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The Role of Glutathione Transferases in the Development of Insecticide Resistance

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Abstract

Glutathione transferases are multifunctional enzymes. Some of the known functions of the enzymes are biotransformation of xenobiotics, countering oxidative stress and participating in cell regulatory functions. As the isoforms present in number of classes the purification of a particular isoform for characterization is a challenging task. In insect, the study of GSTs is focusing on their roles in development of insecticide resistance. There were evident that certain classes of the enzymes are reactive towards conjugating the pesticides. This makes GSTs one of the enzymes of intention in the discipline of pesticide control management.

Keywords: Glutathione transferases, detoxification, insecticide resistance

1. Introduction

This chapter will review literatures concerning glutathione S-transferases from a broad point of view but with an emphasis on their properties, functions, and purification strategies and its challenges. The focus will be on the occurrence of GSTs in insects and the understanding of their role in insecticide resistance. The intention of this review will also be to look into the relationship of particular isoforms of the GSTs to responses to most used insecticides in agriculture.

2. Glutathione-dependent enzymes

Glutathione (GSH, γ -glutamylcysteinylglycine) is a low molecular weight sulfhydryl compound. It is a tripeptide with the sequence glutamic acid, cysteine, and glycine. GSH is a

crystalline solid with a melting point of 192–195°C and molecular weight of 307.33. It dissolves readily in water. There are two peptide bonds, two carboxylic acid groups ($pK_{\text{COOH}} = 3.53$ and 2.12), one amino group ($pK_{\text{NH}_3^+} = 8.66$), and one thiol group ($pH_{\text{SH}} = 9.66$). GSH is found intracellularly in all mammalian tissues and is the major nonprotein thiol compound present in the cell, with concentrations ranging from 0.1 to 10 mM. It is involved in a variety of metabolic processes, for instance, detoxication of xenobiotics, reduction of hydroperoxides, synthesis of leukotrienes and prostaglandins, maintenance of protein and membrane structures, and regulation of numerous enzyme activities. This functional diversity is due to the properties of the thiol group that participates in redox transitions, thiol exchange reactions, thioether formation, and radical scavenging.

A variety of different enzymes utilize glutathione in a variety of biotransformations [1]. Glutathione reductase (GR) catalyses the reduction of GSSG (oxidized glutathione) using NADPH as a reductant. GR is important in maintaining the high cellular reduction potential.

Selenium-dependent glutathione peroxidase (GPOX) is another type of GSH-requiring enzyme that catalyses the reduction of peroxides using GSH as the reducing agent. There are the glutathione S-transferases (GSTs) that are also GSH dependent enzymes with many catalytic activities including the conjugation of GSH to xenobiotics [2,3].

3. Glutathione S-transferases (GSTs, E.C. 2.5. 1.18) with diverse functions

GSTs are found in almost every species, including plants [4] microorganisms [5,6], and animals [7]. GSTs are divided into classes based on their amino acid sequence, immunological, kinetic, and structural properties. In mammals, at least nine classes of GSTs have been identified, namely, Alpha, Mu, Pi, Theta, Omega, Sigma, Zeta, Kappa, and a microsomal class. Human GSTs have been reviewed in reference [8, 9], and [10]. The majority of GSTs are found mainly in the cytosol. Each class consists of one or more protein isoforms. The classes are defined such that the amino acid identity between two isoforms of the same class is more than 50% but more than 30% if they are in different classes [11]. Human cytosolic GSTs are not only in cytoplasm but may also be localized in the mitochondria or the nucleus [12]. The microsomal family of membrane-bound GSTs is also reported and is different from cytosolic GSTs in molecular weight, subunit structure, and immunological reactivity [13-15]. The microsomal GSTs are trimeric, membrane-bound proteins. Mitochondrial GST 13-13 previously purified from rat liver [16] has been later characterized as GSTK1-1 of a Kappa class GST [17]. The Kappa class GSTs are located in mammalian mitochondria and peroxisomes [18,19] and are structurally distinct from the microsomal and cytosolic GSTs [20].

