Chapter 10
Importance of Metabolic Enzymes and Their Role in Insecticide Resistance

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Abstract Insects are a vital component in the world as they do harmful and harmless effects on human beings. The medically and agriculturally essential insects occupy more space for their habitats and better surveillance. Consequently, insects' population increased and reduced agricultural products' productivity and served as a vector for many threatening diseases. The use of chemical insecticides to combat pests has resulted in the creation of resistance in many insect species. This may respond to either resistance to other chemicals with the same action mode and sometimes produce multiple resistance and cross to different insecticide classes. However, insects develop resistance to various chemical groups; the mechanism and mode method of insecticide resistance action are similar. Insects become intoxicated at four different stages of pharmacological interactions: behavioral alteration, increased enzymatic metabolism, altered target site response, ingestion of the toxicant or decreased penetration. Metabolic resistance, which is regulated by advanced enzymes and results in transforming more complex toxic molecules into less toxic compounds, is a more general resistance process. The resistance mediated by metabolic mechanisms results from enhanced production of enzymes and the increased rate and expression levels of some related metabolic enzymes. Studying insecticide resistance among insects will help us understand its response to particular chemical compounds and the resistance mechanism.

Keywords Metabolic resistance · Detoxification · Cytochrome P450 · Esterase · Glutathione –S transferase

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10.1 Introduction

Insects/pests are dangerous to crops and forests and are directly associated with food availability. These pests interfere with agriculture productivity and storage, processing, marketing, transport, etc. According to the recent report, an estimated 7–50% of crop loss has occurred annually (Oliveira et al. 2014). Apart from the direct damage and losses caused by the insect, indirectly, they served as a vector for pathogens like viruses and bacteria, thereby threatening the public and environment. Hence it is essential to control such pest's population to protect the economy.

There are different methods available for pest control, such as:

(a) Cultural control
(b) Mechanical/Physical control
(c) Biological control and
(d) Chemical control.

A cultural pest control method involves a modified farm process to avoid insect pests or make them unsuitable to their habituating environment. Mechanical pest control methods practice a manual hand collection and killing of the larval caterpillar to reduce its populations. Biological control uses natural enemies of insect pests. These natural enemies are categorized into predators, parasites, and pathogens. Chemical insecticides and their use are one of the most effective pest control techniques. These insecticides are chemical substances that can be used to destruct and control the pest, and every year a billion kilogram of insecticides are being used (Alavanja 2009). Pesticide overuse harms agriculture and human health. The extensive and discriminative uses of pesticides create resistance mechanisms in insects. Functionally resistance can be defined as an organism's ability to survive a dose of toxicants that is lethal to the susceptible one. There have been 500 different insect pests' species that target major crops such as tobacco, peanuts, cotton etc., has developed resistance to the novel insecticides. Moreover, the constant spread of this resistance in the future population poses a serious challenge towards controlling these pests (Connor et al. 2011; Stratonovitch et al. 2014).

10.2 Insecticide Resistance and Its Evolution in Insects

Insecticide tolerance can be evolved by four stages of pharmacological interactions in which insects become intoxicated: improved enzymatic metabolism, altered target site insensitivity, behavioral alteration, decreased penetration, or ingestion of the toxicant. Pest organisms can evolve more than one of these mechanisms simultaneously, or the mechanism can operate on more than one category of insecticides (e.g. oxidative metabolism), resulting in cross resistance.

The first case of resistance to insecticide in scale insects was reported by Melander (1914). The evolution of DDT an organic insecticide developed resistance

Table 10.1 Insecticide resistance cases in different insect species and its mechanism

