator is currently under development [27].

The efficiency of monopyridinium oximes is further improved with the attachment of a ligand that can strongly bind to the AChE, thus orienting the oxime group in the active site [28]. This finding has led to the synthesis of potential bispyridinium oximes between 1959 and 1968. The examples of bispyridinium oximes are MMB-4 (methoxime) and TMB4 (trimedoxime) [29]. Both oximes were reported to be able to reactivate tabun poisoning [30, 31]. A clinical trial study has been performed for the treatment of parathion poisoning using obidoxime, which is another example of bisquaternary oximes. Obidoxime is the TMB4 analog in which its structure contains one oxygen heteroatom in the bridging alkyl chain in between the two pyridinium rings. The oxime potential is affected by this heteroatom. Obidoxime has been certified as safe and exhibits the potential to reactivate parathion-inhibited AChE [32]. 2-PAM and obidoxime have been introduced into clinical use in the 1950s and 1960s, respectively [33–37].

Since TMB4 shows higher potency compared to monopyridinium oximes, another aldoxime, HI6, has been synthesized as a derivative of TMB4 structure [38]. HI-6 is not effective against all reported nerve agents since its effectiveness depends on the nature of the phosphoryl group of the inhibited AChE. For soman poisoning, HI-6 (asoxime) in combination with atropine is the chosen therapy [39]. HLö 7, the analog of HI-6 which carries two oxime functions in positions 2 and 4 at a single pyridinium ring, had a greater reactivation potential compared to HI-6. Hence, this oxime has been considered as a broad-spectrum oxime and displayed better therapeutic effectiveness towards several nerve agents as well as tabun [40, 41]. However, since this compound is hard to synthesize, unstable in aqueous solutions, and exhibits higher toxicity, there has been limited interest in the further development of HLö 7. Consequently, HI-6 remains a key for the broad-spectrum candidate [42–44]. Reiner and Rudolph have described the combination of their screening compounds (consisting of pyridinium, imidazolium, and quinuclidinium ring with different substituents and chains linking rings) with atropine to be effective antidotes against the organophosphate nerve agent's tabun or soman. The therapeutic factor ≥2.0 has been shown through animal study [45].

The development of oximes continues for the treatment of aging since 1966 (Figure 5). Pretreatment of aging via AChE effectors is one of the approaches to lower the aging rate since it cause aging retardation [46]. However, these effectors must be consumed before AChE is completely aged. Gallamine triethiodide and propidium iodide are the reported AChE effectors since these compounds act as allosteric ligands of AChE and bind at a peripheral anionic site [47, 48]. Besides, 2, 4-dimethylimidazole has been reported by Sterri to lower the aging rate by 70% towards the AChE inhibited with sarin [49]. These efforts were continued until 2008. Nonetheless, the aforementioned effectors have not been clinically utilized to slow down aging, which might be due to their low activities. The effective concentration of the clinical treatment is on the mM scale, which is too high and may exhibit toxicity [50].

In addition, aged AChE can be realkylated by suitable alkylators which might help in postaging treatments (Figure 6). The alkylators reverse this dealkylation reaction by realkylation of the oxyanion on the phosphoryl adduct. Thus, after realkylation, the negative charge on the phosphoryl group will be neutralized, and the reactivation by oxime reoccurs. The examples of electrophilic alkylating agents include sulfonates, haloketones, methoxypyridiniums, sulfoniums, and quinone methide precursors [51–55].

The other two approaches are by upregulation of AChE expression which can be activated by the exogenous AChE and some peptides. The exogenous AChE can be whole blood or purified AChE, either from human or nonhuman species. However, this approach does not revive aged AChE but may recompense for lowered active AChE levels [50].

The strategies to produce oximes that can penetrate BBB include incorporating oximes with sugar moiety which will be recognized by the facilitative glucose transporters. Hence, these novel sugar-oxime conjugates can be transported across the BBB (Figure 7). Literally, several oximes have been reported to have the ability to penetrate the BBB, for example, sugar conjugated-pyridinium aldoximes in which the sugar conjugated to the pyridine ring [57, 58]. More recently, N-[(3-β-d-glucopyranosyloxy) octyl]-2-pyridiniumaldoxime chloride has been synthesized by Garcia et al. and shown to be a potential BBB-penetrating reactivator [59]. This oxime is tested towards AChE and BChE inhibited with DFP, paraoxon, sarin, and VX. The *in vitro* and *in vivo* studies of the reactivator show the ability to reactivate the inhibited AChE and BChE from humans, guinea pigs, and mice, either in the blood or CNS. However, it is suggested that high treatment doses may increase the efficiency of the reactivator. The development progress of the BBB-penetrating oxime is slow, and there are no reported novel compounds that are suitable for advanced development or into clinical use [36].

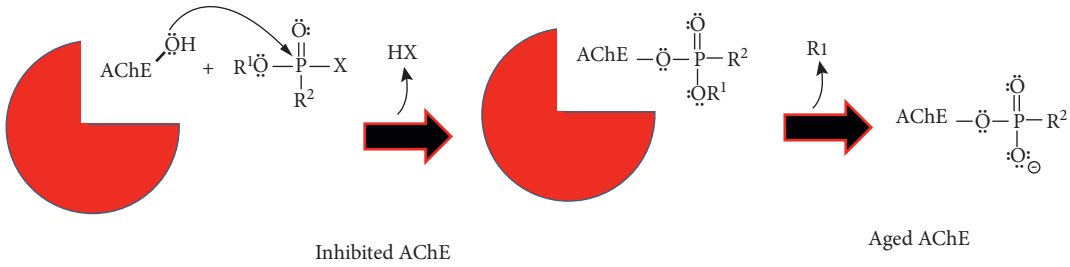

Figure 5: Scheme illustrating aging of AChE.