GSTs have a broad and overlapping specificity. Among the reactions catalyzed by GSTs are the substitution of halogens in halogenohydrocarbon, the addition to double bonds, the cleavage of epoxides, and the reduction of organic peroxides. 1-Chloro-2,4-dinitrobenzene (CDNB) is the most common substrate used to assay GSTs in the laboratory as most, but not all, GSTs show catalytic activity with it. Other substrates that have been commonly used to characterize the enzymes are 1,2-dichloro-4-nitrobenzene (DCNB), trans-4-phenyl-3-butene-2-

one (PBO), ethacrynic acid (EA), 1,2-epoxy-3-nitrophenoxypropane (EPNP), *p*-nitrobenzyl chloride (NBC), and sulfobromophthalein (BSP) (Figure 1).

GSTs catalyze the nucleophilic attack by the thiol group of reduced glutathione (GSH) on a wide range of electrophilic substrates. GSTs play important roles in the development of resistance to a variety of exogenous xenobiotics, such as chemotherapeutic drugs [21], chemical carcinogens [22], herbicides [4], and insecticides [7].

3.1. Conjugation of exogenous toxins (Biotransformation)

GSTs play important roles in the protection of macromolecules from attack by reactive electrophiles. The enzymes generally exist in dimeric forms with a subunit molecular weight of approximately 26 kDa. GSTs occur both as homo- and heterodimers. The cytosolic isoenzymes have two active sites per dimer that behave independently of one another [23]. Each active site consists of at least two ligand-binding regions, namely, the GSH binding site (hydrophilic G-site), which is specific for GSH, and the electrophile-binding site (hydrophobic H-site), which is less specific and thus enables GSTs to react with a wide variety of xenobiotics [24]. A review in reference [25] listed xenobiotics that could be conjugated by GSTs. These include halogenonitrobenzenes, organophosphorus compounds, steroids, $\alpha\beta$ -unsaturated carbonyl compounds, aryl halides epoxides, quinones, isothiocyanates, and aryl nitro compounds.

The conjugations catalyzed by the GSTs occur between the nucleophilic GSH and the compounds possessing a sufficiently electrophilic center [25]. The GSTs function by decreasing the pK_a of GSH, thereby allowing its deprotonation and the formation of a more reactive thiolate anion. In most GST classes (Pi, Mu, Alpha, and Sigma), a tyrosine residue in the N-terminal region interacts with GSH to stabilize the thiolate anion. In Theta and Omega classes, this role is carried out by serine and cysteine residues, respectively [9].

This GSH conjugation has been shown to occur in mammals, birds, reptiles, amphibians, fish, insects, and other invertebrates [26], and it is the first step of mercapturic acid formation that is one of the metabolic pathways for detoxication of xenobiotics *in vivo*. The glutathione conjugates, which are water soluble and generally nontoxic, may be converted to the corresponding cysteine conjugate following sequential removal of glutamate and glycine. The cysteine conjugate is either N-acetylated to be excreted as a mercapturic acid or cleaved to a mercaptan by β -lyase. The thiol can be then further metabolized, for example, to be excreted as a glucuronide [26, 27].

Prostaglandin D-synthase, the enzyme involved in production of the D and J series of prostanooids, was characterized as belonging to the Sigma class of GSTs [28]. GSTs also participate in the isomerization of biologically active molecules. A prostaglandin-H E-isomerase of *Ascaridia galli* [29] and prostaglandin-H D-isomerase of rat spleen [30] were identified as Sigma class GSTs. GSTs can also catalyze *cis-trans* isomerizations, for example, the isomerization of maleylacetoacetic acid to fumarylacetoacetic acid. The maleylacetoacetate isomerase activity of hGSTZ1-1 (human GST Zeta 1-1) has been investigated [31] using a spectrophotometric assay with ($\pm$)-2-bromo-3-(4-nitrophenyl)propanoic acid (BNPP) as substrate. Some GSTs

