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# Defence against Oxidative Stress and Insecticides in *Musca domestica*

Tan Yong Hao, Siti Nasuha Hamzah and Zazali Alias

## Abstract

This review is looking at the way *Musca domestica* defends itself against harmful molecules. One of the most notable enemies is against oxidative stress. Over the years there were reports that indicated the development of resistance on range of pesticides that are used against the flies. Researches have demonstrated that there are several functional protein molecules which contribute directly or indirectly as a response to oxidative stress and resistance against insecticides. As currently, the whole genome sequencing of the organisms has enabled future study to be conducted in evaluating the behaviour of the targeted protein/enzyme in response to oxidative stress and intake of insecticides in the flies.

**Keywords:** *Musca domestica*, oxidative stress, insecticide resistance

## 1. Introduction

An estimated 150,000 of species of Diptera have been described [1], and houseflies (*Musca domestica*) are one of the wonderfully evolved organism. A notorious vector, houseflies are associated with more than 100 pathogens [2], and resistance towards insecticides of houseflies have been reported all over the world. According to Scott et al., *Musca domestica* is suitable as a model organism for resistance studies and development of new insecticides. The knowledge on cellular metabolism in recent years has been expanded to understand the metabolic aspect of oxidative stress. In *Musca domestica* alone, a few families of proteins have been more or less associated with oxidative stress response: glutathione S-transferases (GST) [3–5], superoxide dismutase (SOD) [6] and glutathione peroxidases [7–9].

## 2. *M. domestica* response towards insecticide

Naturally houseflies' main ecosystem role is to decompose and recycle organic material. Houseflies are synanthropic insect in urban areas where high densities of human waste are their food source [10, 11]. It has been known to be vectors of various diseases of over 30 bacteria, protozoan, viruses and helminth eggs [12]. It also transfers viruses such as polioviruses [13] and *Coxsackie* viruses, as well as numerous bacteria such as *Campylobacter jejuni*, *Helicobacter pylori* [14], *Salmonella* sp. [14], *Listeria* sp., *Yersinia pseudotuberculosis* [15], *Shigella* sp. [16], *Escherichia coli* [17], and *Vibrio* sp. [13]. Flies may also be vectors of protozoan flies such as *Giardia* and

*Entamoeba* [16] and eggs of several tapeworms [18]. In 2010, there were further proof on transmission of Newcastle disease virus (NDV—*Paramyxoviridae*), a highly infectious virus shed in the faeces in infectious birds [19] with *Musca domestica* as vector in both field and laboratory. More recently, *Musca domestica* were also reported to carry antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus* and ticarcillin-resistant *Pseudomonas* [20], which possess threat in hospitals and health-care facilities [18]. Flies are causing 6 million cases of childhood blindness each year (<http://www.who.int/topics/trachoma/en/>). *Musca domestica* also create implications in economical ways, and costs of pesticides were estimated at more than US\$200 million yearly in the United States [21] and US\$1.6 million in 1998 [22].

The types of insecticides used to control houseflies on field are adulticides and larvicides ([www.flycontrol.novartis.com](http://www.flycontrol.novartis.com)). Adulticides are carbamates (e.g. propoxur and methomyl), organophosphates (e.g. fenitrothion, azamethiphos and dimethoate), pyrethroids (e.g. cyfluthrin, deltamethrin and permethrin) and recently neonicotinoids (e.g. imidacloprid, thiamethoxam). Larvicides are insect growth regulators (IGRs) (e.g. triflumuron, diflubenzuron, cyromazine [23], and novaluron and juvenile hormone synthetic analogues (e.g. methoprene, fenoxycarb, pyriproxyfen [23] ([www.flycontrol.novartis.com](http://www.flycontrol.novartis.com))). Since the first case of DDT resistance is reported on the housefly [24], resistance of adult *Musca domestica* towards various insecticides in various sites (agricultural, wild and urban) is a fast-growing global issue. There has been an increasing resistance profile report from various places in the world.

In the United Kingdom, a resistance risk assessment done by [25] showed that although farmers claimed they had reduced using insecticides (a measure to reduce selective stress on field housefly strains), there was no sign of decrease of housefly resistance towards piperonyl butoxide synergized pyrethrins. Flies with high fenitrothion and dimethoate resistance were also discovered in Denmark [26]. In 1997, an increase in pyrethroid-resistant strains and widespread of azamethiphos-resistant strains in 21 different farms all over Denmark were confirmed [27]. In Argentina, a first insecticide survey was reported [28]. Several *Musca domestica* populations were found to be permethrin-, dichlorovinyl dimethyl phosphate (an organophosphate)- and cyromazine-resistant. In the neighbouring Brazil, [29] led a first evaluation of cyromazine resistance of houseflies in five different sites, and three out of the five sites indicated cyromazine resistance. There was a report suggesting the occurrence of insecticide tolerance in tsunami-hit villages in India [30]. With hygiene at minimum provision, immediate fly control was imposed by spraying 76% dichlorvos, and LD90 of adult housefly was 3.5–3.9 times higher than the flies from control sites. As in the United States, in a study tested against nine insecticides, the fly strains showed high resistances in tetrachlorvinphos, permethrin and cyfluthrin [31], while in southeastern Nebraska, houseflies are shown to be moderately resistant to permethrin yet extremely resistant to stirofos and methoxychlor [32]. Deltamethrin-resistant flies were discovered in urban garbage dump of cities of Beijing, Tianjin and Zhangjiakou [33].

