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Review

Insecticide Use, Resistance Status and Mechanism in Indian Mosquito Vectors

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Abstract

Mosquito-borne diseases such as malaria, dengue, chikungunya, and filariasis continue to pose a serious public health challenge in India. Vector control remains central to managing these diseases, with insecticides forming the backbone of control programs. However, the effectiveness of these chemicals has declined as mosquito populations have developed resistance, while drug resistance has also emerged in pathogens. Resistance in mosquitoes is driven by multiple mechanisms, including enhanced detoxification processes and mutations that reduce insecticide sensitivity. This review traces the history of insecticide use in India, focusing on the five major classes - organochlorines, organophosphates, pyrethroids, carbamates, and neonicotinoids. Prolonged use has led to widespread resistance in key species such as *Anopheles culicifacies*, *An. stephensi*, *Culex quinquefasciatus*, and *Aedes aegypti*. The review highlights target-site mutations (such as kdr L1014F/S, F1534C), metabolic resistance (CYP450s, GSTs, esterases), behavioral changes, and cuticular thickening. Resistance patterns vary across regions and often involve multiple classes of insecticides. Recent molecular findings offer important insights for surveillance and provide direction for integrated and sustainable resistance management strategies in India.

Keywords: mosquito vectors; mosquito-borne disease; indoor residual spraying; insecticide resistance; knockdown resistance (kdr); metabolic detoxification

Introduction

Vector-borne diseases continue to be a major public health concern in India, contributing significantly to morbidity and mortality. Mosquitoes belonging to the groups *Anopheles*, *Aedes*, and *Culex* are the main carriers that transmit malaria, dengue, chikungunya, Zika virus, and lymphatic filariasis. (Raghavendra et al., 2011). For decades, vector control in India has relied heavily on chemical insecticides, particularly organochlorines, organophosphates, carbamates, and pyrethroids. However, the extensive and often indiscriminate use of these compounds has led to the emergence and spread of insecticide resistance, posing a significant challenge to vector management and disease control programs (Hemingway et al., 2016).

Insecticide resistance refers to the heritable decrease in the sensitivity of mosquito populations to chemicals that were previously effective at controlling them. This is an evolutionary response facilitated by the selection pressure exerted by sustained exposure to insecticides. Resistance mechanisms are broadly categorized into four types: metabolic resistance (enhanced detoxification), target site insensitivity (mutations in genes such as kdr for pyrethroids), behavioral resistance, and cuticular resistance (Liu, 2015).

In India, resistance has been widely reported in vector mosquitoes in multiple states. For example, *An. culicifacies*, the major malaria vector in rural India, has shown resistance to DDT and pyrethroids in various regions (Raghavendra et al., 2011). *Aedes aegypti, the main mosquito responsible for spreading dengue and chikungunya,* has developed resistance to temephos and pyrethroids, raising concerns regarding the efficacy of current control strategies (Kushwah et al., 2015). Similarly, *Cx. quinquefasciatus*, the vector of filariasis, has exhibited widespread resistance to organophosphates and pyrethroids, complicating efforts to eliminate lymphatic filariasis (Thomas et al., 2013).

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The challenge of managing insecticide resistance is compounded by the lack of alternative tools and the limited development of new insecticidal compounds. The World Health Organization's Global Plan for Insecticide Resistance Management (GPIRM) has emphasized the need for integrated vector management (IVM), rotation of insecticides, and the use of combination interventions to delay the evolution of resistance (WHO, 2020). In India, the National Centre for Vector Borne Diseases Control (NCVBDC) has initiated periodic resistance surveillance to inform and optimize vector-control policies.

This literature review aims to synthesize the knowledge on the status, mechanisms, and patterns of insecticide resistance in Indian vector mosquitoes.

Historical Overview of Insecticide Use for Vector Control in India

Since the mid-20th century, insecticides have been a cornerstone of vector control strategies aimed at managing vector-borne diseases. The introduction of synthetic insecticides has revolutionized vector control programs by providing potent and relatively affordable tools for suppressing vector populations. Based on their chemical composition, insecticides are generally categorized into five major groups. a) Organochlorines, b) Organophosphates, c) Pyrethroids, d) Carbamates, e) Neonicotinoids (Nayak and Solanki, 2021).

Organochlorines: In India, commonly used organochlorine insecticides for vector control include DDT, BHC (banned since 1997), and dieldrin (banned since 2001) (NIMR, 2006). Among these, DDT is the principal agent in the fight against malaria. Owing to its excito-repellent properties, DDT not only kills mosquitoes but also drives them away upon contact (NCVBDC, 2016).

DDT was first introduced in India in 1944 by American and British soldiers in Odisha and Karnataka. In 1953, the Government of India mandated the use of DDT in Indoor Residual Spraying (IRS) at a dosage of 1 g/m² under the National Malaria Control Programme (NMCP). At the time, malaria accounted for approximately 75 million cases and 800,000 deaths annually, but by 1960, cases had dropped to 108394 with zero fatalities. Despite its initial effectiveness, malaria resurgence, particularly due to *Plasmodium falciparum*, was observed in the 1990s (Sharma, 2003; Betne and Rajankar, 2011). Between 2000 and 2008, although nearly 6 million kilograms of DDT were distributed annually across Indian states, the malaria incidence plateaued, indicating the emergence of insecticide resistance among vectors (Betne and Rajankar, 2011).

Currently, India has significantly reduced DDT usage. It is restricted to a maximum of 10,000 metric tons annually and is employed only in public health programs, particularly during outbreaks or epidemics. According to the WHO recommendations, DDT use is strictly limited to Indoor Residual Spraying (IRS) (NCVBDC, 2016). Notably, DDT has been banned for agricultural purposes since 1989 (Betne and Rajankar, 2011).

Organophosphates: Common organophosphate insecticides used for vector control in India include Malathion, Fenthion, Fenitrothion, Pirimiphos-methyl, and Temephos (NIMR, 2006). Malathion is primarily used for mosquito and fruit fly control.

Temephos (1%) granules are widely used to manage dengue and chikungunya vectors. Its 50% emulsifiable concentrate formulation is noted for its low toxicity to mammals and non-lethality to aquatic organisms, such as fish (NCVBDC, 2016).

Organophosphates were first introduced in India in the 1960s (Kumar et al., 2016). In 1969, malathion was deployed in regions where mosquitoes had developed resistance to DDT (WHO, 2015). However, the current use of organophosphates remains limited because of their toxicological risks and the development of resistance among vector species (Kumar et al., 2016).

Pyrethroids: Synthetic pyrethroids are among the newer insecticides used for vector control in India. The Central Insecticide Board has recommended deltamethrin (2.5% WP), cyfluthrin (10% WP), alphacypermethrin (5% WP), lambdacyhalothrin (10% WP), and bifenthrin (10% WP) as adulticides (NCVBDC, 2016). The use of pyrethroids in India commenced in the 1980s (Kumar et al., 2016). These compounds are favored for Long-Lasting Insecticidal Nets (LLINs) and IRS due to their rapid

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knockdown effect and low toxicity to mammals. However, widespread resistance has become a significant concern (Hemingway et al., 2016; WHO, 2015).

Carbamates: The most commonly used carbamate insecticide for vector control in India is propoxur. It was initially introduced by the Union Carbide Corporation in 1956 for agricultural use (Paul, 2018), and its application in mosquito control began in the 1970s (Kumar et al., 2016), particularly in areas with resistance to organochlorines such as DDT. Resistance to propoxur has been reported in major vector species, such as *Cx. quinquefasciatus* (vector of filariasis) (Shetty et al., 2013) and *An. stephensi* (a key malaria vector) (Mukhopadhyay et al., 1996).

Neonicotinoids: Neonicotinoids are being explored as novel alternatives to conventional insecticides for vector control. Compounds such as dinotefuran, thiamethoxam, and imidacloprid exhibit a high binding affinity for nicotinic acetylcholine receptors in mosquitoes, making them promising candidates for effective vector management (Natarajan et al., 2014). Due to increasing resistance, a neonicotinoid called clothianidin is being explored for IRS as a pyrethroid replacement (Kumar et al., 2024).