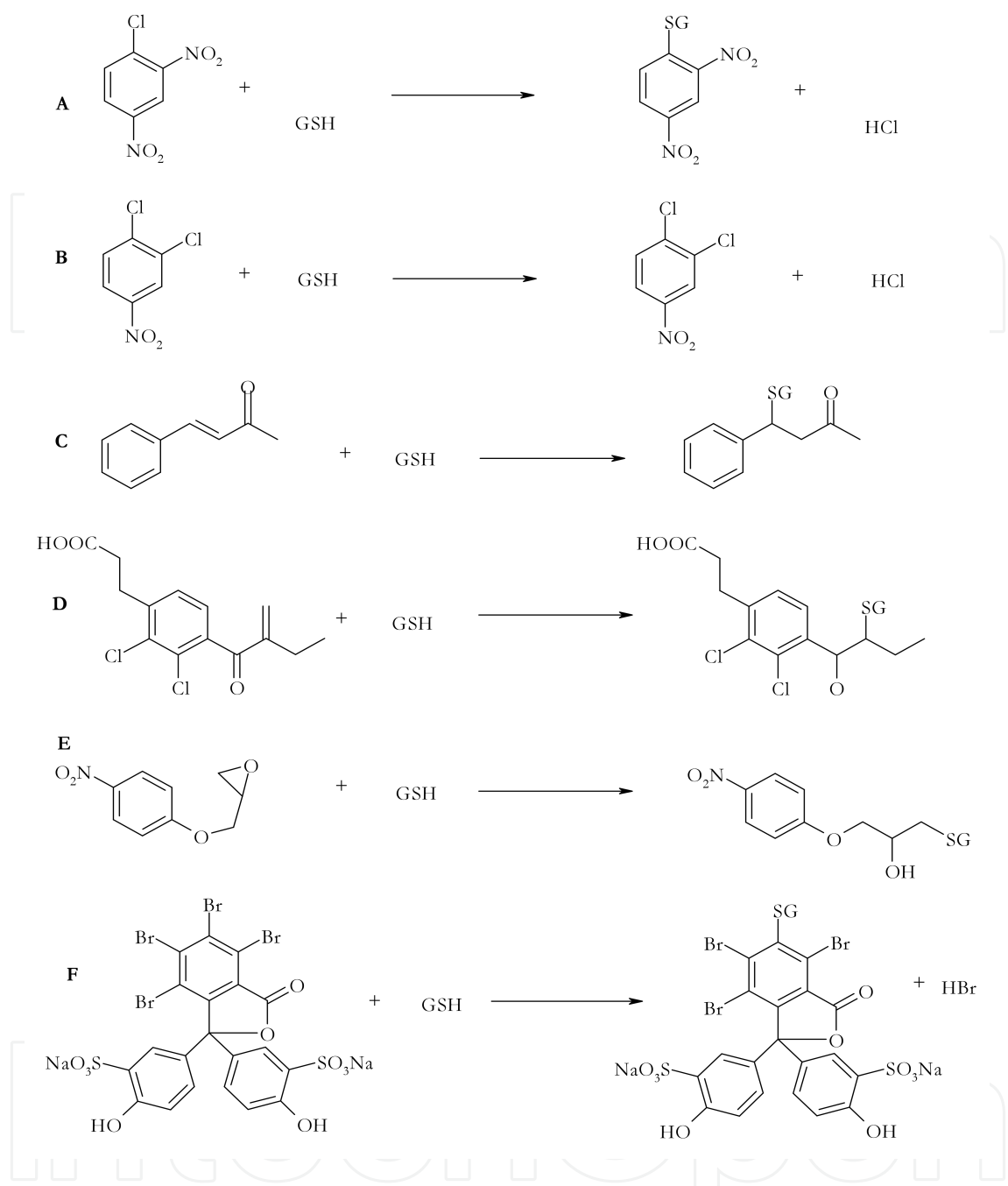


Figure 1. Enzymatic conjugation of common substrates by GST in the presence of GSH. (A) CDNB, (B) DCNB, (C) PBO, (D) EA, (E)EPNP, and (F) BSP.

possess keto-steroid isomerase activity and catalyze the conversion of Δ^5 -3-androstene-3,17-dione to Δ^4 -3-androstene-3,17-dione [21,32].

