REVIEW



The power of Drosophila genetics in studying insect toxicology and chemical ecology



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Abstract

Insect toxicology and chemical ecology are inherently interconnected disciplines, both dedicated to unraveling the intricate relationships between insects and the diverse array of chemical compounds that pervade their surroundings. *Drosophila melanogaster*, owing to its genetic and physiological similarities to other insects, serves as a robust model system in the study of insect toxicology. Moreover, state-of-the-art techniques in Drosophila neurobiology have extensively probed the chemosensory system of insects, providing significant insights into their adaptation to chemical environments. In this review, we emphasize the advancements achieved through the application of Drosophila genetics in investigations spanning both of these fields, significantly enhancing our understanding of the mode of action and resistance mechanisms of insecticides, as well as unraveling the molecular and cellular mechanisms underlying insect chemosensation and associated behaviors. The profound insights derived through this tiny fly not only enrich our understanding of the broader world of insects but also hold the potential to develop more effective and sustainable strategies for pest management.

Keywords Insect toxicology, Chemical ecology, Drosophila melanogaster, Genetics, Insecticide, Receptor

Introduction

Drosophila melanogaster, commonly known as the fruit fly, has served as a model organism in genetics research for well over a century. The utilization of Drosophila genetics has proven invaluable in exploring fundamental biological processes such as development, behavior, and disease, as well as more applied fields such as toxicology and chemical ecology. One of the key advantages of employing *D. melanogaster* as a model organism lies in its well-characterized genome and the availability of powerful genetic tools. The fruit fly possesses a relatively small

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² Department of Bio & Fermentation Convergence Technology, Kookmin University, Seoul 02707, Republic of Korea genome that lends itself to facile manipulation through techniques such as gene editing and RNA interference. Additionally, *D. melanogaster* exhibits a short generation time, facilitating rapid genetic analysis and high-throughput screening. The application of Drosophila genetics has yielded numerous pivotal discoveries in biological research, encompassing the identification of key developmental genes, the elucidation of the role of genetic mutations in disease, and the unraveling of molecular mechanisms underlying behavior and memory [1].

Insect toxicology and chemical ecology are closely related fields that both focus on understanding the interactions between insects and the chemical compounds present in their environment, but they approach this interaction from slightly different angles. Insect toxicology primarily deals with the study of how chemical substances, including insecticides and other toxic compounds, affect insects. It aims to understand the mechanisms of toxicity, how insects develop resistance to toxic



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substances, and the impact of these compounds on insect populations, ecosystems, and even human health. Insect chemical ecology, on the other hand, focuses on the role of chemical compounds in mediating interactions between insects and their environment. It investigates how insects use chemical cues for finding mates, locating suitable habitats, identifying hosts or prey, and avoiding predators. Therefore, comprehending insect toxicology and chemical ecology is important for developing effective pest management strategies that minimize the use of harmful chemicals. Furthermore, understanding the ecological roles of insects and their interactions with other organisms is equally vital.

Here, we compile and organize existing research about the applications of Drosophila genetics in insect toxicology and chemical ecology, serving as a centralized resource for researchers, students, and professionals in these fields. This consolidation helps individuals access a comprehensive overview of the state of the art in this specific area of study and allows for the exchange of ideas and methodologies between researchers to encourage interdisciplinary collaboration.

Elucidating the mode of action of insecticides with Drosophila genetics

Chemical pesticides have been widely employed for pest control in agriculture, horticulture, forestry, as well as residential and urban areas. They have also played a crucial role in preventing the transmission of vector-borne diseases that affect both humans and animals. While the modes of action of most insecticides are known (www.irac-online.org), the precise molecular targets still remain elusive. Merely establishing an in vitro biochemical interaction between an insecticide and a protein is insufficient to confirm that the protein is indeed the target responsible for the insecticidal effect in vivo. Genetic evidence, demonstrating the impact of mutating the candidate receptor, is essential before conclusively identifying a specific protein as the target of an insecticide. Therefore, the utilization of forward/reverse genetics in D. melanogaster has proven to be a powerful approach in identifying protein targets for insecticides (Table 1). In cases where an insecticide does not exhibit toxicity towards flies, behavioral assays can be employed to characterize potential targets. For instance, climbing assays have been used to identify a Drosophila TRPV channel as the target for two insecticides, pymetrozine and pyrifluquinazon [2]. Similar strategies have also revealed the molecular target of flonicamid to be nicotinamidase [3]. Behavioral assays involving Drosophila null mutants of octopamine receptors have pinpointed Octβ2R, a receptor subtype, as the sole target of amitraz in vivo [4].

Actually, the mode of action of insecticides is well conserved between *D. melanogaster* and other insects, probably because insecticides disrupt essential physiological functions. For instance, the nAChR gene family, encoding the direct targets of neonicotinoids, spinosyns and many other insecticides, exhibits slow evolution, and the core groups of nAChR subunits exhibit significant conservation across diverse insect species, spanning approximately 300 million years of evolution, underscoring their essential functions in the nervous system. The majority of Drosophila nAChR subunit genes have oneto-one orthologs in the genomes of other insects, and the sequence identities between these orthologs are likewise considerable. For some subunit genes, even alternative splicing and RNA editing are conserved [7].

Besides utilizing various target gene alleles, Drosophila offers sophisticated genetic toolboxes that enable the manipulation of candidate target genes and target-expressing neurons with high spatial and

 Table 1
 Insecticide molecular targets identified and/or confirmed with Drosophila genetics

IRAC groups	Molecular targets	Drosophila strains	Reference
2 GABA-gated chloride channel blockers	Rdl	A301S point-mutation allele	[5, 6]
4 Nicotinic acetylcholine receptor competitive modulators	α1α2β1β2; α1β1β2; α3β1; α1α3β1 heterooligomers	a1, a2, a3, β 2 null and β 1 R81T point-mutation alleles	[7]
5 Nicotinic acetylcholine receptor allosteric modu1 lators—Site I	a6 homooligomer	a6 null allele	[7, 8]
6 Glutamate-gated chloride channel allosteric modulators	GluCl	P299S point-mutation allele	[9]
7 Juvenile hormone mimics	Met	Met null alleles	[10, 11]
9 Chordotonal organ TRPV channel modulators	Nan/lav	Nan and lav null alleles	[2]
10 Mite growth inhibitors affecting CHS1; 15 Inhibitors of chitin biosynthesis affecting CHS1	CHS1	11056M/F point-mutation alleles	[12]
14 Nicotinic acetylcholine receptor channel blockers	a6 homooligomer	α6 null allele	unpublished
19 Octopamine receptor agonists	Octβ2R	<i>Octβ2R</i> null allele	[4]
29 Chordotonal organ nicotinamidase inhibitors	Naam	A265E point-mutation allele	[3]

temporal resolution. For example, using UAS-controlled transgenes that express RNAi-inducing or ORF constructs can lead to tissue-specific RNAi or overexpression. Another important tool in *D. melanogaster* is the thermogenetics reagents, such as UAS-trpA1 and UAS-Shibire^{ts}. Expressing the thermosensitive cation channel Drosophila TRPA1 with the Gal4/UAS system to acutely hyperstimulate neurons expressing Octβ2R within a narrow time frame mimics the effects of amitraz on target pests, providing evidence that in vivo pharmacological activation of $Oct\beta 2R$ by amitraz leads to toxicity and eventual mortality [4]. Electrophysiological studies conducted on native tissues or recombinant receptors have demonstrated that low concentrations of neonicotinoids can inhibit nAChR, while higher concentrations result in receptor activation. Consequently, it has remained unclear whether the insecticidal activity stems from nAChR inhibition or activation in vivo. However, through the utilization of Drosophila thermogenetics tools, it has been discovered that transient artificial activation, rather than inhibition, of nAChR-expressing neurons is sufficient to induce symptoms resembling neonicotinoid poisoning in flies. Hence, the overall effect of neonicotinoids involves neuronal depolarization through nAChR activation, which is more physiologically relevant [7].

