基于神经多受体复合物新视角的杀虫剂抗药性*

万岩然[1**] 王茂源[1] 陈可为[1] 钱康华[2] 杨浩岚[2] 吴青君[2***]

（1. 河北农业大学植物保护学院，保定 071000；2. 中国农业科学院蔬菜花卉研究所，蔬菜生物育种全国重点实验室，北京 100081）

摘 要 神经毒性杀虫剂对全球粮食安全和公共卫生有重要作用，但其广泛应用已引发害虫抗性问题。传统靶点突变与代谢解毒理论已阐明多种抗性机制，但对不同作用机理杀虫剂间的非预期交互抗性、功能代偿等复杂现象，经典“单一靶点”研究范式解释力不足，提示昆虫神经系统存在比现有认知更复杂的靶标组织模式与调控网络。脊椎动物神经研究显示，神经受体可组装为功能性“神经多受体复合物”，通过变构调节、信号串扰协同调控神经元功能。鉴于神经系统进化高度保守，本研究将该理论引入昆虫毒理学与抗药性研究，认为神经递质受体通过蛋白质相互作用组装为超分子复合物，协同调控神经元功能。本研究分析典型抗药性案例，构建昆虫抗药性新假说，整合了昆虫体内存在功能性神经多受体复合物并介导抗药性的间接证据：跨靶标交互抗性及神经受体功能代偿。构建了基于神经多受体复合物抗性理论框架，提出昆虫神经系统中 nAChR、VGSC、GABAR、GluR 等关键杀虫剂靶点形成功能整合的受体网络，针对任一节点的持续选择压力不仅会引发该节点适应性改变，还会通过复合物内相互作用将影响传递至其他节点，最终形成复杂广谱抗性表型。“神经多受体复合物”理论为理解杀虫剂作用机制与抗性演化提供了全新视角，将研究范式从“单一分子”提升至“系统网络”层面，既为传统模型难以解释的非预期交互抗性和功能代偿提供了分子框架，也为未来杀虫剂研发开辟了新方向，对制定科学的抗性治理策略具有重要理论指导意义与应用前景。

关键词 神经多受体复合物；神经毒性杀虫剂；信号串扰；交互抗性

New perspectives on insecticide toxicology and resistance based on neural multireceptor complexes

WAN Yan-Ran[1**] WANG Mao-Yuan[1] CHEN Ke-Wei[1]
QIAN Kang-Hua[2] YANG Hao-Lan[2] WU Qing-Jun[2***]

(1. College of Plant Protection, Hebei Agricultural University, Baoding 071000, China;
2. State Key Laboratory of Vegetable Biobreeding, Institute of Vegetable and Flower, Chinese Academy of Agricultural Sciences, Beijing 100081, China)

Abstract Neurotoxic insecticides play vital roles in safeguarding global food security and public health, however, their widespread application has triggered the development of pest resistance. Multiple resistance mechanisms have been clarified using the theories of conventional target-site mutation and metabolic detoxification. Nevertheless, the classical "single-target" research paradigm lacks explanatory power for complex phenomena, such as unintended cross-resistance and functional compensation among insecticides with disparate modes of action. This indicates that the insect nervous system possesses more sophisticated target organization patterns and regulatory networks than are currently understood. Neuroscientific research on vertebrates has demonstrated that neural receptors can assemble into functional "multineuroreceptor complexes", which

*资助项目 Supported projects：国家自然科学基金（32472562）；中国农业科学院科技创新工程（CAAS-ASTIP-IVFCAAS）

**第一作者 First author，E-mail：wanyanran@hebau.edu.cn

***通讯作者 Corresponding author，E-mail：wuqingjun@caas.cn

收稿日期 Received：2026-06-22；接受日期 Accepted：2026-08-07

collaboratively regulate neuronal functions through allosteric modulation and signal crosstalk. Given the high evolutionary conservation of nervous systems across species, the present study introduces this theory into insect toxicology and insecticide resistance research. We hypothesize that neurotransmitter receptors assemble into supramolecular complexes via protein-protein interactions to cooperatively govern neuronal activity. By analyzing representative cases of insecticide resistance, this work establishes a novel hypothesis for insect resistance, assembling indirect evidence supporting the existence of functional multineuroreceptor complexes mediating resistance in insects, namely cross-target cross-resistance and functional compensation of neural receptors. A theoretical framework of resistance rooted in the multineuroreceptor complex is postulated: Key insecticide targets within the insect nervous system, including nAChRs, VGSCs, GABARs and GluRs, form an integrative functional receptor network. Continuous selection pressure acting on any single node of this network induces adaptive alterations at that node, the impacts of which propagate to other nodes via intramolecular interactions within the complexes, ultimately generating complex broad-spectrum resistance phenotypes. The multineuroreceptor complex theory offers an innovative perspective for deciphering insecticide modes of action and the evolution of resistance, elevating the research paradigm from the "single-molecule" level to the “systematic network” level. It furnishes a molecular framework to interpret unexpected cross-resistance and functional compensation that cannot be explained by traditional models, pioneers new avenues for future insecticide development, and has important theoretical significance and prospects for the formulation and application of scientific strategies to manage resistance.

Key words　neural multireceptor complexes; neurotoxic insecticides; signal cross-talk; cross-resistance

自 20 世纪中叶以来，化学杀虫剂在全球粮食生产和病媒生物控制中发挥着重要作用，对保障农业产量和人类健康具有实际贡献（Liang *et al*., 2025）。其中，神经毒性杀虫剂因其作用迅速、杀虫谱广等优点，占据了市场主导地位。然而，杀虫剂的长期和大规模使用对害虫种群施加了持续的选择压力，导致抗性在全球范围内广泛发展，已成为现代农业和公共卫生领域最严峻挑战之一（Liu, 2015; Liang *et al*., 2025）。目前，对杀虫剂抗性机制的研究主要归纳为两大类，即靶点抗性和代谢抗性（Li *et al*., 2007; Bass *et al*., 2015）。靶点抗性主要由编码靶标蛋白的基因发生点突变引起 （Ffrench-Constant *et al*., 2000）。例如，电压门控钠离子通道（Voltage-gated sodium channels, VGSC）的突变导致对 DDT 和拟除虫菊酯类杀虫剂的击倒抗性（Dong *et al*., 2014; Silva *et al*., 2014）。代谢抗性则是指昆虫体内解毒酶系统（如细胞色素 P450 单加氧酶、谷胱甘肽 *S*-转移酶和羧酸酯酶）活性增强，加速杀虫剂的代谢分解，使其在到达靶点前即被清除（Li *et al*., 2007）。在众多抗性现象中，交互抗性（Cross-resistance）尤为棘手。交互抗性指害虫对一种杀虫剂产生抗性后，同时对其他化学结构或作用机理不同但之前未接触过的杀虫剂也表现出抗性 （Beckie and Tardif, 2012）。这种现象使得通过轮换使用不同作用模式杀虫剂来延缓抗性发展的策略变得复杂甚至失效（Sparks and Nauen, 2015）。

代谢抗性被认为是交互抗性的主要驱动力（Liu, 2015），核心是昆虫体内解毒酶系统代谢杀虫剂的能力增强。例如褐飞虱 *Nilaparvata lugens* 单个 P450 基因 *CYP6CS1* 过表达可介导对吡蚜酮及其他几种农药的中低水平交互抗性（Lin *et al*., 2025）；疟疾媒介芬斯特按蚊 *Anopheles funestus* 中，GSTe 基因簇的过表达和等位基因变异是其对 DDT 和拟除虫菊酯产生抗性的关键因素（Kouamo *et al*., 2025）。与代谢抗性不同，靶标抗性源于杀虫剂作用靶点蛋白基因突变引发的结构改变，传统观点认为其特异性强，仅引发作用于同一靶点或相似位点杀虫剂间的交互抗性。例如 DDT 和拟除虫菊酯类杀虫剂的靶点电压门控钠离子通道（VGSC），其基因点突变（如 L1014F，即 kdr 突变）是这类杀虫剂最主要的抗性机制之一。除上述两大机制外，还有辅助性抗性机制也可引发交互抗性：昆虫体壁改变产生的穿透抗性可减缓多种脂溶性杀虫剂进入（Balabanidou *et al*., 2018）；近年来研究证实，气味结合蛋白（Odorant binding protein,

OBPs）、化学感受蛋白（Chemosensory protein, CSPs）等非解毒蛋白可结合隔离杀虫剂分子形成隔离/封存抗性，这类蛋白可容纳多种疏水性小分子，过表达也可能引发广谱交互抗性（Tsouri and Douris, 2025; Wang *et al*., 2025）。

尽管以代谢抗性为主导的理论框架已解释大量交互抗性现象，但随检测技术发展与抗性案例积累，其局限性日益凸显，部分复杂交互抗性模式无法用单一代谢理论解释，主要体现在两方面：第一，预期交互抗性缺失。根据广谱代谢酶理论，抗性品系中高表达的 P450 或 GST 基因，应使该品系对该酶可代谢的所有杀虫剂都产生抗性，但实际并非如此。对多杀菌素类杀虫剂 1 100 余个抗性案例的回顾分析显示，多杀菌素抗性品系与其他主要杀虫剂类别不存在交互抗性相关性（Sparks *et al*., 2025）；氟啶虫胺腈与新烟碱类同属 IRAC 第 4 组，但对新烟碱类高水平抗性的烟粉虱 *Bemisia tabac*i 品系，对氟啶虫胺腈几乎无交互抗性（Watson *et al*., 2021）。这些案例说明，即便存在抗性背景，交互抗性产生仍有高度选择性与特异性，与单一广谱解毒酶作用模式相悖。第二，意外交互抗性出现。部分交互抗性谱系难以解释：吡虫啉长期筛选的 B 型烟粉虱抗性品系，除对其他新烟碱类有预期交互抗性外，还对多杀菌素、阿维菌素产生低水平交互抗性（Wang *et al*., 2009），虽已明确 P450 介导代谢增强是机制之一，但很难存在一个 P450 可同时高效降解结构、作用机理差异极大的多种化合物。此外，棉铃虫 *Helicoverpa armigera* 中发现的 Bt 毒素广谱抗性也挑战传统认知：CryIA（c）筛选的抗性品系，不仅对 CryIA 类毒素有抗性，还对 CryIIA 毒素产生交互抗性，且该抗性与经典靶标结合位点改变无关（Gould *et al*., 1992），代谢增强仅为抗性表型的贡献因素之一，还存在其他协同机制。