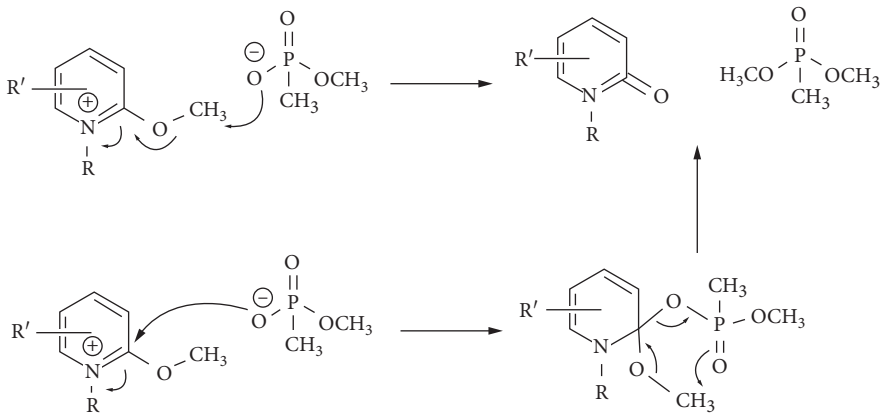

Figure 6: The alkylation of aged AChE with methoxypyridiniums. Two possible mechanisms of methyl transfer from methoxypyridiniums to phosphonates were proposed in [51]. Pictures were adapted from [50].

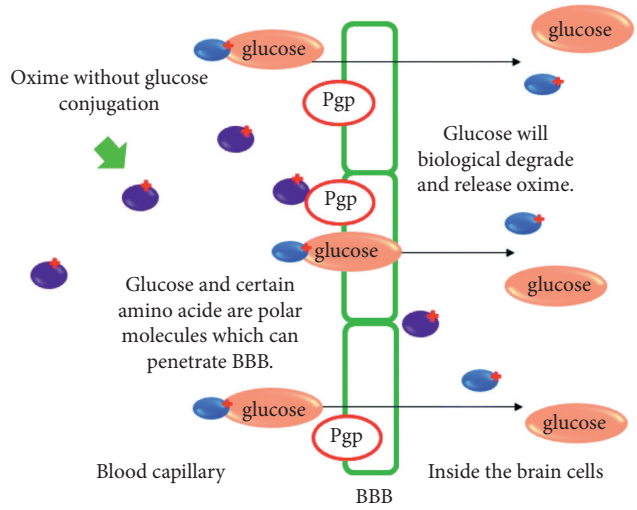

Figure 7: Schematic diagram of BBB penetration of glucose-conjugated oxime. The picture was adapted from [56].

The searching and exploration of enhanced uncharged oximes with the ability to reactivate human AChE are still needed [60, 61]. Recently, seven candidates of uncharged acetamido bis-oximes have been synthesized as reactivators [62]. Bis-oximes consist of two oxime groups that are connected to the same central, saturated heterocyclic core. Diverse protonation of the heterocyclic amines and oxime groups of these bis-oximes lead to the equilibration up to 16 different ionization forms. The compounds are in uncharged forms that can penetrate the CNS and also numerous zwitterionic forms optimal for the reactivation to occur [62]. They modified these bis-oximes from the X-ray structures of the monoxime RS194B reversibly bound to native and VX-inhibited human AChE (*h*AChE) [62]. Previously, the potential of a novel zwitterionic and centrally acting oxime RS194B to reactivate sarin- and paraoxon-inhibited

macaque AChE and butyrylcholinesterase (BChE) has been successfully tested *in vitro and in vivo* [62].

The improvement of the reactivation potential was in agreement with the prolific position of one of the two nucleophilically reactive aldoxime groups. Additionally, the dynamic charge distribution and the correct binding orientation between the three or four ionizable groups of the novel heterocyclic bis-oxime leads to better diversity of the zwitterionic forms which are supposed to be mostly in charge of the nucleophilic reactivation of OP-*h*AChEs.

A recent study by Zorbaz et al. has reported the efficiency of bispyridinium oximes with one (K865, K866, and K867) or two (K868, K869, and K870) ortho-positioned chlorine moieties, to reactivate human butyrylcholinesterase (BChE) inhibited by sarin, cyclosarin, VX, and tabun [63]. These compounds are similar to the previously known K027, K048, and K203 oximes which are potent reactivators of human AChE inhibited by nerve agents. With their ability to reactivate both AChE and BChE, these compounds have the potential of pseudocatalytic scavenging of most nerve agents.

