narra j

Review Article

Resistance status of *Aedes* mosquitoes as dengue vectors and the potential of plant larvicides from Indonesia for biological control: A narrative review

Kasman Kasman[1,2], Hasanuddin Ishak[3*], Gemini Alam[4], Ridwan Amiruddin[5], Poedji Hastutiek[6], Andi A. Arsin[5], Sudirman Nasir[7], Muhammad R. Ridha[8] and Isra Wahid[9]

[1]Doctoral Program in Public Health Sciences, Faculty of Public Health, Universitas Hasanuddin, Makassar, Indonesia; [2]Department of Epidemiology, Faculty of Public Health, Universitas Islam Kalimantan, Banjarmasin, Indonesia; [3]Department of Environmental Health, Faculty of Public Health, Universitas Hasanuddin, Makassar, Indonesia; [4]Department of Pharmaceutical Sciences and Technology, Faculty of Pharmacy, Universitas Hasanuddin, Makassar, Indonesia; [5]Department of Epidemiology, Faculty of Public Health, Universitas Hasanuddin, Makassar, Indonesia; [6]Department of Veterinary Parasitology, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia; [7]Department of Health Promotion and Behavioral Science, Faculty of Public Health, Universitas Hasanuddin, Makassar, Indonesia; [8]Vector-borne and Zoonotic Diseases Research Group, Research Center for Public Health and Nutrition, National Research and Innovation Agency, Jakarta, Indonesia; [9]Departement of Parasitology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia

*Corresponding author: hasanuddin.ishak@unhas.ac.id

Abstract

Dengue fever remains a major public health threat in Indonesia, exacerbated by rising insecticide resistance in *Aedes aegypti*. Strategies relying on chemical insecticides, while initially effective, have led to widespread resistance in mosquito populations. This resistance is particularly pronounced in areas such as Java, where the extensive use of insecticides, including organophosphates and pyrethroids, has been documented. To address this challenge, one promising alternative is the utilization of biolarvicides derived from local Indonesian plant materials. Biolarvicides are environmentally friendly, safe, and have the potential to mitigate the adverse impacts associated with chemical insecticides. Numerous studies have explored the larvicidal properties of indigenous plants native to Indonesia, demonstrating their efficacy against *A. aegypti*. The aim of this study was to examine insecticide resistance in *Aedes* mosquitoes across Indonesia, highlighting geographical variations and underexplored regions, and exploring plant-based biolarvicides as sustainable alternatives. Biolarvicides derived from native Indonesian plants could be eco-friendly alternative for dengue vector management. Their integration into existing control strategies could significantly enhance efforts to control dengue while reducing the environmental and health risks posed by chemical insecticides.

Keywords: *Aedes aegypti*, biolarvicides, dengue fever control, insecticide resistance, Indonesian plants

https://narraj.org/

Introduction

Dengue fever represents a persistent global public health challenge, particularly in tropical and subtropical regions [1]. World Health Organization (WHO) estimates that approximately 390 million individuals are infected with dengue annually, with Southeast Asia, including Indonesia, among the most severely affected areas [2]. Dengue is primarily transmitted by *Aedes* mosquitoes, notably *Aedes aegypti* and *A. albopictus*, which serve as the principal vectors [3,4].

Received: November 27, 2024 - Accepted: March 17, 2025 - Published online: April 17, 2025

Vector control strategies have predominantly relied on chemical insecticides; however, the efficacy of these measures has been significantly compromised by the emergence of insecticide resistance among mosquito populations [3].

In Indonesia, dengue poses a substantial burden, with cases occurring year-round due to the tropical climate that supports the continuous proliferation of *Aedes* mosquitoes [5]. Stagnant water sources, including rainwater puddles, serve as ideal breeding habitats for *A. aegypti* [6,7]. In 2020, the Indonesian Ministry of Health reported over 100,000 dengue cases, resulting in approximately 800 deaths [8]. Despite continuous efforts to mitigate transmission, vector control measures face substantial challenges, with insecticide resistance being a critical issue [9]. The emergence of resistance to commonly used insecticides has undermined existing control efforts, highlighting the urgent need for innovative and sustainable strategies to effectively manage *Aedes* mosquito populations.

Insecticide resistance in *Aedes* mosquitoes is not a recent phenomenon; however, its prevalence has intensified in recent years. Previous studies conducted globally, including in Indonesia, have reported the development of resistance in *Aedes* populations to various insecticide classes, including pyrethroids, organophosphates, and carbamates [10,11]. Pyrethroids, widely employed in vector control programs, have become increasingly ineffective due to genetic mutations in *Aedes* populations [12]. These mutations, particularly in the *kdr* (knockdown resistance) genes, reduce mosquito sensitivity to insecticides, thereby diminishing the efficacy of conventional vector control strategies [13].

Despite extensive documentation of insecticide resistance in *Aedes* mosquitoes, significant gaps persist in understanding resistance patterns across Indonesia. The country's diverse geographic, climatic, and urbanization profiles suggest considerable variability in resistance across different regions [14]. Current studies predominantly focus on urban centers such as Jakarta and Surabaya, while rural and peripheral regions remain largely underexplored [15]. Furthermore, limited research on the molecular mechanisms underlying resistance in Indonesian *Aedes* populations hampers the development of targeted interventions tailored to specific resistance profiles.

Reliance solely on chemical insecticides has demonstrated long-term unsustainability due to the progressive development of resistance [16]. Consequently, integrated vector management strategies, which combine biological controls with environmentally sustainable alternatives to complement chemical insecticides, have gained increasing importance [16]. In response to the challenges posed by insecticide resistance, research efforts are shifting toward identifying alternative solutions for vector control.

