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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 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 one-to-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	α1, α2, α3, β2 null and β1 R81T point-mutation alleles	[7]
5 Nicotinic acetylcholine receptor allosteric modu1 lators—Site I	α6 homooligomer	*α6* 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/Iav	*Nan* and *Iav* null alleles	[2]
10 Mite growth inhibitors affecting CHS1; **15** Inhibitors of chitin biosynthesis affecting CHS1	CHS1	I1056M/F point-mutation alleles	[12]
14 Nicotinic acetylcholine receptor channel blockers	α6 homooligomer	*α6* null allele	unpublished
19 Octopamine receptor agonists	Octβ2R	*Octβ2R* 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 Octβ2R 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 (7*Z*,11*Z*)-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.

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

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]
		I4758M + Y4667C[a]	19.5–172.1	
		Y4667D[a]	6.2–117.2	
		I4758M + Y4667D[a]	21.2- 1542.8	
		I4758M[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	I4790M[b] = I4758M[a]	2.3–15.3	
Fipronil/Rdl	*Laodelphax striatellus; Sogatella furcifera*	A2'N	1099	unpublished
Benzoylureas/CHS1	*Plutella xylostella* *Culex pipiens*	I1042F/M[b]	111–15,625	[12, 18]
Etoxazole; Clofentezine; Hexythiazox/CHS1	*Tetranychus urticae*	I1042F[b]	1077	
Indoxacarb; Metaflumizone/Para	*Plutella xylostella; Tuta absoluta*	V1848I[c]	6–8.4	[19]
		F1845Y[c]	10.2–3441.2	
Pyrethroids; DDT/Para	*Aedes aegypti*	I1011M[c]	> 3	[20, 21]
		V1016G[c]	3	
	Many species	L1014F[c]	12.7	
Spinosyns/nAChR	*Frankliniella occidentalis; Thrips palmi; Tuta absoluta*	α6 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]

[a] *Chilo suppressalis* numbering. [b] *Plutella xylostella* numbering. [c] Housefly 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 sweet-sensing, 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