Common insecticides and their recommended dosages are presented in Table 1.

Table 1. List of different insecticides with recommended doses against different mosquito vectors.

Insecticide	Formulation	Dosage	Application method	Duration of action	Target vector	Ref.
Organochlorines						
DDT	50% WP*	1.0-1.5 g/m²	Indoor Residual Spraying (IRS)	Up to 6 months	*Anopheles* (malaria), *Phlebotomus*	WHO, 2015; NCVBDC, 2022
Organophosphates						
Malathion	25% WP*	1-2 g/m²	IRS	2-3 months	*Anopheles*, *Aedes*, *Culex*	WHO, 2015; NCVBDC, 2022
Malathion	50% EC*	1:100 (fogging dilution)	Fogging	2-3 months	*Anopheles*, *Aedes*, *Culex*	NIMR, 2006; NCVBDC, 2022

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Temephos	50% EC*	2.5 cc in 10 L	Larvicide in Water	1 Week	*Anopheles*, *Aedes*, *Culex*	NIMR, 2006; NCVBDC, 2022
Fenthion	100% EC*	5 cc in 10 L	Larvicide in Water	1 Week	*Mosquitoes*, *flies*	NIMR, 2006
Fenitrothion	50% or 25% WP*	2 g/m²	IRS	3-6 months	*Anopheles*, *Aedes*	WHO, 2015
Pirimiphos-methyl	50% WP*, 50% EC*,	1-2 g/m²	IRS	2-3 months	*Anopheles*, *Aedes*, *Culex*	WHO, 2015
Pyrethroids						
Deltamethrin	2.5% WP*, 62.5 SC*	20-25 mg/m²	IRS, ITN	6 months	*Anopheles*, *Phlebotomus*	WHO, 2015; NCVBDC, 2022
Alpha-Cypermethrin	5% WP*, 10% SC*	25 mg/m²	IRS	4-6 months	*Anopheles*, *Phlebotomus*	WHO, 2015; NCVBDC, 2022
Lambda-Cyhalothrin	10% WP*	25 mg/m²	IRS, ITN	3-6 months	*Anopheles*	NIMR, 2006; WHO, 2015; NCVBDC, 2022
Cyfluthrin	10% WP*	20-50 mg/m²	IRS, ITN	3-6 months	Mosquitoes, Houseflies	NIMR, 2006; WHO,

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						2015; NCVBDC, 2022
Bifenthrin	10% WP*	20-50 mg/m²	IRS	3-6 months	Mosquitoes	WHO, 2015; NCVBDC, 2022
Etofenprox	5% WP*	100-300 mg/m²	IRS	3-6 months	Mosquitoes, flies	WHO, 2015
Permethrin	10% EC*	1:100 dilution for fogging	Space spraying, Fogging	1 month	*Aedes*	NIMR, 2006
Cyphenothrin	5% EC*	0.50 mg/m² for spraying 0.35 mg/m² for fogging	Space spraying, Fogging	1-3 months	Mosquitoes, flies	NCVBDC, 2022
Carbamates						
Propoxur	20% WP*	1-2 g/m²	IRS	3-6 months	Mosquitoes, Houseflies	WHO, 2015
Bendiocarb	80% WP*	100-400 mg/m²	IRS	2-6 months	Mosquitoes, flies	WHO, 2015
Neonicotinoids						

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Clothianidin	50% WDG*		IRS	up to 6-9 months	Mosquitoes	WHO, 2017

*WP = Wettable powder; EC = Emulsifiable concentrate; SC = Suspension concentrates; WDG = Water Dispersible Granules.

Insecticide Resistance Among Mosquito Vectors in India

Insecticide resistance is the heritable reduction in sensitivity to an insecticide in a pest population, such that normal dosages fail to achieve expected control. It arises through genetic changes (e.g., mutations, enhanced detoxification) driven by repeated exposure. Resistance can be specific, cross, or multiple, depending on mechanisms and insecticide classes (IRAC, 2023).

Anopheles culicifacies, the primary malaria vector in India, has shown widespread resistance. Recent studies reported a 39% mortality rate and confirmed resistance to DDT (4%) across all surveyed regions. Mortality rates generally range between 49% and 78%, with resistance also observed to deltamethrin (0.05%) and malathion (5%). Notably, *An. culicifacies* populations are triple-resistant (to DDT, malathion, and deltamethrin) in nine Indian states (Rahi et al., 2024).

Anopheles stephensi, another major malaria vector, exhibits resistance to DDT and malathion in seven regions and to deltamethrin in one area (Rahi et al., 2024). Anopheles fluviatilis shows variable susceptibility patterns, with resistance differing across several states in India (Rahi et al., 2024).

Aedes aegypti and *Aedes albopictus,* important vectors of dengue, chikungunya, and Zika, are generally resistant to DDT but remain susceptible to certain pyrethroids (Kumar et al., 2024).

Culex mosquitoes, including *Cx. quinquefasciatus*, have been reported to be resistant to multiple classes of insecticides, including pyrethroids, carbamates, DDT, and organophosphates (Bharadwaj et al., 2025).

Historical Perspective: India has one of the earliest records of mosquito insecticide resistance. *Cx. quinquefasciatus* (formerly *Cx. fatigans*) was the first species reported resistant to DDT in 1952 in Bombay and Uttar Pradesh (Mehrotra, 1989; Sharma and Moin, 2021). *An. stephensi* from Tamil Nadu was reported DDT-resistant in 1956, followed by *An. culicifacies* in Gujarat in 1957. In 1964, *An. fluviatilis* populations from Mumbai and Mysore also developed DDT resistance. Among *Aedes* species, *A. aegypti* in Calcutta showed DDT resistance in 1963, while *A. vittatus* in Baroda and *A. albopictus* in Lucknow demonstrated resistance in 1964 and 1965, respectively. Resistance of *Aedes* mosquitoes to BHC and DDT is now well documented (Mehrotra, 1989).

The status of insecticide resistance among various vector mosquito species across different states of India is summarized in Tables 2, 3, and 4 for Anopheles, Aedes, and *Culex species, respectively.*

Table 2. The status of insecticide resistance in Anopheles mosquito vectors in various Indian states.

State	Mosquito Species	Insecticides Resistant	Reference(s)
Assam	*An. minimus*	Possible Resistant to Organochlorine (DDT)	Singh et al., 2014
Chhattisgarh	*An. culicifacies*	Organochlorine (DDT), Organophosphate (Malathion), Pyrethroid (Deltamethrin)	Singh et al., 2014

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Gujarat	*An. culicifacies*	Organochlorine (DDT), Organophosphate (Malathion), Pyrethroid (Deltamethrin)	Raghavendra et al., 2022
	An. stephensi	Resistant to Organochlorine (DDT), Organophosphate (Malathion) and Possible Resistant to Pyrethroid (Deltamethrin)	Singh et al., 2014
Haryana	*An. culicifacies*	Organochlorine (DDT), Organophosphate (Malathion), Pyrethroid (Deltamethrin)	Raghavendra et al., 2022
	An. stephensi	Organochlorine (DDT)	Raghavendra et al., 2022
Jharkhand	*An. culicifacies, An. annularis*	Resistant to DDT (Organochlorine) and Possible Resistant to Organophosphate (Malathion)	Singh et al., 2014; Raghavendra et al., 2022
	An. fluviatilis,	DDT (Organochlorine)	Singh et al., 2014; Raghavendra et al., 2022
Karnataka	*An. culicifacies*	Organochlorine (DDT), Organophosphate (Malathion), Pyrethroid (Deltamethrin, alpha-cypermethrin)	Raghavendra et al., 2022
	An. stephensi	Organophosphate (Malathion)	Singh et al., 2014
Kerala	*An. stephensi*	DDT (Organochlorine)	Singh et al., 2014
Madhya Pradesh	*An. culicifacies*	Resistant to Organochlorine (DDT), Organophosphate (Malathion) and Possible Resistant to Pyrethroid (Deltamethrin)	Singh et al., 2014; Raghavendra et al., 2022
	An. stephensi	Resistant to Organochlorine (DDT) and Possible Resistant to Organophosphate (Malathion)	Singh et al., 2014
Maharashtra	*An. culicifacies*	Resistant to Organochlorine (DDT), Organophosphate (Malathion), Pyrethroid (Deltamethrin, cyfluthrin, alpha-cypermethrin, and lambda-cyhalothrin)	Raghavendra et al., 2022
	An. fluviatilis, An. annularis	Organochlorine (DDT)	Singh et al., 2014