Human GST A3-3 was shown to efficiently catalyze the double-bond isomerization of Δ^5 -androstene-3,17-dione and Δ^5 -pregnene-3,20-dione [12]. Human GSTs were reported to act as retinoic isomerases that catalyze the steric conversion of 13-*cis*-retinoic acid (13-cRA) to all-*trans*-retinoic acid (t-RA) [33].

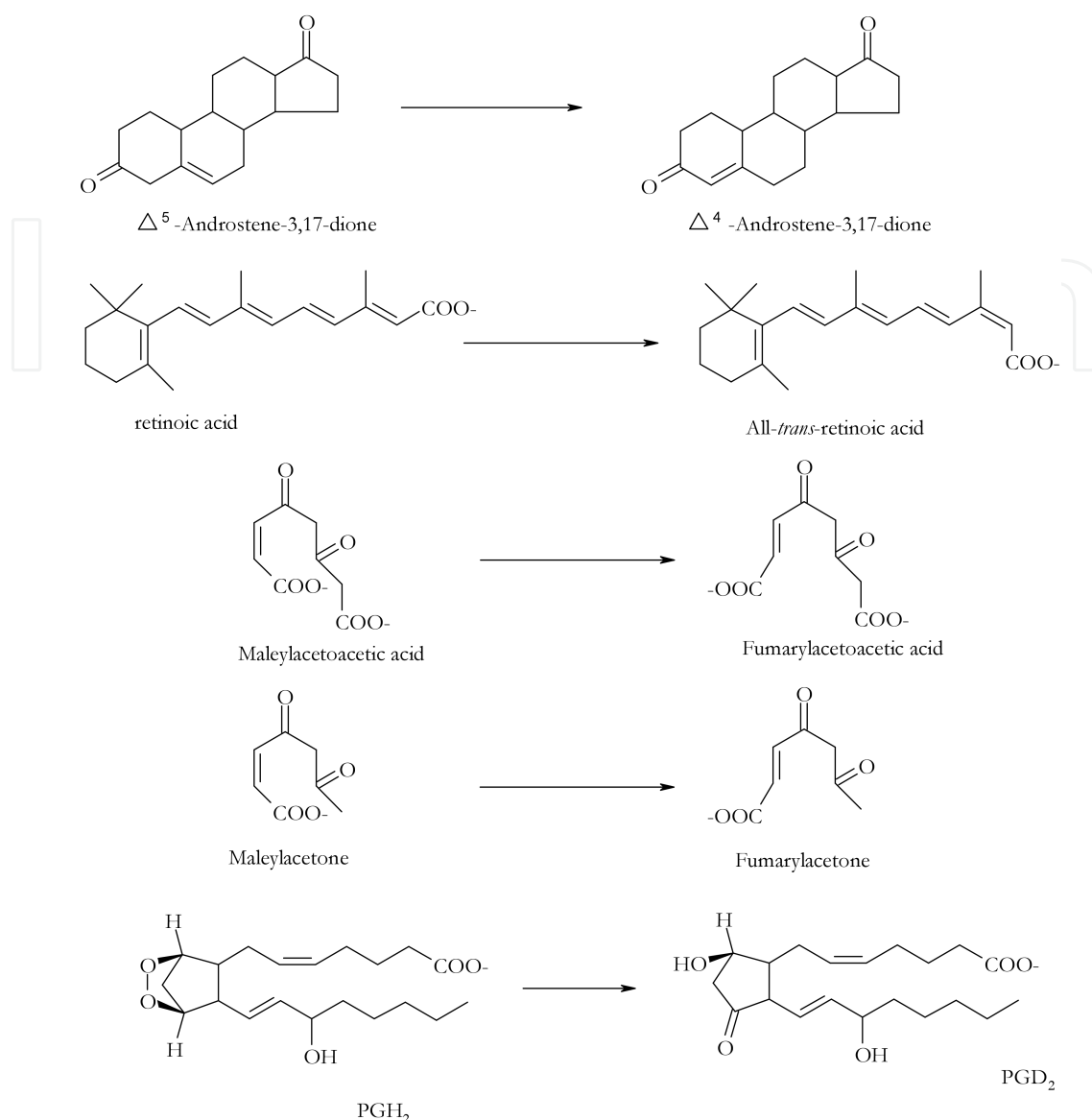


Figure 2. Some examples of GSTs with isomerase and synthase functions. (adapted from [9])