One promising approach involves the use of plant-based biolarvicides [17]. These natural products, derived from botanical sources, have insecticidal or larvicidal properties that target mosquito larvae, thereby reducing mosquito populations at the pre-adult stage [18,19]. The application of biolarvicides offers several advantages over chemical insecticides, including a reduced environmental footprint, a lower likelihood of resistance development, and the utilization of renewable natural resources [20]. Such attributes make biolarvicides an attractive and sustainable component of modern vector control strategies.

Indonesia, recognized as one of the most biodiverse countries globally, harbors an extensive repository of plant species with significant untapped potential for biolarvicide development [21]. Ethnobotanical studies have documented the traditional use of various indigenous plants by local communities in Indonesia for insect control [22]. Notable examples include *Azadirachta indica* (neem) [23], *Euphorbia hirta* [24], and *Ocimum sanctum* (holy basil) [25], which have demonstrated larvicidal activity against mosquito species in laboratory studies. However, despite these promising findings, there is a substantial gap in research on the large-scale application and field efficacy of these plant-based larvicides against *Aedes* mosquitoes.

Further research gap exists in the standardization and formulation of plant-derived biolarvicides. Previous research emphasized the effects of crude plant extracts under laboratory conditions, but limited information is available about efficacy in natural environments or when scaled for public health interventions [26]. Therefore, the aim of this study is to address gaps in dengue vector control strategies by summarizing the status of insecticide resistance in *Aedes* mosquitoes across Indonesia, with particular emphasis on geographical variations and underexplored regions. Additionally, this study presents the potential of plant-based biolarvicides as sustainable alternatives, incorporating ethnobotanical evidence, laboratory findings, and challenges in large-scale implementation. By highlighting these aspects, this review might contribute to the development of more effective and sustainable vector control strategies.

Historical overview of *Aedes* mosquito resistance in Indonesia: Trends, contributing factors, and implications for vector control

Larvicidal agents were introduced in Indonesia in the mid-20th century to combat rising dengue cases [27]. During this time, dichlorodiphenyltrichloroethane (DDT) became the primary choice for mosquito control, including efforts to reduce *A. aegypti* larval populations [28]. DDT was extensively applied in dengue-endemic areas through indoor and outdoor spraying and direct application to mosquito breeding sites [29]. Prolonged use of DDT led to resistance in *A. aegypti* populations across various regions [30], diminishing its effectiveness and prompting a gradual phase-out [15]. This resistance was attributed to sodium channel mutations, which reduced mosquito sensitivity to the insecticide [11]. DDT was eventually replaced by alternative insecticides, such as organophosphates (e.g., temephos) and pyrethroids (e.g., permethrin) [15]. However, resistance to these newer insecticides has also been reported, particularly in urban centers such as Jakarta, Indonesia, where significant resistance to pyrethroids has been identified [11].

1980s: Preliminary surveillance

Vector resistance to dengue was first documented in Indonesia during the early 1980s when *A. aegypti* began showing resistance to various insecticide classes [31]. This marked the initial recognition of resistance as a significant issue [15]. Concurrently with the escalating application of insecticides for population management of *A. aegypti* mosquitoes [15]. The extensive use of insecticides, particularly temephos as a larvicide, was implemented to control *A. aegypti* populations. Although initially effective, prolonged and repeated use led to resistance in certain regions [15]. Resistance to temephos and malathion emerged in *A. aegypti* populations across urban Indonesia [30], particularly in Jakarta, due to extensive use of malathion since the 1970s and temephos since the 1980s [32]. Prolonged exposure to these insecticides facilitated the survival and reproduction of resistant individuals [33]. By 1983, report highlighted insecticide resistance in *A. aegypti* populations in specific regions, particularly Java Island, where resistance to malathion and temephos had developed [15]. Resistance was not limited to these insecticides but also extended to other classes, including pyrethroids such as permethrin, which have been in use since the 1980s [34].

1990s: Worsening resistance

In the 1990s, dengue vector resistance in Indonesia intensified, with *A. aegypti* mosquitoes developing resistance to commonly used pyrethroid insecticides [35]. A study conducted between 1995 and 1998 in Salatiga and Semarang, Central Java, confirmed the emergence of resistance to permethrin in these mosquito populations [36].

2000s: Escalating resistance

During the 2000s, dengue vector resistance spread across various regions of Indonesia. Resistance to permethrin was detected in Semarang, Central Java, in 2003, with a notably high resistance level [36]. The highest resistance was observed in Salatiga, Central Java, with a 296-fold increase in the lethal concentration required to kill 95% of the tested population (LC_{95}) [36]. A 2007 investigation in Palembang, South Sumatra, and Surabaya, East Java, highlighted *A. aegypti* resistance to both permethrin and deltamethrin [37]. In Bandung, West Java, resistance to both insecticides was also evident, with resistance ratio (RR_{90}) values of 79.3 for permethrin and 23.7 for deltamethrin [37]. Augmented resistance transpires not solely to pyrethroids but also to organophosphate and carbamate insecticides [12].