Insect species	Insecticides and class	Resistance mechanism
Bemisia tabaci	Deltamethrin (type II pyrethroid) and Monocrotophos (organophosphate)	Metabolic resistance (Ahmad et al. 2002)
Aedes aegypti	Temephos (organophosphate) and Deltamethrin (type II pyrethroid)	Metabolic resistance & *kdr* Knock down resistance (Marcombe et al. 2009)
Spodoptera littoralis	Methoxyfenozide (Diacylhydrazine)	Metabolic resistance (Mosallanejad and Smagghe 2009)
Plutella xylostella	Cypermethrin (type II Pyrethroid)	Metabolic resistance (Baek et al. 2010)
Spodoptera litura	Chlorantraniliprole (Anthranilic diamide)	Metabolic resistance (Muthusamy et al. 2014)
Aedes aegypti	Temephos (organophosphate)	Metabolic resistance & AChE insensitivity (Muthusamy and Shivakumar 2015a, b, c, d)
Aedes aegypti	Permethrin (type I Pyrethroid)	Metabolic resistance & *kdr* Knock down resistance (Muthusamy and Shivakumar 2015a)
Cimex lectularius and *Cimex hemipterus*	Dichloro-diphenyl-trichloroethane (organochlorine) & Imidacloprid (neonicotinoid)	Metabolic resistance, AChE insensitivity, Knock down resistance, GABA receptor insensitivity and altered nAChRs (Dang et al. 2017)
Helicoverpa armigera	Indoxacarb (organochlorine)	Metabolic resistance (Cui et al. 2018)
Anopheles stephensi	Permethrin (type I Pyrethroid) Deltamethrin (type II pyrethroid) and malathion (organophosphate)	Metabolic resistance, AChE & *kdr* insensitivity (Safi et al. 2017)
Odontotermes brunneus	Cypermethrin (type II Pyrethroid)	Metabolic resistance (Mamatha et al. 2020)
Amsacta albistriga	Cypermethrin (type II Pyrethroid)	Metabolic resistance (Mathiyazhagan et al. 2020)
Drosophila melanogaster	Propoxur (carbamate)	AChE insensitivity (You et al. 2020)

was an issue of the past. Unfortunately, by 1947 housefly (*Musca domestica*) resistance to DDT was documented. Resistance to insecticides has increased dramatically in recent decades, owing to introducing new insecticide classes such as carbamates, cyclodienes, pyrethroids, formamidines, organophosphates and microbial biological pest control agents. *Bacillus thuringiensis* (www.irac-nline.org 2010). Examples of insecticide resistance cases in different insect species and its mechanism are given in Table 10.1.

Insecticide resistance affects many species and affects all large insecticide types. Today an estimation of 447 cases of arthropod resistance species exists in the world. Several insects have developed resistance to newer insecticide chemistry with a different mode of action. Over the past few decades, 90% of the arthropod resistance

cases reported in different species populations are either Hemiptera (in the broad sense, 14%), Lepidoptera (15%), Diptera (35%), mites (14%) or Coleoptera (14%). Few studies relatively involve the stable tracing of Arthropod resistance. One such classical study was carried out by Sukhoruchenko and Dolzhenko (2008) on agricultural insect pests in Russia. They reported that 36 arthropod species had developed resistance to regularly used plant conservation products. They also report the development of the group, cross, and multiple resistances in economically essential pests.

10.3 Metabolic Resistance Mechanism

Metabolic resistance, which is regulated by advanced enzymes and results in transforming more complex toxic molecules into a less toxic compound, is a more general resistance process. Three main enzyme mechanisms, carboxylesterases, cytochrome P450 regulated monooxygenases, and glutathione S-transferases, are involved in the metabolic tolerance pathway and are responsible for various insecticide metabolism. Increased metabolism can modify enzymes in the available form and make the insecticide more degradable (Siegfried and Scharf 2001).

The metabolic detoxification of insecticide involves three phases. The first phase includes CYPs reducing substrate toxicity. Using GSTs and carboxylesterases (COEs), hydrophobic toxic compounds are converted to hydrophilic materials in phase II, allowing for easier excretion. ATP binding cassette (ABC) and main membrane transporters, which can pump conjugated xenobiotics out of the cell, are involved in phase III. Insects use various strategies to shield themselves from harmful substances, including evasion, sequestration, excretion, target site mutation, susceptibility alteration, overexpression, and the development of various isoforms of detoxifying enzymes (Chapman 2003; Silva et al. 2001). CYP- or COE43-mediated reactions result in toxin reduction or oxidation, which is the most common biochemical pathway for metabolic detoxification of toxic chemicals. GSTs then use glutathione conjugation to convert the detoxified molecule into a more water-soluble form, which aids in eliminating the cell (Enayati et al. 2005). This can be achieved by either overexpression (Silva et al. 2001) or duplicated isoforms of these enzymes are expressed. Alternatively, modifying the target site (mutation an amino acid residue) could cause insects to become insensitive to toxic chemicals or react to them. Sequestration is concerned with the selective transport and preservation of toxic compounds and avoiding their interaction with natural physiological processes (You et al. 2013).