Drosophila genetics as a powerful tool for studying insecticide resistance mechanisms

Invertebrate pest control faces a significant global challenge due to the prevalence of insecticide resistance, with over 600 different insect and mite species demonstrating resistance to at least one insecticide. Moreover, there are documented cases of resistance to more than 335 insecticides/acaricides. To address the potential failure of insecticide-based control methods, it is imperative to understand the underlying resistance mechanisms, which typically include behavioral, penetration, metabolic, and target-site resistance. The majority of the research conducted in the field to date has utilized the genetic tools and resources available in D. melanogaster, although the advent of CRISPR/ Cas9 genome editing now allows for gene modifications in pests. Introducing point mutations identified in target genes of resistant pest populations into homologous sites in Drosophila is quick and straightforward, enabling genetic confirmation of the causal relationships between genotypes and resistance phenotypes (Table 2). Additionally, numerous reports have indicated that insecticide resistance is associated with variations in the overexpression of metabolic enzymes such as cytochrome P450s, carboxylesterases, glutathione-S-transferases, and UDP-glucuronosyltransferases. However, establishing a definitive causal link between overexpression and resistance has often lacked supporting evidence. Therefore, the controlled overexpression of metabolic genes from pests into *Drosophila* has proven to be a valuable tool in establishing connections between enzyme activity and resistance (Table 3).

Drosophila genetics as a model system for studying the chemical ecology of insects

Drosophila genetics has also been employed to investigate the field of chemical ecology in insects. Chemical ecology focuses on studying the interactions between organisms and their chemical environment, including the roles of chemicals in communication, defense, and other ecological interactions. Insect taste and odor receptors are very sensitive detectors to find nutritious food, mates, and safe oviposition sites or avoid any potential predators. D. melanogaster has been used as a model organism in a variety of chemical ecology studies, including those related to pheromones, food odorants/tastants, and plant volatiles/nonvolatiles. Following the first identification of the insect taste or odor receptors in D. melanogaster, similar receptors have been identified in many other insects, including the silk moth, Bombyx mori, the malaria vector mosquito Anopheles gambiae, and the honey bee Apis mellifera.

One advantage of using Drosophila genetics in chemical ecology studies is the ability to identify specific genes and pathways involved in chemical sensing and response. For example, genetic screens have been used to identify chemoreceptors and other genes involved in the detection of specific chemical cues. Additionally, Drosophila genetics allows for the manipulation of specific genes or pathways to investigate their roles in chemical communication and other behaviors.

Insects commonly employ semiochemicals to communicate within their own species or with other species. These semiochemicals include pheromones, allomones, and kairomones. Food trail pheromones, alarm pheromones, and sex pheromones are examples that can significantly influence behavior and physiology. The production of allomones and kairomones allows insects to avoid harmful food sources or predators. Drosophila genetics has been instrumental in identifying the receptor of 11-cis-Vaccenyl Acetate (cVA) as a volatile sex pheromone. Furthermore, there are many contact-mediated pheromones, such as the male dominant monoalkenes, (Z)-7-tricosene and (Z)-9-tricosene, and the female specific (7Z,11Z)-heptacosadiene. These pheromones can be studied as aggregation pheromones to gain insights into their chemical communication. Research involving Drosophila genetics and various tools in chemical ecology provides not only an understanding of how to respond to specific chemicals but also insight into how the chemical signals integrate into the higher brain center.

Insecticides/Targets	Species	Resistance alleles	Resistance ratios in Drosophila mutants	Reference
Avermectins/GluCl	Plutella xylostella	V263I	27.1	[13]
	Tetranychus urticae	I321T	3	[14]
Diamides/RyR	Chilo suppressalis	Y4667C ^a	1.3–8.6	[15, 16]
		14758M + Y4667C ^a	19.5–172.1	
		Y4667D ^a	6.2–117.2	
		14758M + Y4667D ^a	21.2- 1542.8	
		14758M ^a	3.3–22	
		Y4891F ^a	5.9-10.2	
	Plutella xylostella; Tuta absoluta; Chilo suppressalis	G4946E ^b	25.2–153.1	
	Plutella xylostella; Tuta absoluta	G4946V ^b	5.4–194.7	[17]
	Plutella xylostella; Tuta absoluta; Chilo suppressalis; Spodoptera exigua; Spodoptera frugiperda	14790M ^b =14758M ^a	2.3–15.3	
Fipronil/Rdl	Laodelphax striatellus; Sogatella furcifera	A2'N	1099	unpublished
Benzoylureas/CHS1	Plutella xylostella Culex pipiens	11042F/M ^b	111–15,625	[12, 18]
Etoxazole; Clofentezine; Hexythiazox/CHS1	Tetranychus urticae	11042F ^b	1077	
Indoxacarb; Metaflumizone/Para	Plutella xylostella;	V1848I ^c	6–8.4	[19]
	Tuta absoluta	F1845Y ^c	10.2-3441.2	
Pyrethroids; DDT/Para	Aedes aegypti	11011M ^c	>3	[20, 21]
		V1016G ^c	3	
	Many species	L1014F ^c	12.7	
Spinosyns/nAChR	Frankliniella occidentalis; Thrips palmi; Tuta absoluta	a6 G275E	62.2	[22]
Neonicotinoids/nAChR	Myzus persicae; Aphis gossypii	β1 R81T	23.9–398.3	[7, 23]
Spiromesifen; Spirodiclofen; Spirotetramat/Accase	Bemisia tabaci	A2083V	874–3616	[24]

Table 2 Target-site resistance mutations experimentally confirmed with Drosophila genetics

^a Chilo suppressalis numbering. ^bPlutella xylostella numbering. ^cHousefly numbering

Furthermore, the use of Drosophila genetics and many research tools in chemical ecology studies allows for comparisons across species. By studying the genetics and behavior of Drosophila in response to specific chemicals, researchers can gain insights into the evolution of chemical communication and other ecological interactions across different insect species.

Identification of gustatory receptor for various tastants in Drosophila

Taste organs are broadly distributed, such as the mouth parts labellum, legs, wing margins, and a female ovipositor as external organs. In addition, the pharynx also houses gustatory receptor neurons (GRNs) as internal organs. *D. melanogaster* has 31 taste sensilla in each hemisphere. A

taste sensillum has a pore to have both chemosensory and mechanosensory cells. The sensilla on the labellum are the most well studied taste sensilla, categorizing the bristles and the taste pegs. Each taste bristle is typically innervated by two or four bipolar chemosensory neurons and a mechanosensory neuron. The taste sensilla can be categorized as long (L), intermediate (I), and short (S)-types, depending on the size of the bristles. Each bristle was analyzed by the tip recording technique, making contact with the pore at the tip of the sensillum with the taste stimulus and an electrolyte. Experiments with various tastants distinguished at least four types of GRNs such as sweetsensing, water-sensing, bitter-sensing, and salt-sensing GRNs. Alkaline-sensing GRNs have recently been identified. This finding suggests that each type of bristle may be

Table 3 Metabolic resistance genes experimentally confirmed with Drosophila genetics