3.2. Participation in countering oxidative stress

Reactive oxygen species (ROS) such as superoxide anion, hydrogen peroxide, and the hydroxyl radical are constantly produced during normal aerobic metabolism. The free radicals may attack the polyunsaturated fatty acyl moieties and lead to the peroxidation of lipid bio-membranes. The cleavage of polyunsaturated fatty acids is known to be associated with formation of organic hydroperoxides and reactive aldehydes. These include alkanals, alkenals, and malondialdehyde. These may interfere with several biological processes such as DNA and protein synthesis by inhibition of specific enzyme reactions [34,35].

Peroxidized lipids, produced during oxidative stress, are substrates for GSTs. 4-Hydroxyal-kenals are derived from membrane-bound phospholipid hydroperoxides. They were shown

to be efficiently conjugated to GSH by GST A4-4 [36,37]. A membrane-bound mouse GSTA4-4 [38] and a rat GSTA8-8 [39,40] were also shown efficiently conjugating 4-hydroxyalkenals. It was reported that transfected mGSTA4 protects HL 60 [41] and K562 human erythroleukemia cells [42] against 4-hydroxynonenal-induced apoptosis.

Free radicals can also cause DNA peroxidation. The toxicity of thymine propenal, which is generated by oxidative damage to DNA, was shown to be substantially reduced when HeLa cells received GSTP1-1 and GSH [43]. The rat GST6-6 had previously shown active toward thymine hydroperoxide [44].

Within the cells, peroxides occur either as hydrogen peroxide (H_2O_2) or organic hydroperoxides, such as fatty acid and phospholipid hydroperoxides. GSTs protect tissues from endogenous organic hydroperoxides produced during oxidative stress [35,45]. Some GSTs have shown selenium-independent H_2O_2 and organic hydroperoxidase activity, which are involved in free radical reactions during oxidative stress [46]. A microsomal GST A1-1 of sheep liver exhibited peroxidase activity toward fatty acid hydroperoxides such as linoleic and arachidonic acid hydroperoxides [47]. Human GSTs, such as hGSTA1-1 and hGSTA2-2 [48,49], also exhibited glutathione peroxidase activity toward phospholipid hydroperoxide [50]. Other workers observed elevated GSTs in *Nilaparvata lugens* when treated with pyrethroids, which induces oxidative stress and lipid peroxidation in insects [51].

3.3. Involve in cells regulatory functions

Recent studies of GSTs have demonstrated that a Pi class GST is involved in regulation of c-Jun N-terminal kinase (JNK) signaling in mammals. GSTP interacts with c-Jun N-terminal kinase 1 (JNK1) suppressing the basal kinase activity [52,53]. A model of GST inhibition of JNK signaling was proposed [52]. Under a nonstressed condition, GSTp can exist as free dimeric enzyme or complexed with Jun-JNK thus inhibiting JNK. Upon stress, GSTP forms larger aggregates, which are unable to associate with the Jun-JNK complex, thus enabling the JNK phosphorylation of c-Jun. Phosphorylated Jun can act as a stable and active transcription factor. The accumulation of ROS in response to oxidative stress results in the activation of multiple stress kinase cascades and an elevated level of GSTp expression [54].

Apoptosis signal-regulating kinase 1 (ASK 1) can activate the JNK and the p38 signaling pathways. It plays important role in stress-induced apoptosis. Mouse GSTM1-1 was shown to physically interact with ASK1 and repress ASK1-mediated signaling [55,56].