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Odisha	*An. culicifacies*	Resistant to Organochlorine (DDT) and Possible Resistant to Pyrethroid (Deltamethrin)	Singh et al., 2014; Raghavendra et al., 2022
	An. fluviatilis	Possible Resistant to Organochlorine (DDT)	Singh et al., 2014; Raghavendra et al., 2022
	An. minimus	Organochlorine (DDT)	Singh et al., 2014
Rajasthan	*An. culicifacies, An. stephensi*	Resistant to Organochlorine (DDT) and Possible Resistant to Organophosphate (Malathion)	Singh et al., 2014
Tamil Nadu	*An. culicifacies*	Organochlorine (DDT), Pyrethroid (Deltamethrin)	Singh et al., 2014
Tripura	*An. minimus*	Possible Resistant to Organochlorine (DDT)	Singh et al., 2014
Uttar Pradesh	*An. culicifacies*	Resistant to Organochlorine (DDT) and Possible Resistant to Organophosphate (Malathion)	Singh et al., 2014
West Bengal	*An. stephensi*	Organochlorine (DDT), Carbamate (Propoxur), Organophosphate (Malathion)	Mukhopadhyay et al., 1996

Table 3. The status of insecticide resistance in *Aedes* mosquito vectors among different states of India.

State	Mosquito Species	Insecticides	Reference(s)
Andhra Pradesh	*A. aegypti*	DDT (Organochlorine) and Malathion (Organophosphate)	Kumawat et al., 2021
Arunachal Pradesh	*A. Aegypti, A. albopictus*	DDT (Organochlorine)	Kumawat et al., 2021
Assam	*A. aegypti, A. albopictus*	DDT (Organochlorine), Temephos (Organophosphate)	Kumawat et al., 2021
	A. albopictus (Guwahati)	Resistant to DDT (Organochlorine) and Incipient Resistant to Deltamethrin, Permethrin (Pyrethroids)	Kumawat et al., 2021
	A. Aegypti, A. albopictus	DDT (Organochlorine)	Kumawat et al., 2021

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Delhi	*A. aegypti*	Resistant to DDT and Dieldrin (Organochlorine) and Possible Resistant to Temephos (Organophosphate)	Kumawat et al., 2021
	A. albopictus	Resistant to DDT (Organochlorine) and Incipient Resistance to Deltamethrin, Permethrin (Pyrethroids)	Kumawat et al., 2021
Goa	*A. aegypti*	DDT (Organochlorine)	Kumawat et al., 2021
Haryana (Gurgaon)	*A. albopictus*	Resistant to DDT (Organochlorine) and Incipient Resistance to Deltamethrin, Permethrin (Pyrethroids)	Kumawat et al., 2021
Jharkhand	*A. Aegypti, A. albopictus*	DDT (Organochlorine)	Kumawat et al., 2021
Karnataka	*A. aegypti*	DDT (Organochlorine), Propoxur (Carbamate), deltamethrin, and Permethrin (Pyrethroid)	Kumawat et al., 2021
Kerala	*A. Aegypti, A. albopictus*	DDT and Dieldrin (Organochlorine)	Kumawat et al., 2021
	A. albopictus	Resistant to DDT (Organochlorine) and Incipient Resistance to Deltamethrin, Permethrin (Pyrethroids)	Kumawat et al., 2021
Maharashtra	*A. albopictus*	DDT (Organochlorine)	Kumawat et al., 2021
	A. aegypti	Temephos, Fenthion (Organophosphate)	Kumawat et al., 2021
Odisha	*A. albopictus*	DDT (Organochlorine)	Baig et al., 2021; Rath et al., 2018
	A. aegypti	Resistant to DDT (Organochlorine), Deltamethrin (Pyrethroids) and Possible Resistance Malathion (Organophosphate)	Baig et al., 2021; Rath et al., 2018
Rajasthan	*A. aegypti, A. vittatus, A. w-albus*	DDT and Dieldrin (Organochlorine)	Kumawat et al., 2021
	A. aegypti	Possible Resistant to Cypermethrin, Permethrin (Pyrethroids)	Kumawat et al., 2021
Tamil Nadu	*A. aegypti*	Permethrin (Pyrethroid)	Kumawat et al., 2021
Uttarakhand (Haridwar)	*A. albopictus*	Resistant to DDT (Organochlorine) and Incipient Resistance to Deltamethrin, Permethrin (Pyrethroids)	Kumawat et al., 2021

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West Bengal	*A. albopictus*	DDT (Organochlorine), Permethrin (pyrethroid), propoxur (carbamate), and Temephos (Organophosphate)	Kumawat et al., 2021
	A. aegypti	Permethrin (Pyrethroid) and Propoxur (Carbamate)	Kumawat et al., 2021

Table 4. The status of insecticide resistance in Culex mosquito vectors in various Indian states.

State	Mosquito Species	Insecticides	Reference(s)
Assam	Cx. *gelidus*, Cx. *vishnui*	Suspected Resistant to DDT (Organochlorine), Sensitive to Deltamethrin (Pyrethroid)	Dhiman et al., 2013
	Cx. *quinquefasciatus*	Resistant to DDT (Organochlorine), Susceptible to Deltamethrin (Pyrethroid)	Sarkar et al., 2009
Bihar (Patna)	Cx. *quinquefasciatus*	Organochlorine (DDT and dieldrin)	Mukhopadhyay et al., 1993
Delhi	Cx. *tritaeniorhynchus*	Organochlorine (DDT), Organophosphate (Malathion, Fenitrothion), Carbamate (Propoxur)	Thomas et al., 2000
	Cx. *quinquefasciatus*	Temephos (Organophosphate)	Thomas et al., 2013
Gujarat (Jamnagar)	Cx. *quinquefasciatus*	Lower resistant to Pyrethroid (alpha-cypermethrin) and Organophosphate (fenthion)	Suman et al., 2010
Karnataka (Bengaluru)	Cx. *quinquefasciatus*	Highly resistant to Propoxur (Carbamate), Susceptible to Temephos (Organophosphate)	Paul, 2018
Odisha	Cx. *vishnui*, Cx. *tritaeniorhynchus*	DDT (Organochlorine), Deltamethrin (pyrethroids), and malathion (Organophosphate)	Sahu et al., 2019
	Cx. *bitaeniorhynchus*	Remains susceptible to DDT (organochlorine), deltamethrin (pyrethroids), and malathion (organophosphate).	
Punjab (Bathinda)	Cx. *quinquefasciatus*	High larval Resistant to Organophosphate (temephos and	Suman et al., 2010

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		fenthion) and pyrethroids (Lambda Cyhalothrin, alpha cypermethrin, and Cypermethrin)	
Rajasthan (Jodhpur)	Cx. *quinquefasciatus*	High Resistant to Organophosphate (Temephos, Fenthion), Neemarin (a neem-based insecticide), pyrethroids (Cypermethrin)	Suman et al., 2010
Rajasthan (Bikaner)	Cx. *quinquefasciatus*	Moderately resistant to organophosphates (temephos, fenthion), Neemarin (a neem-based insecticide), and pyrethroids (alpha-cypermethrin).	
Tamil Nadu (Thiruvarur)	Cx. *gelidus*	Possible Resistant to Deltamethrin (pyrethroids) and malathion (Organophosphate)	Krishnan et al., 2021
West Bengal	Cx. *quinquefasciatus*	organophosphate (temephos and malathion), carbamate (propoxur), synthetic pyrethroids (deltamethrin, lambdacyhalothrin and permethrin) and organochlorine (DDT)	Rai et al., 2019
	Cx. *tritaeniorhynchus*	organochlorine (DDT), Deltamethrin (Pyrethroids), malathion (Organophosphate)	Saha et al., 2018
	Cx. *pseudovishnui*	organochlorine (DDT), Deltamethrin (Pyrethroids),	Saha et al., 2018
	Cx. *vishnui*	organochlorine (DDT), Deltamethrin (Pyrethroids)	Saha et al., 2018
	Cx. *gelidus*	Resistant to organochlorine (DDT) and Possible Resistant to Deltamethrin (Pyrethroids)	Saha et al., 2018

Mechanisms of Insecticide Resistance in Indian Vector Mosquitoes

Insecticide resistance in vector mosquitoes (e.g. *Anopheles*, *Aedes*, *Culex*) arises through biochemical, genetic, and behavioral adaptations that allow them to survive exposure, undermining control efforts. The major mechanisms are target-site resistance, metabolic resistance, behavioral resistance, and cuticular resistance (Elanga Ndille et al., 2023).