In Malaysia, [34] resistance of housefly from a garbage dump, poultry farm and agricultural farm was evaluated. It was shown that garbage dump and poultry farm fly samples were more resistant than agricultural farm. It was also shown that two poultry farms in the state of Penang against malathion, propoxur and DDT, with resistance ratio, have been found with strong correlations against relative humidity, which is a first in field discovery [35]. However, on housefly larvae, resistance assessment has been relatively scarce with only a handful of feeding and toxicity tests done. A report on an increase in diflubenzuron resistance and new-found cyromazine resistant strain was also obtained [36]. A dip test-emergence test of *Musca domestica* third instar larvae on eucalyptol extracts has been done [37] with LD50 values of 118 mg/fly and 177 mg/fly on male and female flies, respectively.

### 3. Impact of oxidative stress-induced resistance

In an oxidative stress-induced insecticide resistance research, rats [38–40], humans [41], fresh water fish *Brycon cephalus* [42] and black tiger shrimp *Penaeus monodon* [43] have been used as models to investigate insecticide inflicted oxidative stress. Insecticides including pyrethroids [44, 45], organophosphates [46–48] and organochlorines [49] have known to be inducing oxidative stress. It was reported that there were changes in activities of the antioxidative enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase and in GSH level changes both in the liver and erythrocyte homogenate [39]. Molecular resistances are consisted of target site resistance and metabolic-based resistance [50]. Yet, most of the works, as far as *Musca domestica* is concerned, have been more in top-down approach. While genome sequencing was still ongoing for that time being, specific gene family is identified and sequenced before getting into expression studies. With other fly species such as the dipteran *Drosophila melanogaster* and *Anopheles* genome as comparable reference database, it was also concluded three groups of gene superfamilies are involved in metabolic-based resistance [51], i.e. glutathione S-transferases, cytochrome P450 and acetylcholinesterase.

In cytochrome P450, [52] it was revealed that three P450 genes, CYP4D4v2, CYP4G2, and CYP 6A38, were up-regulated in response to permethrin treatment on permethrin-resistant ALHF strains. By using PCR technology, constant overexpression of CYP 6A1, CYP 6D1 and CYP 6D3 in neocotinoid-resistant strains in Denmark during thiomethoxam challenge was demonstrated [53]. CYP6D1 was also found to be implicating more than 5000-fold of cypermethrin resistance in Learn pyrethroid-resistant strain found in New York [54]. Significant increase in non-specific esterases and glutathione S-transferases activities were also evaluated [34]. A remarkable drop on GST activity has been reported on a DDT-resistant strain 698ab [27]. Point mutation was reported as the cause of insecticide sensitivity in the case of acetylcholinesterases (E.C 3.1.1.7) [55]. As far as metabolic-based resistance is concerned, there are still much more questions to be addressed. A study [31] stated that there is very little knowledge about the mechanism of the pyrethroid resistance (monooxygenase/CYP450), although pathways have been elucidated via genomic means. There was a significant correlation between *kdr* allele (i.e. genes reducing the sensitivity of the nervous system to pyrethroids) frequencies and the levels of knockdown resistance by deltamethrin via a PCR-based assay [33]. It was also demonstrated that a behavioural resistance might be playing a role in contributing such resistance and such traits are still being inherited in the field [25]. The upregulation mediated by changes to transacting factors reveals that these mechanisms were underlying in some cases of resistances of P450, GSTs, and acetylcholinesterases [56, 57].

#### 3.1 Enzymatic removal of cellular hydrogen peroxide

It was suggested that aerobic organisms survive due to their evolved antioxidant capability [58]. Catalase (EC 1.11.1.6) was discovered in tobacco extracts [59]. Catalase detoxifies  $\text{H}_2\text{O}_2$  into water and oxygen [60]. Catalase is one of the well-described enzymes, and it is a class of enzyme including the iron-heme enzyme, catalase-peroxidases and a small group of manganese enzymes [61]. Superoxide dismutase (EC 1.15.1.1) is a well-known enzyme against oxidative stress. SOD1, the first superoxide dismutase to be identified, uses free radical as a substrate [62]. A metalloenzyme, superoxide dismutase catalyses the dismutation of superoxide anion ( $\text{O}_2^{\cdot-}$ ) to hydrogen peroxide and oxygen, as the first defence line against oxidative stress [63]. They are also known to exhibit additional peroxidase activity when hydrogen peroxide level is at its large. It has been suggested that the removal of superoxide



anion will reduce SOD alternate toxic behaviour [6]. Copper-zinc and manganese SODs scavenge and dismutate superoxide anion in mitochondrial electron transport systems. It was demonstrated that a manganese superoxide dismutase-deficient yeast thrived in hyperoxia conditions (95% oxygen, 5% carbon dioxide) under the removal of electron transport system [64]. A copper-zinc SOD1 in baker's yeast was characterized at the intermembrane space of mitochondria [65].