2010s: Growing concern over resistance development

In this decade, the spread of dengue vector resistance has become increasingly concerning [38]. The prevalence of resistance is rising in various regions, particularly in large islands such as Java, Sumatra, and Kalimantan [39]. *A. aegypti* mosquitoes are showing resistance to newer, more potent insecticides [11]. In 2015, a correlation between permethrin and deltamethrin resistance and the *V1023G* mutation was identified in Yogyakarta Province, suggesting that the efficacy of pyrethroids could diminish in the region, necessitating the implementation of resistance management strategies [40]. In 2017, *A. aegypti* populations in dengue-endemic areas of Central Java, including Semarang, Surakarta, Kudus, and Jepara, showed high resistance to pyrethroids [41]. Resistance also emerged outside Java, as observed in Denpasar, Bali, in 2017, where mortality rates of *A. aegypti* were less than 90%, with the highest resistance noted for permethrin 0.75% [42]. A study in Toraja Regency, South Sulawesi, revealed that *A. aegypti* mosquitoes (high endemic strain) were resistant to 0.8% malathion and tolerant to 5% malathion, while larvae remained susceptible to 1% temephos [43]. In contrast, non-endemic *A. aegypti* strains were susceptible to malathion (0.8% and 5%) and temephos (1%) [43] Resistance to temephos in Padang, West Sumatra, indicated that some *A. aegypti* populations were resistant, while others were tolerant, with no populations being susceptible [44]. In Banjarmasin, South Kalimantan, resistance levels varied, with mortality rates below 90% for most insecticides, except for malathion 5%, and the highest resistance recorded for 0.75% permethrin and 0.1% bendiocarb, where mortality rates were under 50% [45]. In Kuningan, Sunda Island, *A. aegypti* larvae showed resistance to diagnostic doses of chlorpyrifos, malathion, temephos, and DDT, with mortality rates ranging from 0% to 74.67% [46].

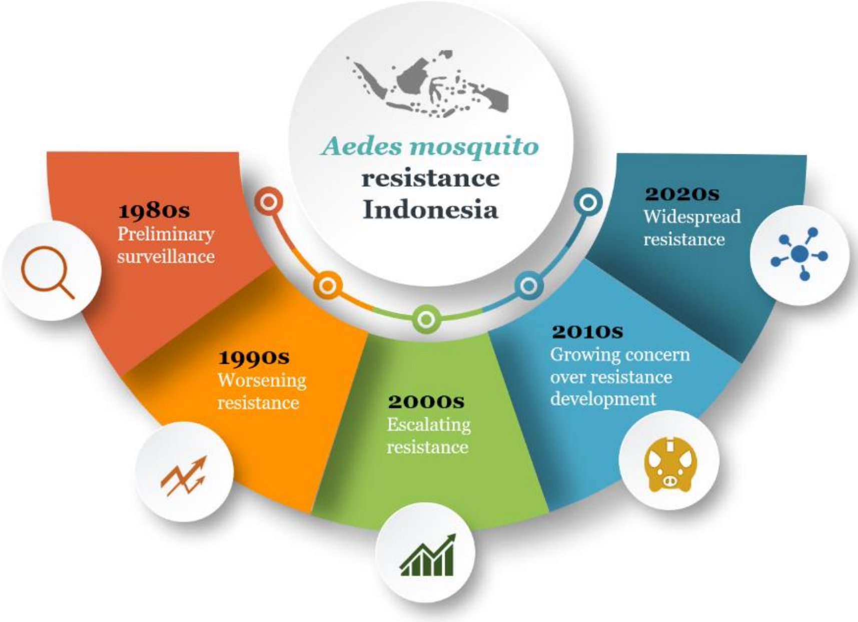

Figure 1. Historical development of *Aedes* mosquito resistance to insecticides in Indonesia.

2020s: Widespread resistance

In the 2020s, dengue vector resistance has become more widespread across Indonesia [47]. *A. aegypti* in Riau Province showed resistance to temephos and adult mosquitoes to 5% malathion [48]. A large-scale study in 2022 across 32 regencies and cities found low to moderate resistance to pyrethroids in strains from urbanized cities on Java Island, such as Banten, Jakarta, Bandung, Semarang, Yogyakarta, and Surabaya [39], while strains from less populated cities in Borneo Island showed high resistance to pyrethroids [49]. In 2023, resistance in Central Java was observed, with *A. aegypti* mortality rates following exposure to cypermethrin, malathion, and temephos ranging from 16–86%, 75–100%, and 6–51%, respectively. These findings indicate resistance to cypermethrin and temephos, while susceptibility to malathion was noted in 23.08% of strains from various elevations [31]. In Magetan Regency, East Java, resistance levels ranged from 25% to 79.16% for malathion and 41.66% to 64.16% for alpha-cypermethrin. The summary of the dengue vector resistance studies in Indonesia is presented in **Table 1**.