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Target Site Resistance:

Structural alterations or point mutations in genes encoding target proteins that interact with insecticides cause target-site resistance. Pyrethroids and dichlorodiphenyltrichloroethane (DDT) are insecticides that target sodium channels. Both organophosphate and carbamate insecticides target acetylcholinesterase (AChE). γ-Aminobutyric acid (GABA) receptors are the targets of insecticides such as cyclodiene and fipronil (*Liu, 2015*).

Voltage-gated sodium channel (VGSC): Mutations in the voltage-gated sodium channel (VGSC), commonly referred to as *knockdown resistance (kdr)*, are a well-established mechanism of insecticide resistance in mosquitoes. These mutations, mainly concentrated in the IS6, IIS6, and IIIS6 domains of the VGSC, reduce sensitivity to pyrethroids and DDT. The most critical substitution occurs at codon 1014 in domain IIS6, where leucine (L) is replaced by phenylalanine (F), serine (S), or histidine (H), conferring resistance (Gan et al., 2021).

In *Anopheles* species, kdr mutations have been widely documented. *An. culicifacies* populations carry L1014F and L1014S mutations, which are associated with resistance to pyrethroids and DDT (Singh et al., 2009; Dykes et al., 2015). *An. stephensi* populations in northern India carry both L1014F and L1014S mutations (Dykes et al., 2016), and *An. subpictus* has been found with the L1014F mutation, exhibiting notable geographic variation in its prevalence (Sindhania et al., 2023).

In Aedes species, several distinct kdr mutations have been identified. In *A. albopictus*, the T1520I and F1534C mutations in the VGSC gene are linked to resistance to DDT and pyrethroids, with F1534C first reported in northern West Bengal (Modak et al., 2022). *A. aegypti* frequently displays kdr mutations such as S989P, V1016G, T1520I, F1534C, and F1534L, which collectively reduce susceptibility to these insecticides (Kumawat et al., 2021). The V1016G + F1534C double mutation in *A. aegypti* is associated with high resistance and genetic polymorphism in West Bengal (Saha et al., 2019). The Delhi population of *A. aegypti* has exhibited resistance to DDT, deltamethrin, and permethrin, with both F1534C and a novel T1520I mutation detected (Kushwah et al., 2015). Further studies from Punjab have identified V1016G and L1006S mutations in *A. aegypti* (Kaura et al., 2022).

In *Cx. quinquefasciatus* populations from West Bengal, both L1014F and L1014S mutations in the VGSC gene have been detected, conferring resistance to DDT and pyrethroids. Notably, L1014S was reported for the first time in this species from the region (Rai & Saha, 2022; retracted 2023). The L1014F mutation was also confirmed in *Cx. quinquefasciatus* from the sub-Himalayan areas of West Bengal (Modak et al., 2024).

Kdr mutations in the VGSC gene (Figure 1) are widespread in many mosquito species and reduce their sensitivity to insecticides such as pyrethroids and DDT. A word diagram (Figure 2) is provided to explain how these mutations affect the VGSC.

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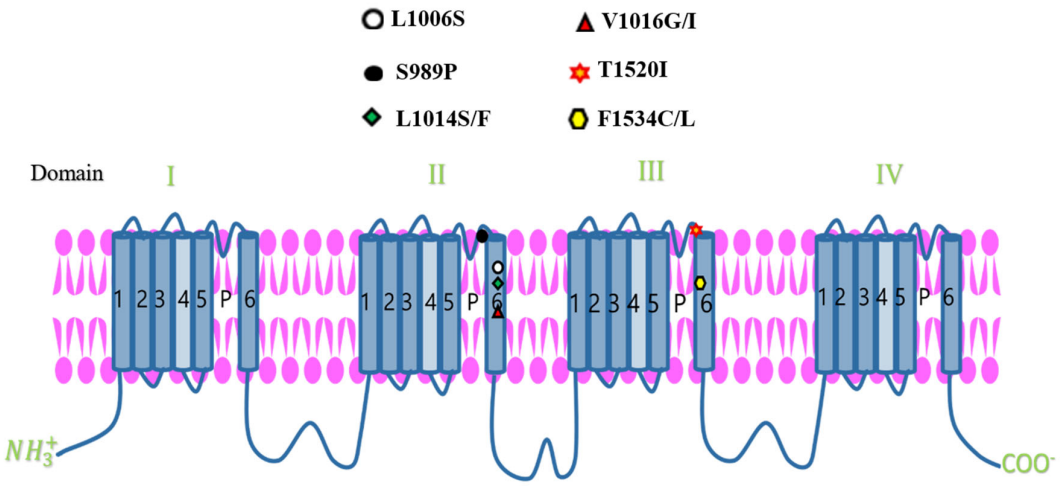

Fig. 1: Various VGSC mutation in different Indian vector mosquitoes

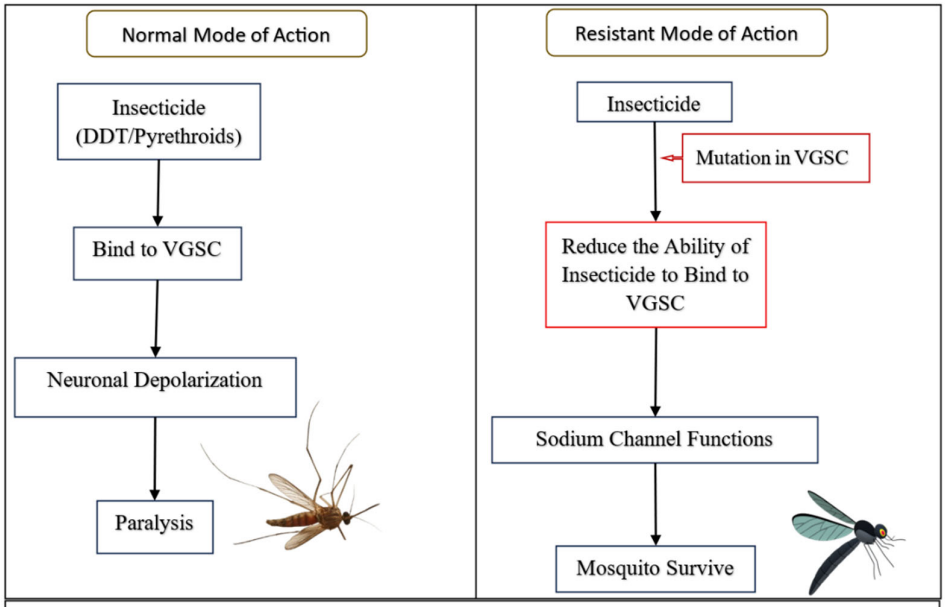

Fig. 2: Mode of Action of VGSC in Vector Mosquitoes

Acetylcholinesterase (AChE): Carbamate and organophosphate pesticides primarily target acetylcholinesterase (AChE), preventing nerve transmission at cholinergic synapses. Resistance arises from amino acid substitutions in the ace-1/ace-2 gene, rendering AChE insensitive to inhibition (Gan et al., 2021). Numerous mosquito species, including An. gambiae, An. albimanus, Cx. vishnui, Cx. pipiens, and Cx. quinquefasciatus, have been found to exhibit the G119S substitution (Liu, 2015).