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Sulfoxaftor CYP380C4Q: UGT344P2 ActSC-GAL4 [35] Bernisia tabaci CYPACCI 57] Imidacloprid CYPACCI 57] Imidacloprid CYPACCI 57] Imidacloprid, Nitenpyram CYPACCI 57] Plutella sylostella chlorantraniliprole FWQ2 ActSC-GAL4 59] P-opermethnic phosim bifenthrin; chlorpyrifos, fervalerate; malathion; aE14 41] 41] B-opermethnic phosim aE3 41] 42] Anopheles coluzzi Permethrin; DDT GSTe2 ActSC-GAL4 43] Anopheles funestus Deltamethrin; DTT permethrin GyrEy171 4ctSC-GAL4 45] Anopheles funestus Deltamethrin; permethrin CYPBV92; CYPBP9b 4ctSC-GAL4 45] Anopheles funestus Deltamethrin; permethrin CYPBV92; CYPBP9b 4ctSC-GAL4 45] Actes adbopictus Heedoxan A CYPBV92; CYPBP9b 4ctSC-GAL4 51] Actes adbopictus Heedoxan A CYPBV92; CYPBV92 4ctSC-GAL4 51] Actes adbopictu	Myzus persicae	Nicotine; clothianidin	СҮР6СҮ3	Direct insertion	[34]
Bernisia tabaci Cynattaniliptole CYP6C/3 Actin-GAL4 [36] Imidacloprid CYP8C/1 IS Plutella xylostella chiorantaniliptole RMO2 Act5C-GAL4 [39] Plutella xylostella chiorantaniliptole RMO2 Act5C-GAL4 [40] Plutella xylostella chiorantaniliptole RPAC [41] Porpermethrin; phoxim blenthrin; chiorgn/rios ferwalentar smalathior; chiorantaniliptole CYP86G1 [42] Anopheles coluzzi Permethrin; chiorantaniliptole CYP86G2 Act5C-GAL4 [43] Anopheles coluzzi Permethrin; DDT GSTe2 Act5C-GAL4 [44] Anopheles funestus Deltamethrin; DTT permethrin; chiorarb CYP8692, CYP6995 [46] [47] Anopheles funestus Deltamethrin; permethrin CYP8092, CYP6995 [48] [46] Acta all all all all all all all all all a		Sulfoxaflor	CYP380C40; UGT344P2	Act5C-GAL4	[35]
ImidaclopridCVP402C1InterparationSTAPlutella xylostellaimidacloprid, NtenpyramCVP6CM/HR-GAL4SBPlutella xylostellachlorantraniliproleFM02ActSC-GAL4SBPlutella xylostellaCVpemethrin, phosim bifenthrin; actionarytifes, termalerate; malathion; actionarytifes, termalerate; malathion; actionarytifes, termalerate; malathion; bergemethrin, phosim bifenthrin; B-cypermethrin, chlorantraniliproleCVP68G1LLAnopheles coluzziPermethrin; DDTGSTe2ActSC-GAL4LAnopheles coluzziPermethrin; DDTGSTe2ActSC-GAL4LDDTGstE2HR-GAL4LLAnopheles funestusDeltamethrin; DTT permethrin; DEltamethrin; permethrinC/P69793ActSC-GAL4LAnopheles funestusBendiocarbC/P69790HR-GAL4LLAcdes albopictusBendiocarbC/P69792C/P66902HHLAcdes albopictusHaedoxan AC/P69792C/P66023HR-GAL4LLLAcdes albopictusOttamethrinC/P6792ActSC-GAL4LLL <td>Bemisia tabaci</td> <td>Cvantraniliprole</td> <td>СҮР6СХ3</td> <td>Actin-GAL4</td> <td>[36]</td>	Bemisia tabaci	Cvantraniliprole	СҮР6СХ3	Actin-GAL4	[36]
Inidactorict, NitenpyramCYP6CM1HR-GAL4[3]Plutella xylostellachlorantraniliproleFMO2ActSC-GAL4[3]Plutella xylostellap-cypermethrin; phoximaE14Actin-GAL4[4]P-cypermethrin; phoximaE14Actin-GAL4[4]P-cypermethrin; phoximaE14Actin-GAL4[4]P-cypermethrin; phoximaE8[4]P-cypermethrin; phoximGSTe2ActSC-GAL4[4]Anopheles coluzziiPermethrin; DDTGSTe2ActSC-GAL4[4]Anopheles coluzziiDeltamethrin; DDTGstE2HR-GAL4[8]Anopheles funestusDeltamethrin; DTP remethrin; bendiocarbCYP6P93CYP6P96[4]Anopheles funestusDeltamethrin; permethrinCYP6P90; CYP6P96[4][4]Acdes ablopictusIberlamethrin; permethrinCYP6P90; CYP6P96[4][4]Acdes adsoptictusDeltamethrinCYP6P9112ActSC-GAL4[5]Acdes adsoptictusDeltamethrinCYP6P92; CYP6P96[4][5]Acdes adsoptictusDeltamethrinCYP6P93; CYP6P10ActSC-GAL4[5]Anopheles albimanus-cypermethrin; DetermethrinCYP6P3ActSC-GAL4[5]Anopheles albimanus-cypermethrin; DetermethrinCYP6P3ActSC-GAL4[5]Anopheles albimanus-cypermethrin; DetermethrinCYP6P3ActSC-GAL4[5]Anopheles albimanus-cypermethrin; DetermethrinCYP6P3ActSC-GAL4[5]Anopheles albimanus-cyp		Imidacloprid	CYP402C1		[37]
Plutella vylostella chlorantraniliprole FMO2 ActSC-GAL4 [39] Plutella vylostella C-spermethrin; phoxim bilenthrin; chloraprifos fervalerate; malathion; b-cypermethrin; chlorantraniliprole C/PBBG1 ActSC-GAL4 [41] Anapheles caluzzi Permethrin; chlorantraniliprole C/PBBG1		Imidacloprid: Nitenpyram	CYP6CM1	HR-GAL4	[38]
β-cypermethrin; phoxim bifenthrin; hlorsprifos, fervalerate; malathion; β-cypermethrin; phoximaE14Actin-GAL4[4]β-cypermethrin; phoxim β-cypermethrin; phoximaB8[4]Anopheles caluzziiPermethrin; DDTG5r2ActSC-GAL4[4]Anopheles gambiaeDeltamethrin; DDTG5r2ActSC-GAL4[4]Anopheles gambiaeDeltamethrin; DDTG5r2ActSC-GAL4[4]Anopheles gambiaeDeltamethrin; DTT permethrin; DETG5r2HR-GAL4[3]Anopheles funestusDeltamethrinCYP6P32HR-GAL4[4]Deltamethrin; permethrinCYP6P32, CYP6P3b[4][4]Aedes albopictusHaedoxan ACYP6P32, CYP6P3b[4]Aedes albopictusHaedoxan ACYP6P12ActSC-GAL4[5]Aedes albopictusHaedoxan ACYP6P12ActSC-GAL4[5]Anopheles albimanu acscpermethrin; DeltamethrinCYP6P12ActSC-GAL4[5]Anopheles albimanu acscpermethrin; DeltamethrinCYP6P424CYP6CH2; CYP6CH3; CYP6CH3CGC-GAL4[5]Aphis gosspiiPermethrin; DeltamethrinCYP6424; CYP6A36; CYP6CH3; CYP6C	Plutella xvlostella	chlorantraniliprole	FMO2	Act5C-GAL4	[39]
Args G-cypermethrin; chlorantraniligroled8[41]Anopheles coluzitG-cypermethrin; chlorantraniligroleCVP86G1[42]Anopheles coluzitPermethrin; DDTGSTe2Act5C-GAL4[43]Anopheles gambiaDTGste2HR-GAL4[8]Anopheles funestusDDTGste2HR-GAL4[4]Anopheles funestusDeltamethrin; DT permethrin; bendiocarbCVP699;CVP699b[4]Anopheles funestusBelamethrin; permethrinCVP699;CVP699b[4]Aedes albopictusHaedoxan ACVP699;CVP699b[5]Aedes albopictusHaedoxan ACVP6972;CVP699b[5]Aedes albopictusHaedoxan ACVP6972;CVP6972[5]Aedes albopictusHaedoxan ACVP6972;CVP6972[5]Aedes albopictusHaedoxan ACVP6972;CVP6972[5]Aedes albopictusHaedoxan ACVP6972;CVP6721[5]Anopheles albimanuc-cypermethrin; DeltamethrinCVP672;CVP6010[5]Aphis gossypiiIniamethoxamCVP679;CVP672;[5]Musca dornesticIniamethoxamCVP679;CVP672;[5]Spodopter aviguaInloreyrifosCVP320;CVP672;[5]Spodopter aviguaInloreyrifosCVP320;CVP672;[5]Spodopter aviguaInloreyrifosCVP320;CVP672;[5]Spodopter aviguaInloreyrifosCVP320;CVP672;[5]Spodopter avigu	, ,	β-cypermethrin; phoxim bifenthrin; chlorpyrifos; fenvalerate; malathion;	aE14	Actin-GAL4	[40]