这些理论上的“裂痕”促使我们必须重新审视交互抗性的分子基础，并探索超越代谢抗性的新机制。靶标抗性，这一曾被认为高度特异的机制，是否可能以一种我们尚未认识到的方式，介导跨作用模式的交互抗性？神经受体是当前杀虫剂研发领域的生理学靶标之一（El-Helw *et al*., 2025; Haikal *et al*., 2025），也是杀虫剂抗性机制研究的重点方向（El-Helw *et al*., 2025; Ramadan *et al*., 2025）。围绕不同神经毒剂的作用靶标及其作用机制已有一系列研究报道（Goulson, 2013; Gao *et al*., 2025; Yan *et al*., 2025），针对单一神经受体靶标发生基因突变及异常剪接引发昆虫抗药性的相关报道较为丰富（Ffrench-Constant *et al*., 1993）。然而，传统的“单一靶点”研究范式在解释日益复杂的田间抗药性现象时存在显著局限，无法解释跨靶标交互抗性也无法解释受体缺失后的功能代偿。部分作用机制被证实存在显著差异的杀虫剂之间，偶有出现不符合预期的交互抗性（Sparks *et al*., 2025），该现象无法仅通过已知的靶标突变（Lin *et al*., 2025; Choi *et al*., 2026）或广谱代谢解毒酶进行充分阐释（Khan *et al*., 2025; Huang *et al*., 2025b；朱雅婷等, 2024）。上述结果提示，昆虫神经系统中杀虫剂靶标的组织模式与作用机制可能比现有认知更为复杂（Soderlund and Knipple, 2003; Thany, 2025）。与此同时，脊椎动物神经科学领域逐步提出“神经多受体复合物”（Neural multireceptor complexes）的概念。相关研究显示，神经递质受体并非独立分布于细胞膜上，而是可与其他受体或信号蛋白组装形成稳定或动态的超分子复合物（Rodbell, 1980; Rasmussen *et al*., 2011; Martinez-Sanchez *et al*., 2021）。这类复合物可通过变构调节（Zhang *et al*., 2025）和信号串扰（Signal cross-talk）（Hunter, 2007）等方式协同调控胞内信号通路（Verona *et al*., 2025），拓展神经元的信息处理功能（Yuasa-Kawada *et al*., 2026）。例如，G 蛋白偶联受体（G protein-coupled receptors，GPCRs）的二聚化或寡聚化（Maurel *et al*., 2008）、离子通道型受体与代谢型受体之间的功能偶联均已得到实验验证，并成为药物设计的靶点之一（George *et al*., 2002）。

目前，昆虫神经多受体复合物的直接研究仍较为有限。鉴于神经递质系统在物种进化过程中的高度保守性，可推测昆虫神经系统中可能存在类似的复合物组织方式。昆虫已演化出结构复杂

的神经系统，其行为调控同样依赖多种神经递质的协同作用（Schoofs *et al*., 2017）。因此，以神经多受体复合物概念为视角重新审视杀虫剂的作用机制与抗性问题，具有理论创新意义。本文拟系统阐释神经多受体复合物概念对杀虫剂毒理学及昆虫抗药性研究的潜在启示：首先梳理神经多受体复合物的基本结构与功能特征，其次归纳主流神经毒性杀虫剂的作用机制与交互抗性，最终通过分析典型抗药性案例，提出昆虫体内存在功能性神经多受体复合物的假说，并对该方向未来的研究路径与应用前景进行讨论。

1　神经多受体复合物

1.1　定义与互作机制

神经元间的信息传递依赖于多种神经受体与神经递质构成的“活性微环境”，该微环境参与神经元适应性反应的塑造（Semyanov and Verkhratsky, 2021）。神经多受体复合物是指由两个及以上神经递质受体（同源或异源）通过直接蛋白质-蛋白质相互作用，或经由支架蛋白、信号分子介导间接结合，所形成的稳定或动态超分子组装结构（Husi *et al*., 2000）。该组装模式改变了传统认为受体以独立单元行使功能的认知，凸显了受体互作网络在信号整合过程中的作用（Dale *et al*., 2022）。受体间的相互作用可归纳为两类机制：其一为直接物理结合，即不同受体蛋白在细胞膜上组装形成异聚体（De Bosscher *et al*., 2020），烟碱型乙酰胆碱受体（Nicotinic acetylcholine receptors, nAChRs）与多巴胺受体（Dopamine receptors, DRs）的相互作用是该机制的典型代表（Jiang *et al*., 2025; Touponse *et al*., 2026）；其二为功能性串扰，即受体间不存在直接物理连接，但可通过共享或汇聚的下游信号通路、膜电位改变等途径产生相互调控作用（Hunter, 2007），nAChRs 与谷氨酸受体（Glutamate receptor, GluRs）之间的功能性串扰即属此类（Mondragón-García *et al*., 2024）。

1.2　脊椎动物神经多受体复合物研究进展

现阶段脊椎动物神经多受体复合物领域的研究已取得显著进展（Bibel and Barde, 2000; Gimpl and Fahrenholz, 2001; Dechant and Barde, 2002）。G 蛋白偶联受体的同源二聚化与异源二聚化是最早被鉴定的多受体复合物组装形式（Devi *et al*., 2001; Angers *et al*., 2002; Milligan, 2004）。已有研究证实，多巴胺 D1 受体与 D2 受体、腺苷 A2A 受体与多巴胺 D2 受体（Canals *et al*., 2003）均可形成异源二聚体，此类受体间的相互作用可影响配体亲和力、信号转导效率（Campaña *et al*., 2025; Jayachandran *et al*., 2025）以及受体内吞与转运过程（Wiley , 2003; Lidke *et al*., 2004）。近年来，依托单分子荧光共振能量转移（Single molecule fluorescence resonance energy transfer, smFRET）等生物物理技术，研究者已可在活细胞内对受体复合物动态构象变化进行实时解析（Ha *et al*., 2022），明确其功能调控的分子基础。除 GPCRs 自身的相互作用外，离子通道型受体与 GPCRs 之间（Beaulieu and Gainetdinov, 2011; Luo *et al*., 2025）、不同类型离子通道之间同样可组装形成功能复合物（Traynelis *et al*., 2010）。例如，属于离子型谷氨酸受体的 N-甲基-D-天冬氨酸（N-Methyl aspartic acid 或 N-methyl-D-aspartic acid, NMDA）受体与多巴胺 D1 受体的相互作用，在学习记忆与突触可塑性调控过程中发挥关键作用（Cepeda and Levine, 1998）。该类复合物的组装使得一种受体激活后可通过变构效应快速调控另一受体的功能（Changeux and Edelstein, 1998），进而实现细胞内信号的快速整合。

受体间组装通常发生于蛋白质合成的早期阶段，具体发生在内质网层面（Chen *et al*., 1999; Luo and Lee, 2013）。GPCR 寡聚体主要通过高度保守的跨膜螺旋（TM4、TM5、TM6）（Simpson *et al*., 2010; Orzeł *et al*., 2025）、羧基末端及第 3 个胞内环（ICL3）介导分子间相互作用（Klco *et al*., 2003）。此外，带相反电荷的胞内结构域之间的静电相互作用，在包括 GPCR 与非 GPCR 异聚化在内的大多数受体相互作用过程中发挥调控作用（Navarro *et al*., 2010）。此类受体复合物的结构基础具有异质性：既包括受体蛋白特定

结构域（如 C 端尾部或跨膜螺旋）间的直接接触（de Vos *et al*., 1992; Schlessinger *et al*., 2000; Stamos *et al*., 2002），也存在突触后致密区（Postsynaptic density, PSD）支架蛋白（如 PSD-95、Homer）作为“分子胶水”锚定不同受体与下游效应蛋白的间接组装模式。近年来，冷冻电子断层扫描（Cryo-electron tomography, cryo-ET）技术已可在接近原生生理状态下，以纳米级分辨率解析突触间隙中连接突触前囊泡与突触后受体的跨突触蛋白复合体（Orozco-Borunda *et al*., 2024; Do *et al*., 2026），为神经多受体复合物的存在提供了直接的结构学证据（Martinez-Sanchez *et al*., 2021）。在众多参与神经受体异聚体组装的受体分子中，烟碱型乙酰胆碱受体的作用尤为关键（Changeux and Edelstein, 1998; Kalamida *et al*., 2007）。现有研究证据表明，烟碱型乙酰胆碱受体可与谷氨酸受体、多巴胺受体（Wittenberg *et al*., 2020）等发生物理相互作用并组装形成受体复合物。

1.3 烟碱型受体与谷氨酸及多巴胺受体的相互作用

烟碱型乙酰胆碱受体与谷氨酸受体常共表达于同一细胞膜（Halevi *et al*., 2002），二者的相互作用是中枢神经系统（Central nervous system, CNS）中重要的功能调控机制之一（Stone, 2021）。该相互作用的功能特性依赖于所参与的受体亚型（Livingstone *et al*., 2009），且 nAChRs 的激活通常发生于 GluRs 功能调控之前（Meyer *et al*., 2002）。分布于突触前神经末梢的 nAChRs 可通过诱导含谷氨酸的突触囊泡发生胞吐，促进谷氨酸释放（Dickinson *et al*., 2008; Dorostkar and Boehm, 2008）；而由神经元内源释放的谷氨酸可同时激活代谢型与离子型谷氨酸受体（Nusser *et al*., 1994; Scanziani *et al*., 1997; Crupi *et al*., 2019; Bono *et al*., 2023; Hunjan and Aran, 2025）。谷氨酸能神经末梢可表达 CNS 中最具典型性的 nAChR 亚型，主要包括 α4β2 亚型与 α7 亚型（Stone, 2021）。其中 α7 亚型 nAChRs 可上调突触前 N-甲基-D-天冬氨酸受体（N-methyl-D-aspartate receptors, NMDARs）的膜表面表达水平，进而在突触发育早期阶段促进谷氨酸释放。在成熟的谷氨酸能突触体中，尼古丁预处理可诱导 NMDARs 发生功能性上调，该效应由 α7-nAChRs 介导（Bono *et al*., 2023）。

在多巴胺能神经元中，DRs 与 nAChRs 共存于同一神经元，二者在功能层面存在关联性（Parish *et al*., 2005），可通过形成异聚体发挥协同作用（Bono *et al*., 2022），共同调控 DA 释放、神经元营养代谢与神经保护过程（Guan, 2024）。已有研究证实，nAChR 的 β2 亚基可与 D2 样多巴胺受体（D2SR）及 D3 多巴胺受体（D3R）发生物理相互作用，进一步组装形成 D2R-nAChR 与 D3R-nAChR 两种不同的异聚体（Bono *et al*., 2022; Sbrini *et al*., 2024）。目前已有诸多研究在小鼠与人类 DA 能神经元中探究了该异聚体的生理功能（Bono *et al*., 2022）。其中，D3R-nAChR 异聚体是介导 nAChR 与 D2R/D3R 激动剂诱导 DA 能神经元可塑性及神经保护效应的核心功能单元（Mutti *et al*., 2022; Sbrini *et al*., 2024）。DA 的释放受到 nAChRs 的精准调控（Zhou *et al*., 2001），在中脑腹侧被盖区（Ventral tegmental area, VTA）与黑质（Substantia nigra, SN）的 DA 能神经元中，nAChRs 呈高表达状态（Azam *et al*., 2002; Wooltorton *et al*., 2003），其中 α4β2 与 α6β3 亚型可通过调节突触前膜兴奋性促进 DA 释放（Bono *et al*., 2023）。此外，nAChRs 还可与毒蕈碱受体（Muscarinic receptors）（Kawashima and Fujii, 2000）以及 γ-氨基丁酸受体（Gamma-aminobutyric acid receptor, GABAR）发生交互对话（Schmiedhofer *et al*., 2022）。

2 作用于神经受体的杀虫剂

神经毒性杀虫剂通过干扰昆虫神经系统的正常功能而发挥作用，其靶点主要集中在神经信号传递的关键环节，包括神经递质受体和离子通道。根据杀虫剂抗性行动委员会（Insecticide Resistance Action Committee）公布的杀虫剂作用机理分类，靶向神经受体的药剂的靶标、作用机理代表性化合物以及代表性药剂如表 1 所示。