Acetylcholinesterase (ace-1) mutations have been documented in several Indian vector mosquitoes and are associated with resistance to organophosphates and carbamates. In *Culex quinquefasciatus*, the G119S mutation in the ace-1 gene has been reported from eastern Uttar Pradesh, where it was linked to malathion resistance. The same study also identified the F331W substitution in *Culex tritaeniorhynchus*, along with evidence of altered ace gene activity that indicated an insensitive AChE mechanism (Misra and Gore 2015). In *Aedes aegypti*, populations from Tamil Nadu (Namakkal district) were found to carry the G119S mutation at a frequency of about 0.24. This mutation, together with elevated esterases, contributed to larval resistance against the

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organophosphate temephos (Muthusamy and Shivakumar 2015). These findings confirm that ace-1 mutations play a significant role in insecticide resistance in Indian mosquito vectors, although their prevalence appears to vary across species and regions. A word diagram (Figure 3) illustrating the mode of action of Acetylcholinesterase is shown below.

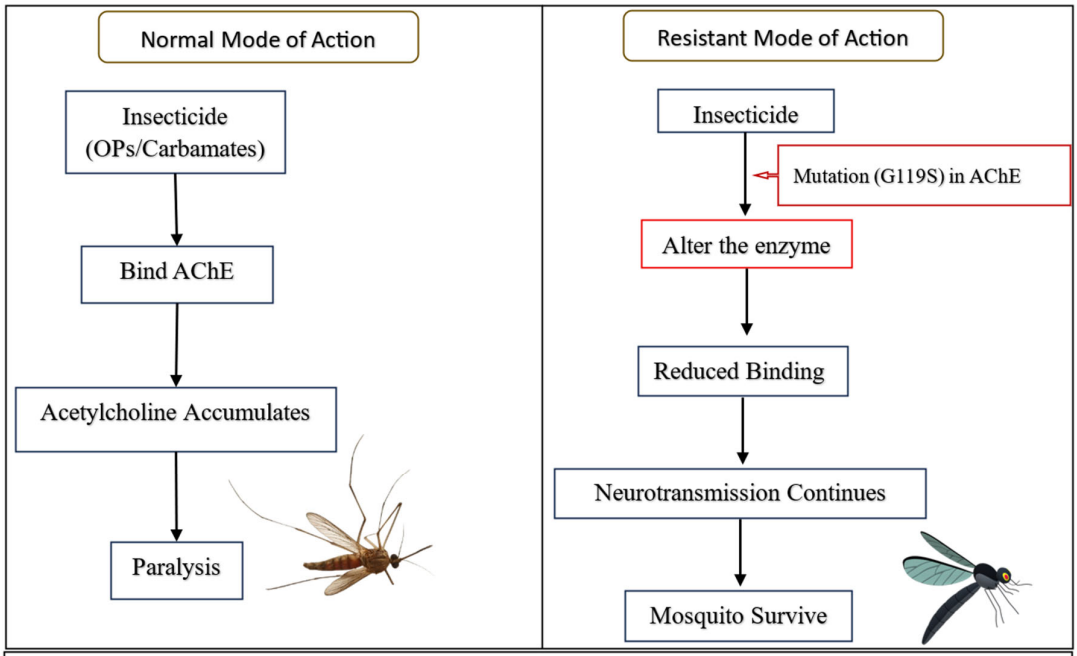

Fig. 3: Mode of Action of Acetylcholinesterase in Vector Mosquitoes

GABA Receptor (Rdl Gene): Neuronal signalling involves the resistance to dieldrin (RDL) gene, which encodes the GABA receptor. The rdl receptor belongs to the Cys-loop ligand-gated ion channel superfamily and has an N-terminal extracellular domain for GABA binding. Each of the five subunits of this receptor has four transmembrane domains and an external cysteine loop (M1 - M4). Numerous pesticides, including cyclodiene, fipronil, and pyrethroids, target rdl, and their effects are influenced by post-translational changes. GABA receptors, integral chloride channels targeted by cyclodiene insecticides (dieldrin) and phenyl pyrazoles (fipronil), display mutations such as A296S/G that confer resistance (Liu, 2015). There is no specific evidence confirming the presence of these mutations in Indian vectors like *Anopheles stephensi*, *Aedes aegypti*, or *Culex quinquefasciatus*. The mode of action of the GABA receptor is shown in the word diagram (Figure 4) below.

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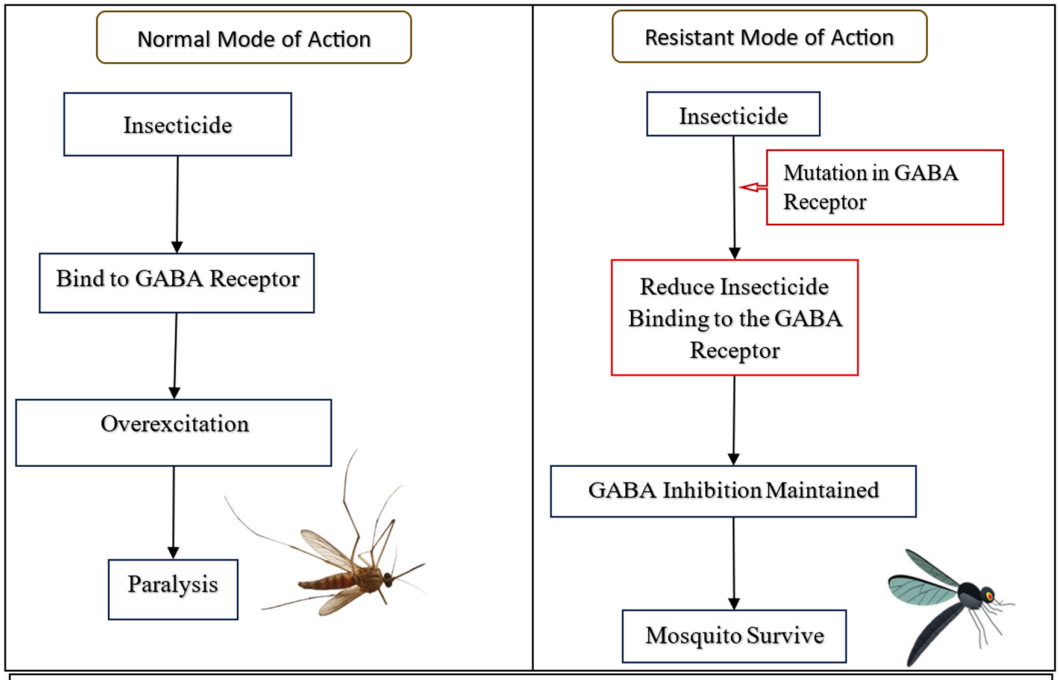

Fig. 4: Mode of Action of GABA Receptor in Vector Mosquitoes

Below is a list of all target site mutations reported in Indian mosquitoes.

Table 5. Major target-site mutations observed in different mosquito vectors in India.