It has also been reported that human GST class Omega, GSTO1-1, modulates calcium channel (ryanodine receptors, RyRs) protecting mammalian cells from apoptosis induced by calcium (Ca^{2+}) mobilization [57]. It was suggested that RyRs has two binding sites for GSTO1-1. The mammalian protein Bax (21 kDa) is an inducer of apoptosis. A study [58] has reported a plant GST (Theta class) as one of the Bax-inhibiting plant proteins, which prevent apoptosis in plants. GSTP1-1 was proposed [59] interacting with physiological nitric oxide (NO) carriers such as S-nitrosoglutathione (GSNO) and dinitrosyl-diglutathionyl iron complex (DNDGIC). In the absence of GSH, GSNO interacts with and modifies Cys⁴⁷ and Cys¹⁰¹ residues of GSTP1-1 by an S-nitrosylation reaction. Thus, in the cellular depletion of GSH, GSTP1-1 acts directly as an

NO carrier without losing its detoxication activity. The expression of 'tissue' transglutaminase (tTG) is induced in cells programmed to die such as in cells undergoing apoptosis. It was reported that [60] the overexpression of tTG in human neuroblastoma cells increases apoptosis. The study showed that tTG interacts with β -tubulin, histone H2B, and GSTP1-1 to form a protein complex. It was proposed that the interaction with tTG resulted in oligomerization of GSTP1-1. The formation of multimers of GSTP1-1 leads to inactivation of the enzyme toward ROS.

4. GSTs in insects

In insects, GSTs are classified into two groups, class I and class II GSTs [61]. According to a recent proposed classification [62], an insect-specific Delta class GST is classified as a class I GST. This includes those from *Drosophila melanogaster*, DmGSTD1 to DmGST10 [62,63]; *Musca domestica*, MdGSTD1 to MdGSTD5 [49,61] and *Anopheles gambiae*, AgGSTD1 to AgGSTD6 [64,65]. Class II consists primarily of Sigma class GSTs as identified in *D. melanogaster*, DmGSTS1 [66] and *A. gambiae*, AgGSTS1 [67]. A third proposed class of insect's GSTs (class III) [68] that comprises GSTs classified as the Epsilon class in *Drosophila* and the AgGST3-1 and AgGST3-2 of *Anopheles gambiae*.

Studies on insect GSTs were reviewed in detail [7,23,69]. GSTs have been detected in Lepidoptera, Diptera, Coleoptera, Dictyoptera, and Hymenoptera [23]. At present, only few insect GST structures are known. These include that from the Australian sheep blowfly, *L. cuprina* (Theta class) [66], mosquito, *Anopheles dirus* (isoenzymes 1–3 and 1–4 by [70,71] and fruit fly, *D. melanogaster* (GSTS1) [72,73].

4.1. Characterization of GSTs and its challenges

A problem faced during the extraction of insect GSTs is the possible presence of endogenous inhibitors [74]. Quinones and catecholamines released during homogenization can inhibit the GSTs' activity [75]. The last-named authors suggested the inclusion of GSH in the homogenizing buffer to protect the GSTs from inhibition. Polyphenol pigments have also been shown to inactivate the GSTs. The inclusion of 5–10 mM cysteine in the homogenate prevents the formation of polyphenol. The endogenous inhibitors can also be removed by initial loading of the crude homogenate through an ion exchange or gel filtration column [7]. There are many different strategies employed to purify the GSTs from insects. One of those is by using affinity chromatography with several different affinity matrices. A ligand, sulfobromophthalein-glutathione conjugate (BSP), has been immobilized to an agarose matrix by using either cyanogen bromide [76] or epichlorohydrin activation [77]. The enzymes bind selectively to the resulting matrices when a crude homogenate is applied directly to the columns. The bound enzymes can be eluted by using 0–5 mM of BSP [77] or 1–5 mM GSH solution [76]. The matrix has been used to purify a GST to homogeneity from *Galleria mellonella* [76,78], *Costelytra zealandica* [79], *Musca domestica* [77,80,81], *Drosophila melanogaster* [82] and *Wiseana cervinata* [83]. Another form of affinity matrix that has been used widely is the immobilized GSH-

agarose matrix [84]. The bound enzymes are best eluted from this support with GSH solution. This technique has been used to purify GSTs from a number of insects. These include *Drosophila* [85]. In another instance, a study [86] had used another form of affinity column, namely immobilized S-hexylglutathione [87] to purify GSTs from *Drosophila*.