As it was described many times, there are only few commercially available AChE reactivators on the market: pralidoxime (2-PAM; P2S; and 2-hydroxyiminomethyl-1-methylpyri-dinium chloride or methansulphonate), trimedoxime (Fosan®, 1, 3-bis (4-hydroxyiminomethylpyridinium)-propane dichloride or dibromide), obidoxime (Toxogonin®; LüH-6; 1,3-bis(4-hydroxyiminomethylpyridinium)-2-oxapropane dichloride), methoxime (MMC-4; MMB-4; and 1, 1-bis (4-hydroxyiminomethylpyridinium)-methane dichloride or dibromide), and HI-6 (1-(2-hydroxyiminomethylpyridinium)-3-(4-carbamoylpyridinium)-2-oxapropane dichloride or dimethanesulfonate). Although thousands of oximes have been investigated and developed from 1955 to date, only few oximes are applied for clinical purposes or advanced development. An improved reactivator with a closer and more critical approach to the oxime concept along with the factors determining its *in vivo* effectiveness is needed.

The application of oxime varies between countries. For example, in the USA, 2-PAM Cl is a licensed oxime. However, most of Europe and Iran preferred obidoxime as their licensed oxime [64]. Iran used this oxime in small quantities. Due to the carcinogenic intermediate being formed during the synthesis process of obidoxime, this oxime is not licensed in the USA. TMB-4 is preferred in Israel while Canada is in the middle of changing its licensed 2-PAM Cl to HI-6. Rather than using 2-PAM Cl, Japan preferred 2-PAM iodide due to cultural reasons. Thyroid disease with a high baseline rate predisposes physicians to treat with iodides where feasible. A higher dosage of 2-PAM Cl (≥2000 mg) can also trigger dangerous hypertension; thus, in the USA, this oxime can only be found at poison control centres [65]. Atropine alone is used if there is a need for prolonged treatment during that time.

1.2. Limitations of Oxime Therapy for OP Poisoning. Several factors contribute to the challenges of using reactivators as a treatment in OP poisoning. Firstly, the probability of the presentation's differences in the acute toxicity symptoms of both aliphatic and aromatic OP pesticides as well as their phosphyl moiety has not been fully understood yet. Secondly, AChE's side chains and aromatic rings may present structural and thermodynamic properties disadvantageous towards current and next therapeutic modalities. This has become a subject of concern, and consequently, new therapeutic is hard to develop.

Apart from that, the stability of the reactivation intermediate product has also been an issue. Generally, in some cases, AChE reactivation has resulted in the stable production of phosphoryloxime intermediate which inhibits AChE at higher rates compared to the parent oxons and is eliminated gradually. However, this condition is likely to occur towards 4-pyridinium aldoximes in comparison to the phosphoryloximes from 2-pyridinium aldoximes which is easily altered [34]. Another limitation of oximes, specifically 2-PAM, is that this oxime is not a broad-spectrum antidote and is restricted in its usage against OP toxicity, either from OP pesticides, OP chemical weapon agents, OP chemicals (only those with anticholinesterase activity), or cholinesterase inhibitors.

While oximes cannot penetrate the BBB, even with the latest design of oxime, OP nerve agents can simply do so [65]. Even with the latest strategy to enhance the lipophilicity of oximes by structural modifications, the attempt was only successful via *in vitro* study. Based on *in vitro* results, K869 oxime exhibits slightly higher effective permeability values in the parallel artificial membrane permeability assay (PAMPA). However, further *in vivo* evaluation shows the penetration of the oxime towards BBB recorded only a small amount of oxime (~60 ng/g of tissue) was found in the brain about 30 min after oxime administration. The penetration of K869 into the brain did not exceed conventionally used oximes since the brain/plasma ratio calculated is less than 1% [66].

Hence, oxime primarily acts at nerve junctions and works best to reverse the paralysis of respiratory muscles but does not affect centrally mediated respiratory depression. As a consequence, 2-PAM is administered together with atropine which can penetrate the BBB. During the treatment of OP poisoning, atropine is given before the administration of 2-PAM since atropine can antagonize the muscarinic effects of OPs. The efficiency of atropine in OP poisoning is well established compared to 2-PAM where its clinical use is still being researched to improve its ability to provide therapeutic relief.

Throughout this period, broad research efforts have led to the preparation of unlimited experimental oximes and, more recently, certain nonoxime reactivators. The intention is to use as a substitute or as an adjunct to the established and licensed oximes. However, none of them are yet to be manufactured. New oxime's structure, uncharged oximes, conjugation of uncharged oximes, and sugar-oxime moieties are among several strategies to increase the BBB penetration efficiency of oximes [61]. It has been reported that oximes get access into the brain and, thus, reactivate inhibited local AChE. Even the oximes in the central nervous system exhibit significantly lower concentration than in the plasma, and

they can reduce the effect of OP-induced brain using other than the AChE reactivation method of action. The method of action might involve centrally neuroprotective mechanisms.

In some cases, 2-PAM is attracted to the aromatic residues of inhibited AChE in the nonproductive configuration to reactivate AChE, while the structural diversity of OPs hinders the effective reactivation [56]. To overcome this problem, the reactivators should be improved to optimize its nucleophile within the AChE active-center gorge. An example of the reactivator that has been reported to overcome the nonproductive configuration issue of oxime is the aforementioned monoxime RS194B.