表 1　神经毒性杀虫剂

Table 1　Neurotoxic insecticides

神经系统 Nervous system	作用机理 Mechanism	代表性化合物 Representative compounds	代表性杀虫剂 Representative insecticides
胆碱能神经元 Cholinergic neurons	nAChR 竞争性调节剂 nAChR competitive modulators	新烟碱类 Neonicotinoids	吡虫啉、噻虫嗪等 Imidacloprid, thiamethoxam *et al*.
		砜亚胺类 Sulfonylimides	氟啶虫胺腈 Sulfoxaflor
		丁烯羟酸内酯类 Butenolides	氟吡呋喃酮 Flupyradifurone
		介离子类 Mesoionics	三氟苯嘧啶 Triflumezopyrim
	nAChR 变构调节剂 nAChR allosteric modulators	多杀菌素类 Spinosyns	多杀霉素、乙基多杀菌素 Spinosad, spinetoram
	nAChR 通道阻断剂 nAChR channel blockers	杀蚕毒素类似物 Nereistoxin analogues	杀螟丹、杀虫双等 Cartap hydrochloride, thiosultap *et al*.
	乙酰胆碱酯酶抑制剂 Acetylcholinesterase inhibitors	氨基甲酸酯类 Carbamates	涕灭威、克百威等 Dichlorvos, carbaryl *et al.*
		有机磷酸酯类 Organophosphates	毒死蜱、乐果等 Deltamethrin, parathion *et al*.
	囊泡乙酰胆碱转运蛋白抑制剂 Vesicular acetylcholine transporter inhibitors	噁唑磺酰虫啶 Oxadiazinylurea	噁唑磺酰虫啶 Oxadiazinylurea
GABA 受体 GABA receptors	GABA 受体拮抗剂 GABA receptor antagonists	环戊二烯有机氯类 Cvclodiene organochlorines	氯丹、硫丹等 Chlordane, endosulfan *et al*.
		苯基吡唑类 Phenylpyrazoles	氟虫腈、乙虫腈 Fipronil, ethipronil
	GABA 受体变构调节剂 GABA receptor allosteric modulators	间二酰胺类和异噁唑啉类 Meta-diamides and isoxazolines	溴虫氟苯双酰胺、氟噁唑酰胺 Broflanilide, fluxametamide
谷氨酸受体 Glutamate receptor	谷氨酸受体变构调节剂 Glutamate receptor allosteric modulators	阿维菌素类及弥拜菌素类 Avermectins and milbemycins	阿维菌素、甲氨基阿维菌素苯甲酸盐等 Abamectin and emamectin benzoate
章鱼胺受体 Octopamine receptor	章鱼胺受体激动剂 Octopamine receptor agonists	双甲脒 Amitraz	双甲脒 Amitraz
鱼尼丁受体 Ryanodine receptor	鱼尼丁受体调节剂 Ryanodine receptor modulators	双酰胺类 Diamides	氯虫苯甲酰胺、四唑虫酰胺等 Chlorantraniliprole, etraniliprole *et al.*
钠离子通道 Sodium channel	钠离子通道调节剂 Sodium channel modulators	拟除虫菊酯类除虫菊素类 Pyrethroids and pyrethrins	联苯菊酯、高效氯氟氰菊酯等 Bifenthrin, lambda-cyhalothrin *et al*.
		DDT	DDT
	钠离子通道阻断剂 Sodium channel blockers	噁二嗪类 Oxadiazines	茚虫威 Indoxacarb
		缩氨基脲类 Semicarbazones	氰氟虫腙 Metaflumizone

靶向胆碱能的杀虫剂主要包括作用于烟碱型乙酰胆碱受体的竞争性调节剂、变构调节剂以及通道阻断剂（Buisson and Bertrand, 1998; Young *et al*., 2008; Williams *et al*., 2011; Cartereau *et al*., 2024），作用于乙酰胆碱酯酶的抑制剂（Wu *et al*., 2026），以及作用于囊泡乙酰胆碱转运蛋白的抑制剂，如图 1 所示。靶向 GABA 能的杀虫剂主要包括作用于 GABA 门控氯离子通道的拮抗剂和变构剂（Cole *et al*., 1993; Bloomquist *et al*., 1996; Olsen, 2015; Akinnawo *et al*., 2025）。靶向谷氨酸能的杀虫剂主要是作用于谷氨酸门控氯离子通道（Glutamate-gated chloride channel, GluCl）的变构调节剂，代表性药剂为阿维菌素（Walton *et al*., 2000; Huang *et al*., 2025a）。作用于章鱼胺受体（Octopamine receptor, OARs）的为 OARs 受体激动剂，代表性化合物为甲脒类（Baxter and Barker, 1999），其中双甲脒是广泛应用于害螨和害虫防治的品种之一（Casida and Durkin, 2013）。作用于鱼尼丁受体（Ryanodine receptor, RyR）的调节剂通过锁定 RyR 耗尽细胞内钙库，导致肌肉持续收缩、麻痹和死亡（Casida, 2015），代表性化合物为双酰胺类杀虫剂（Boaventura *et al*., 2020; Huang *et al*., 2020; 杨浩岚等, 2024; 李亚迎等, 2024）。电压门控钠离子通道（Voltage-gated sodium ion channel, VGSC）调节剂通过改变 VGSC 的动力学特性，延长通道的开放时间，导致神经元持续去极化和重复放电。代表性药剂包括 DDT 及拟除虫菊酯类杀虫剂（Davies *et al*., 2007）。噁唑磺酰虫啶是一种新型磺酰类杀虫剂，最初被认为通过阻断 VGSC 的慢失活状态发挥作用（Suzuki and Yamato, 2021）。近期研究显示，其主要靶点可能是囊泡乙酰胆碱转运体（Vesicular acetylcholine transporter, VAChT），表明其作用机理的复杂性，有待进一步阐明（Goodchild *et al*., 2024）。

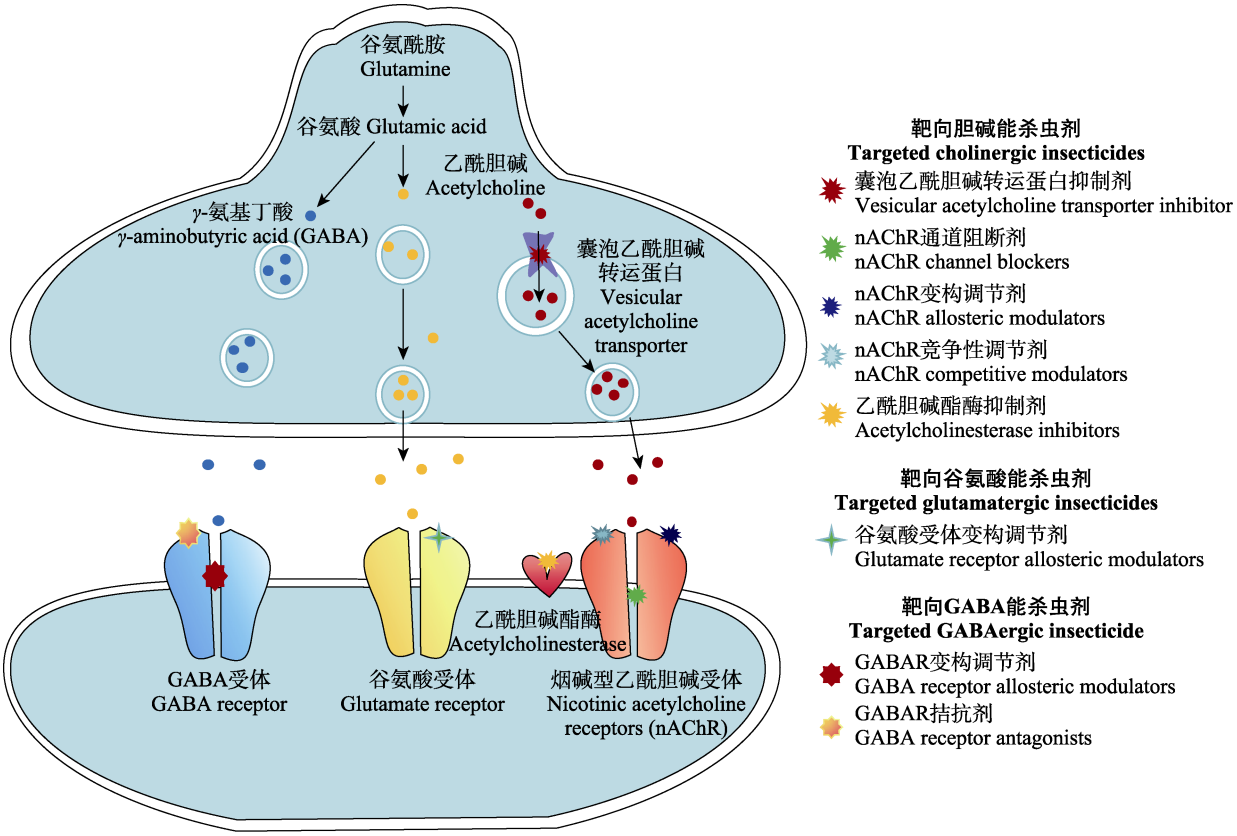


图 1　作用于胆碱能、谷氨酸能和 GABA 能的杀虫剂作用位点示意图

Fig. 1　Schematic diagram of insecticide action sites targeting cholinergic, glutamatergic and GABAergic synapses

3　神经毒性杀虫剂中的跨受体交互作用及其应用

3.1　神经受体互作介导的不同作用机理杀虫剂交互抗性案例

新烟碱类与 DDT/拟除虫菊酯类两种作用靶标不同的杀虫剂之间同样存在交互抗性现象（Daborn *et al*., 2001）。两类杀虫剂的作用靶点分别为 nAChR 与 VGSC，前者介导突触后膜的化学门控过程（Cecchini and Changeux, 2015; Wu *et al*., 2015），后者介导轴突膜的电信号传导，二者通常被认为是功能独立的两个系统。针对家蝇 *Musca domestica* 的研究证实，经氯菊酯（拟除虫菊酯类）筛选获得的高抗性家蝇品系同样对吡虫啉产生了交互抗性，且该品系对吡虫啉的抗性无法被 P450 抑制剂胡椒基丁醚（PBO）或酯酶抑制剂 DEF 抑制。上述研究结果提示，该交互抗性并非由代谢解毒机制介导，而可能源于不同靶点层面的潜在功能关联（Liu and Yue, 2000）。此外，携带 GABA 门控氯离子通道 A301S 突变（Rdl A301S）的黑腹果蝇 *Drosophila melanogaster* 品系，在对环戊二烯类、苯基吡唑类以及异噁唑啉类杀虫剂产生抗性的同时（Xie *et al*., 2024），其胆碱能系统中乙酰胆碱酯酶的基因表达量与酶活性均显著上调，进而引发神经生理改变，最终导致该品系对靶向 AChE 的氨基甲酸酯类与有机磷类杀虫剂产生交互抗性。该结果也证实，胆碱能神经与 GABA 能神经之间存在交互调控作用。

3.2　神经受体之间的功能补偿案例

除不同靶标杀虫剂间的交互抗性案例外，神经毒性杀虫剂抗性机制的相关研究也为神经多受体复合物假说提供了支撑。nAChR α6 亚基发生缺失型转录可导致翻译提前终止，产生无功能的 nAChRs α6 蛋白，进而使西花蓟马 *Frankliniella occidentalis*、桔小实蝇 *Bactrocera dorsalis* 以及小菜蛾 *Plutella xylostella* 等多种田间与室内种群害虫对多杀菌素类杀虫剂产生抗性（Wan *et al*., 2018; Grant *et al*., 2019; Zhang *et al*., 2023）。该抗性机制与受体亚基单位点氨基酸突变不同，西花蓟马中截短型 nAChRs α6 蛋白缺失了膜锚定所需的全部 4 个跨膜结构域，导致所有含 α6 亚基的受体均无法在细胞膜上正常组装，目前该亚基所介导受体聚合物的功能代偿机制尚不明确（Wan *et al*., 2018; Zhang *et al*., 2023）。本实验室前期研究发现，西花蓟马抗性种群中多种离子型谷氨酸受体-海人藻酸受体（Kainate receptors, KARs）的表达量显著上调，且其必需辅助蛋白神经纤毛-特罗德样蛋白（Neuropilin and tolloid-like, NETO）在抗性种群中形成与敏感种群不同的可变剪接体，干扰 NETO 基因的表达可显著提高多杀菌素对西花蓟马的毒力，据此推测，当 nAChRs α6 受体无法正常表达时，谷氨酸能神经元受体可通过上调表达以及形成不同转录本等方式补偿胆碱能神经系统的功能突变，进而维持神经正常传递与高水平抗性之间的功能平衡（万岩然等, 2026）。