β-cypermethnin, blorantraniliproleCYP6BG1(42)Anopheles coluzziiPermethnin, DDTGSTe2ActSC-GAL4[43]Anopheles gambieDeltamethnin, DTT permethnin, bendiocarbCyp6M2, CYP6P3ActSC-GAL4[44]Anopheles funestusDDTGstE2HR-GAL4[38]Anopheles funestusDeltamethninCYP6P9a, CYP6P9b[46]Deltamethnin, permethninCYP6P9a, CYP6P9b[49]ActSC-GAL4[41][41]Aedes albopictusBendiocarbCYP6P9a, CYP6P9b[49]Aedes albopictusHaedoxan ACYP6P12ActSC-GAL4[51]Deltamethnin, permethninCYP6P12ActSC-GAL4[51]Aedes albopictusDeltamethnin, coffnoroxCYP6P2C, CYP6D9b[41]Aedes albopictusDeltamethnin, coffnoroxCYP6P2C, CYP6D9b[51]Aedes albopictusDeltamethnin, CYP9228, CYP6BQ23HR-GAL4[51]Musca domesticaPermethnin, CP19228, CYP6B023HR-GAL4[51]Musca domesticaPermethnin, CP1924, CYP6A36, CYP6D10ActSC-GAL4[51]Anopheles albinanusa-cypermethnin, DeltamethninCYP647, CYP6D29, CYP6C71ActSC-GAL4[51]Anopheles albinanusa-cypermethnin, DeltamethninCYP647, CYP6D33, CYP6D10ActSC-GAL4[51]Anopheles albinanusa-cypermethnin, DeltamethninCYP647, CYP6D21, CYP6D21ActSC-GAL4[51]Anopheles albinanusa-cypermethnin, DeltamethninCYP2147, CYP6D31, CYP6D21ActSC-GAL4[51]Aphis gossypii<		β-cypermethrin; phoxim	aE8		[41]
Anopheles coluzziiPermethrin; DTGSTe2ActSC-GAL4[43]Anopheles gambiaeDeltamethrin; DT permethrin; bendiocarbCyp6M2; CYP6P3ActSC-GAL4[44]DDTGstE2HR-GAL4[38]Anopheles funestusDeltamethrin; DT permethrinCYP8P3q; CYP6P9b[46]Dettamethrin; permethrinCYP8P3q; CYP6P9b[46]Dettamethrin; permethrinCYP8P3q; CYP6P9b[49]Aedes albopictusHaedoxan ACYP804A1Tub-Gal80 ¹⁶ +Tub-Gal4[50]Aedes albopictusHaedoxan ACYP804A1Tub-Gal80 ¹⁶ +Tub-Gal4[51]Aedes albopictusDeltamethrin; etofenproxCYP6P12ActSC-GAL4[51]Aedes adospictusDeltamethrin; etofenproxCYP6P12ActSC-GAL4[52]Anopheles albimanusc-cypermethrin; DeltamethrinCYP6P5ActSC-GAL4[53]Musca domesticaPermethrinCYP6G42; CYP6A36; CYP6D10ActSC-GAL4[54]propoxurCYP6G42; CYP6C18; CYP6C11[57][57]Aphis gossypiiThiamethoxamCYP23D46; CYP6C12; CYP6C712; CAGL4[58]Spodoptera ituraIndoxacrbCOE090; COE092; COE074; CYP6C727; CFGA14[59]Spodoptera fugiperdatricinCYP32D416; CYP6D12ActSC-GAL4[51]Spodoptera fugiperdatricinCYP32D416; CYP6C722; CYP6C718; CFGC71[57]Spodoptera fugiperdaIndoxacrbCOE090; COE092; COE092; COE074Tub-GAL4[60]Spodoptera fugiperdatricinCYP32D416; CYP32D41ActSC-GAL4[β-cypermethrin; chlorantraniliprole	CYP6BG1		[42]
Anopheles gambiae bendiocarbDetamethrin; DTT permethrin; bendiocarbCyp6M2; CYP6P3Act5C-GAL4[44]Anopheles funestusDDTGst52HR-GAL4[38]Anopheles funestusDetamethrin; permethrinCYP6P11Act5C-GAL4[45]Detamethrin; permethrinCYP6P30; CYP6P9b[46][47]Aedes albopictusBendiocarbCYP6P30; CYP6P9b[49]Aedes albopictusBendiocarbCYP6P30; CYP6P9b[51]Aedes albopictusBelamethrin; etofenproxCYP6P12Act5C-GAL4[51]Aedes albopictusDetamethrin; etofenproxCYP6P12Act5C-GAL4[52]Anopheles albimanuc-cypermethrin; DetamethrinCYP4524; CYP6A36; CYP6D10Act5C-GAL4[53]Musca domesticaPermethrinCYP6Q4HR-GAL4; ActS-GAL4[54]propoxurCYP6G4HR-GAL4; ActS-GAL4[55][57]Aphis gossypiiThiamethoxamCYP6G9; CYP6C12; CYP6C716; CYP6C21Act5C-GAL4[56]propoxurCYP321A16; CYP6D12; CYP6C72; CYP6C745; CYP6C74[57][57]Spodoptera ituraIndoxacrabCVP209; COE034; COE034; CYP6C72; CYP6C745; CYP6C745; CYP6C72; CYP6C745; CYP6C745; CYP6C72; CYP6C745; CYP6C	Anopheles coluzzii	Permethrin; DDT	GSTe2	Act5C-GAL4	[43]
DDTGstE2HR-GAL4[8]Anopheles funestusDeltamethrinCYP9/11ActSC-GAL4[45]Deltamethrin; permethrinCYP6Pa; CYP6Pbb[46, 47]Deltamethrin; permethrinCYP6Pa; CYP6Pbp[47]Aedes albopictusHaedoxan ACYP6Pa; CYP6Pb2[41]Aedes albopictusDeltamethrin; etofenproxCYP6Pa; CYP6Pb2ActSC-GAL4[51]Aedes albopictusDeltamethrin; etofenproxCYP6P2; CYP6BQ23HR-GAL4[52]Anopheles albimanuso-cypermethrin; DeltamethrinCYP6P3; CYP6BQ23HR-GAL4, Act-GAL4[53]Musca domesticapermethrinCYP6P42; CYP6A36; CYP6D10ActSC-GAL4[54]Musca domesticapropoxurCYP6P42; CYP6A36; CYP6D10ActSC-GAL4[55]Aphis gossypiiHiamethoxamCYP699; CYP4CK1; CYP6DB1; CYP6C21ActSC-GAL4[56]Aphis gossypiiIniadelopridCYP3204C1; CYP6D21; CYP6C71[57]Spodoptera luruaIndopxarbCYP321A16; CYP32A1ActSC-GAL4[59]Spodoptera luruaIndopxarbCYP321A6; CYP4C11; CYP6D42; CYP6C71[50]Spodoptera luruaIndopxarabCYP321A6; CYP32A1ActSC-GAL4[61]Spodoptera luruaIndopxarbCYP321A6; CYP32A1ActSC-GAL4[61]Spodoptera luruaIndopxarbCYP321A6; CYP32A1ActSC-GAL4[61]Spodoptera luruaIndopxarabCYP321A6; CYP32A1ActSC-GAL4[61]Spodoptera luruaIndopxarabCYP321A6; CYP32A1[Act-GAL4[62] <t< td=""><td>, Anopheles gambiae</td><td>Deltamethrin; DTT permethrin; bendiocarb</td><td>Сур6М2; СҮР6Р3</td><td>Act5C-GAL4</td><td>[44]</td></t<>	, Anopheles gambiae	Deltamethrin; DTT permethrin; bendiocarb	Сур6М2; СҮР6Р3	Act5C-GAL4	[44]
Anopheles funesturDeltamethrin; permethrinCYP9J11Act5C-GAL4[45]Deltamethrin; permethrinCYP6P90[46,47]BendiocarbCYP6P90[43]Acdes albopictusHaedoxan ACYP304A1Tub-Gal80 ¹⁵ +Tub-GalDeltamethrin; teofenproxCYP6P12Act5C-GAL4[51]Acdes aegyptiDeltamethrin; teofenproxCYP4D24Act5C-GAL4[52]Anopheles albinanauc-ypermethrin; DeltamethrinCYP4D24Act5C-GAL4[53]Musca domesticaPermethrinCYP6A24Act5C-GAL4[53]Musca domesticaPorpoxurCYP6A24CYP6A24[54]Aphis gosspriiThiamethoxamCYP6A24CYP6A24[54]Aphis gosspriiThiamethoxamCYP6A24CYP6A24[54]Spodoptera reliqueActorcanat[57][57]Spodoptera fuignesIcinantCYP3116'CYP321A1Act5C-GAL4[51]Spodoptera fuignesIcinantaCYP321A16'CYP321A1Act5C-GAL4[51]Spodoptera fuignesIcinantaCYP321A16'CYP321A1Act5C-GAL4[51]Spodoptera fuignesIcinantaCYP321A16'CYP321A1Act5C-GAL4[61]Spodoptera fuignesIcinantaCYP321A16'CYP321A1Act5C-GAL4[51]Spodoptera fuignesIcinantaCYP321A16'CYP321A1Act5C-GAL4[51]Spodoptera fuignesIcinantaCYP321A16'CYP321A1Act5C-GAL4[51]Spodoptera fuignesIcinantaCYP321A16'CYP321A1Act5C-GAL4[51]<		DDT	GstE2	HR-GAL4	[38]