Another issue that is of concern is an effect called "aging" which is the result of the OP-inhibited AChE that has undergone dealkylation reaction. The dealkylation reaction can follow inhibition, thus producing an oxyanion on the phosphoryl group [50]. Due to this aging event, the oxime must be administered before this event occurs. There is no clinically relevant spontaneous reactivation of AChE occurring before aging has occurred in the case of soman poisoning since the aging occurs so fast. In other words, resynthesize of AChE is the only way to recover the function. Consequently, it is a must that an oxime is administered quickly after soman exposure so that some reactivation of AChE occurs before all the enzymes become aged [67]. However, in cases of acute OP poisoning, even when the oxime is administered before AChE aging is thought to occur, the clinical benefits are not very encouraging [34, 67]. Therefore, it is vital to develop new therapies for patients presenting severe OP poisoning. Each nerve agent has a different period of aging. Several aging side reactions are very slow that they can be clinically eliminated. The aging halftime of VX, sarin, tabun, and soman is 40 hours, 3-4 hours, 13-14 hours, and 2 minutes, respectively [68]. Consequently, if the patient is poisoned by soman, oxime therapy is useless unless the patient is given treatment directly. Efforts to replace 2-PAM with more efficient AChE reactivators by the United States and other countries are ongoing, but there are none that are close to FDA approval.

Although new improved oximes are needed to treat OP poisoning, the assortment and applications of novel oximes encounter several problems. Usually, intentional intoxications of OP pesticide happen in developing countries facing limited financial resources [69, 70]. Notwithstanding the number of patients requiring effective medical treatment is extremely large, the continuing controversy on the virtue of oximes [67, 71], the effort in designing meaningful phase II clinical studies [70], and the hesitancy of the pharmaceutical industry to involve in oximes hinders a wider and optimized use of the recognized oximes 2-PAM and obidoxime. Hence, the intensified research on improved reactivators against OP pesticides is unlikely.

Several cases of OP poisoning involved the ingestion of OP pesticides in large quantities, thus resulting in very high OP concentrations in blood. The ingested OP is spread to the entire body with the highest amount being stored in fat-rich tissues [72]. Usually, several weeks after OP exposure and adsorption, this OP will leach out from the fatty tissues. The leaching of OP from this stored fat will eventually cause serious issues to treat the severe OP poisoning victims as the OP will return into the blood circulation. Consequently, OP continues to inhibit AChE at the neuromuscular junctions throughout the body. Besides, due to the lipid reservoir of pesticide, patients frequently need to continue 2-PAM therapy for several weeks after they ingest pesticides with the highly lipophilic property such as diazinon.

Based on the cohort study of patients poisoned with dimethoate in Sri Lanka, it is proven that patients with blood dimethoate concentrations of above 750 μM cannot survive, regardless of maximal conventional therapy with oximes [73]. It is assumed that the degradation or functional inhibition of the ingested OP will decrease the blood OP concentrations, thus allowing a higher percentage of patients to survive. This prolonged deposition of OP in body tissues is one of the factors highlighting the importance of the enzymatic degradation of OPs.

1.3. Applications of Enzyme Therapy for OP Poisoning and Its Limitations. The emerging of two unique protein classes in the treatment of OP poisoning such as stoichiometric bioscavengers that can trap OPs and catalytic bioscavengers which can degrade OPs has started in early 1957. These enzymes were particularly studied since they allow effective detoxification and decontamination without toxicity or environmental impact [74]. Apart from that, bioscavengers also have a rapid and wide range of actions towards a variety of toxic OPs including sarin, soman, and tabun [75]. They are readily absorbed from the injection sites and exhibit extended circulatory retention time [76]. A combination treatment for skin decontamination in which OP hydrolases are incorporated with oxime is preferred to detoxify all phosphonylated oximes with little substrate specificity [77].

Catalytic bioscavengers are capable in hydrolyzing OPs in a relative high turnover which indicates better protection compared to large doses of costly low-activity enzymes. An OP-hydrolytic enzyme is widely used in detoxification, for example, phosphotriesterases (PTE) and glutathione-S-transferases (GST) [78, 79] (Figure 8). The importance of PTE towards the toxicity of OP insecticides has been discovered to be critical as its activity can drastically influence the toxicity. The destruction of diazinon, on the other hand, is carried out by glutathione S-transferase [80–86]. The hydrolysis products of this reaction are the nontoxic metabolites glutathione conjugate S-(2-isopropyl-4-methyl-6-pyrimidinyl) glutathione and diethylphosphorothioic acid.

A test on the ability of OpdAs to hydrolyze OP insecticides in the sample consisting human serum and clinically appropriate minipig models has been carried out [87]. The results show that the hydrolysis rate between 856 (SD 44) down to 0.107 (SD 0.01) moles of substrate hydrolyzed/mole of enzyme/sec (kcat) for quinalphos and phenthoate has been achieved, respectively. The highly efficient production of all the aforementioned enzymes from this prokaryotic system leads to the idea of producing it commercially such as streptokinase. However, due to the consequent risk of unfavourable reactions and immunogenicity, the subsequent application in humans will be limited over the next 12