Species	Insecticides	Transgenes	GAL4 drivers	References
Apis mellifera	Chlorantraniliprole	*CYP9Q2/3*	Hsp70-GAL4	[25]
	Flupyradifurone	*CYP9Q2/3*		[26]
	Thiacloprid	*CYP9Q1/2/3*	Malp-tub-GAL4	[27]
Nilaparvata lugens	*Imidacloprid*	*CYP6ER1 variants*	Act5C-GAL4	[28]
		CYP6ER1		[29]
		Mdr49-like	Actin-GAL4	[30]
	Buprofezin	*CYP6ER1vA; CYP439A1*	da-GAL4	[31]
	Chlorpyrifos	*CarE17*	Tub-GAL80^{ts} + Tub-GAL4	[32]
	Pymetrozine	*CYP6CS1*	Actin-GAL4	[33]
Myzus persicae	Nicotine; clothianidin	*CYP6CY3*	Direct insertion	[34]
	Sulfoxaflor	*CYP380C40; UGT344P2*	Act5C-GAL4	[35]
Bemisia tabaci	Cyantraniliprole	*CYP6CX3*	Actin-GAL4	[36]
	Imidacloprid	*CYP402C1*		[37]
	Imidacloprid; Nitenpyram	*CYP6CM1*	HR-GAL4	[38]
Plutella xylostella	chlorantraniliprole	*FMO2*	Act5C-GAL4	[39]
	β-cypermethrin; phoxim bifenthrin; chlorpyrifos; fenvalerate; malathion;	*aE14*	Actin-GAL4	[40]
	β-cypermethrin; phoxim	*aE8*		[41]
	β-cypermethrin; chlorantraniliprole	*CYP6BG1*		[42]
Anopheles coluzzii	Permethrin; DDT	*GSTe2*	Act5C-GAL4	[43]
Anopheles gambiae	Deltamethrin; DTT permethrin; bendiocarb	*Cyp6M2; CYP6P3*	Act5C-GAL4	[44]
	DDT	*GstE2*	HR-GAL4	[38]
Anopheles funestus	Deltamethrin	*CYP9J11*	Act5C-GAL4	[45]
	Deltamethrin; permethrin	*CYP6P9a; CYP6P9b*		[46, 47]
		CYP6M7		[48]
	Bendiocarb	*CYP6P9a; CYP6P9b*		[49]
Aedes albopictus	Haedoxan A	*CYP304A1*	Tub-Gal80^{ts} + Tub-Gal4	[50]
	Deltamethrin; etofenprox	*CYP6P12*	Act5C-GAL4	[51]
Aedes aegypti	Deltamethrin	*CYP9J28; CYP6BQ23*	HR-GAL4	[20]
	Permethrin	*CYP4D24*	Act5C-GAL4	[52]
Anopheles albimanus	α-cypermethrin; Deltamethrin	*CYP6P5*	Act5C-GAL4	[53]
Musca domestica	Permethrin	*CYP4S24; CYP6A36; CYP6D10*	Act5C-GAL4	[54]
	propoxur	*CYP6G4*	HR-GAL4; Act-GAL4	[55]
Aphis gossypii	Thiamethoxam	*CYPC6Y9; CYP4CK1; CYP6DB1; CYP6CZ1*	Act5C-GAL4	[56]
	Imidacloprid	*CYPC6Y9; CYP6CY22; CYP6CY18; CYP6D*		
	cyantraniliprole	*CYP380C6; CYP4CJ1*		[57]
	Spirotetramat	*CYP380C6; CYP4CJ1; CYP6DA2; CYP6CY7; CYP6CY21*	Esg-GAL4	[58]
Spodoptera exigua	chlorpyrifos	*CYP321A16; CYP332A1*	Act5C-GAL4	[59]
Spodoptera litura	Indoxacarb	*COE090; COE050; COE093; COE074*	Tub-GAL4	[60]
Spodoptera frugiperda	tricin	*CYP321A9*	Act5C-GAL4	[61]
Ceratitis capitata	Deltamethrin; λ-cyhalothrin	*CYP6A51*	HR-GAL4	[62]
Bombus terrestris	Thiacloprid	*CYP9Q4/5*	Hsp70-Gal4	[27]
	Thiacloprid; acetamiprid	*CYP9Q6*		[63]
Osmia bicornis	Thiacloprid	*CYP9BU1; CYP9BU2*	Hsp70-Gal4	[64]
Lucilia cuprina	Diazinon; malathion	*aE7*	HR-GAL4	[38]
Tribolium castaneum	Deltamethrin	*CYP6BQ9*	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 (Synthetic compounds)	Denatonium	*Gr22e*, *Gr32a*, *Gr33a*, *Gr59c*, and *Gr66a*	Labellum	[76, 77]
	DEET	*Gr32a*, *Gr33a*, *Gr66a*, and *Gr89a*	Labellum	[78, 79]
	IR3535	*Gr47a*	Labellum	[80]
Bitter (Natural or plant derived compounds)	Caffeine	*Gr33a*, *Gr39a.a*, *Gr66a*, and *Gr93a*	Labellum	[77, 81, 82]
	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	*Ir76b*, *Gr9a*, *Gr22e*, and *Gr98a*	Labellum	[89, 90]
Salty	High salt (Aversive)	*Ir7c*, *Ir25a*, and *Ir76b*	Labellum	[91]
	Low salt (Attractive)	*Ir25a*, *Ir56b*, and *Ir76b*	Labellum, leg	[92, 93]
Sour	Acetic acid (Aversive)	*Ir7a*	Labellum	[94]
	Carboxylic acid (lactic acid, citric acid, glycolic acid, and HCl) (Attractive)	*Gr5a*, *Gr61a*, *Gr64a-f*, *Ir25a*, and *Ir76b*	Labellum, leg	[95–97]
	HCl	*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)	*Ir25a*, *Ir62a*, and *Ir76b*	Labellum	[104]
Ammonia and polyamine	Ammonium salt, urea, and putrescine (Aversive)	*Ir25a*, *Ir51b*, and *Ir76b*	Labellum	[105]
	Polyamines (putrescine and cadaverine) (Aversive)	*Ir76b*	Labellum	[106]
Fatty acid	Hexanoic acid (Aversive)	*Gr32a*, *Gr33a*, and *Gr66a*	Labellum	[107]
	Hexanoic acid (Attractive)	*Ir56d*	Labellum	[107–109]
	Carbonation and fatty acids	*Ir25a*, *Ir56d, and Ir76b*	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	*Or7a, Or42b, Or59b,* and *Or98a*	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	*Ir8a*	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	*Gr21a* and *Gr63a*	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	*Ir92a*	Antennae	[129]
	Polyamines (spermidine, putrescine, cadaverine, and others)	*Ir41a* and *Ir76b*	Antennae	[106]
Volatile Fatty acid (FA) pheromone	*cis*-vaccenyl acetate, cVA	*Or65a* and *Or67d*	Antennae	[130]
Olfactory responses of other insect species to plant derived compounds and pheromone components	*D. sechellia* to odor bouquet of noni fruit	*DsecOrco, DsecOr22a, DsecIr8a,* and *DsecIr75b*	Antennae	[131]
	Locusta migratoria to body pheromone phenylacetonitrile (PAN)	*LmOr70a*	Antennae	[132]
	Scaptomyza flava 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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Availability of data and materials
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Declarations

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