PeltamethrinCYP6P9a, CYP6P9b[46, 47]RediocarbCYP6P9a, CYP6P9b[4]Aedes albopictusHaedoxan ACYP6P9a, CYP6P9b[4]Deltamethrin, etofenproxCYP6P12ActbC-GAL4[5]Aedes albopictusDeltamethrin, etofenproxCYP6P12ActbC-GAL4[5]Aedes albimanusocypermethrinCYP6P28, CYP6B023HR-GAL4[5]Anopheles albimanusacypermethrin, DeltamethrinCYP6P24, CYP6A36, CYP6D10ActbC-GAL4[5]Musca domesticaPermethrinCYP6G4HR-GAL4[5]Musca domesticaPermethrinCYP6G4HR-GAL4, Act-GAL4[5]Mis gosspilThiamethoxamCYP6G9, CYP4C17, CYP6D81, CYP6C21ActbC-GAL4[5]Spodoptera eruguaInlorqvifosCYP380C6; CYP4C11, CYP6D81, CYP6C71ActbC-GAL4[5]Spodoptera furgiperaIcinCYP380C6; CYP4C11, CYP6D718, CYP6C71Esg-GAL4[5]Spodoptera furgiperaIcinCYP311A16, CYP332A1ActbC-GAL4[6]Spodoptera furgiperaIcinCYP6A51CYP6072Tub-GAL4[6]Spodoptera furgiperaIcinCYP6A51CYP321A16, CYP32D4HR-GAL4[6]Spodoptera furgiperaIcinCYP6A51CYP6A51Icin[6]Spodoptera furgiperaIcinCYP6A51HR-GAL4[6]Spodoptera furgiperaIcinCYP6A51HR-GAL4[6]Spodoptera furgiperaIcinCYP6A51HR-GAL4[6]Spodoptera furgiperaIcin	Anopheles funestus	Deltamethrin	CYP9J11	Act5C-GAL4	[45]
CYP6M7(48)BendiocarbCYP6P9a; CYP6P9b(49)Aedes albopictusHaedoxan ACYP394A1Tub-Gal80 ⁵ +Tub-Gal4Deltamethrin; etofenproxCYP6P12Act5C-GAL4[51]Aedes aegyptiDeltamethrinCYP6912Act5C-GAL4[52]Anopheles albimanusa-cypermethrinCYP6923HR-GAL4[52]Anopheles albimanusa-cypermethrin; DeltamethrinCYP655Act5C-GAL4[53]Musca domesticaPermethrinCYP664HR-GAL4; Act-GAL4[54]Musca domesticaPermethrinCYP669; CYP4C/1; CYP6D10Act5C-GAL4[55]Aphis gossypiiThiamethoxamCYP669; CYP4C/1; CYP6D17; CYP6D17; Act5C-GAL4[56]ImidaclopridCYP308C6; CYP4C/1; CYP6DA2; CYP6C72; CYP6C721Seg-GAL4[59]Spodoptera kriugholoxacarbCOE09; CVP321A16; CYP332A1Act5C-GAL4[59]Spodoptera fruignetticinCYP321A9Act5C-GAL4[61]Spodoptera fruignetticinCYP321A9; CYP8G23; CDE074Tub-GAL4[61]Spodoptera fruignetticinCYP321A9; CYP8G23HR-GAL4[62]Spodoptera fruignetTicinCYP321A9; CYP8G23HR-GAL4[62]Spodoptera fruignetThiaClopridCYP321A9; CYP8G23HR-GAL4[63]Spodoptera fruignetThiaClopridCYP9Q6HR-GAL4[61]Spodoptera fruignetThiaClopridCYP9Q6HR-GAL4[63]Spodoptera fruignetThiaClopridCYP9Q6HR-GAL4[63]	,	Deltamethrin; permethrin	СҮР6Р9а; СҮР6Р9b		[46, 47]
Aedes albopictusBendiocarb(YP6P9; CYP6P9b(YPAedes albopictusHaedoxan ACYP304A1Tub-Gal80 ¹⁵ +Tub-Gal4(50)Aedes aegyptiDeltamethrin; etofenproxCYP6P12Act5C-GAL4(51)Aedes aegyptiDeltamethrinCYP028; CYP6B023HR-GAL4(20)Anopheles albimanuso-cypermethrin; DeltamethrinCYP0424; CYP6A36; CYP6D10Act5C-GAL4(53)Musca domesticaPermethrinCYP654Act5C-GAL4(53)Musca domesticaPropoxurCYP664HR-GAL4, Act-GAL4(55)Aphis gossppiiThiamethoxamCYP669; CYP4CK1; CYP6D10; CYP6C71Act5C-GAL4(56)Aphis gossppiiThiamethoxamCYP669; CYP4CK1; CYP6D31; CYP6C71Act5C-GAL4(56)Spodoptera exiguachlorpyrifosCY93026; CYP4C/11; CYP6DA2; CYP6C77; CYP6C71Esg-GAL4(59)Spodoptera fuigreetricinCYP321A9; CYP332A1Act5C-GAL4(59)Spodoptera fuigreetricinCYP321A9; CYP332A1Act5C-GAL4(51)Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6A51HR-GAL4(52)Bombus terrestrisThiaclopridCYP302CYP9Q4/55Hsp70-Gal4(52)Cyria bicornisThiaclopridCYP9Q4/55Hsp70-Gal4(52)Cyria capitataDeltamethrin; λ-cyhalothrinCYP6A51Hsc302(53)Cyria capitataDeltamethrin; λ-cyhalothrinCYP9Q6(53)(53)Cyria capitataDeltamethrin; λ-cyhalothrinCYP9Q6(53)(СҮР6М7		[48]
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Aedes aegyptiDeltamethrinCYP9J28; CYP6BQ23HR-GAL4[2]Anopheles albimanusa-cypermethrin; DeltamethrinCYP4D24Act5C-GAL4[5]Musca domesticaPermethrinCYP6P5Act5C-GAL4[5] <i>propoxur</i> CYP6G4HR-GAL4; Act-GAL4[5]Aphis gossypiiThiamethoxamCYP6GY9; CYP4CK1; CYP6D10Act5C-GAL4[5] <i>propoxur</i> CYP6GY9; CYP4CK1; CYP6D11; CYP6CZ1Act5C-GAL4[5] <i>propoxur</i> CYP6GY9; CYP4CK1; CYP6D11; CYP6CZ1Act5C-GAL4[5] <i>propoxur</i> CYP6GY9; CYP4CK1; CYP6D11; CYP6CZ1Act5C-GAL4[5] <i>propoxur</i> CYP380C6; CYP4CJ1Esg-GAL4[5] <i>propoxur</i> CYP380C6; CYP4CJ1; CYP6DA2; CYP6CY2;Esg-GAL4[5] <i>propoxur</i> CYP380C6; CYP4CJ1; CYP6DA2; CYP6CY7; CYP6CY21Esg-GAL4[6] <i>propoxur</i> CYP321A16; CYP32A1Act5C-GAL4[6] <i>propoxur</i> CYP321A9; CYP6D10Tub-GAL4[6] <i>propoxur</i> CYP21A9CYP6D10[6] <i>propoxur</i> CYP321A9Act5C-GAL4[6] <i>propoxur</i> ThiaclopridCYP321A9Act5C-GAL4[6] <i>propoxur</i> ThiaclopridCYP9Q4/5Hsr-GAL4[6] <i>propoxur</i> ThiaclopridCYP9Q4/5Hsp-70-Gal4[6] <i>propoxur</i> ThiaclopridCYP8Q9Hsp-70-Gal4[6] <i>propoxur</i> Deltamethrin; A-cyhalothrinCYP6Q9CNS-GAL4; Act5C-GAL4[6] <i>propoxur</i> ThiaclopridCYP9Q6Hsp-70-Gal4[6] <td></td> <td>Deltamethrin; etofenprox</td> <td>CYP6P12</td> <td>Act5C-GAL4</td> <td>[51]</td>		Deltamethrin; etofenprox	CYP6P12	Act5C-GAL4	[51]
Dr.PermethrinCYP4D24ActSC-GAL4[5]Anopheles albimanusa-cypermethrin; DeltamethrinCYP6P5ActSC-GAL4[53]Musca domesticaPermethrinCYP4S24; CYP6A36; CYP6D10ActSC-GAL4[54]propoxurCYP6G4HR-GAL4; Act-GAL4[55]Aphis gossypiiThiamethoxamCYPC6Y9, CYP4CK1; CYP6DB1; CYP6CZ1ActSC-GAL4[56]imidaclopridCYPC6Y9, CYP4CV1; CYP6DB1; CYP6CZ1ActSC-GAL4[56]cyantraniliproleCYP380C6; CYP4CJ1; CYP6DA2; CYP6CY2;Esg-GAL4[56]Spodoptera exiguachlorpyrifosCYP321A16; CYP332A1ActSC-GAL4[59]Spodoptera lituraIndoxacarbCOE090; COE050; COE093; COE074Tub-GAL4[60]Spodoptera fuigiperadtricinCYP6A51HR-GAL4[61]Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6Q45HR-GAL4[62]Bombus terrestrisThiacloprid, acetamipridCYP9Q45HSp70-Gal4[63]Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[63]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tibolium castaneumDeltamethrinCYP6B09CNS-GAL4; ActSC-GAL4[65]Bactrocera dorsalismalathionG5T88-Bda-Gal4[66]	Aedes aegypti	Deltamethrin	СҮР9J28; СҮР6ВQ23	HR-GAL4	[20]
Anopheles albimanusα-cypermethrin; DeltamethrinCYP6P5ActSC-GAL4[53]Musca domesticaPermethrinCYP6P5ActSC-GAL4[54]propoxurCYP6G4HR-GAL4; Act-GAL4[55]Aphis gossypiiThiamethoxamCYP6G9; CYP4CK1; CYP6DB1; CYP6C21ActSC-GAL4[56]ImidaclopridCYP6G9; CYP4CK1; CYP6DB1; CYP6C71; cyantaniliproleCYP380C6; CYP4C11; CYP6DB1; CYP6C72; CYP820C6; CYP4C11; CYP6DA2; CYP6C77; CYP6C721Esg-GAL4[57]Spodoptera exiguachlorpyrifosCYP321A16; CYP332A1ActSC-GAL4[59]Spodoptera fuigipedatricinCYP321A9; CYP6C721Tub-GAL4[60]Spodoptera fuigipedatricinCYP6A51HR-GAL4[61]Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6A51HR-GAL4[62]Osmia bicornisThiaclopridCYP9Q6[58][53]Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; ActSC-GAL4[61]	371	Permethrin	CYP4D24	Act5C-GAL4	[52]