Among resistance mechanisms, metabolic enzyme-mediated resistance poses a significant challenge to pest control. Resistant individuals possessing this mechanism can render more toxic substances to less toxic to escape from its effect.

10.3.1 Carboxylesterases

Carboxylesterase is an important enzyme which metabolizes the exogenous and endogenous chemical compounds. This large enzyme family can be characterized by substrate specificities and inhibitors or electrophoretic mobilities (Dauterman 1985; Soderlund 1997). Insect carboxylesterase plays a significant part in the biotransformation and detoxification of exogenous xenobiotics through hydrolysis. Synthetic pesticides, like pyrethroids, are an important class of xenobiotics metabolized by this enzyme (Crow et al. 2012). The non-insecticidal 1-napthyl acetate, an artificial substrate, is often used to detect the carboxylesterase activity in a colorimetric biochemical assay (Fig. 10.1). The quantitative alterations in the esterase coding region, like mutational substitution, may change the esterase specificity to its naphthyl acetate substrate; by changing enzymatic nature could cause resistance to insecticide (Claudianos et al. 2006). The great substitution (Trp224Ser) in the OP resistance *Culex* esterase gene revealed a modified enzymatic nature of esterase that decreased the carboxylesterase activity in resistance mosquito and other insect species (Cui et al. 2011).

In many insect species, the higher activity of the esterase enzyme has been correlated with insecticide resistance (Latif and Subrahmanyam 2010; Muthusamy and Shivakumar 2015b).

Since most chemical insecticides contain an ester moiety in their composition, improved detoxification and sequestration by carboxylesterase confers tolerance to organophosphate, pyrethriod, and carbamates in insects (Hemingway et al. 2004; Oakeshott et al. 2005; Li et al. 2007). In many studies of pyrethroid metabolic resistance, an exalted esterase activity or synergism by esterase enzyme inhibitors revealed the contribution of esterase to the resistance in insects (Oakeshott et al. 2010). Most notably, non-denaturing PAGE studies revealed that the staining intensity of one or more esterase bands with various electrophoretic mobilities could be involved (Farnsworth et al. 2010). In addition to these pathways in insects, higher esterase activities can result in gene amplification, which can lead to insecticide tolerance. In some cases, over-expression of carboxylesterase with higher fold amplification was found in some insect species (Small and Hemingway 2000; Cui et al. 2007; Muthusamy and Shivakumar 2015a, b, c, d).

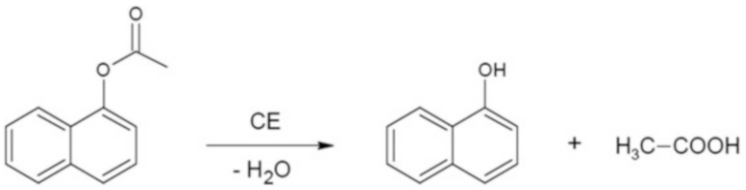

Fig. 10.1 Carboxylesterases catalyze the hydrolysis of 1-naphthyl acetate (artificial substrate). (Modified from Konanz (2009))