Glutathione peroxidase (EC 1.11.1.9) utilizes reduced glutathione (GSH) to decompose hydrogen peroxide [66–68]. This enzyme was discovered [66] and identified as selenocysteine enzymes at first [69], better known as GPx1. Later, more selenocysteines were identified such as GPxs-GPx2, GPx3, and GPx4 [70]. It was also found in mammals [68, 71]. Later, a catalytic cysteine residue on rat was discovered [72], known as GPx5, and followed by GPx6 [73] which is a selenocysteine proteins in humans but not in rats or mice [74]. Mammalians GPx7 and GPx8 were the last to be elucidated but have a low GPx activity [75].

Peroxiredoxins (EC 1.11.1.15) are another group of enzymes worth mentioning when discussing about oxidative stress in cellular organisms. Peroxiredoxins are a family of antioxidant enzymes [76]. Highly specific in reducing hydrogen peroxide [77], its cysteine residue makes up the active site of peroxiredoxins, which in turn are being oxidized into sulfenic acid and recycled back to thiol, via sulfiredoxins [78]. They also control cytokine-induced peroxide levels which, in turn, mediate signal transduction in mammalian cells [79].

#### 4. Oxidative stress-related proteins in *Musca domestica*

There are several possible candidates of oxidative stress defence proteins. Those are superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferases, GSSG reductase, thiol transferases, gamma-glutamylcysteine synthetase, and glucose-6-phosphate dehydrogenase. Oxidative stress hypothesis is evident on aging and has always been raising questions from researchers. *Musca domestica* [80], *Drosophila melanogaster* [81, 82] and *Caenorhabditis elegans* [83] are made as model tested on hyperoxia conditions. Aging is resulted from oxidative damage from cellular macromolecules [81]. It was stated that the main prediction of this hypothesis is that the rate of aging cannot be slowed down without corresponding attenuation of oxidative damage/stress [84].

GST gene family and their isoforms have been discovered to participate in oxidative stress pathway. Overexpression and peroxidase activity of GSTs in peroxide treatment were observed [85]. Other than oxidative stress resistance, GSTs detoxify xenobiotics, protect from tissue damage, participate in Jun-kinase signaling pathway and act as non-catalytic carrier proteins (ligandins) in the intracellular transport of hydrophobic compounds [3–5]. Glutathione synthetase (GSHs) are responsible in the antioxidant defence as the dominant non-protein sulphhydryls in the cell [86] forming conjugates non-enzymatically or more by the catalysis and mediation of GSTs.  $H_2O_2$  oxidizes thiolate group in cysteine residues (-S-) into thiols (-SOH), which is present in the exposing active site. Reaction against peroxidants is also energy-consuming due to the inhibition of oxidative phosphorylation [87] and deprives energy to maintain the recycling of NADPH during pentose phosphate pathway and glucose 6-phosphate dehydrogenase, making cells hyperglycaemic [88] and able to topple the condition of cell redox levels in levels of lactate/pyruvate ratio [89]. Most of the cases above were investigated towards organophosphates and pyrethroids. In cadmium ion treatment, concentration ranging from 0.2 to 5 mM in the medium, widely known to enhance reactive oxygen species in cell, increases the levels of superoxide dismutase [90]. Lowering the intake of selenium

via diet increases the events of a peroxidative injury. The group further purified the selenium-independent glutathione peroxidase [8] and suggested this enzyme and the related pathways should be in the picture during the investigation of insect antioxidant defence system. There was no direct research work on peroxiredoxins with relation to houseflies, and its mechanisms and activities *in vivo* are not much of knowledge. However, it was discovered that there was no increase in catalase activity even though the diet of selenium in *Musca domestica* was lowered [7]. Another investigation [9] in houseflies revealed that the total inhibition of catalase also did not affect the survival of the flies, although slight increase in the level of SOD activity was observed.

## 5. Conclusion

Despite such remarkable immunity and rising insecticide tolerance exhibited by *Musca domestica*, and being such prominence as model for biochemistry and insect physiology, no genome project has been launched till 2009 [2]. More importantly, to the best of our knowledge, only a handful of *Musca domestica*-related proteomic work has been reported. However, in this last 5 years, there is an increasing interest unravelling the inner molecular workings of this insect. A genome project was launched [2], and a full genome of *Musca domestica* was successfully sequenced [91]. The sequenced genome is 691 MB, and some gene sequences notably 771 putative immune-related, 86 CYP450-related, and 33 glutathione S-transferase and 92 are predicted to have esterase activities. In comparison, this genome contained a plethora of shared and novel sequences than its *Drosophila* counterparts, supporting the fact of an exemplary ability of *Musca domestica* of associating closely with numerous amounts of pathogens living in a septic environment. Pioneering transcriptomic works have been done on *Musca domestica* larvae, by massive cDNA parallel pyrosequencing [92]. Thus with the help of recent advancement, a better insight on the mechanisms that are associated with oxidative stress and resistance against insecticides in *Musca domestica* is better understood.

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