Musca domesticaPermethrinCYP4S24; CYP6A36; CYP6D10ActSC-GAL4[54]Musca domesticapropoxurCYP6G4HR-GAL4; Act-GAL4[55]Aphis gossypiiThiamethoxamCYPC6Y9; CYP4CK1; CYP6DB1; CYP6CZ1ActSC-GAL4[56]ImidaclopridCYPC6Y9; CYP4CV1; CYP6DV22; CYP6CY18; CYP6D[57][57]cyantraniliproleCYP380C6; CYP4CJ1; CYP6DA2; CYP6CY2;[58][58]Spodoptera exiguachlorpytifosCYP321A16; CYP32A1ActSC-GAL4[59]Spodoptera firuiperaIndoxacarbCOE090; COE050; COE093; COE074Tub-GAL4[60]Spodoptera firuiperatricinCYP6A51HR-GAL4[61]Ceratitis capitataDeltamethrin; A-cyhalothrinCYP6Q4/5Hs-GAL4[62]Osmia bicornisThiaclopridCYP9Q6/5Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; ActSC-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Anopheles albimanus	q-cypermethrin: Deltamethrin	CYP6P5	Act5C-GAL4	[53]
propoxurCYP6G4HR-GAL4; Act-GAL4[55]Aphis gossypiiThiamethoxamCYP6GY9; CYP4CK1; CYP6DB1; CYP6C21Act5C-GAL4[56]ImidaclopridCYP26(Y9; CYP6CY22; CYP6CY18; CYP6D[57][57]cyantraniliproleCYP380C6; CYP4CJ1; CYP6DA2; CYP6CY7; CYP6CY21Esg-GAL4[58]Spodoptera exiguachlorpyrifosCYP321A16; CYP332A1Act5C-GAL4[59]Spodoptera furuaIndoxacrbCOE090; COE050; COE093; COE074Tub-GAL4[60]Spodoptera fuigiperatricinCYP321A9Act5C-GAL4[61]Ceratitis capitataDeltamethrin; A-cyhalothrinCYP6A51HR-GAL4[62]Bombus terrestrisThiaclopridCYP9Q4/5Hsp70-Gal4[27]Thiacloprid; acetamipridCYP9Q6[59][63]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6B29CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	, Musca domestica	Permethrin	CYP4S24; CYP6A36; CYP6D10	Act5C-GAL4	[54]
Aphis gossypiiThiamethoxam ImidaclopridCYPG(Y); CYP4CK1; CYP6DB1; CYP6CZ1 CYP6CY2; CYP6CY18; CYP6DAct5C-GAL4[56]ImidaclopridCYP26Y9; CYP6CY22; CYP6CY18; CYP6D[57][57]cyantraniliproleCYP380C6; CYP4CJ1[58][58]SpiotetramatCYP380C6; CYP4CJ1; CYP6DA2; CYP6CY7; CYP6CY21Esg-GAL4[59]Spodoptera exiguachlorpyrifosCYP321A16; CYP332A1Act5C-GAL4[59]Spodoptera lituraIndoxacarbCOE090; COE050; COE093; COE074Tub-GAL4[60]Spodoptera frugiperdatricinCYP321A9Act5C-GAL4[61]Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6A51HR-GAL4[62]Bombus terrestrisThiacloprid; acetamipridCYP9Q4/5Hsp70-Gal4[27]Cosmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDeltamethrinAE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]		propoxur	CYP6G4	HR-GAL4: Act-GAL4	[55]
ImidaclopridCYPC6Y9; CYP6CY22; CYP6CY18; CYP6D[57]cyantraniliproleCYP380C6; CYP4CJ1[57]SpirotetramatCYP380C6; CYP4CJ1; CYP6DA2; CYP6CY7; CYP6CY21Esg-GAL4Spodoptera exiguachlorpyrifosCYP321A16; CYP332A1Act5C-GAL4Spodoptera lituraIndoxacarbCOE090; COE050; COE093; COE074Tub-GAL4Spodoptera fuigiperdatricinCYP321A9Act5C-GAL4Spodoptera fuigiperdatricinCYP6A51HR-GAL4Bombus terrestrisThiaclopridCYP9Q4/5Hsp70-Gal4Cosmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4Lucilia cuprinaDeltamethrinAct5C-GAL4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolum castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Aphis aossvpii	Thiamethoxam	CYPC6Y9: CYP4CK1: CYP6DB1: CYP6CZ1	Act5C-GAL4	[56]
cyantraniliproleCYP380C6; CYP4CJ1[57]SpirotetramatCYP380C6; CYP4CJ1; CYP6DA2; CYP6CY7; CYP6CY21Esg-GAL4[58]Spodoptera exiguachlorpyrifosCYP321A16; CYP332A1Act5C-GAL4[59]Spodoptera lituraIndoxacarbCOE090; COE093; COE093; COE074Tub-GAL4[60]Spodoptera frugiperdatricinCYP321A9Act5C-GAL4[61]Ceratitis capitataDeltamethrin; A-cyhalothrinCYP6A51HR-GAL4[62]Bombus terrestrisThiaclopridCYP9Q4/5Hsp70-Gal4[27]Thiacloprid; acetamipridCYP9Q6[63][64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrin;CYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	F J-JF	Imidacloprid	CYPC6Y9; CYP6CY22; CYP6CY18; CYP6D		
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Spodoptera exiguachlorpyrifosCYP321A16; CYP332A1ActSC-GAL4[59]Spodoptera lituraIndoxacrbCOE090; COE050; COE093; COE074Tub-GAL4[60]Spodoptera frugiperadtricinCYP321A9ActSC-GAL4[61]Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6A51HR-GAL4[62]Bombus terrestrisThiacloprid; acetamipridCYP9Q4/5Hsp70-Gal4[27]Osmia bicornisThiaclopridCYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6B02CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTE8-Bda-Gal4[66]		Spirotetramat	CYP380C6; CYP4CJ1; CYP6DA2; CYP6CY7; CYP6CY21	Esg-GAL4	[58]
Spodoptera lituraIndoxacarbCOE090; COE050; COE093; COE074Tub-GAL4[60]Spodoptera lituraIndoxacarbCVP321A9Act5C-GAL4[61]Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6A51HR-GAL4[62]Bombus terrestrisThiaclopridCYP9Q4/5Hsp70-Gal4[27]Thiacloprid; acetamipridCYP9Q6[63]Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Spodoptera exigua	chlorpyrifos	CYP321A16; CYP332A1	Act5C-GAL4	[59]
Spodoptera frugiperdatricinCYP321A9Act5C-GAL4[61]Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6A51HR-GAL4[62]Bombus terrestrisThiaclopridCYP9Q4/5Hsp70-Gal4[27]Thiacloprid; acetamipridCYP9Q6[63]Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Spodoptera litura	Indoxacarb	COE090; COE050; COE093; COE074	Tub-GAL4	[60]
Ceratitis capitataDeltamethrin; λ-cyhalothrinCYP6A51HR-GAL4[62]Bombus terrestrisThiaclopridCYP9Q4/5Hsp70-Gal4[27]Thiacloprid; acetamipridCYP9Q6[63]Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Spodoptera fruaiperda	tricin	CYP321A9	Act5C-GAL4	[61]
Bombus terrestrisThiaclopridCYP9Q4/5Hsp70-Gal4[27]Thiacloprid; acetamipridCYP9Q6[63]Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Ceratitis capitata	Deltamethrin: λ -cyhalothrin	CYP6A51	HR-GAL4	[62]
Thiacloprid; acetamipridCYP9Q6[63]Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Bombus terrestris	Thiacloprid	CYP904/5	Hsp70-Gal4	[27]
Osmia bicornisThiaclopridCYP9BU1; CYP9BU2Hsp70-Gal4[64]Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]		Thiacloprid: acetamiprid	CYP906		[63]
Lucilia cuprinaDiazinon; malathionaE7HR-GAL4[38]Tribolium castaneumDeltamethrinCYP6BQ9CNS-GAL4; Act5C-GAL4[65]Bactrocera dorsalismalathionGSTe8-Bda-Gal4[66]	Osmia bicornis	Thiacloprid	CYP9BU1: CYP9BU2	Hsp70-Gal4	[64]
Tribolium castaneum Deltamethrin CYP6BQ9 CNS-GAL4; Act5C-GAL4 [65] Bactrocera dorsalis malathion GSTe8-B da-Gal4 [66]	l ucilia cuprina	Diazinon: malathion	aF7	HR-GAL4	[38]
Bactrocera dorsalis malathion GSTe8-B da-Gal4 [66]	Tribolium castaneum	Deltamethrin	CYP6BO9	CNS-GAL4: Act5C-GAL4	[65]
	Bactrocera dorsalis	malathion	GSTe8-B	da-Gal4	[66]