10.3.2 Cytochrome P450 Dependent Monooxygenases

Cytochrome P450-dependent monooxygenases are ubiquitous enzymes occurring in microbes, plants, mammals, and insects involved in the digestion of xenobiotics such as pesticides and plant toxins (Nelson 2011). These are hemoprotein-related microsomal oxidases named after their reduced form showed a typical absorbance peak at 450 nm when complexed with carbon monoxide. P450 is responsible for the metabolism of a wide range of xenobiotic compounds in insects and is also involved in their growth, development, and reproduction. P450 also plays a key role in converting herbicide molecules in plants through oxidation and peroxidation reactions (Feyereisen 2005; Hlavica and Lehnerer 2010; Li et al. 2012; Muthusamy and Shivakumar 2015b). Monooxygenases can be present in various tissues of insects, including the fat body, Malpighian tubules, and the midgut (Hodgson 1985; Scott 1999). P450 system activation was found in microsomes (endoplasmic reticulum-bound) and mitochondria in the insect subcellular distribution (Hodgson 1985). Many model substrates, such as p-nitroanisole, methoxyresorufin, NADPH cytochrome c reductase, TMBZ peroxidation, p-Nitroanisole O-Demethylase, and ethoxyresorufin, were commonly used for the biochemical identification of monooxygenase activity in insects. The oxidation of Tetramethylbenzidine (TMBZ) by peroxidase is used to measure the resistant in insects (Kranthi 2005) (Fig. 10.2).

In insect P450s are grouped into four major clades based on their evolutionary relationship: the mitochondrial P450s, CYP2, CYP3, and CYP9). Among them, the CYP3 clade, CYP6, and CYP9 P450 families, Insecticide detoxification and metabolism are critical in various insect species (Poupardin et al. 2010; Musasia et al. 2013). Overexpression of cytochrome P450 genes from various families has been shown to impart insecticide resistance in various insect species. Deltamethrin resistance in *Tribolium castaneum* was also documented when the expression of CYP6BQ9 was knocked down (Zhu and Snodgrass 2003). The overexpression of *Cyp12a4 I* associated with the lufenuron *resistance in Drosophila melanogaster* (Bogwitz et al. 2005). Similarly, the detoxification ability and expression level of four novel P450s were studied in honey bees of *Apis cerana cerana* (Zhang et al. 2019). The P450s also help in the detoxification of the toxic phytochemical, including aflatoxin B1 present in the diet of honey bees (Mao et al. 2009; Niu et al. 2011; Zhang et al. 2019). The *CYP4G11* gene has been reported to protect honeybees from the damage caused by insecticides (Shi et al. 2013). Also, the CYP9Q family of

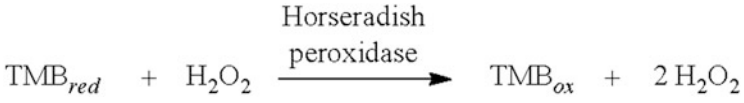

Fig. 10.2 Microsomal proteins catalyze peroxidation of Tetramethylbenzidine with hydrogen peroxide as co-substrate. (Modified from Kranthi (2005))

bumblebees P450 plays a significant role in studying the insecticide sensitivity to different classes (Manjon et al. 2018).

In many cases, regulatory changes of insects are responsible for the metabolic resistance mechanism. Up-regulation of metabolic enzymes through mutations in trans and cis-acting regulatory loci or gene amplification encoding the enzyme is typically the mechanism for increased development (Hemingway and Karunaratne 1998); monooxygenases confer resistance to a wide range of insecticides, including organophosphates, carbamates, pyrethroids, and inhibitors of chitin biosynthesis (Li et al. 2007; Atoyebi et al. 2020; Mamatha et al. 2020). It has been reported that Neonicotinoid resistance is linked with CYP6A1, CYP6D1, and CYP6D3 genes are overexpressed in *Musca domestica* where the CYP6D1 and CYP6D3 males are overexpressed and female resistant housefly, respectively (Markussen and Kristensen 2010). Similarly, the DDT resistance by *Drosophila melanogaster* is associated with the two resistance loci of p-450 gene subunits, i.e., CG10737 and Cyp6w1 (Schmidt et al. 2017). It has also been reported that the overexpression of 3 cytochrome P450 genes, *CYP6CY14, CYP6CY22*, and *CYP6UN1,* are responsible for the dinotefuran (the third-generation neonicotinoid) resistance in *Aphis gossypii* Glover in China (Chen et al. 2020). Similarly, the resistant *Anopheles mosquitoes* showed overexpressed P450 enzymes, *CYP4G16* and *CYP4G17* (Ingham et al. 2014).