Investigation of multiple forms of GSTs with different isoelectric points could be performed by using isoelectrofocusing [78,88,89] or chromatofocusing [90]. Purification by affinity chromatography followed by isoelectrofocusing revealed the existence of multiple forms of GSTs [91], in house fly strains Rutgers, Cornell R, and Hirokawa. The presence of multiple isoenzymes of GSTs have also been reported in other species, such as *Aedes aegypti* [92], *G. mellonella* [78], *Plutella xylostella* [92], *C. zealandica* [79] and *Tenebrio molitor* [94].

4.2. GSTs and insecticide resistance

The majority of studies on insect GSTs have focused on their role in conferring insecticide resistance. A review [95] has indicated the importance of genetic and biochemical mechanisms in *Drosophila* in countering toxins and thus developing resistance. There are two types of biochemical mechanism of insecticide resistance outlined [96,97]. The first is by selection of an altered target molecule so that no interaction between the molecules and the toxins occurs, resulting in target site resistance. The target sites of insecticides in insects include the GABA receptor, sodium channel, acetylcholine esterase, acetylcholine receptor, and juvenile hormone receptor. Second, through the process of metabolism, these toxins may be converted to less toxic and more easily excretable derivatives before reaching the target sites. This is a metabolic resistance. Several enzymes play important roles in these types of resistance, such as hydrolases, mixed function oxidases, and glutathione S-transferases and a variety of other conjugating (Phase II) enzymes.

High levels of GSTs have consistently been observed in resistant insect strains and play a major role in insecticide resistance [77,98,99]. Increased activity of GSTs in housefly was found to be associated with resistance to azinphosmethyl [100], parathion [98], pyrethroids [101], tetrachlorovinphos [102] and malathion [103]. *D. melanogaster* develops resistance toward several insecticides. These include malathion [104,105] and 1,1,1-trichloro-2,2-bis-(p-chlorophenyl)ethane (DDT) dehydrochlorinase [106]. Resistance to diazinon, chlorpyrifos, propanthos, and dichlofenthion and their correlation to increased GST activity has also been reported in larval *L. cuprina* [107].

GSTs have been shown to play an important role in insecticide resistance. The catalysis of conjugation of insecticides, such as organophosphorus compounds, chlorinated hydrocarbons, and carbamate insecticides is shown in Figure 3. It was classified three types of reactions catalyzed by GSTs in metabolism of organophosphorus insecticides [108]. The detoxification of organophosphates (OP) occurs by the conjugation of GSH to OP via an O-dealkylation or O-dearylation conjugation, which later forms O-alkyl, O-aryl, and phosphonate conjugates which are all less toxic derivatives.

For the organochlorine insecticides the process involves dehydrochlorination and the GSH conjugation to the parent molecules [97]. Pyrethroids, however, trigger oxidative damage in

cell. Therefore, GSTs role has been detoxifying the lipid peroxidation products resulted by the insecticide [51]. It is well known that some classes of GSTs have shown peroxidases activities. For example, a Delta class GST of *N. lugens* [51] and Epsilon class GST of *A. aegypti* mosquitoes [109,110] and Sigma class GST of *D. melanogaster* [111,112]. There was however report to suggest that protection against pyrethroids can be achieved through a passive sequestration process in which GSTs are capable to bind to various pyrethroids [113,114].