Table 3 (continued)

Species	Insecticides	Transgenes	GAL4 drivers	References
Tetranychus urticae	Fenpyroximate	CYP392A11	HR-GAL4	[67]
	Abamectin	CYP392A16		[68]

more diverse and complex than previously thought, leaving the possibility of discovering uncharacterized GRNs in the future.

During the last two decades, many research groups have deorphanized GRs (Table 4). For example, GR43a has been identified as a fructose receptor that functions in the brain to detect fructose levels in hemolymph [69]. The Drosophila genome contains nine sweet GRs, primarily responsible for detecting sugars and other attractive chemicals. GR8a, GR66a, and GR98b were first characterized as a full repertoire of L-canavanine receptors [70, 71].

In insects, ionotropic receptors (IRs) are also very popular taste receptors that mainly function to detect salty and sour tastants (Table 4). Recent behavioral and physiological studies have revealed that GRs and IRs may function together to detect the same chemicals, such as amino acids, metal ions, hexanoic acids, and attractive carboxylic acids, although the pathway and the exact mechanism are not clear. One study utilized in vivo calcium imaging from the subesophageal zone (SEZ), which is the first place to receive all the peripheral taste information, to demonstrate the simultaneous activation and deactivation of IR25a and sweet GRs, respectively, in response to lactic acid stimuli [95]. Mutants lacking specific receptors exhibited defects in calcium imaging during the corresponding phases.

Most chemoreceptors, such as sweet and bitter taste receptors, detect a chemical in a dose-dependent manner. In contrast, depending on the concentration of salt and sour, *D. melanogaster* likes low concentrations and dislikes high concentrations. This preference is mediated by the specific GRNs that harbor the corresponding receptors. For example, IR56b and IR7c work in attractive or aversive GRNs to detect salt, respectively [91, 92]. Recent studies also provide the evidence that arginine, proline, and lysine among amino acids as well as low fatty acids such as hexanoic acid also work as attractive or aversive tastants depending on the concentrations.

Except GRs and IRs, other highly well conserved ion channels in the animal kingdom, such as pickpocket ion channels (PPKs), transient receptor potential ion channels (TRPs), otopetrins, and alkaliphile participate in contact chemosensation to detect water, pungent chemicals, inorganic protons, and basic solutions (Table 4).

Identification of olfactory receptors for various odorants with Drosophila genetics

Olfactory receptor neurons (ORNs) in insects are found in the antennae and maxillary palps. Each sensillum contains ORN dendrites that can detect odors through pores. The axons of the ORNs innervate the glomeruli in the antennal lobes of the brain. The ORNs expressing the same receptor project to a single glomerulus in each hemisphere. They synapse with the projection neurons to transmit signals to the higher olfactory centers, such as the mushroom body and the lateral horn. The olfactory sensilla of the antennae can be divided into three morphological types: basiconic, coeloconic, and trichoid.

A bioinformatic search for *olfactory receptor* (Or) genes identified 60 Or genes that mainly function in the antennae or maxillary palps. Orco is unusually expressed in most olfactory neurons and is the most well conserved chemoreceptor gene in insects. ORCO is a coreceptor to detect specific odors with another specific OR, which results in the role of ORCO in the transport or function of another specific OR. Insect ORNs have been analyzed by extracellular recording techniques. Loss of Or genes does not affect the survival of ORNs. The deletion of Or22a and Or22b results in an empty neuron that is unresponsive to odors. Therefore, the empty neuron system has been widely used to identify unknown receptors by misexpressing them. ORs are required for detecting aversive odorants such as DEET, IR3535, picaridin, and pyrethrum as well as nutrient yeast, alcohol, and volatile sex pheromone, cVA (Table 5). IRs are another important clade to work in sensory neurons in ORNs but do not generally coexpress ORs. Olfactory sensory neurons housed in coeloconic sensilla do not express Orco and are tuned to acids, ammonia, and humidity. The most broadly expressed IRs (IR8a and IR25a) in the antennae mainly function to detect acids and organic compounds such as 1,4-diaminobutane, pyrrolidine, phenethylamine, ammonia, and polyamines (Table 5).

Recent interesting findings include a geosmin receptor, OR56a. Geosmin is an earthy or musty flavor from toxic microbes, triggering an aversive response in Drosophila flies. The geosmin detection system allows flies to generally inhibit feeding and oviposition [115]. In contrast, *D. sechillia* is an extreme specialist on *Morinda citrifolia* (noni fruit), while *D. melanogaster* is a generalist.