10.3.3 Glutathione S-Transferase

Glutathione S-transferases (GST) are a multifunctional intracellular enzyme present in most aerobic microorganisms, plants, and animals, including insects, and play an important role in intracellular transportation, hormone biosynthesis, and oxidative stress protection (Ketterman et al. 2011; Listowsky et al. 1998; Enayati et al. 2005). GST proteins are also recognized as MAPEG proteins and belong to the superfamily of mitochondrial, cytosolic, and microsomal proteins. Subclasses of the cytosolic superfamilies are included in the detoxification process and include Delta, Epsilon, Omega, Sigma, Theta, Mu, and Zeta (Che-Mendoza et al. 2009). In insects, GSTs are categorized as microsomal and cytosolic. The number of cytosolic GSTs is much higher than the number of microsomal GSTs divided into six classes. The subclasses (Delta) and (Epsilon) are insect-specific, while the Omega, Sigma, Theta, and Zeta are present in a variety of species types (Low et al. 2007). GST can detoxify various chemical compounds by glutathione conjugation and plays a key role in the resistance production of various insecticide groups, including organophosphates and pyrethroids, due to the availability of a wide variety of substrates for individual enzymes (Yamamoto et al. 2009). Furthermore, they aid in the removal of harmful oxygen-free radicals produced by pesticides (Fig. 10.3).

Many endogenous, hydrophobic and foreign compounds form water-soluble conjugates with GSH, making detoxification easier. In many vertebrate and non-vertebrates systems, GSTs are responsible for detoxifying chemical substances;

Fig. 10.3 The conjugation of the artificial substrate 1-hcloro-2, 4-dinitrobenzene with GSH was induced by glutathione S-transferase. (Modified from Konanz (2009))

protect them against oxidative damage, and transporting numerous endogenous metabolites and intracellular hormones (Sanil et al. 2014). Insecticides may also be metabolized by promoting reductive dehydrochlorination or eliminating oxygen free radicals generated by pesticides (Hayes et al. 2005). Increased GST enzyme production using gene amplification or overexpression is also associated with GST-based insecticide resistance (Vontas et al. 2002).

The high activity GSTs in organophosphate and DDT resistance has been studied in *Musca domestica* (Motoyama and Dauterman 1980). The number of cytosolic GSTs is much higher than the number of microsomal GSTs divided into six classes. The subclasses (Delta) and (Epsilon) are insect-specific, while the Omega, Sigma, Theta, and Zeta are present in a variety of species types (Low et al. 2007). Studies have shown that GSTs were responsible for many detoxifying classes of chemical insecticides such as organophosphate (OPs), synthetic pyrethroids (SPs), and chlorine (Ketterman et al. 2011; Mamatha et al. 2020). Increased activity and expression level of one or more GST genes was described to cause insecticide resistance in many insects (Hemingway 2000; Ranson et al. 2001). In many studies, the GST was associated with resistance and other enzymes (Pavlidi et al. 2018; Mathiyazhagan et al. 2020).

10.4 Behavioral Resistance

Behavioral resistance mechanism necessitates alteration in the insect behavior by which they can avoid insecticides. The ability of an insect's resistance to behavioral and penetration response is the least mechanism. Insects' behavioral resistance can be (1) stimulus-dependent following direct contact or without contact (2) stimulus-independent like zoophily or exophily (Chareonviriyaphap et al. 2013). Stimulus-dependent habits necessitate the insect's sensory restoration in order to reveal a toxin-nursed surface before receiving a lethal dose, causing a delayed response. In insecticide resistant mosquito vectors, stimulus-independent activity has been observed, accompanied by extensive insecticide use (Meyers et al. 2016; Moiroux et al. 2012). Similar behavior resistance has been reported in numerous insect pests. In such a study, Sarfraz et al. (2005) observed that the laboratory developed *P. xylostella* laid more eggs near the soil instead of laying eggs on the stem and leaves of the host plant exposed to the insecticide.