3.3　基于神经受体复合物的抗药性理论体系

综上所述，昆虫神经元中的 nAChR、VGSC、GABAR 以及 GluR 并非独立发挥功能，而是可组装形成功能性受体复合物。该复合物可通过受体间直接的物理相互作用，或经支架蛋白、信号分子介导的间接连接，形成稳定或动态的超分子结构。在该结构框架下，长期针对单一神经受体的选择压力可引发该受体发生构象或功能层面的适应性改变，这种改变不仅影响受体自身功能，还可传递给复合物中的其他伴侣受体。一方面，这种一个靶点改变引发其他靶点功能变化的机制，可合理解释家蝇与黑腹果蝇中观测到的不同靶标间非代谢性交互抗性现象；另一方面，该机制也可解释神经受体亚基缺失后，非同家族受体介导的功能代偿现象。

神经多受体复合物理论将抗性研究的视角从单个分子提升到了神经回路乃至整个系统的层面。这与现代神经科学和系统生物学的发展趋势相一致，即强调网络属性和涌现行为（Simon *et al*., 2006）。在哺乳动物中，神经和精神疾病的

机制研究早已超越了单一受体理论，转向关注多神经递质系统的失衡和神经回路的功能障碍（Liu *et al*., 2014; Li, 2020）。类似地，昆虫神经系统也具备相当的复杂性和可塑性。例如，单一受体可以同时介导快速的离子型反应和较慢的代谢型信号通路（Sinclair and Kabbani, 2023），而不同受体系统之间也存在广泛的串扰。这种网络的冗余性和多效性（Ozaki and Leonard, 2002）正是“神经多受体复合物”框架所强调的抗性产生的生物学基础。该框架能够为一些传统理论难以解释的现象提供新的解释。首先，它可以解释低水平、多基因抗性的形成。在这种情况下，可能没有任何一个基因发生显著的高抗突变，而是网络中多个节点的微小变化累积起来，共同导致了表型上的抗性。其次，它有助于理解不同作用模式杀虫剂之间的非预期交叉抗性或负交叉抗性。如果两种杀虫剂作用于同一复合物中的不同组分，它们可能会通过网络相互作用产生协同或拮抗效应。再次，该框架可以解释击倒后的快速恢复现象。即使主要靶点被抑制，神经网络也可能通过激活代偿通路，在短时间内恢复部分功能，从而使昆虫存活。这种系统层面的稳健性是单个分子模型所无法捕捉的。

3.4 基于神经受体复合物研发新型杀虫剂的应用前景

神经多受体复合物可作为新型杀虫剂分子设计的潜在靶标。靶向受体-受体互作界面可设计特异性结合于两个受体结合域的小分子化合物，分析靶向昆虫受体异聚物的蛋白质-蛋白质相互作用（Protein-protein interaction, PPI）界面作为杀虫剂设计新策略的可行性，为开发新一代绿色、高效的杀虫剂开辟了全新路径。

相较于传统作用于单一靶点的杀虫剂，靶向受体异聚体相互作用界面的小分子抑制剂在延缓害虫抗药性演化、提升靶标物种选择性层面具备显著的理论优势。其一，蛋白质-蛋白质相互作用界面通常比酶活性中心或离子通道孔道区域更大、构象更平坦，且在进化层面可能具有更高的变异性（Agogo-Mawuli *et al*., 2025）。这意味着害虫需要累积多个协同突变才能有效破坏抑制剂与结合界面的相互作用，进而产生抗药性，该过程发生的概率远低于单点突变介导的抗性产生。此外，该类结合界面对维持受体正确四级结构与生理功能具有关键作用（Hebert *et al*., 1996），任何改变界面构象或性质的突变都会使害虫付出极高的适合度代价（Kliot and Ghanim, 2012），进而在自然选择过程中被淘汰。这种内在的进化约束使得靶向 PPI 界面的设计策略具备延缓抗性产生的显著潜力。其二，不同昆虫物种的受体亚基组成与界面结构可能存在显著分化。例如，γ-氨基丁酸（GABA）受体由 α、β、γ 等多种亚基组装而成，其药理学特性随亚基组成的不同发生变化（Philip *et al*., 2025），这种亚基组合的多样性为设计物种特异性或类群特异性抑制剂提供了结构基础。通过靶向特定害虫类群（如鳞翅目或半翅目）特有的受体亚基结合界面，可开发出对传粉昆虫、害虫天敌等非靶标生物影响极低的高选择性杀虫剂。该设计原理与新烟碱类杀虫剂选择性作用于昆虫烟碱型乙酰胆碱受体（nAChRs）的机制相似（Jeschke *et al*., 2011），且有望实现更高精度的靶向特异性。该策略不仅可实现害虫抗性的有效管理，也符合现代农业对环境友好型植保产品的迫切需求。

尽管靶向昆虫受体界面的药物开发策略具备广阔应用前景，但其向实际生产应用的转化仍面临多重挑战，挑战主要集中于结构生物学解析与高效化合物筛选两个核心方向：其一，昆虫受体（尤其是膜蛋白受体复合物）的三维结构信息目前仍极为匮乏。蛋白质-蛋白质相互作用界面通常具有动态性与构象柔性特征，这对利用 X 射线晶体学等传统结构生物学方法解析其高分辨率结构造成了极大阻碍。近年来，冷冻电子显微镜（Cryo-electron microscopy, Cryo-EM）技术的发展为该问题的解决提供了新的技术路径，该技术可解析大型柔性蛋白复合物的近原子分辨率结构（Wang *et al*., 2025）。但就昆虫研究体系而言，获得足量且稳定的受体复合物纯化样品仍是尚未突破的技术瓶颈。精确三维结构信息的缺失导致基于结构的药物设计难以开展，现

有研究大多依赖计算模型与同源建模方法（Nagasubramanian *et al*., 2025），这显著提升了先导化合物发现过程的不确定性。其二，PPI 界面通常被归类为“难成药”靶点（Raavi Koehler and Vegas, 2025），其具有作用表面积大、缺乏清晰深度结合口袋的结构特征（Thitayanuwat *et al*., 2025），导致传统小分子化合物难以实现高亲和力与高特异性的结合，进而造成传统高通量筛选（High-throughput screening, HTS）的筛选效率处于较低水平。针对这一问题，计算化学与虚拟筛选（Virtual screening, VS）方法的作用日益受到关注（Khalid *et al*., 2025），该类方法可通过分子对接（Alhudaithi *et al*., 2026）、分子动力学（Molecular dynamics, MD）模拟（Wang *et al*., 2025）与机器学习（Alencar Filho *et al*., 2025）等技术，从大规模化合物库中完成潜在活性候选分子的初筛，可显著提升筛选效率与筛选成功率（Akter *et al*., 2025）。但此类计算方法的预测准确性高度依赖靶点结构质量与打分函数精度，其筛选结果仍需通过后续生物学实验完成活性验证。

为推动该创新策略的实际应用，需构建整合计算科学、生物物理学、化学生物学与昆虫学等多学科技术的综合性研发体系。后续研究需首先完成关键害虫核心受体复合物的结构解析，为新型杀虫剂分子设计提供结构基础；同时，需着力发展并优化靶向蛋白质-蛋白质相互作用的虚拟筛选流程，例如，可采用诱导契合对接（Induced-fit docking）或基于系综的对接（Ensemble-based docking）方法纳入受体界面的柔性效应（Sun *et al*., 2021; Zifruddin *et al*., 2023），并结合分子动力学模拟评估复合物的稳定性（Qin and Yuchi, 2024）。经虚拟筛选获得的候选化合物需通过多轮体外实验完成活性验证：表面等离子共振（Surface plasmon resonance, SPR）（Wang *et al*., 2025）或生物膜干涉（Bio-layer interferometry, BLI）等技术可精准测定化合物与靶蛋白的结合动力学参数；继而可在细胞水平验证化合物对受体功能的抑制效应（Liu *et al*., 2025）；最终通过 RNA 干扰（RNA interference, RNAi）与基因编辑等功能基因组学工具（端木浩南等, 2025），在活体昆虫中验证靶点功能并评估化合物的杀虫活性（Paschapur *et al*., 2026）。这种从计算模拟到活体验证的多层次整合筛选验证体系，是加速杀虫剂先导化合物发现与优化的核心路径。

此外，变构调控是靶向 PPI 界面极具潜力的替代策略。变构抑制剂通过结合于受体界面以外的变构位点，诱导受体构象改变，进而间接破坏受体亚基间的相互作用或稳定受体的非活性构象（Chen *et al*., 2016; Zhang *et al*., 2018）。与 PPI 界面相比，变构位点通常具有更小的尺寸与更明确的结构特征，更易实现小分子结合，为克服 PPI 界面“难以成药”的瓶颈提供了新的研究方向。

4　挑战与展望

将神经多受体复合物概念引入杀虫剂研究领域，可为杀虫剂抗性机制的理解提供新的视角。从抗性机制研究维度看，神经多受体复合物的存在提示，特定抗性表型可能源于受体复合物的整体功能失调，而非单一受体的基因突变或表达异常所致。未来研究需突破单一受体的分析框架，转向基于系统生物学的研究思路。在应用层面，神经多受体复合物可作为新型杀虫剂分子设计的潜在靶标。靶向受体-受体互作界面可设计特异性结合于 2 个受体结合域的小分子化合物，该类小分子本身可不具备激动或拮抗活性，但可通过改变复合物的整体构象调控神经信号传导，最终发挥杀虫效用。这类“界面抑制剂”具备更高的作用特异性，且不易与传统杀虫剂产生交互抗性。

神经多受体复合物概念的提出可为杀虫剂抗性治理策略提供重要理论指导。传统杀虫剂抗性治理策略主要依赖于轮换施用不同作用模式的杀虫剂，以延缓单一抗性机制的定向选择（Sparks and Nauen, 2015）。尽管该策略在多数场景下已被证实有效（Gao *et al*., 2012），但现有研究进展表明，仅以主要作用靶点差异制定治理方案存在局限性，有必要从神经网络层面深入解析不同杀虫剂间的相互作用关系。基于神经多受体复合物的研究框架，未来杀虫剂抗性治理策略可向以下方向拓展：1. 开发“网络破坏剂”：除

靶向致死性靶点的传统杀虫剂外，可开发以破坏神经多受体复合物结构稳定性或功能代偿能力为作用方式的新型化合物。该类化合物本身杀虫活性可能较低，但可作为增效剂恢复现有杀虫剂对抗性种群的毒力效力。2. 设计具协同效应的杀虫剂组合：基于对受体复合物内部相互作用机制的解析，可合理构建杀虫剂组合，使组分同时或序贯作用于信号网络中的关键节点，产生显著的协同致死效应，从而降低单一药剂的选择压力。3. 优化杀虫剂轮换策略：基于对害虫神经信号网络响应模式的解析，可设计更科学的杀虫剂轮换方案。例如，需避免连续施用作用于同一功能模块或具有相似下游效应的药剂，即便此类药剂归属于不同的作用机理分类。该优化方向对管理日趋复杂的杀虫剂抗性问题至关重要（Ranson and Lissenden, 2016; Moyes *et al*., 2017）。