Table 4 Information of the gustatory receptors required for detecting tastants

Taste	Stimulus	Receptors	Organs responsible for sensation	References
Sweet	Sucrose	Gr64a, Gr64b, Gr64c, Gr64d, Gr64e, and Gr64f	Labellum	[72–75]
	Maltose	Gr64a, Gr64b, Gr64c, Gr64d, Gr64e, and Gr64f	Labellum	[72–75]
	Glucose	Gr5a, Gr61a, Gr64a, Gr64b, Gr64d, Gr64e, and Gr64f	Labellum	[72–75]
	Fructose	Gr64a, Gr64b, Gr64d, Gr64e, and Gr64f	Labellum	[74, 75]
Bitter	Denatonium	Gr22e, Gr32a, Gr33a, Gr59c, and Gr66a	Labellum	[76, 77]
(Synthetic compounds)	DEET	Gr32a, Gr33a, Gr66a, and Gr89a	Labellum	[78, 79]
	IR3535	Gr47a	Labellum	[80]
Bitter	Caffeine	Gr33a, Gr39a.a, Gr66a, and Gr93a	Labellum	[77, 81, 82]
(Natural or plant derived compounds)	L-canavanine	Gr8a, Gr66a, and Gr98b	Labellum	[70, 71]
	Strychnine	Gr22e, Gr32a, Gr33a, Gr47a, and Gr66a	Labellum	[77, 83, 84]
	Saponin	Gr28b.c	Labellum	[85]
	Nicotine	Gr10a, Gr32a, and Gr33a	Labellum	[86]
	Cucurbitacin B	Gr33a	Labellum	[87]
	Azadirachtin	Gr32a and Gr33a	Labellum	[77]
	Umbelliferon	Gr33a, Gr39a, Gr66a, and Gr93a	Labellum	[77, 88]
	Quinine	Gr32a, Gr33a, and Gr66a	Labellum	[77]
	Histamine	<i>Ir76b, Gr9a, Gr22e,</i> and <i>Gr98a</i>	Labellum	[89, 90]
Salty	High salt (Aversive)	<i>Ir7c, Ir25a,</i> and <i>Ir76b</i>	Labellum	[91]
	Low salt (Attractive)	Ir25a, Ir56b, and Ir76b	Labellum, leg	[92, 93]
Sour	Acetic acid (Aversive)	lr7a	Labellum	[94]
	Carboxylic acid (lactic acid, citric acid, glycolic acid, and HCl) (Attractive)	Gr5a, Gr61a, Gr64a-f, Ir25a, and Ir76b	Labellum, leg	[95–97]
	HCI	otopla	labellum	[98]
Alkali	Hydroxide (Aversive)	Alka	Labellum, leg	[99]
Amino acid	Low concentration of arginine, lysine, proline (Aversive)	Ir25a, Ir51b, and Ir76b	Labellum	[100]
	Low and high concentration of valine, tryptophan, isoleucine, and leucine (Aversive)	Ir25a, Ir51b, and Ir76b	Labellum	[100]
	Low concentration of arginine, proline, lysine, low and high concentration of glycine, alanine, serine, threonine, and cysteine (Attractive)	Gr5a, Gr61a, Gr64f, Ir20a, Ir25a, and Ir76b	Labellum, leg	[100, 101]
	Low and high concentration of methionine and glutamine (Attractive)	Ir25a and Ir76b	Labellum	[100]
Metals	Copper and zinc (Aversive)	Gr33a, Gr66a, Ir25a, Ir56b, and Ir76b	Labellum	[102, 103]
Minerals	Calcium (Aversive)	<i>Ir25a, Ir62a,</i> and <i>Ir76b</i>	Labellum	[104]
Ammonia and polyamine	Ammonium salt, urea, and putrescine (Aversive)	<i>Ir25a, Ir51b,</i> and <i>Ir76b</i>	Labellum	[105]
	Polyamines (putrescine and cadaverine) (Aversive)	lr76b	Labellum	[106]
Fatty acid	Hexanoic acid (Aversive)	<i>Gr32a, Gr33a,</i> and <i>Gr66a</i>	Labellum	[107]
	Hexanoic acid (Attractive)	lr56d	Labellum	[107–109]
	Carbonation and fatty acids	lr25a, lr56d, and lr76b	Labellum	[110]
	Hexanoic acid, octanoic acid, oleic acid, linoleic acid	Gr64e, Gr64a-f, Ir25a, and Ir76b	Labellum, leg	[111, 112]

Table 4 (continued)

Taste	Stimulus	Receptors	Organs responsible for sensation	References
Other attractive organic compounds	Glycerol	Gr43a, Gr64a, Gr64b, Gr64c, Gr64d, Gr64e, and Gr64f	Labellum	[74, 75, 111]
	Vitamin C	Gr5a, Gr61a, Gr64b, Gr64c, Gr64e, Ir25a, and Ir76b	Labellum	[74]

 Table 5
 Information about the olfactory receptors required for sensing odorants

Smell	Stimulus	Receptors	Organs responsible for sensation	References
Aversive	DEET	Or59b and Orco (Or83b)	Antennae	[113]
	DEET, IR3535, and picaridin	Or42a	Antennae and maxillary palp	[114]
	Geosmin	Or56a	Antennae	[115]
	Pyrethrum	<i>Or7a, Or42b, Or59b</i> , and <i>Or98a</i>	Antennae	[116]
Acidic	Carboxylic acid (acetic acid, propionic acid, and HCl)	Ir8a and Ir64a	Antennae	[117–119]
	2-oxovaleric acid, propionic acid, phenylacetic acid and phenylacetaldehyde	lr8a	Antennae	[119, 120]
	Acetic acid, propionic acid, and butyric acid	Ir75a	Antennae	[121]
	Hydroxycinnamic acid	Or71a	Maxillary palp	[122]
Organic compounds	1,4-diaminobutane, pyrrolidine, phenethylamine, and ammonia	Ir25a and Ir76b	Antennae	[120]
Nutrient source	Yeast	Or35a and Orco	Antennae	[123]
Drosophila stress odorant (dSO)	CO ₂	<i>Gr21a</i> and <i>Gr63a</i>	Antennae	[124–126]
Alcohol	Hexanol	Orco and Or35a	Antennae	[120]
Courtship pheromones	Phenylacetic acid and phenyladehyde	Ir84a	Antennae	[127]
	9-tricosene	Or7a	Antennae	[128]
Ammonia and polyamines	Ammonium and amine	lr92a	Antennae	[129]
	Polyamines (spermidine, putrescine, cadaverine, and others)	<i>Ir41a</i> and <i>Ir76b</i>	Antennae	[106]
Volatile Fatty acid (FA) pheromone	cis-vaccenyl acetate, cVA	<i>Or65a</i> and <i>Or67d</i>	Antennae	[130]
Olfactory responses of other insect species to plant derived compounds and pheromone components	<i>D. sechellia</i> to odor bouquet of noni fruit	DsecOrco, DsecOr22a, DsecIr8a, and DsecIr75b	Antennae	[131]
	<i>Locusta migratoria</i> to body pheromone phenylacetonitrile (PAN)	LmOr70a	Antennae	[132]
	<i>Scaptomyza flava</i> to Isothiocyanate (ITC) derived from mustard oil	SflaOr67b1, SflaOr67b2, and SflaOr67b3	Antennae	[133]
	Campoletis chlorideae to sex pheromone (tetradecanal (14:Ald) and 2-heptadecanone (2-Hep))	CchlOR18 and CchlOR47	Antennae	[134]

The characterization of the Or22a pathway and comparative studies of the circuit from specialists and generalists provide how animal behavior evolves [131]. *DsecOrco*, *DsecOr22a, DsecIr8a,* and *DsecIr75b* are needed for detecting odor bouquets from noni fruit. *Scaptomyza flava,* an herbivorous leaf mining fly species in the family

Drosophilidae, specializes in isothiocyanate (ITC)-producing plants, Brassicales. *Sfla* Or67bs mediate ITC responses [133], although *D. melanogaster* is known to detect ITC via TRPA1.

Recent pheromone studies in olfaction from parasitoids and locusts have provided interesting insights. *Campoletis chlorideae* is one of most common hymenopteran parasites emerging from *Helicoverpa armigera*. A recent study showed that *CchlOr18* and *CchlOr47* are selectively tuned to two female-derived pheromones, tetradecanal and 2-heptadecanone, to elicit strong responses from males [134]. These pheromones can be developed to control specific pests. In addition, cannibalism in migratory locusts is known to be mediated by phenylacetonitrile and its receptor, *LmOr70a* [132]. Researchers can gain insight into the mechanisms of chemical communication and other ecological interactions across diverse insect species.

Perspectives

Our review emphasizes the pivotal role this model organism has played in advancing our understanding of insect responses to chemicals, including breakthroughs in the mode of action of insecticides, resistance mechanisms, and the molecular basis of chemosensation. Understanding how Drosophila research informs strategies for pest management, crop protection and sustainable agriculture is vital for addressing the practical challenges associated with chemical control of insect pests. This type of review can also help students and early-career scientists gain a deeper understanding of the foundational principles and recent advances. While genome modification becomes increasingly accessible in non-model species and related resources continue to accumulate, the value of D. melanogaster as a model organism for studying insect toxicology and chemical ecology is still expected to persist well into the future. The expanding repertoire of genetic and genomic resources, along with the accompanying technologies, presents numerous opportunities for researchers in this field.

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Authors' contributions

J. H. and Y. L. both contributed equally to this work.

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Availability of data and materials

All data analyzed during this study are included within the paper.

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