Table 1. Summary of dengue vector resistance in Indonesia

Location	Insecticides	Findings	Reference
Salatiga and Semarang	Permethrin 0.75%	The highest level of permethrin resistance was observed, with a 296-fold increase at lethal concentration (LC)$_{95}$	[36]
Bandung, Palembang, and Surabaya	Permethrin 0.75% and deltamethrin 0.05%	Reduced susceptibility to permethrin and deltamethrin was observed in Palembang and Surabaya	[37]
Surabaya	Temephos 0.012 mg/L	All field strains were resistant to temephos at 0.012 mg/L, with 24-hour mortality ranging from 22% to 60%	[50]
Yogyakarta	Permethrin 0.75% and deltamethrin 0.05%	*V1023G* mutation in Yogyakarta was associated with permethrin and deltamethrin resistance, indicating reduced pyrethroid efficacy	[40]
Semarang, Surakarta, Kudus, and Jepara	α-Cypermethrin 0.05%, deltamethrin 0.05%, λ-cyhalothrin 0.05%, and malathion 0.8%	*Aedes aegypti* populations in dengue-endemic areas of Central Java Province demonstrated high resistance to pyrethroid insecticides	[41]
Wonosobo	Malathion 0.8%	Biochemical resistance was detected in 50% of *Aedes* sp. samples collected	[51]
Jakarta	Permethrin 0,75%	*A. aegypti* in Jakarta is resistant to multiple pyrethroid insecticides used in control programs	[11]
Denpasar	Permethrin 0.75%	*A. aegypti* mortality remained below 90%, with the highest resistance to permethrin 0.75%	[42]
Toraja Regency	Malathion (0.8% and 5%) and temephos 1%	High-endemic strains of *A. aegypti* demonstrated resistance to 0.8% malathion and tolerance to 5% malathion, whereas the larvae remained susceptible to 1% temephos. In contrast, non-endemic strains were susceptible to 0.8% and 5% malathion, as well as 1% temephos	[43]
Yogyakarta	Cypermethrin 10 µg/bottle	*A. aegypti* from Yogyakarta City (93% mortality) and Sleman Regency (88% mortality) demonstrated potential resistance to cypermethrin	[52]
Padang	Temephos 0.02 mg/L	Temephos exposure indicated resistance in some *A. aegypti* populations, tolerance in others, and no susceptibility across all populations	[44]
Ciamis, Purwakarta, Bogor, Bandung, Denpasar, Mataram, Kuningan, Padang, and Samarinda	Permethrin 0.75% and deltamethrin 0.05%	Strains from Denpasar, Mataram, Kuningan, Padang, Samarinda, and East Sumba demonstrated resistance (<80% mortality), whereas those from West Manggarai, Dompu, and Pontianak were susceptible (>98% mortality)	[12]
Banjarmasin	Malathion 5%, deltamethrin 0.05%, permethrin 0.75%, λ-cyhalothrin 0.05%, bendiocarb 0.1%, and cyfluthrin 0.15%	*A. aegypti* demonstrated varying resistance to insecticides, with mortality rates below 90% for most compounds, except for 5% malathion. The highest resistance was observed with 0.75% permethrin and 0.1% bendiocarb, with mortality rates below 50%	[29]
Bengkulu	Malathion 5% and cypermethrin 0.05%	*A. aegypti* from endemic and sporadic dengue areas in Bengkulu City remain susceptible to malathion and cypermethrin; however, signs of emerging resistance mechanisms have been observed	[45]
Kuningan	DDT, chlorpyrifos, malathion 5%, and temephos	*A. aegypti* larvae demonstrated resistance to diagnostic doses of chlorpyrifos, malathion, temephos, and dichlorodiphenyltrichloroethane	[46]

Location	Insecticides	Findings	Reference
		(DDT), with mortality rates ranging from 0% to 74.67%	
Magelang	Pyrethroid	Several *kdr* mutations associated with pyrethroid resistance were identified in *A. aegypti*, with urbanization potentially contributing to their development	[53]
Pekanbaru	Temephos 0.02 mg/L and malathion 5%	*A. aegypti* larvae were resistant to temephos, while adult mosquitoes were resistant to 5% malathion	[48]
Pesisir Selatan Regency	Temephos 0,02 mg/L	*A. aegypti* larvae demonstrated tolerance to 0.012 mg/L temephos, with a mortality rate of 91.67%	[54]
32 regencies/cities in Indonesia	Deltamethrin 0.05%, permethrin 0.75%, bendiocarb 0.1%, and pyrimiphos-methyl	*A. aegypti* strains from highly urbanized cities in Java (Banten, Jakarta, Bandung, Semarang, Yogyakarta, and Surabaya) had low to moderate resistance to pyrethroids, whereas strains from less populated regions of Borneo demonstrated high resistance.	[49]
Central Java	Cypermethrin 0.05%, malathion 5%, and temephos 0.02 mg/L	*A. aegypti* mortality following exposure to cypermethrin, malathion, and temephos ranged from 16% to 86%, 75% to 100%, and 6% to 51%, respectively	[31]
Magetan Regency	Malathion 5% and cypermethrin 0.05%	Resistance to malathion ranged from 25% to 79.16%, while resistance to alpha-cypermethrin ranged from 41.66% to 64.16%	[55]

Types of resistance in *Aedes* mosquitoes: Pyrethroid, malathion, and temephos resistance mechanisms across Indonesia

Resistance of *Aedes* mosquito to pyrethroids

Pyrethroid insecticides, synthetic derivatives of pyrethrin found in chrysanthemum flowers (*Chrysanthemum cinerariifolium*), are designed to mimic the structure and mechanism of pyrethrin but showed greater stability under solar radiation and prolonged efficacy [56]. These compounds disrupt the insect nervous system by modifying sodium channels on nerve cell membranes, causing continuous depolarization, nerve dysfunction, paralysis, and ultimately insect death [57]. Pyrethroids are widely used for controlling *A. aegypti* mosquitoes, which are primary vectors of diseases such as dengue hemorrhagic fever (DHF) [58]. In Indonesia, commonly used pyrethroid formulations include permethrin, deltamethrin, cypermethrin, and lambda-cyhalothrin [39].

Permethrin is widely employed to control adult mosquitoes through insecticide-infused mosquito nets and sprays. However, prolonged use has resulted in resistance in *A. aegypti* mosquitoes [59]. Numerous studies have reported permethrin resistance in Indonesia. In 2003, resistance levels were notably high in Salatiga and Semarang, Central Java [36]. *A. aegypti* in Palembang, South Sumatra, and Surabaya, East Java, showed tolerance to permethrin, while the Bandung, West Java, strain demonstrated resistance with RR_{90} of 23.7 [37]. The resistance in the Bandung strain is attributed to elevated activity of detoxifying enzymes [37]. Other cities in Indonesia with documented permethrin resistance include Yogyakarta [40,52], Jakarta [11], Denpasar [42], and Banjarmasin [29].