Behavioral resistance to insecticides on simple repellency or avoidance has been observed in German cockroach gel bait with sucrose, maltose and fructose, which

are commonly feedants to sensitive laboratory strains of *B. germanica* (Wang et al. 2004). Whereas in the resistant strain of *B. germanica* excluded all of these semiochemicals from their diet. Despite studies documenting insecticide resistance to insect behavior, the gene responsible for toxic chemical metabolism is unknown (Mamidala et al. 2011).

10.5 Penetration Resistance

This type of resistance involves the modifications in the cuticle leading to the slowdown in the penetration of insecticide inside the insects' body. Cuticle thickening and cuticle structure change are two distinct pathways for resistance to penetration. The event of resistance to penetration in insects through physiological changes is basic reason. However, in some instances, reduced insecticide penetration through the insect cuticle has been identified as an alternative resistance mechanism. Only a few studies have reported the association of insecticide penetration or cuticular thickness with resistance (Strycharz et al. 2013).

Many insect species overcome insecticides' effects through reduced cuticular penetration (Pan et al. 2009; Wood et al. 2010). This style of resistance is often linked to other types of opposition (Zhu et al. 2013; Dang et al. 2017). Balabanidou et al. (2016) made significant strides in understanding cuticular tolerance, identifying the basic changes observed in resistant mosquito cuticles, and, more importantly, expanding on previous research to include further evidence of a role for the CYP4G subfamily of P450s in this process. The thickening of cuticle in the *Triatoma infestans* vector has been associated with pyrethroid resistance and is deduced from the transcriptional gene analysis in *An. stephensi* (Vontas et al. 2007). Another study from West Africa revealed pyrethroids and DTT resistance in *An. gambiae*, the overexpression of CPLCG3 and CPRs have been linked to a thicker procuticle in the femur leg segment and a phenotype (Yahouédo et al. 2017). It has been reported that the femur cuticle was thicker in the resistant strain of *Culex pipiens* compared to the susceptible one. The CPLCG5 gene is silenced, resulting in a thinner cuticle and greater insecticide resistance. This demonstrates CPLCG5's function in insect resistance (Huang et al. 2018). Pedrini et al. (2009) revealed that the decreased penetration rates across the cuticle are associated with the lower insecticide inoculation in the internal organs, leading to metabolically-mediated detoxification.

10.6 Resistance by Target-Site Insensitivity

In insects, exposure to altered target site insensitivity is a critical mechanism. A genetically-based modification is made to the target-site where the insecticide normally binds, such as a single-nucleotide polymorphism that causes difference in the amino acid sequence within the target protein's binding region (Liu 2015). The

resistance can also be thought of as a preadaptive phenotype. A small number of individuals have one or more resistance alleles that allow them to survive exposure to the stressor. As a result, effective insecticide resistance testing and a thorough understanding of the factors that contribute to and the processes that regulate resistance growth are critical to the effectiveness of pest management and vector-borne disease control (Butler 2011).

10.6.1 Altered Acetylcholinesterases

Acetylcholinesterase is a crucial enzyme that hydrolyzes acetylcholine in cholinergic synapses rapidly (Rosenberry 1975). Organophosphate (OP) insecticides mainly attack AChE, which phosphorylates the serine residues in its active site and blocks the hydrolysis of acetylcholine, causing the insect to die (Menozzi et al. 2004). AChE is used in two ways in insects. A globular disulfide-linked dimeric protein (ca. 150 kDa) is one of the most common forms, with a glycolipid anchor connecting it to the membrane. The AChE active site is divided into two subsites: the esteratic catalytic site, which has a distinct catalytic triad of amino acid residues (serine, glutamic acid, and histidine), and the anionic choline-binding site (Fournier et al. 1992; Fournier and Mutero 1994). In several pest species, the insensitive AChE has become an important tool for insecticide resistance (Chen et al. 2001; Weill et al. 2002; Muthusamy et al. 2013). According to molecular studies, in AChE encoding genes, point mutations associated with target-site insensitivity confer structural modifications (Kozaki et al. 2001). According to the findings, in *Drosophila melanogaster* (Brochier et al. 2001), decreased AChE insensitivity was found to be a typical resistance mechanism to OP/carbamates in other insect species (Lee et al. 2006; Seong et al. 2012).