Mosquito species	Mutation	Transmembrane Domain / gene	Reference(s)
A. *Aegypti*	V1016G, S989P, L1006S	II	Kumawat et al., 2021; Saha et al., 2019; Kaura et al., 2022
	F1534C, F1534L, T1520I,	III	Kumawat et al., 2021; Kushwah et al., 2015; Saha et al., 2019
	G119S	Ace-1	Muthusamy and Shivakumar, 2015
A. *albopictus*	T1520I, F1534C	III	Modak et al., 2022
An. *culicifacies*	L1014F, L1014S	II	Singh et al., 2009; Dykes et al., 2015
An. *subpictus*	L1014F	II	Sindhania et al., 2023

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An. *stephensi*	L1014F, L1014S	II	Dykes et al., 2016
Cx. *quinquefasciatus*	G119S	Ace-1	Misra and Gore 2015
	L1014F, L1014S	II	Rai & Saha, 2022; Modak et al., 2022
Culex tritaeniorhynchus	F331W	Ace-1	Misra and Gore 2015

Metabolic Resistance:

As a result of point mutations in the cis/trans loci of the enzymes, metabolically resistant strains detoxify toxins or insecticides by overexpressing the enzymes or changing their conformation. Three main enzymatic processes are typically linked to metabolic detoxification: cytochrome P450 monooxygenases (P450s), carboxylesterases and glutathione S-transferases (GSTs) (Gan et al., 2021). Insecticide detoxification in mosquitoes involves a multi-step biochemical process (Figure 5). These are-

1. Uptake: Insecticides penetrate the cuticle or are ingested.
2. Phase I (functionalization): Oxidation, reduction, or hydrolysis introduces or exposes polar groups to the substrate. The key actors are cytochrome P450 monooxygenases (P450s) and carboxyl/cholinesterases (esterases) (David et al., 2013).
3. Phase II (conjugation): Conjugating enzymes (notably glutathione S-transferases, GSTs) attach polar groups (e.g., glutathione) to Phase I products, increasing their solubility (Ranson and Hemingway, 2005).
4. Phase III (transport/excretion): Transporter proteins (ATP-binding cassette (ABC) transporters and other efflux systems) move metabolites out of cells and across barriers for excretion (Dermauw and Van Leeuwen, 2014).

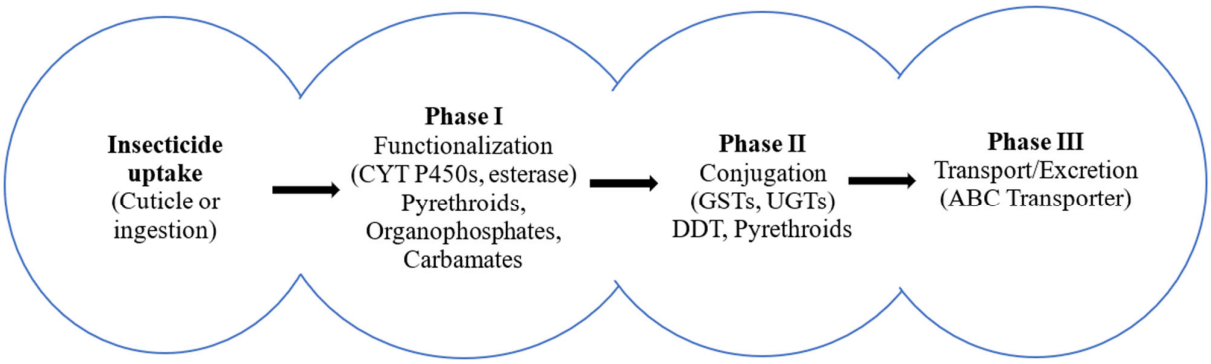

Fig. 5: Biochemical pathway of metabolic resistance in Indian vector mosquitoes

Cytochrome P450 Monooxygenases (CytP450s): The overexpression of cytochrome P450 (CYP) genes, particularly those belonging to the CYP6 and CYP9 families, is a well-established marker of metabolic resistance in mosquitoes (Bharadwaj et al., 2025). CYP450 enzymes play a crucial role in

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broad-spectrum detoxification, including the metabolism of pyrethroids and carbamates (Ballav et al., 2022).

In Indian vector mosquitoes, cytochrome P450s (CYPs) are consistently implicated in insecticide resistance, particularly against pyrethroids and organochlorines. In *Anopheles culicifacies*, metabolic resistance has been linked to the strong overexpression of CYP6Z1, which is associated with resistance to deltamethrin (Kareemi et al., 2022).

In *Culex quinquefasciatus*, permethrin-resistant populations from India showed significant upregulation of multiple CYP genes. Notably, CYP6AA7 was upregulated about 10-fold in both larvae and adults, CYP9J34 nearly 9-fold, and CYP6Z2 approximately 5-fold compared to susceptible strains (Ramkumar et al., 2023).

Field studies from northern West Bengal further confirmed these trends. Wild *Culex quinquefasciatus* larval populations from the sub-Himalayan region exhibited widespread resistance to cyphenothrin. Biochemical assays revealed high monooxygenase activity, while gene expression analysis showed elevated levels of CYP6AA7 and CYP9J40 (Saha et al., 2025). P450-mediated resistance has been documented against a number of pesticide classes, including as organophosphates and pyrethroids. Below is a general mechanism of this resistance (Figure 6).

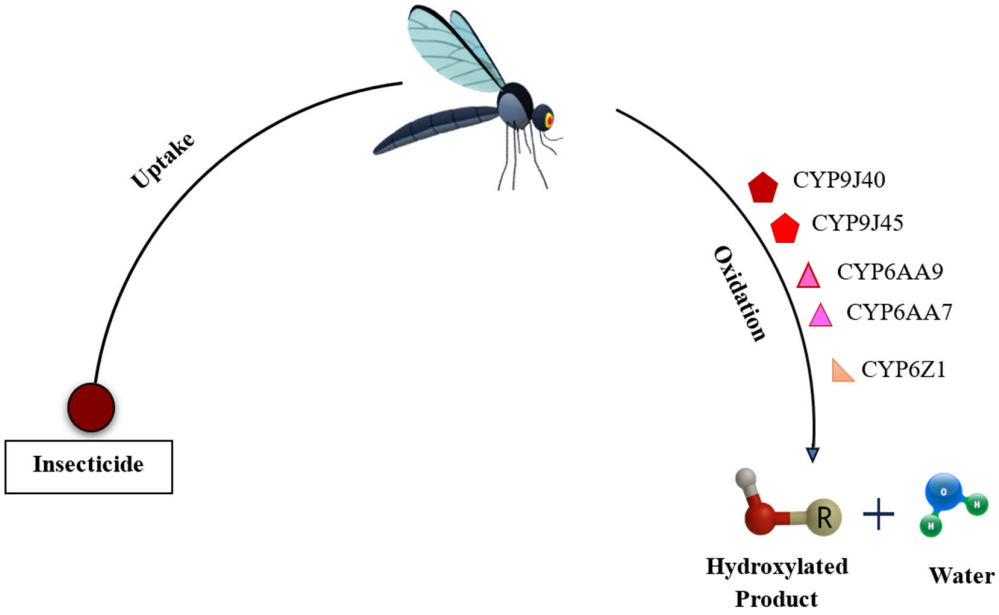

Fig. 6: Cytochrome P450s mediated detoxification pathway in mosquitoes

Carboxylesterases (esterases): Enzymes that hydrolyse ester bonds, such as esterases, contribute to insecticide resistance through gene duplication and overexpression, thereby amplifying detoxification capacity (Liu, 2015).

Esterase activity has been widely implicated in insecticide resistance among Indian vector mosquitoes. In Culex quinquefasciatus from the sub-Himalayan districts of West Bengal, wild larval populations resistant to cyphenothrin and temephos demonstrated high levels of carboxylesterase activity, with gene expression analysis confirming the overexpression of esterase genes (Saha et al., 2025).

In Aedes aegypti, α- and β-esterase activities were reported to be 1.2–3.1-fold and 2.0–23.0-fold higher, respectively, in field populations from the Dooars and Terai regions of West Bengal compared with a susceptible laboratory strain. Isozyme profiles further revealed notable population variation (Bharati et al., 2018). Similarly, in Pondicherry, A. aegypti collected from Lawspet showed elevated

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β-esterase activity associated with malathion resistance, likely driven by repeated thermal fogging, whereas populations from Abishegapakkam displayed lower activity (Ramesh et al., 2023).

More than 50% and up to 80% of all four Japanese encephalitis (JE) vector species (Cx. tritaeniorhynchus, Cx. vishnui, Cx. pseudovishnui, and Cx. gelidus) showed elevated levels of both α- and β-esterases (Ballav et al., 2022). Furthermore, A. aegypti populations in West Bengal and Assam have demonstrated esterase-mediated resistance (Kumawat et al., 2021).