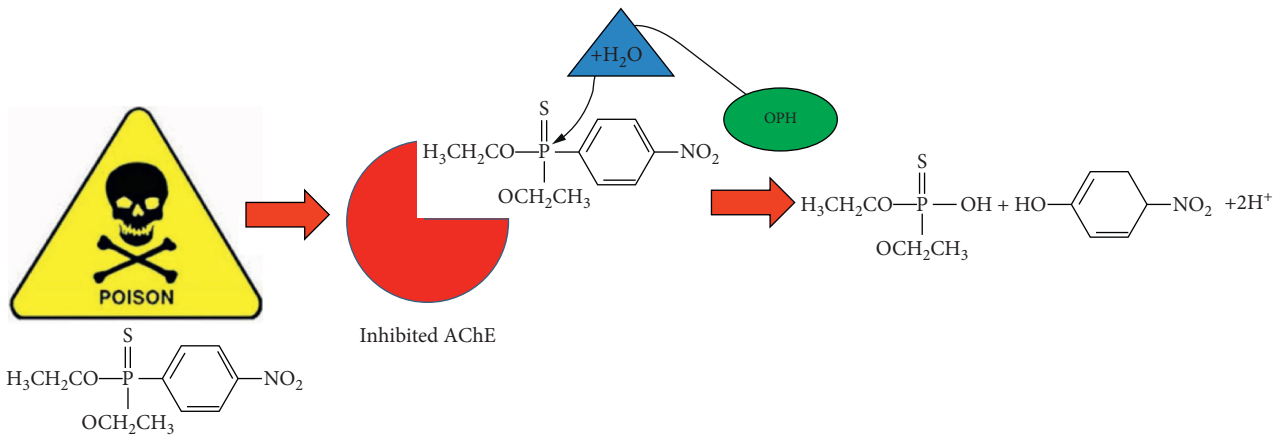

Figure 8: Schematic of OP insecticide hydrolysis by OP hydrolases. The products of hydrolysis do not inhibit acetylcholinesterase.

months [88]. Before clinical use, some parameters such as human safety, immunogenicity, and tolerance must be tested.

Plasma paraoxonase-1 (PON1) is one of the examples of OP-hydrolytic enzymes in human plasma. To increase its efficiency against OPs, this enzyme has been mutated at the catalytic site as what has been reported by Kirby et al. [89]. The hydrolysis activity of PON1 has improved 9-fold compared to its native. Nevertheless, the absence of a proper hydrophobic environment affects the catalytic efficiency. Thus, for immune acceptance and half-life modulation, PEGylation is needed.

OP acid anhydrolase (OPH) is originated from *Alteromonas undina*. This enzyme with a molecular weight of 53,000 kDa composed of a single polypeptide chain has been successfully purified [90]. The substrate for OPH, diisopropylfluorophosphate, is hydrolyzed with a specific activity of ~575 μmol/min/mg of protein with its optimum activity at pH 8.0 and 55°C by this OPH. This enzyme prefers sulfhydryl reducing agents and manganese as its inducer.

The important of enzymatic degradation of OP is also applied in foodstuffs. As what we acknowledge, in order to control agricultural and domestic pests, organophosphorus pesticides (OPPs) are widely used. Through consumption of contaminated foods and water, the exposure towards OPP residues poses serious health threats to human health. Hence, the removal of the OPP residues from foodstuffs to enhance food safety is required. Probiotic microorganisms in contaminated foodstuffs have also been claimed to exhibit the functional capacity to degrade pesticides. A review by Sarlak et al. has provided the interactions between different OP pesticides (OPPs) and phosphatase from probiotics in various food and organism models. The toxicity and gut absorption of OPPs are decreased in food supplemented with probiotic strains via binding and/or metabolizing mechanisms. Mechanisms of action used by probiotics against OPPs are mostly associated to phosphatase capability. However, lactic fermentation by probiotics that can exclusively be used in fermented foods is crucial in this biological detoxification. Therefore, factors such as inoculated probiotic levels, initial pesticide concentrations, fermented food types, and environmental conditions on bioremediation activity of probiotics are important to be further investigated [91].

The second group is cholinesterases and other related enzymes in which these enzymes stoichiometrically bind and neutralize OP. This group of enzymes that act naturally to defend our body from OP intoxication is known as stoichiometric bioscavengers. They naturally and sufficiently protect low exposure doses of OP but ineffective for high-dose exposition [92]. These specific molecules irreversibly bind to pesticide OP in a mole-to-mole ratio. Human butyrylcholinesterase is the most advanced stoichiometric bioscavenger and known as pseudocholinesterase and it is found in the liver and plasma (Figure 9). Although the administration of exogenous butyrylcholinesterase can protect humans, however, by increasing the amount of the administered enzymes, certain metabolic processes or enhanced immunogenic reaction will occur. For that reason, protection such as PEGylation or the inclusion of these enzymes in nanocontainers should avoid immune responses.

Larger doses of these stoichiometric bioscavengers have been proven to act efficiently against soman and VX [93, 94]. Since the effective required doses are highly expensive, production of human butyrylcholinesterase on a larger scale has become the main focus.

Hence, this enzyme has been produced in a recombinant form. Unfortunately, the plasma half-lives of the recombinant butyrylcholinesterase are shorter as compared to its native form. Several studies are conducted to overcome this issue such as PEGylation, addition of peptides and fusion to albumin [95, 96]. PEGylation is also useful for protein stability.