现有研究表明，“神经多受体复合物”目前仍主要处于理论框架构建阶段，其具体分子组成与作用机制仍有待大量实验证据进一步明确与完善，对该框架的验证与完善仍存在显著技术瓶颈。相较于哺乳动物，昆虫神经系统具有结构微小、调控网络复杂的特征，开展在体功能研究（如电生理记录、钙成像）的技术难度更高。此外，神经多受体复合物的组成具有动态异质性，可随物种、组织类型及发育阶段发生变化。尽管上述研究方向仍存在诸多挑战，但现代生物学技术的快速发展为探索该领域提供了前所未有的研究机遇。未来研究可重点聚焦于以下方向：

（1）系统性多组学分析：整合转录组学、蛋白质组学与代谢组学技术，系统比较杀虫剂处理前后抗性品系与敏感品系的分子表达差异，识别与神经功能相关的共调控基因网络与信号通路（Ingham, 2018; Rosli *et al*., 2024）。该研究策略不仅可挖掘新的抗性候选基因，还有助于阐明候选基因间的功能关联。

（2）功能验证与神经生理学表征：利用 CRISPR/Cas9 基因编辑、RNA 干扰等技术，在体内精准调控候选基因的表达水平，结合电生理等功能分析手段，直接验证候选基因在抗性调控网络中的功能（Lamberti *et al*., 2025）。例如，可在靶点抗性突变的遗传背景下，验证敲低代偿性受体是否可恢复害虫对杀虫剂的敏感性。

（3）计算建模与人工智能分析：随着多组学数据的持续积累，利用计算生物学与人工智能技术（尤其是图神经网络）构建并分析复杂生物分子网络已具备技术可行性（Liu *et al*., 2024）。此类模型可实现多源数据的整合，预测调控网络中的关键节点与分子相互作用，模拟杀虫剂胁迫下的网络动态变化，进而为实验设计与害虫抗性治理（IRM）策略制定提供理论指导（Duan *et al*., 2025; Zeng and Jia, 2025）。

（4）新型调控机制挖掘：除经典受体与离子通道外，还需重点关注其他潜在调控元件在网络稳态调控中的作用，包括多巴胺、5-羟色胺等神经调质（Hoyt *et al*., 2019）、G 蛋白偶联受体（Ma, 2025）以及化学感应蛋白等非经典抗性相关蛋白（Tsouri and Douris, 2025）。

将神经多受体复合物假说从理论层面推进至实验验证与实践应用阶段，仍面临诸多挑战。一方面，相较于哺乳动物，昆虫神经系统的研究方法与资源相对匮乏，分离鉴定具有动态特征的蛋白质复合物存在技术难度。另一方面，田间害虫种群中靶点抗性、代谢抗性与“复合物抗性”往往共存，如何量化复合物抗性对整体表型的贡献是实验设计的核心难点。尽管如此，该研究方向有助于将神经科学前沿概念与昆虫毒理学经典科学问题相结合，为理解杀虫剂作用机制与抗性演化提供新的理论工具。神经多受体复合物概念将研究对象从单一靶点蛋白拓展至功能整合的受体网络层面，为阐释传统理论难以解释的复杂交互抗性现象提供了可能的分子框架，同时也为靶向受体互作界面的新型杀虫剂研发提供了思路。

参考文献 (References)

Agogo-Mawuli PS, Sadiya I, Abramyan TM, Bosch DE, Emmitte KA, Colón-Pérez LM, Kosloff M, Siderovski DP, 2025. Developing inhibitors of the guanosine triphosphate hydrolysis accelerating activity of regulator of G protein signaling-14. *Journal of Biological Chemistry*, 301(10): 110611.

Akinnawo S, Oluwole A, Ediagbonya T, 2025. Organochlorine and pyrethroid residues: Occurrence, potential sources, degradation path, ecological and health risk assessment in maize plantation: A pilot study from southwest Nigeria. *Environmental Pollution and Management*, 2: 245–255.

Akter B, Uddin MS, Islam MR, Ahamed KU, Aktar MN, Hossain MK, Salamatullah AM, Bourhia M, 2025. Computational drug design approaches for the identification of novel antidiabetic compounds from natural resources through molecular docking, ADMET, and toxicological studies. *Cell Biochemistry and Biophysics*, 83(1): 1057–1070.

Alencar Filho EB, Guimarães RP, Santos VC, Bispo ABP, Paranhos BAG, Aquino NC, Nascimento R, Oliveira Neto RF, 2025. Converging XGboost machine learning and molecular docking strategies to identify attractants for *Ceratitis capitata*: Molecular characterization and database curation of natural ligands for in vitro/in vivo tests. *Archives of Insect Biochemistry and Physiology*, 120(1): e70095.

Alhudaithi SS, Salih MHR, AlHusseini ZH, Almufadhili SM, Alelayani N, Bakheit AH, Alkahtani HM, Asiri HH, Alshamrani AA, Alhoshani AR, Alotaibi MR, As Sobeai HM, 2026. Poliovirus receptor (PVR) expression as a predictor of relapse in colorectal cancer: Bioinformatics and virtual screening. *Experimental Biology and Medicine*, 251(1): 10745.

Angers S, Salahpour A, Bouvier M, 2002. Dimerization: An emerging concept for G protein-coupled receptor ontogeny and function. *Annual Review of Pharmacology and Toxicology*, 42: 409–435.

Azam L, Winzer-Serhan UH, Chen Y, Leslie FM, 2002. Expression of neuronal nicotinic acetylcholine receptor subunit mRNAs within midbrain dopamine neurons. *Journal of Comparative Neurology*, 444(3): 260–274.

Balabanidou V, Grigoraki L, Vontas J, 2018. Insect cuticle: A critical determinant of insecticide resistance. *Current Opinion in Insect Science*, 27: 68–74.

Bass C, Denholm I, Williamson MS, Nauen R, 2015. The global status of insect resistance to neonicotinoid insecticides. *Pesticide Biochemistry and Physiology*, 121: 78–87.

Baxter GD, Barker SC, 1999. Isolation of a cDNA for an octopamine-like, G-protein coupled receptor from the cattle tick *Boophilus microplus*. *Insect Biochemistry and Molecular Biology*, 29(5): 461–467.

Beaulieu JM, Gainetdinov RR, 2011. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacological Reviews*, 63(1): 182–217.

Beckie H, Tardif F, 2012. Herbicide cross resistance in weeds. *Crop Protection*, 35: 15–28.

Bibel M, Barde YA, 2000. Neurotrophins: Key regulators of cell fate and cell shape in the vertebrate nervous system. *Genes & Development*, 14(23): 2919–2937.

Bloomquist JR, 1996. Ion channels as targets for insecticides. *Annual Review of Entomology*, 41: 163–190.

Boaventura D, Bolzan A, Padovez FE, Okuma DM, Omoto C, Nauen R, 2020. Detection of a ryanodine receptor target-site mutation in diamide insecticide resistant fall armyworm *Spodoptera frugiperda*. *Pest Management Science*, 76(1): 47–54.

Bono F, Fiorentini C, Mutti V, Tomasoni Z, Sbrini G, Trebesova H, Marchi M, Grilli M, Missale C, 2023. Central nervous system interaction and crosstalk between nAChRs and other ionotropic and metabotropic neurotransmitter receptors. *Pharmacological Research*, 190: 106711.

Bono F, Missale C, Fiorentini C, 2022. Induced pluripotent stem cells for defining Parkinsonian patient subtypes: A further step toward precision medicine. *Neural Regeneration Research*, 17(4): 767–769.

Buisson B, Bertrand D, 1998. Open-channel blockers at the human alpha4beta2 neuronal nicotinic acetylcholine receptor. *Molecular Pharmacology*, 53(3): 555–563.

Campaña MB, Perkins MR, McCabe MC, Neumann A, Larson ED, Fantauzzo KA, 2025. PDGFRα/β heterodimer activation negatively affects downstream ERK1/2 signaling and cellular proliferation. *Nature Communications*, 16(1): 4754.

Canals M, Marcellino D, Fanelli F, Ciruela F, de Benedetti P, Goldberg SR, Neve K, Fuxe K, Agnati LF, Woods AS, Ferré S, Lluis C, Bouvier M, Franco R, 2003. Adenosine A2A-dopamine D2 receptor-receptor heteromerization: Qualitative and quantitative assessment by fluorescence and bioluminescence energy transfer. *Journal of Biological Chemistry*, 278(47): 46741–46749.

Cartereau A, Bouchouireb Z, Kaaki S, Héricourt F, Taillebois E, Le Questel JY, Thany SH, 2024. Pharmacology and molecular modeling studies of sulfoxaflor, flupyradifurone and neonicotinoids on the human neuronal α7 nicotinic acetylcholine receptor. *Toxicology and Applied Pharmacology*, 492: 117123.

Casida JE, 2015. Golden age of RyR and GABA-R diamide and isoxazoline insecticides: Common genesis, serendipity, surprises, selectivity, and safety. *Chemical Research in Toxicology*, 28(4): 560–566.

Casida JE, Durkin KA, 2013. Neuroactive insecticides: Targets, selectivity, resistance, and secondary effects. *Annual Review of Entomology*, 58: 99–117.

Cecchini M, Changeux JP, 2015. The nicotinic acetylcholine receptor and its prokaryotic homologues: Structure, conformational transitions & allosteric modulation. *Neuropharmacology*, 96(Pt

B): 137–149.

Cepeda C, Levine MS, 1998. Dopamine and N-methyl-D-aspartate receptor interactions in the neostriatum. *Developmental Neuroscience*, 20(1): 1–18.

Changeux JP, Edelstein SJ, 1998. Allosteric receptors after 30 years. *Neuron*, 21(5): 959–980.

Chen YN, LaMarche MJ, Chan HM, Fekkes P, Garcia-Fortanet J, Acker MG, Antonakos B, Chen CH, Chen Z, Cooke VG, Dobson JR, Deng Z, Fei F, Firestone B, Fodor M, Fridrich C, Gao H, Grunenfelder D, Hao HX, Fortin PD, 2016. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. *Nature*, 535(7610): 148–152.

Chen YT, Stewart DB, Nelson WJ, 1999. Coupling assembly of the E-cadherin/beta-catenin complex to efficient endoplasmic reticulum exit and basal-lateral membrane targeting of E-cadherin in polarized MDCK cells. *Journal of Cell Biology*, 144(4): 687–699.

Choi M, Khan M, Jeong IH, Kim J, 2026. RNAseq-based molecular insights into three insecticide resistances in *Laodelphax striatellus*: Structural perspective on CYP6ER2 in detoxification. *Pesticide Biochemistry and Physiology*, 217: 106854.

Cole L, Nicholson R, Casida J, 1993. Action of phenylpyrazole insecticides at the GABA-gated chloride channel. *Pesticide Biochemistry and Physiology*, 46(1): 47–54.

Crupi R, Impellizzeri D, Cuzzocrea S, 2019. Role of metabotropic glutamate receptors in neurological disorders. *Frontiers in Molecular Neuroscience*, 12: 20.