Deltamethrin is another widely used pyrethroid insecticide for controlling *A. aegypti* mosquitoes [60], applied as an aerosol for outdoor fumigation to target flying adult mosquitoes [61]. Residual spraying of deltamethrin on walls and surfaces, commonly used as mosquito resting sites, creates a thin insecticidal layer that kills mosquitoes upon contact [61]. Additionally, mosquito nets impregnated with deltamethrin provide protection by exposing mosquitoes to the insecticide upon landing, leading to their death [62]. Mosquitoes landing on impregnated nets are exposed to deltamethrin, resulting in mortality [62]. Deltamethrin is highly effective against adult *A. aegypti* mosquitoes, demonstrating a rapid knockdown effect [11]. However, continuous application has led to resistance development [15]. Resistance to deltamethrin has been reported in Yogyakarta in 2015 [40] and Banjarmasin in 2018 [29].

Resistance of *Aedes* mosquitoes to malathion

Organophosphate insecticides, including malathion, are used less frequently than pyrethroids due to their higher toxicity risk. Resistance to malathion emerges in initially susceptible *A. aegypti* populations when mosquitoes survive exposure to the insecticide. This resistance trait is subsequently inherited by subsequent generations [63]. The development of malathion resistance has become increasingly evident, particularly in fogging programs targeting *A. aegypti* larvae. According to the US Centers for Disease Control and Prevention (CDC) guidelines, mosquito populations that survive exposure to standard doses of insecticides for more than 60 minutes are considered resistant [64].

A study in Makassar, South Sulawesi, and other regions of Indonesia revealed that *A. aegypti* larvae from non-fogged areas demonstrated 100% mortality rates significantly faster than larvae from fogged or frequently fogged areas, where mortality rates were notably reduced and often failed to reach 100% by the end of the trials [64]. Similar findings were observed in Toraja Regency, South Sulawesi, where adult *A. aegypti* from high-endemic areas demonstrated resistance to 0.8% malathion [43].

In Wonosobo Regency, a highland area in Central Java, mosquito density exceeded dengue control standards (house index (HI): 14.75%; container index (CI): 6.8%; breteau index (BI): 15.6; ovitrap index (OI): 11.30%), and biochemical resistance was detected in 50% of *Aedes* species, contributing to ongoing dengue transmission despite the elevated location [51]. Resistance test in Banjarmasin, South Kalimantan, involving 402 *A. aegypti* samples, revealed a tolerant status with mortality rates below 98% [29]. In Bengkulu, a study in endemic and sporadic areas indicated susceptibility to malathion and cypermethrin, although signs of emerging resistance mechanisms were observed [45]. In the Kuningan, Sunda Islands, *A. aegypti* larvae demonstrated resistance to malathion, with mortality rates below 74.67% [46]. High resistance levels were also recorded in Magetan Regency, East Java, with mortality rates ranging from 25% to 79.16% [55]. In Central Java, exposure to malathion resulted in mortality rates ranging from 75% to 100% [31].

Resistance of *Aedes* larvae to temephos

Prolonged use of temephos has led to the development of resistance in mosquito larvae against this larvicide. According to WHO guidelines, susceptibility to temephos is assessed based on the lethal concentration required to kill 99% of the tested population (LC_{99}) within 24 hours. If the required dose to achieve LC_{99} exceeds 0.02 mg/L within 24 hours, the mosquito larvae are classified as resistant to temephos [65]. Studies investigating the susceptibility of *A. aegypti* larvae to temephos in regions such as Thailand, Trinidad and Tobago, as well as the United Kingdom, demonstrated varying results [66,67]. Mosquito populations frequently exposed to temephos had prolonged mean times to death, attributed to elevated nonspecific esterase enzyme levels, and these resistance mechanisms could be mitigated by incorporating anti-esterase components to reduce larval resistance [66,67]. Similar findings were observed in Riau, Indonesia, where alpha esterase activity tests indicated high sensitivity in most mosquitoes, while beta esterase activity tests revealed moderate resistance [48].

Resistance to temephos in *A. aegypti* larvae has also been reported in several dengue-endemic cities in Indonesia. For instance, in Surabaya, East Java, susceptibility testing across 12 sub-districts using WHO protocol revealed resistance at a dose of 0.012 mg/L (**Table 2**). Mortality rate within 24 hours ranged from 22% to 60%, necessitating further tests to determine the median lethal time (LT_{50}), with resistance ratios ranging from 2.2 to 8.5 [50]. Resistance has also been documented in other Indonesian cities, including Toraja, with a tolerant status toward temephos [43], Padang [44], Kuningan [46], Pekanbaru [48], Painan [54], and Semarang [31].

Factors contributing to insecticide resistance in *Aedes*: Biological, environmental, operational, and exposure-related determinants

Extensive research has demonstrated that the development of insecticide resistance is primarily driven by mutations in insecticide receptor sites and alterations in detoxification mechanisms. These changes involve qualitative and quantitative modifications in enzymatic processes responsible for detoxifying or neutralizing insecticidal compounds [71]. Biological factors such as temperature, high humidity, rainfall, and population density create optimal breeding conditions for *A. aegypti* mosquitoes [64,65], facilitating their proliferation [72]. Operational factors, including inappropriate insecticide use, also contribute to resistance [73]. Examples include the administration of abate based solely on community requests or in response to dengue cases, suboptimal dosing of abate, improper fogging practices (e.g., incorrect insecticide concentrations, mixing, or application timing), and insufficient adherence to recommended guidelines [64]. Furthermore, frequent exposure to insecticides, particularly in rural areas where agricultural use is higher, has been associated with resistance development, as evidenced by domestic and international studies [74].