10.6.2 Altered GABA Receptors

The GABA receptor belongs to a family of ligand-gated ion channels that act as fast inhibitory neurotransmission in insects. According to molecular studies, point mutations in genes encoding insecticide targets have been linked to insensitivity to the target site (Bloomquist 2001). A single common point mutation (alanine to serine at position 302) in the dieldrin resistance (Rdl) subunit is well defined in many insect organisms (Soderlund 1997; Ozoe and Akamatsu 2001; Wondji et al. 2011; Heong et al. 2013). In fly (*D. melanogaster*) and other insects, the dieldrin (Rdl) gene, which primarily functions in encoding GABA receptors composed of five subunits arranged around a central gated ion channel, showed insecticide resistance (cyclodiene) (Remnant et al. 2014). There is only one Rdl gene in most pests, but certain insects/pests have Rdl genes in various allelic variants. The natural function of (Rdl) is affected by a single nucleotide polymorphism (SNP). A single mutation of alanine

to serine at position 302 in the second transmembrane region of the Rdl subunit causes the resistant phenotype. *Myzus persicae* has four types of alleles, with the wild form (called allele A) encoding 'Ala302,' while the other three alleles encoding 'Gly302,' also known as allele 'G,' TCG codon encoding 'Ser302,' and 'AGT' codon encoding 'Ser302' (known as allele 'S'). The central causes of resistance are alanine and glycine, while resistance is not caused by the other loci of two serine-containing "s" alleles (Assel et al. 2014). Resistance is caused by the S/S locus, while A/G has a resistance function to GABA receptors and is resistant to dieldrin (Bass et al. 2014).

10.6.3 Altered Sodium Channel Proteins: Nerve Insensitivity

Voltage-gated sodium channels (vgSChs) are transmembrane proteins responsible for electrical conductivity in the nervous system by inducing action potentials in the neuronal membranes of most excitable cells. When these channels open, Na+ current is produced in the insect nervous system, which causes the membrane potential to depolarize. Many insecticides, such as synthetic pyrethroids, DDT, and oxadiazines, as well as a few synthetic and natural toxins, target insect sodium channels (Narahashi 2000; Vais et al. 2001; Dong 2003). The voltage-gated Na+ channel in a cell membrane has four homologous domains from I to IV, each with six hydrophobic segments (S1 to S6). The S4 and S6 segments are voltage sensors that create a pore in the channel when combined with the S5 segment, connecting the P-loops (Martins and Valle 2012).

Resistance has developed in many species due to the widespread use of pyrethroids and DDT in insect control. Reduced target-site vulnerability, also known as knockdown resistance or kdr, is an essential mechanism that confers resistance to all insecticides in insects (Zlotkin 2001). The housefly was the first species to be tested for this kind of tolerance (*Musca domestica*). Pyrethroid insecticide tolerance in insects was investigated by comparing the coding sequences of para orthologous sodium channel genes in susceptible and resistant animals (Whalon et al. 2008, 2010). Kdr resistance in insects was discovered to be caused by a mutation(s) in the sodium channel gene, according to molecular studies. Several mutations linked to kdr or super-kdr resistance in the housefly have been discovered in recent years (Williamson et al. 1993) and some other essential pest species (Soderlund 2010; Dong 2007; Davies et al. 2007; Thiaw et al. 2018; Kushwah et al. 2020).

10.7 Future Prospective/Conclusion

Insecticide resistance has become an increasing problem in the world today. However, the pest control program mainly relies on synthetic insecticides. In general, insect resistance has developed mainly by increasing pesticide quantity or replacing

the older one with a modern, more significant compound. It is also essential to gather information about the resistance mechanism underlying the insecticide in the population before deciding on alternative insecticides or increasing the doses. However, insects' resistance can be delayed either by applying insecticide with different chemical groups, and the addition of synergist, plant growth regulators and biological pesticides derived from natural products can also be made possible.

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