Daborn P, Boundy S, Yen J, Pittendrigh B, ffrench-Constant R, 2001. DDT resistance in *Drosophila* correlates with Cyp6g1 over-expression and confers cross-resistance to the neonicotinoid imidacloprid. *Molecular Genetics and Genomics*, 266(4): 556–563.

Dale NC, Johnstone EKM, Pfleger KDG, 2022. GPCR heteromers: An overview of their classification, function and physiological relevance. *Frontiers in Endocrinology*, 13: 931573.

Davies TG, Field LM, Usherwood PN, Williamson MS, 2007. DDT, pyrethrins, pyrethroids and insect sodium channels. *IUBMB Life*, 59(3): 151–162.

De Bosscher K, Desmet SJ, Clarisse D, Estébanez-Perpiña E, Brunsveld L, 2020. Nuclear receptor crosstalk: Defining the mechanisms for therapeutic innovation. *Nature Reviews Endocrinology*, 16(7): 363–377.

de Vos AM, Ultsch M, Kossiakoff AA, 1992. Human growth hormone and extracellular domain of its receptor: Crystal structure of the complex. *Science*, 255(5042): 306–312.

Dechant G, Barde YA, 2002. The neurotrophin receptor p75(NTR): Novel functions and implications for diseases of the nervous system. *Nature Neuroscience*, 5(11): 1131–1136.

Devi LA, 2001. Heterodimerization of G-protein-coupled receptors: Pharmacology, signaling and trafficking. *Trends in Pharmacological Sciences*, 22(10): 532–537.

Dickinson JA, Kew JN, Wonnacott S, 2008. Presynaptic alpha 7- and beta 2-containing nicotinic acetylcholine receptors modulate excitatory amino acid release from rat prefrontal cortex nerve terminals via distinct cellular mechanisms. *Molecular Pharmacology*, 74(2): 348–359.

Do TT, Siegert A, Domart F, Hahn F, Zeising C, Muth S, Pape C, Kusch K, Dresbach T, Rizzoli SO, Petrovic A, Fernández-Busnadiego R, 2026. A correlative workflow for synaptic imaging by cryo-electron tomography. *Structure*, 34(5): 839–852.e6.

Dong K, Du Y, Rinkevich F, Nomura Y, Xu P, Wang L, Silver K, Zhorov BS, 2014. Molecular biology of insect sodium channels and pyrethroid resistance. *Insect Biochemistry and Molecular Biology*, 50: 1–17.

Dorostkar MM, Boehm S, 2008. Presynaptic ionotropic receptors. *Handbook of Experimental Pharmacology*, 184: 479–527.

Duan L, Hashemi M, Ngom A, Rueda L, 2025. Ligand-receptor dynamics in heterophily-aware graph neural networks for enhanced cell type prediction from single-cell RNA-seq data. *Frontiers in Molecular Biosciences*, 12: 1547231.

Duanmu HN, Guo FY, Liu Y, Li F, 2025. The application of gene co-expression network in entomology. Chinese *Journal of Applied Entomology*, 62(1): 13–22. [端木浩楠, 国芳媛, 刘莹, 李飞, 2025. 基因共表达网络在昆虫学领域的应用. 应用昆虫学报, 62(1): 13–22.]

El-Helw EAE, Abou-Elmagd WSI, Hosni EM, Kamal M, Hashem AI, Ramadan SK, 2025. Synthesis of benzoquinoline derivatives and evaluation of their insecticidal activity against *Culex pipiens* L. larvae. *European Journal of Medicinal Chemistry*, 290: 117565.

Ffrench-Constant RH, Anthony N, Aronstein K, Rocheleau T, Stilwell G, 2000. Cyclodiene insecticide resistance: From molecular to population genetics. *Annual Review of Entomology*, 45: 449–466.

Ffrench-Constant RH, Rocheleau TA, Steichen JC, Chalmers AE, 1993. A point mutation in a *Drosophila* GABA receptor confers insecticide resistance. *Nature*, 363(6428): 449–451.

Gao L, Nowakowska MB, Selby K, Przykopanski A, Chen B, Krüger M, Douillard FP, Lam KH, Chen P, Huang T, Minton NP, Dorner MB, Dorner BG, Rummel A, Lindström M, Jin R, 2025. Botulinum neurotoxins exploit host digestive proteases to boost their oral toxicity via activating OrfXs/P47. *Nature Structural & Molecular Biology*, 32(5): 864–875.

Gao Y, Lei Z, Reitz SR, 2012. Western flower thrips resistance to

insecticides: Detection, mechanisms and management strategies. *Pest Management Science*, 68(8): 1111–1121.

George SR, O'Dowd BF, Lee SP, 2002. G-Protein-coupled receptor oligomerization and its potential for drug discovery. *Nature Reviews Drug Discovery*, 1(10): 808–820.

Gimpl G, Fahrenholz F, 2001. The oxytocin receptor system: Structure, function, and regulation. *Physiological Reviews*, 81(2): 629–683.

Goodchild J, Chen YJ, Blythe J, Firth LC, Hirst E, Bess K, Bristow J, Willis J, Baines R, Cash F, Muehlebach M, Buchholz A, Rendler S, Earley F, Crossthwaite A, 2024. A novel class of insecticidal alkylsulfones are potent inhibitors of vesicular acetylcholine transport. *Pesticide Biochemistry and Physiology*, 201: 105854.

Gould F, Martinez-Ramirez A, Anderson A, Ferre J, Silva FJ, Moar WJ, 1992. Broad-spectrum resistance to *Bacillus thuringiensis* toxins in *Heliothis virescens*. *Proceedings of the National Academy of Sciences of the United States of America*, 89(17): 7986–7990.

Goulson D, 2013. Review: An overview of the environmental risks posed by neonicotinoid insecticides. *Journal of Applied Ecology*, 50(4): 977–987.

Grant C, Jacobson R, Ilias A, 2019. The evolution of multiple-insecticide resistance in UK populations of tomato leafminer, *Tuta absoluta*. *Pest Management Science*, 75(8): 2079–2085.

Guan ZZ, 2024. Alterations in neuronal nicotinic acetylcholine receptors in the pathogenesis of various cognitive impairments. *CNS Neuroscience & Therapeutics*, 30(10): e70069.

Ha T, Kaiser C, Myong S, Wu B, Xiao J, 2022. Next generation single-molecule techniques: Imaging, labeling, and manipulation in vitro and in cellulo. *Molecular Cell*, 82(2): 304–314.

Haikal A, Kamal M, Hosni EM, Amen Y, 2025. Evaluation of hesperidin as a potential larvicide against *Culex pipiens* with computational prediction of its mode of action via molecular docking. *Scientific Reports*, 15(1): 2677.

Halevi S, McKay J, Palfreyman M, Yassin L, Eshel M, Jorgensen E, Treinin M, 2002. The *C. elegans* ric-3 gene is required for maturation of nicotinic acetylcholine receptors. *The EMBO Journal*, 21(5): 1012–1020.

Hebert TE, Moffett S, Morello JP, Loisel TP, Bichet DG, Barret C, Bouvier M, 1996. A peptide derived from a beta2-adrenergic receptor transmembrane domain inhibits both receptor dimerization and activation. *Journal of Biological Chemistry*, 271(27): 16384–16392.

Hoyt JM, Perkel DJ, Portfors CV, 2019. Dopamine acts via D2-like receptors to modulate auditory responses in the inferior colliculus. *eNeuro*, 6(5): ENEURO.0218–19.2019.

Huang JM, Rao C, Wang S, He LF, Zhao SQ, Zhou LQ, Zhao YX, Yang FX, Gao CF, Wu SF, 2020. Multiple target-site mutations occurring in lepidopterans confer resistance to diamide insecticides. *Insect Biochemistry and Molecular Biology*, 121: 103367.

Huang X, Xiao T, Zhao X, Yang Z, Sun Z, Lu K, 2025a. Olfactory perception of trifluralin by GOBP2 decreases the susceptibility of *Spodoptera litura* to insecticides through modulation of 20E signaling pathway-mediated metabolic detoxification. *Journal of Hazardous Materials*, 500: 140417.

Huang Y, Li J, Liu Z, Hu Q, Yao Q, Gan C, Xiong Q, Cui J, 2025b. Dual-coated emamectin benzoate nano-formulation with enhanced systemic translocation and insecticidal activity based on lignin/urea-formaldehyde. *International Journal of Biological Macromolecules*, 331(2): 148498.

Hunjan G, Aran KR, 2025. Role of mGluR7 in Alzheimer's disease: Pathophysiological insights and therapeutic approaches. *Inflammopharmacology*, 33(6): 2977–2995.

Hunter T, 2007. The age of crosstalk: Phosphorylation, ubiquitination, and beyond. *Molecular Cell*, 28(5): 730–738.

Husi H, Ward MA, Choudhary JS, Blackstock WP, Grant SG, 2000. Proteomic analysis of NMDA receptor-adhesion protein signaling complexes. *Nature Neuroscience*, 3(7): 661–669.

Ingham VA, Wagstaff S, Ranson H, 2018. Transcriptomic meta-signatures identified in *Anopheles gambiae* populations reveal previously undetected insecticide resistance mechanisms. *Nature Communications*, 9(1): 5282.

Jayachandran A, Annadurai P, Upadhyay M, Tiwari M, Sajan P, Sibal P, Chatterjee N, Pal K, 2025. Domain-specific N-glycosylation of the adhesion G-protein-coupled receptor ADGRG6 N-terminal fragment regulates trafficking, proteolytic processing, and signaling. *Molecular Biology of the Cell*, 36(8): ar101.

Jeschke P, Nauen R, Schindler M, Elbert A, 2011. Overview of the status and global strategy for neonicotinoids. *Journal of Agricultural and Food Chemistry*, 59(7): 2897–2908.

Jiang J, Li X, Hu AF, Zhou GJ, Gao YH, Xu C, Wu XM, Wang HJ, 2025. Nicotine and neuronal nicotinic acetylcholine receptors: Unraveling the mechanisms of nicotine addiction. *Frontiers in Neuroscience*, 19: 1670883.

Kalamida D, Poulas K, Avramopoulou V, Fostieri E, Lagoumintzis G, Lazaridis K, Sideri A, Zouridakis M, Tzartos SJ, 2007. Muscle and neuronal nicotinic acetylcholine receptors. *The FEBS Journal*, 274(15): 3799–3845.

Kawashima K, Fujii T, 2000. Extraneuronal cholinergic system in lymphocytes. *Pharmacology & Therapeutics*, 86(1): 29–48.

Khalid M, Alqarni MH, Foudah AI, 2025. Bioactive phytoconstituent

millettone as a potential inhibitor of catechol O-methyltransferase: Implications for neuroprotective therapy in Parkinson's disease. *Journal of Pharmacology and Experimental Therapeutics*, 392(6): 103592.

Khan MM, Wang J, Gao Y, Wu D, Qiu B, Zhu Z, 2025. Impact of long-term cadmium exposure on insecticidal cross-resistance and biological traits of brown planthopper *Nilaparvata lugens* (Hemiptera: Delphacidae). *Journal of Hazardous Materials*, 492: 138203.

Klco JM, Lassere TB, Baranski TJ, 2003. C5a receptor oligomerization. I. Disulfide trapping reveals oligomers and potential contact surfaces in a G protein-coupled receptor. *Journal of Biological Chemistry*, 278(37): 35345–35353.

Kliot A, Ghanim M, 2012. Fitness costs associated with insecticide resistance. *Pest Management Science*, 68(11): 1431–1437.