The growing resistance of *A. aegypti* mosquitoes to insecticides in Indonesia poses a significant obstacle to vector control programs aimed at mitigating diseases such as DHF, chikungunya, and Zika virus [15]. Resistance arises when mosquito populations acquire the ability to survive exposure to previously effective insecticides [75]. In tropical regions, including Indonesia, insecticide-based interventions—particularly those utilizing pyrethroids—form the cornerstone of *A. aegypti* control strategies [35]. However, a concerning increase in pyrethroid resistance has been reported across multiple regions in Indonesia over the past few decades [15]. This trend threatens the efficacy of vector control measures and raises the risk of mosquito-borne diseases outbreaks [76]. Factors contributing to resistance include improper insecticide use and environmental conditions that accelerate resistance development [77].

Table 2. Summary of resistance mechanisms, associated genes, and their impact on the efficacy of insecticides used against *Aedes aegypti* mosquitoes in Indonesia

Insecticide class	Resistance mechanism	Associated genes/ enzymes	Impact on efficacy	Reference
Pyrethroids (permethrin, deltamethrin, cypermethrin, and lambda-cyhalothrin)	Target-site *kdr* mutation in sodium channels and metabolic detoxification through elevated esterase and P450 enzymes	*kdr* gene mutations (e.g., *V1016G*, *F1534C*)	Lower mortality rates and reduced knockdown effect	[15,29,37,40]
Organophosphates (malathion)	Increased metabolic detoxification through elevated esterase activity	Esterase genes (e.g., *ester* and *ace-1*)	Decreased efficacy of fogging programs with increased mosquito survival rates	[15,37,68-70]
Temephos	Increased esterase and glutathione-S-transferase (GST) activity	Esterase genes, *GST* genes	Reduced larvicidal effectiveness, leading to prolonged larval mortality time	[48,50,66,67]

Excessive and improper use of insecticides

The overuse of insecticides, characterized by high application frequency and elevated concentrations, can initiate a natural selection process that fosters the development of resistance in *A. aegypti* mosquitoes [77]. Continuous application of insecticides at excessive doses favors the survival and reproduction of mosquitoes with inherent resistance, while susceptible populations are eliminated [78]. Consequently, over time, the mosquito population becomes predominantly resistant to the insecticide [79]. A study conducted in various regions of Indonesia, including Yogyakarta and Surabaya, has reported a significant increase in resistance to pyrethroid insecticides such as permethrin and deltamethrin, attributed primarily to uncontrolled and excessive insecticide use [77].

In addition to overuse, improper practices such as failure to adhere to recommended dosages or inadequate rotation of active ingredients further accelerate resistance development [80]. Sublethal exposure, such as administering doses insufficient to eliminate mosquitoes but capable of inducing genetic adaptations [42,44] promotes the emergence of more resistant mosquito individuals [81]. A study in Central Java demonstrated that infrequent and suboptimal insecticide applications by local communities contributed to resistance, including resistance to carbamates used as alternatives to pyrethroids, highlighting the influence of improper household insecticide use on resistance dynamics [31,53].

Excessive and repeated applications of insecticides, particularly pyrethroids, have resulted in the widespread emergence of resistant mosquito populations [82]. This overreliance on chemical interventions has diminished insecticide efficacy, necessitating the exploration of alternative pest-control strategies [83]. Sublethal insecticide exposure, such as that encountered with mosquito-repellent coils, has been shown to accelerate resistance development [84]. Recurrent exposure has been associated with reduced mortality rates in resistant populations, thereby complicating vector control efforts [85]. The rise of insecticide resistance in *A. aegypti* represents a significant challenge to vector control programs and increases the risk of mosquito-borne disease transmission. Innovative approaches, such as the use of Wolbachia-infected mosquitoes or natural larvicides, are under investigation to address resistance and enhance the efficacy of control measures [86]. To combat these challenges, continuous monitoring of resistance trends and the implementation of integrated vector management strategies are essential.

Lack of rotation and diversification of insecticides

The insufficient rotation and diversification of insecticides constituted a critical factor contributing to insecticide resistance in *A. aegypti* mosquitoes [87]. The repetitive application of the same insecticide or class of insecticides, without incorporating a rotation strategy, imposed substantial selective pressure on mosquito populations, enabling resistant individuals to survive, reproduce, and transmit resistance alleles to subsequent generations [75]. The repeated use of uniform insecticides, particularly pyrethroids such as cypermethrin and malathion, significantly contributed to resistance among *A. aegypti* populations across Southeast Asia, including Indonesia [15]. This resistance undermined the effectiveness of insecticide-based control measures and complicated the management of outbreaks related to mosquito-borne diseases, including dengue, chikungunya, and Zika [88].

Insecticide rotation has been identified as an essential strategy in *A. aegypti* mosquito control to address resistance challenges and maintain the effectiveness of vector control programs [12,39]. Rotation reduces the selective pressure generated by the repeated use of a single insecticide [89]. Continuous application of the same insecticide allowed mosquitoes with resistance genes to survive and proliferate [90], leading to the dominance of resistant individuals within the population [75]. For example, switching from pyrethroid insecticides to organophosphate alternatives after a period of use helped mitigate the development of resistance [39].