Comparative studies in Mysore highlighted species-specific trends: An. stephensi exhibited higher α-esterase activity, while An. culicifacies showed elevated β-esterase levels, correlating with differences in tolerance to deltamethrin and permethrin (Ganesh et al., 2003). Consequently, the reduced efficacy of the insecticide enables insect survival. The general pathway of this resistance is presented below (Figure 7).

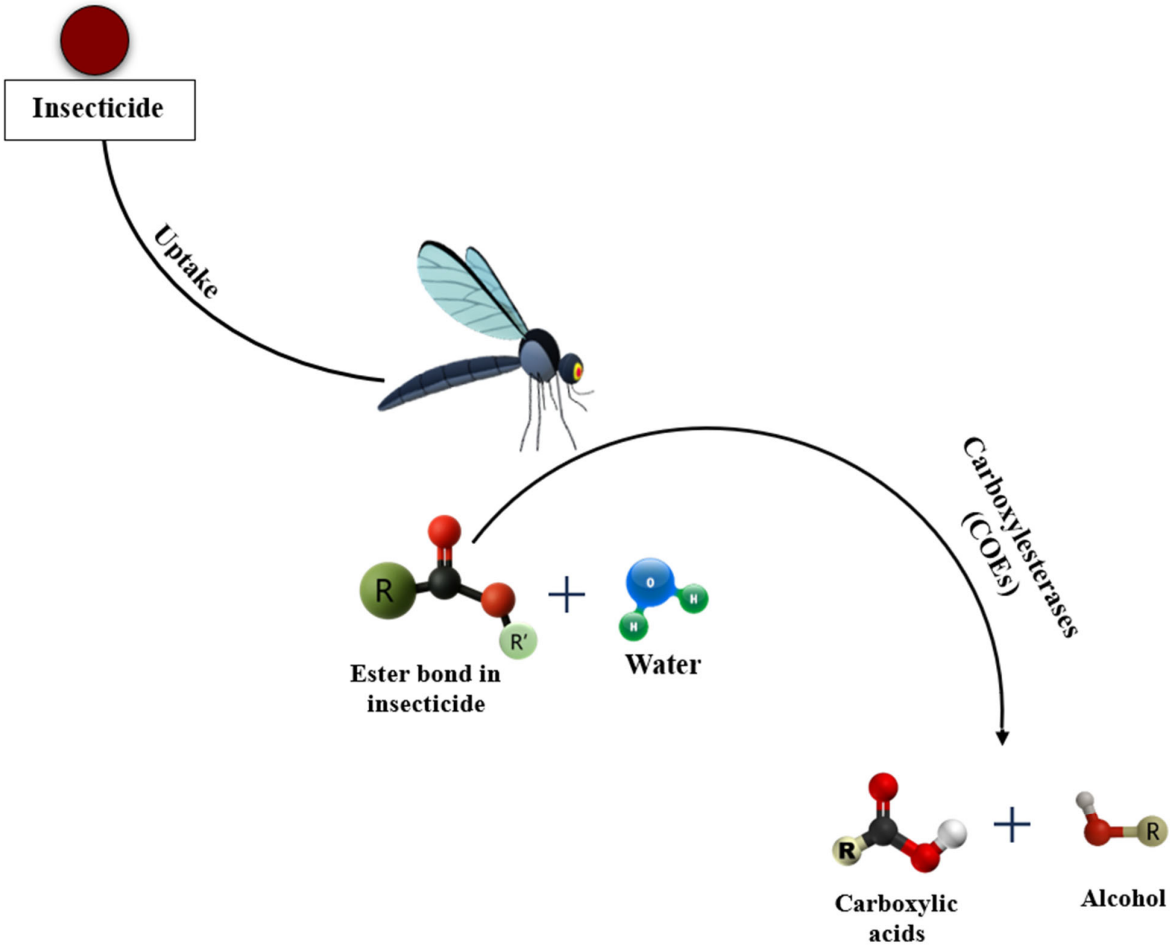

Fig. 7: Esterase-mediated detoxification pathway in mosquitoes

Glutathione-S-transferases (GSTs): Enzymes that conjugate reactive intermediates and are recognized mechanisms of DDT resistance that contribute to pyrethroid metabolism (Dykes et al., 2022). Glutathione S-transferases (GSTs) have been repeatedly implicated in metabolic insecticide resistance across Indian vector mosquitoes, with biochemical, molecular and genomic evidence reported from multiple species and regions. A study showed significantly elevated GST activity in DDT-resistant *Anopheles culicifacies* and *An. annularis* from Malkangiri and Koraput (Odisha), with median GST activities in resistant populations roughly three times those of a susceptible *An. fluviatilis* comparator, supporting a GST-mediated DDT detoxification mechanism (Gunasekaran et al., 2011).

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More recently, molecular and genomic work has directly tied specific GST genes to resistance in Indian *An. Stephensi*, documented a tandem duplication of a genomic region containing *GSTe2* and *GSTe4* in a laboratory-colonized DDT-resistant strain derived from Alwar, India, a structural change likely to increase GST gene dose and enzyme levels and to contribute to DDT resistance (Dykes et al., 2022). Transcriptomic and resistance-mechanism studies in Indian *An. culicifacies* populations have also noted co-upregulation of *GSTe2* alongside cytochrome P450s in pyrethroid- and DDT-resistant samples, further implicating GST epsilon class enzymes in field resistance (Kareemi et al., 2022). Approximately 70–95% of *Culex* mosquitoes across all species exhibited Glutathione S-transferase (GST) activity levels above the threshold, with significant variation observed across sites in northern West Bengal, indicating a strong association with DDT resistance (Bharati et al., 2018). Similarly, *Aedes aegypti* populations from Maharashtra displayed elevated GST activity, which has been linked to organochlorine resistance (Kumawat et al., 2021). Below is a general mechanism of this resistance (Figure 8).

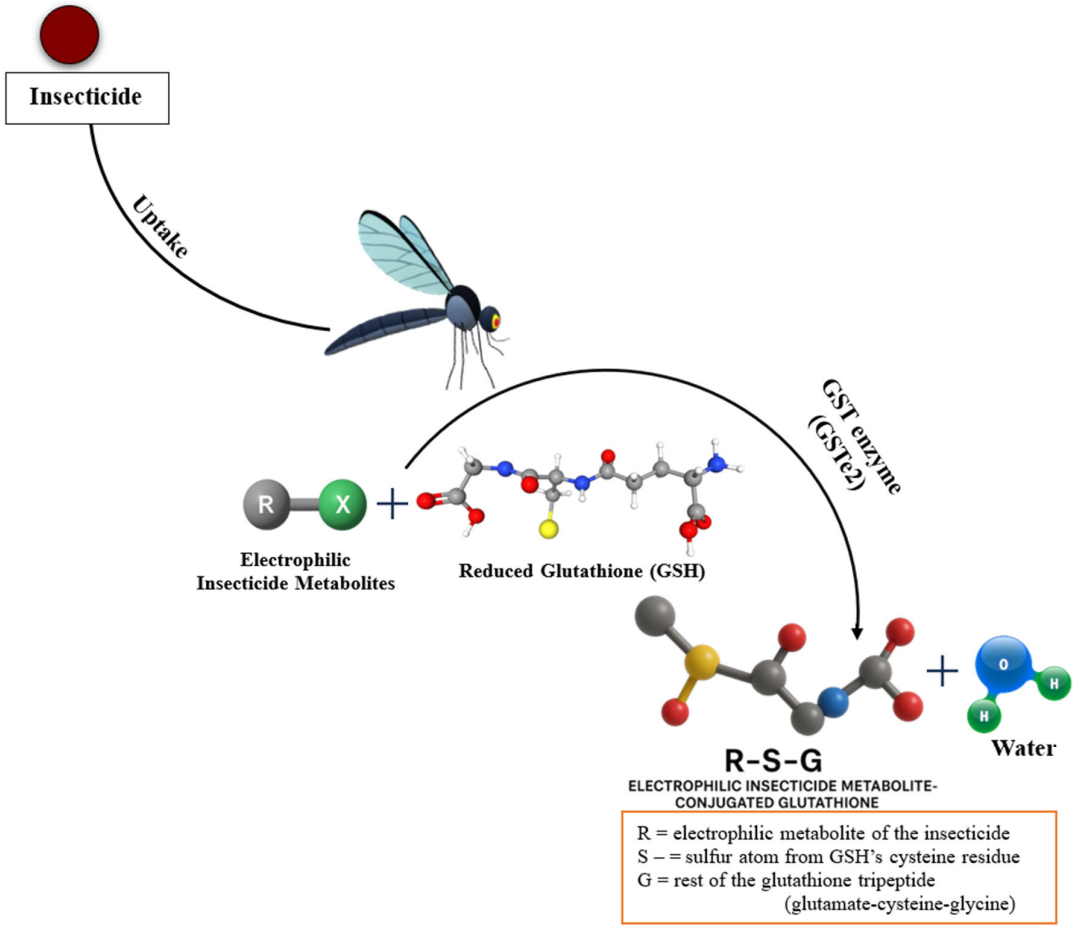

Fig. 8: GSTs mediated detoxification pathway in vector mosquitos

Transport Protein: Transporter proteins, mainly ATP-binding cassette (ABC) family, are membrane pumps that expel insecticide metabolites during Phase III detoxification, contributing to metabolic resistance in mosquitoes