Kouamo MFM, Ibrahim SS, Muhammad A, Gadji M, Hearn J, Wondji CS, 2025. Allelic variation in a cluster of epsilon glutathione *S*-transferase genes contributes to DDT and pyrethroid resistance in the major African malaria vector *Anopheles funestus*. *BMC Genomics*, 26(1): 452.

Lamberti M, van Putten MJAM, Marzen S, le Feber J, 2025. The role of NMDA receptors in memory and prediction in cultured neural networks. *Journal of Neural Engineering*, 22(1): 016018.

Li X, Schuler MA, Berenbaum MR, 2007. Molecular mechanisms of metabolic resistance to synthetic and natural xenobiotics. *Annual Review of Entomology*, 52: 231–253.

Li YF, 2020. A hypothesis of monoamine (5-HT)-glutamate/GABA long neural circuit: Aiming for fast-onset antidepressant discovery. *Pharmacology & Therapeutics*, 208: 107494.

Li YY, Liu mm, Song CX, Li SJ, Ma FF, Zhang KJ, Xiang D, Chen HQ, Nima YZ, Liu H, 2024. Sublethal effect of tetrachlorantraniliprole on the predatory capacity of *Neoseiulus cucumeri*. *Chinese Journal of Applied Entomology*, 61(3): 625–633. [李亚迎, 刘明秀, 宋雪纯, 李士家, 马方芳, 张开军, 相栋, 陈翰秋, 尼玛玉珍, 刘怀, 2024. 四氯虫酰胺亚致死胁迫对胡瓜新小绥螨捕食效能的影响. 应用昆虫学报, 61(3): 625–633.]

Liang J, Xiao F, Ojo J, Chao WH, Ahmad B, Alam A, Abbas S, Abdelhafez MM, Rahman N, Khan KA, Ghramh HA, Ali J, Chen R, 2025. Insect resistance to insecticides: Causes, mechanisms, and exploring potential solutions. *Archives of Insect Biochemistry and Physiology*, 118(2): e70045.

Lidke DS, Nagy P, Heintzmann R, Arndt-Jovin DJ, Post JN, Grecco HE, Jares-Erijman EA, Jovin TM, 2004. Quantum dot ligands provide new insights into erbB/HER receptor-mediated signal transduction. *Nature Biotechnology*, 22(2): 198–203.

Lin PX, Peng YX, Xing JY, Liu ZY, Guo FR, Thia JA, Gao CF, Wu SF, 2025. Cis-regulation of the CYP6CS1 gene and its role in mediating cross-resistance in a pymetrozine-resistant strain of *Nilaparvata lugens*. *Insect Biochemistry and Molecular Biology*, 177: 104261.

Liu J, Buisman-Pijlman F, Hutchinson MR, 2014. Toll-like receptor 4: Innate immune regulator of neuroimmune and neuroendocrine interactions in stress and major depressive disorder. *Frontiers in Neuroscience*, 8: 309.

Liu N, 2015. Insecticide resistance in mosquitoes: Impact, mechanisms, and research directions. *Annual Review of Entomology*, 60: 537–559.

Liu N, Yue X, 2000. Insecticide resistance and cross-resistance in the house fly (Diptera: Muscidae). *Journal of Economic Entomology*, 93(4): 1269–1275.

Liu S, Fu Y, Pan D, Zhan E, Li Y, 2025. APN3 acts as a functional receptor of *Bacillus thuringiensis* Cry1Ac in *Grapholita molesta*. *Journal of Agricultural and Food Chemistry*, 73(22): 13393–13404.

Liu X, Tao Y, Cai Z, Bao P, Ma H, Li K, Li M, Zhu Y, Lu ZJ, 2024. Pathformer: A biological pathway informed transformer for disease diagnosis and prognosis using multi-omics data. *Bioinformatics*, 40(5): btae287.

Livingstone PD, Srinivasan J, Kew JN, Dawson LA, Gotti C, Moretti M, Shoaib M, Wonnacott S, 2009. Alpha7 and non-alpha7 nicotinic acetylcholine receptors modulate dopamine release in vitro and in vivo in the rat prefrontal cortex. *European Journal of Neuroscience*, 29(3): 539–550.

Luo B, Lee AS, 2013. The critical roles of endoplasmic reticulum chaperones and unfolded protein response in tumorigenesis and anticancer therapies. *Oncogene*, 32(7): 805–818.

Luo Y, Sun L, Peng Y, 2025. The structural basis of the G protein-coupled receptor and ion channel axis. *Current Research in Structural Biology*, 9: 100165.

Martinez-Sanchez A, Laugks U, Kochovski Z, Papantoniou C, Zinzula L, Baumeister W, Lučić V, 2021. Trans-synaptic assemblies link synaptic vesicles and neuroreceptors. *Science Advances*, 7(10): eabf0655.

Maurel D, Comps-Agrar L, Brock C, Rives ML, Bourrier E, Ayoub MA, Bazin H, Tinel N, Durroux T, Prézeau L, Trinquet E, Pin JP, 2008. Cell-surface protein-protein interaction analysis with time-resolved FRET and snap-tag technologies: Application to GPCR oligomerization. *Nature Methods*, 5(6): 561–567.

Meyer EL, Gahring LC, Rogers SW, 2002. Nicotine preconditioning antagonizes activity-dependent caspase proteolysis of a glutamate receptor. *Journal of Biological Chemistry*, 277(13):

10869–10875.

Milligan G, 2004. G protein-coupled receptor dimerization: Function and ligand pharmacology. *Molecular Pharmacology*, 66(1): 1–7.

Mondragón-García A, Ramírez-Sánchez E, Francia-Ramírez D, Hernández-González O, Rojano-Posada Y, Ortega-Tinoco S, Garduño J, Verdugo-Díaz L, Hernández-López S, 2024. S-(+)-mecamylamine increases the firing rate of serotonin neurons and diminishes depressive-like behaviors in an animal model of stress. *Neuroscience*, 562: 75–89.

Moyes CL, Vontas J, Martins AJ, Ng LC, Koou SY, Dusfour I, Raghavendra K, Pinto J, Corbel V, David JP, Weetman D, 2017. Contemporary status of insecticide resistance in the major *Aedes* vectors of arboviruses infecting humans. *PLoS Neglected Tropical Diseases*, 11(7): e0005625.

Mutti V, Bono F, Tomasoni Z, Bontempi L, Guglielmi A, Bolognin S, Schwamborn JC, Missale C, Fiorentini C, 2022. Structural plasticity of dopaminergic neurons requires the activation of the D3R-nAChR heteromer and the PI3K-ERK1/2/Akt-induced expression of c-Fos and p70S6K signaling pathway. *Molecular Neurobiology*, 59(4): 2129–2149.

Nagasubramanian K, Govindaraj S, Sivakumar N, Chandrasekaran J, Gupta K, Chandran S, 2025. Identification of small molecule inhibitors targeting wheat dwarf virus Rep protein by virtual screening. *Discover Plants*, 2(1): 12.

Navarro G, Ferré S, Cordomi A, Moreno E, Mallol J, Casadó V, Cortés A, Hoffmann H, Ortiz J, Canela EI, Lluís C, Pardo L, Franco R, Woods AS, 2010. Interactions between intracellular domains as key determinants of the quaternary structure and function of receptor heteromers. *Journal of Biological Chemistry*, 285(35): 27346–27359.

Nusser Z, Mulvihill E, Streit P, Somogyi P, 1994 . Subsynaptic segregation of metabotropic and ionotropic glutamate receptors as revealed by immunogold localization. *Neuroscience*, 61(3): 421–427.

Olsen RW, 2015. Allosteric ligands and their binding sites define γ-aminobutyric acid (GABA) type A receptor subtypes. *Advances in Pharmacology*, 73: 167–202.

Orozco-Borunda D, Papantoniou C, Brose N, Lučić V, 2024. Direct cryo-ET detection of native SNARE and Munc13 protein bridges using AI classification and preprocessing. *bioRxiv*, https://doi.org/10.1101/2024.12.18.629213.

Orzeł U, Barreto CAV, Filipek S, Moreira IS, 2025. GPCR oligomerization across classes: A2AR-mediated regulation of mGlu5R activation. *International Journal of Biological Macromolecules*, 299: 139880.

Ozaki K, Leonard WJ, 2002. Cytokine and cytokine receptor pleiotropy and redundancy. *Journal of Biological Chemistry*, 277(33): 29355–29365.

Parish CL, Nunan J, Finkelstein DI, McNamara FN, Wong JY, Waddington JL, Brown RM, Lawrence AJ, Horne MK, Drago J, 2005. Mice lacking the alpha4 nicotinic receptor subunit fail to modulate dopaminergic neuronal arbors and possess impaired dopamine transporter function. *Molecular Pharmacology*, 68(5): 1376–1386.

Paschapur AU, Pandey D, Singh L, Marella SM, Nebapure SM, Subramanian S, 2026. Integrative screening of plant volatiles through transient receptor potential channel docking, olfactometry, and field validation in *Bemisia tabaci*. *Pest Management Science*, 82(8): 7463–7482.

Philip AB, Brohan J, Goudra B, 2025. The role of GABA receptors in anesthesia and sedation: An updated review. *CNS Drugs*, 39(1): 39–54.

Qin J, Yuchi Z, 2024. Identification of a novel inhibitor of *Cimex lectularius* acetylcholinesterase. *Journal of Agricultural and Food Chemistry*, 72(22): 12498–12507.

Raavi Koehler AN, Vegas AJ, 2025. At the interface: Small-molecule inhibitors of soluble cytokines. *Chemical Reviews*, 125(9): 4528–4568.

Ramadan SK, Abou-Elmagd WSI, Hosni EM, Kamal M, Hashem AI, El-Helw EAE, 2025. Synthesis, in vivo evaluation, and in silico molecular docking of benzo[h]quinoline derivatives as potential *Culex pipiens* L. larvicides. *Bioorganic Chemistry*, 154: 108090.

Ranson H, Lissenden N, 2016. Insecticide resistance in African *Anopheles* mosquitoes: A worsening situation that needs urgent action to maintain malaria control. *Trends in Parasitology*, 32(3): 187–196.

Rasmussen SG, DeVree BT, Zou Y, Kruse AC, Chung KY, Kobilka TS, Thian FS, Chae PS, Pardon E, Calinski D, Mathiesen JM, Shah ST, Lyons JA, Caffrey M, Gellman SH, Steyaert J, Skiniotis G, Weis WI, Sunahara RK, Kobilka BK, 2011. Crystal structure of the β2 adrenergic receptor-Gs protein complex. *Nature*, 477(7366): 549–555.

Rodbell M, 1980. The role of hormone receptors and GTP-regulatory proteins in membrane transduction. *Nature*, 284(5751): 17–22.

Rosli MAF, Syed Jaafar SN, Azizan KA, Yaakop S, Aizat WM, 2024. Omics approaches to unravel insecticide resistance mechanism in *Bemisia tabaci* (Gennadius) (Hemiptera: Aleyrodidae). *PeerJ*, 12: e17843.

Sbrini G, Mutti V, Bono F, Tomasoni Z, Fadel D, Missale C, Fiorentini C, 2024. 17-β-estradiol potentiates the neurotrophic and neuroprotective effects mediated by the dopamine

D3/acetylcholine nicotinic receptor heteromer in dopaminergic neurons. *European Journal of Pharmacology*, 976: 176678.

Scanziani M, Salin PA, Vogt KE, Malenka RC, Nicoll RA, 1997. Use-dependent increases in glutamate concentration activate presynaptic metabotropic glutamate receptors. *Nature*, 385(6617): 630–634.