Diversifying insecticide applications by incorporating products with varying mechanisms of action has been deemed essential for reducing the likelihood of resistance development [91]. Mosquitoes rapidly developed resistance mechanisms when exposed exclusively to a single insecticide [75]. Rotating insecticides at regular intervals alleviated the selective pressure on mosquito populations, thereby slowing resistance progression [12]. Furthermore, incorporating alternative control strategies, such as biological controls and environmental management practices, significantly reduced dependence on chemical insecticides and delayed the onset of resistance [39]. Implementing effective insecticide rotation and diversification strategies is critical, not only for controlling *A. aegypti* populations but also for safeguarding public health from dengue outbreaks [92]. Vector control policies should include routine resistance monitoring and the implementation of appropriate rotation schedules to ensure sustained control efficacy [75]. Through the adoption of a more comprehensive and integrated vector management strategy, the prevalence of dengue fever could be reduced, thereby enhancing public health protection within affected communities [39].

Genetic mutations in mosquitoes

The emergence of resistance in *A. aegypti*, a primary vector for multiple arboviruses, including dengue and Zika, represented a critical public health challenge [93]. Various factors contributed to the development of resistance within mosquito populations, including genetic alterations that reduced the efficacy of insecticidal agents [75]. One significant genetic mutation associated with resistance was the *kdr* mutation [94]. This mutation altered the amino acid configuration of the sodium channel in *A. aegypti*, resulting in a diminished binding affinity for pyrethroid insecticides [95]. Consequently, mosquitoes exposed to pyrethroids demonstrated reduced rates of paralysis and mortality compared to baseline levels [96]. The *kdr* mutation primarily affected the *voltage-gated sodium channel (VGSC)* gene, the primary target of pyrethroid insecticides [96]. Common mutations such as *V1016I* and *F1534C*, associated with increased resistance to both type I and type II pyrethroids, were identified in various regions, including Ghana and USA [97]. Additionally, the overexpression of detoxifying enzymes, such as cytochrome P450, esterases, and glutathione S-transferase, significantly contributed to the development of resistance [72]. These enzymes facilitated the metabolism and neutralization of insecticides, thereby enhancing the survival of resistant mosquitoes [98].

Resistance was not limited to pyrethroids, as genetic mutations in other loci also conferred resistance to different classes of insecticides, including organophosphates and carbamates [99]. For instance, variations in the acetylcholinesterase gene *(ace-1)* conferred resistance to organophosphates and carbamates by reducing the binding affinity of these insecticides to their target enzyme [100]. In Indonesia, this specific mutation was observed in diverse *A. aegypti* populations, broadening the spectrum of resistance mechanisms shown by mosquitoes in response to insecticide exposure [54].

A study conducted in Indonesia identified numerous genetic mutations contributing to *A. aegypti* resistance against various categories of insecticides [15]. For instance, a study in Yogyakarta demonstrated widespread *kdr* mutations in the *VGSC* gene among local mosquito populations, increasing resistance to pyrethroids, including permethrin and deltamethrin [41]. Additionally, prior research identified mutations in the *ace-1* gene, which conferred resistance to organophosphate insecticides, particularly malathion [100]. In Surabaya, East Java, another study revealed that *A. aegypti* had dual resistance to pyrethroids and organophosphates, associated with mutations in both the *VGSC* and *ace-1* genes [101]. These findings indicated that mosquito populations in this region had developed advanced resistance mechanisms, enabling survival despite exposure to multiple insecticide classes [101]. A study in Bali further identified mutations in the *glutathione-S-transferase* (*GST*) gene, which correlated with resistance to organochlorine insecticides such as DDT [102]. Although DDT is rarely used in current practices, the identification of this mutation highlighted a potential resistance that could compromise the efficacy of insecticides with similar modes of action.

The distribution of genetic mutations causing insecticide resistance was not uniform across Indonesia [103]. Areas with intensive insecticide use, such as major cities and urban regions, showed higher mutation frequencies [104]. For example, in Jakarta and Bandung, where vector control programs frequently employed various insecticide classes, *kdr* and *ace-1* mutations were highly prevalent [31]. In contrast, rural areas with limited insecticide exposure demonstrated lower mutation frequencies, although some mosquito populations still harbored these mutations [53]. The dissemination of resistance mutations was also facilitated by human mobility and trade [105]. For instance, mosquitoes carrying resistant mutations spread rapidly through the movement of people and goods, accelerating resistance across Indonesia [106]. Studies in Bali revealed that the previously rare *kdr* mutation proliferated rapidly following increased population mobility and tourist activity [42].

The presence of genetic alterations conferring resistance to diverse categories of insecticides significantly impacts the efficacy of vector management initiatives [97]. As mosquitoes develop resistance to commonly used insecticides, the effectiveness of insecticide applications diminishes, reducing the success of mosquito control measures [75]. This phenomenon can lead to an increase in mosquito populations and an elevated risk of disease transmission, including dengue [107]. Despite intensive spraying, studies reported no significant decline in mosquito populations, with dengue cases remaining elevated during the transmission season [108]. Similarly, in Surabaya, East Java, dual resistance to pyrethroids and organophosphates posed substantial challenges for vector control programs [39]. The decline in insecticide efficacy has necessitated the exploration of alternative strategies. Public health officials have increasingly adopted synergistic approaches combining multiple insecticides with varying mechanisms of action or implemented non-chemical methods to manage mosquito populations effectively. These strategies aim to mitigate resistance and enhance the long-term sustainability of vector control efforts.