Human butyrylcholinesterase (r-HuBuChE; PharmAthene Inc.), which has been successfully produced in a recombinant form and expressed in the milk of transgenic goats, has become commercially available. This recombinant form of r-HuBuChE is similar biochemically to plasma-derived HuBuChE through *in vitro* assays. The pharmacokinetic properties of polyethylene glycol coated (pegylated) form of r-HuBuChE were administered to guinea pigs. From the observation, it was found that the enzyme's half-life (t (1/

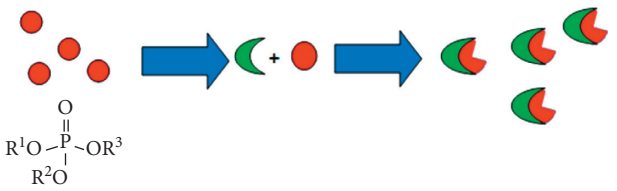

Figure 9: Schematic diagram of the stoichiometric bioscavenger mechanism. The red circle represents nerve agents, and the green represents the scavenger.

2)) and pharmacokinetic profile resembled that of plasma-derived HuBuChE and were rapidly bioavailable [97]. Therefore, in future studies, it is not possible to design a mutant form of HuBuChE with improved activity and stereospecificity towards the most toxic nerve agent isoforms.

Many studies on the successful application of human butyrylcholinesterase (E.C. 3.1.1.8) in providing a stoichiometric nature of the shield in humans against OP nerve agents have been reported [90, 98, 99]. Butyrylcholinesterase has shown the ability to protect up to five and a half times the median lethal dose of OP nerve agents in several animal models. This enzyme has been purified from blood plasma and has been given to animals (26.15 mg/kg ≡ 308 nmol/kg) by the intravascular or intramuscular route prior to either soman or VX uptake. This resulted in the increment of the median lethal dose of soman from 154 nmol/kg to 770 nmol/kg using 308 nmol/kg of human butyrylcholinesterase. Besides, this enzyme was also shown to successfully increase the median lethal dose of VX from 30 nmol/kg to 312 nmol/kg [99]. There were reported enzymes that have been proposed for specific enzymatic treatments such as direct enzyme injection, liposome and erythrocytes carriers, PEGylated preparations, and extracorporeal enzymatic treatments [100].

Carboxylesterases (CarbE, EC 3.1.1.1) is another example of stoichiometric bioscavengers. Malathion and some other OPs are carboxylic acid esters. The toxicity of these OPs in mammals is very low due to the very high activity of carboxylesterases in different tissues of mammals. CarbE can hydrolyze esters of carboxylic acids which are the essential pathways to detoxify malathion and its toxic metabolite malaoxon [101, 102].

Apart from detoxification, enzymes for decontamination towards OPs have been developed using several different approaches which include chemical, physical, and biological decontamination. Enzyme treatment is one of the biological decontamination methods that have been applied [103]. Due to the stability issue in enzymes, the application of enzymes in decontamination is usually incorporated with immobilization strategies. Validated enzyme decontamination with its immobilization strategies are summarized in Table 1. There is emerging interest towards enzyme for OP decontamination which used a biocatalyst, namely, SsoPox, which has been isolated from *Sulfolobus solfataricus* (archaeon). The SsoPox was first described by Merone et al. [104]. Being hyperthermostable, this enzyme appears to be interesting enough to be applied as external decontamination for its stability and catalytic efficiency. Efforts to engineer this enzyme for detoxifying a broad spectrum of toxic OPs are ongoing [105].

The OpdA gene was previously isolated in *Agrobacterium radiobacter* P230 by Horne et al. [105]. Several *in vitro* studies have been performed as well as its use in a field trial [105, 106]. For example, a decontamination test towards 84,000 L of water from an agricultural site polluted with methyl parathion was performed, in which the OpdA successfully fixed to a matrix structure was able to clear> 90% of methyl parathion in a fast-water-flow passage in just 10 minutes [107]. An *in vitro* study shows this enzyme exhibits very high activity towards a broad range of pesticides that may be involved in human poisoning cases [87, 108].

Apart from the aforementioned ability of OPH in detoxification, this enzyme is also nominated as a perfect enzyme for bioremediation of insecticidal OPs with a rate that closes to the diffusion limits [90]. It can also degrade a broad range of nerve agents and some chromogenic phosphinates. Similar to OPH, PTE also has the ability to effectively degrading OP pesticides and G-series nerve agents such as soman, thus showing that PTEs have the potential to be both a therapeutic agent and an environmental decontaminant. Another group of PTE enzymes, OpdA (aryldialkylphosphatase) (EC 3.1.8.1), has also been proven to be useful for the environmental cleansing of OP insecticides and has been found to prevent death among rats and nonhuman primate models if given directly after exposure.

Most of the nerve agents contain a chiral phosphorus center with the SP-enantiomers being significantly more toxic than the RP-enantiomers. PTE which exhibits the ability to detoxify these OP, however, has the stereochemical preference for the RP-enantiomers. Thus, the designation of PTE mutants has been developed to test their hydrolysis ability towards a series of these OP enantiomerical analogs containing the relevant phosphoryl centers. Interestingly, some of the mutants with significantly enhanced, as well as relaxed or reversed, stereoselectivity have been reported [109].

The third group is pseudocatalytic, which is a mixture of ChE and oxime pretreatment [110] (Figure 10). When enzymes react with OPs to form a covalent adduct, in the presence of reactivators, it can act as a catalytic bioscavenger if both phosphylation and reactivation are together. However, the most important rule is the reactivation must occur before aging. Kovaric et al. have reported a study using this pseudocatalytic approach via *in vitro* reactivation of phosphorylated human plasma BChE [111]. They used bispyridinium oximes differ in the length and type of the linker between rings and the position of the oxime group on the ring. K117 [1, 1-(2, 2-oxybis (ethane-2, 1-diyl)) bis (4-hydroxyiminomethyl pyridinium) bromide] and K127 [4-carbamoyl-1-(2-(2-(4-(hydroxyiminomethyl) pyridinium-1-yl) ethoxy) ethyl) pyridinium bromide] show potent reactivators for tabun-inhibited BChE at 1 mM after only 20 min of reactivation. However, reactivation of BChE inhibited with paraoxon by all selected oximes was slow.