Studies on Anopheles mosquitoes have shown that ABC transporters play a role in permethrin tolerance in these species. In Anopheles stephensi larvae, mortality increased when permethrin was combined with the ABC inhibitor verapamil, and the ABCG4 transporter gene was upregulated following exposure (Epis et al., 2014). In adults of the same species, several ABC genes, including

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ABCB2, ABCB member 6, and ABCG4, were upregulated in both males and females after permethrin treatment (Adedeji et al., 2020). Similarly, in Anopheles gambiae larvae, exposure to permethrin in combination with an ABC inhibitor resulted in approximately a 15-fold increase in mortality, further confirming the involvement of these transporters in detoxification (Mastrantonio et al., 2019).

The table displays the various metabolic resistance categories found in Indian vector mosquitoes by species.

Table 6. Major Metabolic Resistance observed in different mosquito vectors in India.

Vector species	Metabolic mechanisms	Insecticide affected	Ref.
Anopheles stephensi	GSTe2 GSTe4 duplication, P450 overexpression, esterase	DDT, Pyrethroids	Dykes et al., 2022
Anopheles culicifacies	P450s (CYP6Z1), esterases, GSTs (GSTe2)	DDT, Pyrethroids, Organophosphates	Sahu et al., 2015; Kareemi et al., 2022
Culex quinquefasciatus	P450s (CYP6/9 families), esterases	Pyrethroids, Organophosphates, Carbamates	Ramkumar et al., 2023
Cx. pipiens	P450s (CYP6AA9)		Bharadwaj et al., 2025

Behavioral Resistance:

Recent entomological investigations have revealed important insights into the resting behavior, host preference, seasonal abundance, and insecticide response of major mosquito vector species in India.

Abdominal Condition and Resting Behavior: Abdominal condition analysis revealed that more than 60% of *Anopheles culicifacies*, *An. stephensi*, and *An. subpictus* were semi-gravid or gravid, suggesting a strong endophilic resting behavior, as these mosquitoes were primarily found resting indoors (Kumar et al., 2024).

Blood Meal Analysis and Host Preference: Blood meal source identification using multiplex PCR indicated that *An. stephensi* exhibited a Human Blood Index (HBI) of 9.09%, with 21.81% of specimens also testing positive for bovine blood, highlighting its zoophilic tendency. In contrast, *An. culicifacies* had a lower HBI of 6.66% and showed no evidence of bovine feeding, suggesting a more anthropophilic feeding behavior (Kumar et al., 2024).

Seasonal Abundance Patterns: Seasonal distribution analysis showed that *An. subpictus* populations peaked during the monsoon season, whereas *An. culicifacies* was more prevalent in the post-monsoon and winter periods, indicating species-specific seasonal preferences (Kumar et al., 2024).

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Excito-repellency and Delayed Mortality: Exposure to synthetic pyrethroids and organophosphates in formulated insecticides induced strong excito-repellency responses in *Aedes aegypti*, *An. stephensi* and *Culex quinquefasciatus*, in addition to causing delayed mortality, suggesting behavioral avoidance mechanisms alongside toxic effects (Dhiman et al., 2021).

Cuticular Resistance:

Cuticular resistance refers to the structural and biochemical modifications in the insect cuticle that reduce insecticide penetration. A primary mechanism involves cuticle thickening, often attributed to increased deposition of cuticular hydrocarbons (CHCs) and chitin. This phenomenon has been observed in resistant populations of *Anopheles gambiae*, *Culex pipiens pallens*, and *Bactrocera dorsalis*. The overexpression of cytochrome P450 genes, particularly *CYP4G16* and *CYP4G17*, in oenocytes enhances hydrocarbon biosynthesis, whereas the upregulation of cuticular protein genes, such as *CPLCG3* and *CPR127*, contributes to the structural thickening of all cuticular layers (Balabanidou et al., 2018).

In India, *Aedes aegypti* mosquitoes selected for resistance to deltamethrin (a pyrethroid) and acetamiprid (a neonicotinoid) exhibited significantly thicker cuticles than susceptible strains, further supporting the role of cuticular thickening in resistance mechanisms (Samal et al., 2021).

Alterations in cuticle composition also contribute to this resistance. Two major biochemical pathways are involved: (1) the overexpression of *laccase 2*, which enhances cuticle sclerotization and hardness, and (2) the upregulation of ATP-Binding Cassette (ABC) transporters, which facilitate the transport of CHCs and lipids to the cuticle surface, thereby increasing cuticular impermeability. ABC transporters, particularly those of subfamily G, have been found to be enriched in the legs of resistant mosquitoes and are implicated in lipid export from epidermal cells (Balabanidou et al., 2018).

Conclusions

The historical and current use of insecticides in India for vector control highlights a complex trajectory shaped by efficacy, resistance evolution, and public health requirements. Initially, organochlorines such as DDT were instrumental in reducing malaria prevalence during the 1950s. However, over time, the efficacy of DDT and similar compounds has declined due to widespread resistance, particularly in species such as An. culicifacies, A. aegypti, and Cx. quinquefasciatus.

India has incorporated other chemical groups, such as organophosphates (e.g., malathion and temephos), synthetic pyrethroids (e.g., deltamethrin and permethrin), carbamates (e.g., propoxur and bendiocarb), and more recently, neonicotinoids. Despite the rotation and combination of these insecticide classes, resistance has become increasingly prevalent in recent years. For example, triple resistance (to DDT, malathion, and pyrethroids) is now observed in several states for major vector species.

Molecular analyses have revealed numerous genetic mutations that confer resistance. Notably, kdr (knockdown resistance) mutations, such as L1014F/S, in An. and Cx. and F1534C, V1016G, and S989P in A. aegypti interferes with the voltage-gated sodium channel targets of DDT and pyrethroids. In addition, resistance to organophosphates and carbamates is associated with mutations in acetylcholinesterase (e.g., G119S), whereas resistance to cyclodienes is linked to mutations in the GABA receptor (e.g., A296G/S).

Metabolic resistance is also widespread and is characterized by the elevated activity of detoxification enzymes, such as cytochrome P450 monooxygenases (e.g., CYP6Z1 and CYP6M2), glutathione S-transferases (e.g., GSTe2), and carboxylesterases. These mechanisms are particularly pronounced in Cx. populations inhabiting polluted environments, and A. aegypti from urban centers.

Behavioral and cuticular resistance further complicate pest control efforts. Excito-repellency and altered host-feeding behaviors reduce insecticide contact, whereas cuticle thickening and altered hydrocarbon composition hinder chemical penetration. These adaptations diminish the overall effectiveness of insecticide-based interventions, such as indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs).

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In conclusion, although insecticides have historically played a critical role in vector control in India, their long-term utility is threatened by the rapid evolution of resistance across all major mosquito vectors. A multifaceted, evidence-based, and adaptive approach is essential to sustain gains in vector-borne disease control.

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