Schlessinger J, 2000. Cell signaling by receptor tyrosine kinases.*Cell*, 103(2): 211–225.

Schmiedhofer P, Vogel FD, Koniuszewski F, Ernst M, 2022. Cys-loop receptors on cannabinoids: All high? *Frontiers in Physiology*, 13: 1044575.

Schoofs L, De Loof A, Van Hiel MB, 2017. Neuropeptides as regulators of behavior in insects. *Annual Review of Entomology*, 62: 35–52.

Semyanov A, Verkhratsky A, 2021. Astrocytic processes: From tripartite synapses to the active milieu. *Trends in Neurosciences*, 44(10): 781–792.

Silva AP, Santos JM, Martins AJ, 2014. Mutations in the voltage-gated sodium channel gene of anophelines and their association with resistance to pyrethroids-A review. *Parasites & Vectors*, 7(1): 450.

Simon SA, de Araujo IE, Gutierrez R, Nicolelis MA, 2006. The neural mechanisms of gustation: A distributed processing code. *Nature Reviews Neuroscience*, 7(11): 890–901.

Simpson LM, Taddese B, Wall ID, Reynolds CA, 2010. Bioinformatics and molecular modelling approaches to GPCR oligomerization. *Current Opinion in Pharmacology*, 10(1): 30–37.

Sinclair P, Kabbani N, 2023. Ionotropic and metabotropic responses by alpha 7 nicotinic acetylcholine receptors. *Pharmacological Research*, 197: 106975.

Soderlund DM, Knipple DC, 2003. The molecular biology of knockdown resistance to pyrethroid insecticides. *Insect Biochemistry and Molecular Biology*, 33(6): 563–577.

Sparks TC, Nauen R, 2015. IRAC: Mode of action classification and insecticide resistance management. *Pesticide Biochemistry and Physiology*, 121: 122–128.

Sparks TC, Wessels FJ, Perry T, Price MJ, Siebert MW, Mann DGJ, 2025. Spinosyn resistance and cross-resistance: A 25 year review and analysis. *Pesticide Biochemistry and Physiology*, 210: 106363.

Stamos J, Sliwkowski MX, Eigenbrot C, 2002. Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor. *Journal of Biological Chemistry*, 277(48): 46265–46272.

Stone TW, 2021. Relationships and interactions between ionotropic glutamate receptors and nicotinic receptors in the CNS. *Neuroscience*, 468: 321–365.

Sun H, Wang J, Liu S, Zhou X, Dai L, Chen C, Xu Q, Wen X, Cheng K, Sun H, Yuan H, 2021. Discovery of novel small molecule inhibitors disrupting the PCSK9-LDLR interaction. *Journal of Chemical Information and Modeling*, 61(10): 5269–5279.

Suzuki T, Yamato S, 2021. Oxazosulfyl, a novel sulfyl insecticide, binds to and stabilizes the voltage-gated sodium channels in the slow-inactivated state. *Journal of Agricultural and Food Chemistry*, 69(14): 4048–4055.

Thany SH, 2025. The mode of action of neonicotinoids and related compounds on insect neuronal nicotinic acetylcholine receptors highlights complex intracellular calcium mechanisms. *Pesticide Biochemistry and Physiology*, 213: 106532.

Thitayanuwat P, Hengphasatporn K, Chankhamhaengdecha S, Shigeta Y, 2025. Mechanistic insights into PRRSV inhibition through CD163-SRCR5 blockade by PRRSV/CD163-IN-1. *The Journal of Physical Chemistry Letters*, 16(25): 6286–6292.

Touponse GC, Pomrenze MB, Yassine T, Denomme N, Wang M, Mehta V, Zhang Z, Malenka RC, Eshel N, 2026. Cholinergic modulation of dopamine release drives effortful behaviour. *Nature*, 651(8107): 1020–1029.

Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R, 2010. Glutamate receptor ion channels: Structure, regulation, and function. *Pharmacological Reviews*, 62(3): 405–496.

Tsouri A, Douris V, 2025. The role of chemosensory proteins in insecticide resistance: A review. *Insects*, 16(5): 496.

Verona F, Di Bella S, Schirano R, Manfredi C, Angeloro F, Bozzari G, Todaro M, Giannini G, Stassi G, Veschi V, 2025. Cancer stem cells and tumor-associated macrophages as mates in tumor progression: Mechanisms of crosstalk and advanced bioinformatic tools to dissect their phenotypes and interaction. *Frontiers in Immunology*, 16: 1529847.

Walton SF, Myerscough MR, Currie BJ, 2000. Studies in vitro on the relative efficacy of current acaricides for *Sarcoptes scabiei* var. *hominis*. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 94(1): 92–96.

Wan Y, Yuan G, He B, Xu B, Xie W, Wang S, Zhang Y, Wu Q, Zhou X, 2018 . Foccα6, a truncated nAChR subunit, positively correlates with spinosad resistance in the western flower thrips, *Frankliniella occidentalis* (Pergande). *Insect Biochemistry and Molecular Biology*, 99: 1–10.

Wan YR, Wan YC, Yuan JJ, Qian KH, Yang HL, Wu QJ, 2026. Function of the NETO gene in spinosad resistance in *Frankliniella occidentalis* (Thysanoptera: Thripidae). *Acta*

Entomologica Sinica, 69(7): 1–10. [万岩然, 王亚超, 袁江江, 钱康华, 杨浩岚, 吴青君, 2026. 西花蓟马 NETO 基因在多杀菌素抗性中的作用. 昆虫学报, 69(7): 1–10.]

Wang Q, Shentu X, Yu X, Liu Y, 2025. Insect odorant-binding proteins (OBPs) and chemosensory proteins (CSPs): Mechanisms and research perspectives in mediating insecticide resistance. *Biology*, 14(10): 892.

Wang Z, Yao M, Wu Y, 2009. Cross-resistance, inheritance and biochemical mechanisms of imidacloprid resistance in B-biotype *Bemisia tabaci*. *Pest Management Science*, 65(11): 1189–1194.

Watson GB, Siebert MW, Wang NX, Loso MR, Sparks TC, 2021. Sulfoxaflor: A sulfoximine insecticide: Review and analysis of mode of action, resistance and cross-resistance. *Pesticide Biochemistry and Physiology*, 178: 104924.

Wiley HS, 2003. Trafficking of the ErbB receptors and its influence on signaling. *Experimental Cell Research*, 284(1): 78–88.

Williams DK, Wang J, Papke RL, 2011. Positive allosteric modulators as an approach to nicotinic acetylcholine receptor-targeted therapeutics: Advantages and limitations. *Biochemical Pharmacology*, 82(8): 915–930.

Wittenberg RE, Wolfman SL, De Biasi M, Dani JA, 2020. Nicotinic acetylcholine receptors and nicotine addiction: A brief introduction. *Neuropharmacology*, 177: 108256.

Wooltorton JR, Pidoplichko VI, Broide RS, Dani JA, 2003. Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. *The Journal of Neuroscience*, 23(8): 3176–3185.

Wu J, Liu X, Peng Y, Huang J, Zhou L, 2026. Molecular insights into the action mechanism, resistance development, and ecological risks of cyantraniliprole. *International Journal of Molecular Sciences*, 27(6): 3218.

Wu ZS, Cheng H, Jiang Y, Melcher K, Xu HE, 2015. Ion channels gated by acetylcholine and serotonin: Structures, biology, and drug discovery. *Acta Pharmacologica Sinica*, 36(8): 895–907.

Xie N, Bickley BA, Gross AD, 2024. GABA-gated chloride channel mutation (Rdl) induces cholinergic physiological compensation resulting in cross resistance in *Drosophila melanogaster*. *Pesticide Biochemistry and Physiology*, 203: 105972.

Yan YY, Wang K, Wang JT, Han QQ, Zhang Z, Yu N, Liu ZW, 2025. Peptide neurotoxins affecting insect voltage-gated calcium channels and possessing insecticidal toxicity: Two ω-atypitoxins from *Calommata signata*. *Pesticide Biochemistry and Physiology*, 208: 106279.

Yang HL, Zhao L, Cao F, Jiang LQ, Liu S, Li MY, Li SG, 2024. Molecular characterization of *Thioredoxin peroxidase* (AiTPX1) from *Agrotis ipsilon* and its response to insecticide stress. *Chinese Journal of Applied Entomology,* 61(2): 258–270. [杨浩岚, 赵乐, 曹付, 江连强, 刘苏, 李茂业, 李世广, 2024. 小地老虎硫氧还蛋白过氧化物酶 AiTPX1 的分子特征及其对杀虫剂胁迫的响应. 应用昆虫学报, 61(2): 258–270.]

Young GT, Zwart R, Walker AS, Sher E, Millar NS, 2008. Potentiation of alpha7 nicotinic acetylcholine receptors via an allosteric transmembrane site. *Proceedings of the National Academy of Sciences of the United States of America*, 105(38): 14686–14691.

Yuasa-Kawada J, Kinoshita-Kawada M, Hiramoto M, Yamagishi S, Mishima T, Yasunaga S, Tsuboi Y, Hattori N, Wu JY, 2026. Neuronal guidance signaling in neurodegenerative diseases: Key regulators that function at neuron-glia and neuroimmune interfaces. *Neural Regeneration Research*, 21(2): 612–635.

Zeng J, Jia X, 2025. Quantifying compatibility mechanisms in traditional Chinese medicine with interpretable graph neural networks. *Journal of Pharmaceutical Analysis*, 15(8): 101342.

Zhang K, Yuan J, Wan Y, Wang J, Zheng X, Zhang Y, Wu S, Liang P, Zhou X, Wu Q, 2023. An insertion in intron 3 of nAChR alpha 6 subunit is associated with spinosad resistance in the western flower thrips *Frankliniella occidentalis*. *Entomologia Generalis*, 43(3): 605–613.

Zhang S, Hu Z, Tanji H, Jiang S, Das N, Li J, Sakaniwa K, Jin J, Bian Y, Ohto U, Shimizu T, Yin H, 2018. Small-molecule inhibition of TLR8 through stabilization of its resting state. *Nature Chemical Biology*, 14(1): 58–64.

Zhang X, Guseinov AA, Jenkins L, Valentini A, Marsango S, Schultz-Knudsen K, Ulven T, Rexen Ulven E, Tikhonova IG, Milligan G, Zhang C, 2025. Allosteric modulation and biased signaling at free fatty acid receptor 2. *Nature*, 643(8074): 1428–1438.

Zhou FM, Liang Y, Dani JA, 2001. Endogenous nicotinic cholinergic activity regulates dopamine release in the striatum. *Nature Neuroscience*, 4(12): 1224–1229.

Zhu YT, Liu YM, Guo XJ, Li Y, Zhang RX, Wu QJ, Feng YT, 2024. Resistance selection of *Tuta absoluta* (Meyrick) to tetraniliprole and cross-realistic analysis. *Chinese Journal of Applied Entomology*, 61(1): 169–176. [朱雅婷, 张雅蒙, 郭晓君, 李娅, 张润祥, 吴青君, 封云涛, 2024. 番茄潜叶蛾对四唑虫酰胺的抗性选育及交互抗性研究. 应用昆虫学报, 61(1): 169–176.]

Zifruddin AN, Mohamad Yusoff MA, Abd Ghani NS, Nor Muhammad NA, Lam KW, Hassan M, 2023. Ensemble-based, high-throughput virtual screening of potential inhibitor targeting putative farnesol dehydrogenase of *Metisa plana* (Lepidoptera: Psychidae). *Computational Biology and Chemistry*, 103: 107811.