Other than HI-6, the efficacy of current oximes is narrow and oxime-induced reactivation of ChEs (human BCHE) is

Table 1: Validated decontamination and detoxification approaches using enzymes.

Authors	Enzyme and matrix for immobilization	Application
Caldwell and Raushel, 1991	PTE from *Pseudomonas diminuta* onto the trityl agarose matrix	Detoxify various OPs with higher affinity towards paraoxon
Raynes et al., 2011	PTE from *Pseudomonas diminuta* using amyloid fibrils generated from insulin and crystallin	Detoxify various OPs with higher affinity towards paraoxon
Gao et al., 2014	OpdA from using covalent immobilization onto polyester textiles	Effectively degrades organophosphate pesticides and environmental remediation (decontamination)
Suthiwangcharoen and Nagarajan, 2014	PTE from *Pseudomonas diminuta* using amphiphilic block copolymer	Detoxify various OPs with higher affinity towards paraoxon
Mechrez et al., 2014	PTE from *D. radiodurans* onto carbon nanotube paper	Environmental remediation of biomedical devices (decontamination)

Figure 10: Schematic diagram of the pseudocatalytic mechanism. The red circle represents the nerve agent, green represents the scavenger, and dark blue represents oxime.

slow for the pseudocatalytic scavenging of OP molecules' efficiency [112]. In contrast, as reported by Sit et al. [113] and Kovaric et al. [114], new imidazole aldoximes show to be promising reactivators for OP-inhibited AChE. The currently designated mutant of AChE, namely, Y337A/F338A, which does not age after phosphylation shows effective potent pseudocatalytic bioscavengers. Another reactivatable serine hydrolase such as human CaE-1 is also found to be of potential interest [115]. Overall, good bioscavengers must have these fundamental properties which are prolonged circulatory residence time and the absence of antienzyme antibodies following repeated injections [110].

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}. \quad (1)$$

1.4. Future Directions in the Treatment of OP Poisoning. Several different structural elements were incorporated into the oxime structure cumulating in uncharged oximes and nonoxime reactivators as recent strategies to develop reactivators that can penetrate BBB [116–119] (Figure 11). These reactivators should further investigate since they show a very promising value of antidotes. Another promising approach is to apply specific BBB transporters such as P-glycoprotein (Pgp) inhibitors and nanoparticles as drug carrier which has also been reported [120]. Due to the inadequate reports focused on the application of these approaches for oximes, the Pgp inhibitors and nanomaterial carriers for oxime delivery into the CNS need to be further studied in the future [61].

Apart from targeting the BBB-penetrating oxime, aging treatment is also one of the researchers' targets for future reactivator development. For aging treatment, Fas2-AChE chimeric proteins were proposed. This Fas2 moiety can anchor the protein to the NMJ and synapses, where endogenous native AChE is naturally located [50]. This work seems to be promising for the development of a new reactivator.

The future direction on the enzymatic treatment is towards the chemical scavengers which have been shown recently with the synthesizing of bifunctional oxime-hydroxamic acid hybrid molecules. These scavengers were proven *in vivo* to protect rat against sarin [121]. However, nearly all chemical scavenger systems depend on functionalized cyclodextrin-bearing nucleophile groups that degrade OP directly with a moiety that reactivates AChE inhibited by OP [122]. Their mechanism has been studied and shows that they belong to the stoichiometric scavenger family [123, 124]. They conclude that based on the *in vivo* data, some hybrids may serve as efficient small-molecule scavengers for mitigating the toxicity of OP nerve agents. Nevertheless, these OP-hydrolyzing catalysts appear more suitable for external decontamination at the moment. However, their usage in the future as economical and universal scavengers is not unimaginable [125].

Another point of view is due to the increments in genomic sequencing and cataloging of environmental microbes, new enzymes and novel pathways will be easier to obtain by researchers for the bioremediation of OPs and other environmental contaminants. By applying molecular biology tools and protein design, researchers have the opportunity to alter these enzymes to increase the substrate-binding ability and catalytic activity. Both current and future OP hydrolases are predicted to be developing due to these rapidly fundamental studies. The commercialization of these enzymes involves large-scale production with high costs, manufacturing, and stabilization. Although these factors have continuously being argued, Novozyme, Gingko Bioworks, and other companies continue to demonstrate the attainability and profitability of enzyme commercialization.