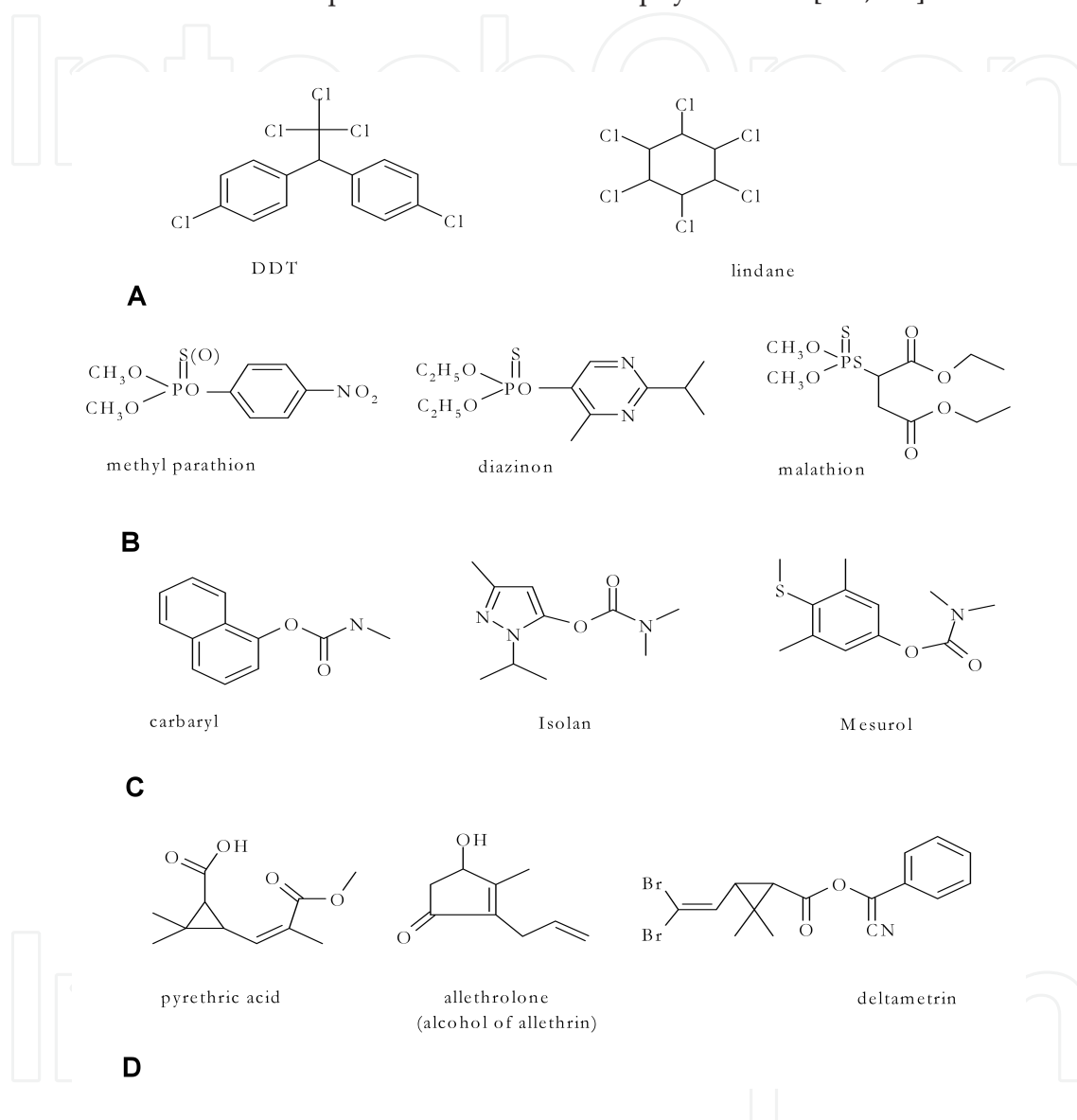


Figure 3. Structures of some (A) halogenated hydrocarbons, (B) organophosphorus, (C) carbamates, and (D) pyrethroids.

5. Summary

GSTs are enzymes of multi-functional roles. Studies in insect have always directed the role of GSTs in conferring resistance toward insecticides resistance. Several classes of GSTs have been

shown to counter the insecticides through direct GSH conjugation process and also their ability to react against lipid peroxidation products. This is due to the fact that some insecticides cause oxidative damage. Direct isolation of responsible GST from insect has been of a challenge due to limited ability of available affinity matrix to capture all classes of GSTs. The characterization of recombinant GSTs could have led to a better understanding of the mechanism of action and thus the regulation of the GSTs upon exposure to insecticides. The availability of fully sequence genomes in model insect such as *D. melanogaster* [115] and recently of *M. domestica* [116] could be of advantage for further studies in glutathione transferase-related insecticides resistance.

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