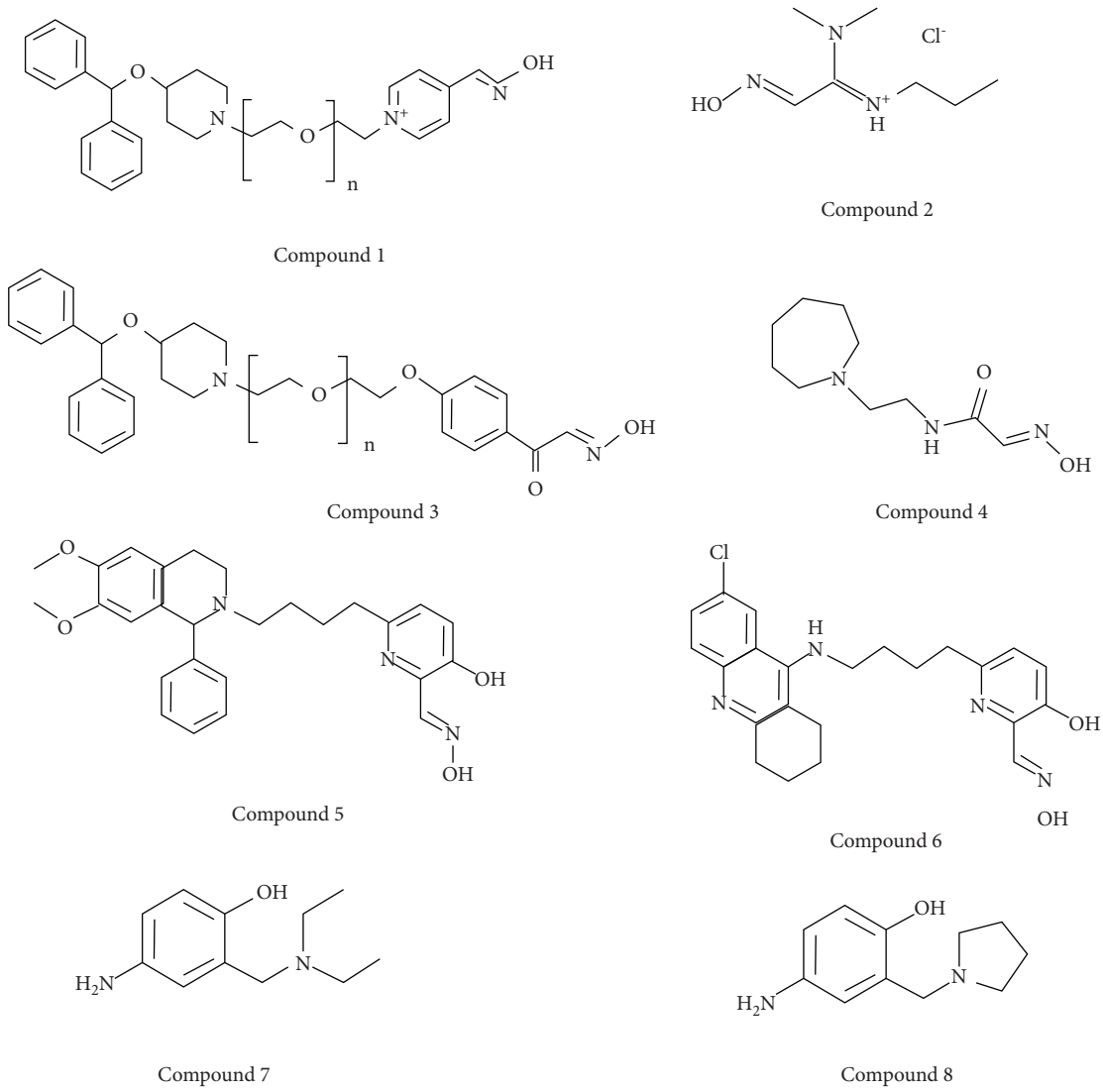

Figure 11: Example of uncharged oxime and nonoxime reactivators. Compounds 1–6 show primarily oximes, while 7-8 show nonoxime reactivators. Pictures were adapted from [36].

Since these companies have been backed up by financial companies and others, it is indisputable that the potential of biological systems has been recognized.

Apart from oximes and enzymes, very recent approach on the toxicity breakdown of OP using the photocatalytic approach has been carried out. A recent study from Filho et al. has proven the degradation of methyl parathion (nerve agent simulant) by a visible photocatalytic NbOFe nanofabric (NbOFe-NF) which has been produced by electrospinning solvent suspension of an iron niobate photocatalyst and polycaprolactone (PCL). After methyl parathion has been exposed to visible radiation for 48 h, 94.52% conversion has been achieved. The advantages of NbOFe-NF are the selectivity for the production of less toxic compounds in which it only cleaves the P-O-Ar system and the demethylation of DMPP by the nanofabric generates nontoxic compounds. This detoxifying process is wholly via photocatalysis, through h^+ and $O^{\bullet}H$ [126].

2. Conclusions

Both oxime and enzyme therapies for OP poisoning are important depending on the circumstances. Although oximes are proven to effectively preventing lethality from OP poisoning, postexposure convulsions, incapacitation, performance deficits, or, in some cases, permanent brain damage are not taken into account. These problems give rise to the development of bioscavengers as a pretreatment to cleave off highly toxic OPs before they get to their physiological targets. In conclusion, it can be seen that extensive studies of both oxime and enzyme therapy for OP poisoning have had a large contribution toward global health issues to date. Oximes remain to have potential as a reactivator for AChE in OP poisoning with the added benefit of being cheap to produce and easy to obtain. Nevertheless, enzymes also show great potential before further exploration as an antidote. However, it has a higher cost and a tedious process for the production of these enzymes, apart from laborious and

the administration of those enzyme proteins into OP exposed individuals. Hence, further research is necessary to overcome these issues.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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