Environmental factors and climate change

The global phenomenon of climate change significantly influences the ecological dynamics of the *A. aegypti* mosquito [109]. Rising global temperatures and changing rainfall patterns affect mosquito life cycles, prolonging the breeding season and increasing the number of reproductive cycles per year [110]. With an increase in mosquito generations within a shorter time frame, the likelihood of genetic mutations leading to resistance also rises [86]. A study demonstrated that elevated temperatures not only accelerate mosquito life cycles but also enhance the rate of larval transformation into adult forms [111]. Analyses conducted in Southeast Asia, particularly in Indonesia, revealed that in areas with higher temperatures, *A. aegypti* mosquitoes show faster development and greater annual generational output compared to regions with more temperate climates [112]. As a result, the selective pressure from insecticide use intensifies, accelerating the evolutionary process of resistance [113]. Additionally, climate-induced changes in precipitation patterns also affect mosquito breeding habitats [114]. More frequent and erratic rainfall creates favorable conditions for mosquito breeding, such as waterlogging in urban areas [110]. This leads to an increase in mosquito populations and greater insecticide exposure, further promoting natural selection and resistance development [115].

The rapid urbanization in Indonesia has significantly altered the natural habitat of the *A. aegypti* mosquito, forcing these organisms to adapt to anthropogenic environments [116]. These mosquitoes have identified optimal breeding sites near human dwellings, including bathtubs, ornamental flower pots, and water retention vessels in urban areas [117]. This adaptation to human environments increased the mosquitoes' exposure to insecticides commonly used by residents for mosquito control [118]. A study showed that *A. aegypti* mosquitoes in metropolitan environments had considerably higher resistance compared to their rural counterparts [119]. This increased resistance was attributed to more frequent exposure to insecticides, both from household use and local government vector control programs [120]. For instance, a study in Jakarta demonstrated that mosquito populations in densely populated urban areas demonstrated higher resistance to pyrethroids and organophosphates than those in suburban regions, which experienced reduced insecticide exposure [11]. Urbanization has also transformed mosquito habitats from natural ecosystems to anthropogenic environments. As natural habitats were cleared for urban expansion, *A. aegypti* mosquitoes adapted to these new environments [121]. These adaptations often involved increased exposure to insecticides used by humans, which further accelerated the evolution of resistance [122].

Environmental factors and climate change contributed to the development of insecticide resistance in *A. aegypti*, posing significant challenges to the effectiveness of vector management strategies [28]. As resistance levels increased, insecticides that were once effective became less capable of controlling mosquito populations, thus increasing the risk of disease transmission [123]. A pronounced increase in insecticide resistance was observed in major urban centers in Indonesia, including Jakarta, Surabaya, and Denpasar [39]. This resistance prompted health authorities to explore more effective control alternatives, such as insecticide rotation, insecticide combinations, or non-chemical control methods [75]. However, without adequate regulation addressing environmental variables and the impact of climate change, resistance was expected to continue escalating [11,42].

Lack of surveillance and monitoring of resistance

Monitoring insecticide resistance is essential in vector control programs, particularly those targeting *A. aegypti* mosquitoes, which are primary vectors for diseases such as DHF, chikungunya, and Zika [124]. In Indonesia, insecticide resistance monitoring has been limited in both geographical coverage and frequency [39]. The lack of sufficient oversight has weakened the effectiveness of vector control efforts and accelerated the development of insecticide resistance in various regions [125].

Effective monitoring enables early detection of changes in mosquito sensitivity to insecticides [126]. With accurate data, health authorities could modify vector control strategies, such as implementing insecticide rotations or alternative control measures, before resistance reaches levels that threaten control effectiveness [12]. In the absence of adequate monitoring, resistance often goes undetected until it reaches critical levels, making interventions more complicated and costly [127].

In Indonesia, surveillance of insecticide resistance remains sporadic and is often limited to areas with high dengue case numbers, such as Jakarta and Yogyakarta [47]. Research conducted in these major cities has revealed that resistance to pyrethroids and organophosphates has reached alarming levels [128]. Monitoring in rural and remote regions has been insufficient due to limited financial resources, a shortage of skilled personnel, inadequate infrastructure, and under-equipped laboratories, which have hindered a comprehensive understanding of insecticide resistance distribution nationwide [129]. These limitations have led to significant data gaps, impeding efforts to develop responsive and targeted control strategies [12].

The lack of insecticide resistance monitoring in Indonesia has had several detrimental effects [29]. Without accurate data, vector control programs often rely on repeated use of the same insecticides, which accelerates the development of resistance [107]. When resistance is not detected early, previously effective insecticides may lose their ability to control mosquito populations, potentially resulting in a surge in mosquito-borne diseases [129]. Furthermore, without sufficient oversight, identifying regions with significant resistance becomes difficult [129]. The use of generalized, non-specific control strategies, such as widespread insecticide application without assessing local resistance levels, often leads to inefficiency and resource waste, failing to achieve desired outcomes [130]

The absence of regular surveillance and monitoring of insecticide resistance in Indonesia has been identified as a key factor contributing to the increase in *A. aegypti* resistance [39]. Without accurate data and consistent monitoring, resistance often goes undetected until it reaches critical levels, reducing the effectiveness of vector control programs [88]. Enhanced surveillance and systematic monitoring are crucial to ensure that vector control strategies can be tailored to specific local contexts and maintain efficacy over time.

Use of insecticides in the non-health sectors

In Indonesia, the application of insecticides extends beyond the health sector's efforts to control disease vectors, encompassing significant use within the agricultural and forestry sectors [131]. The use of insecticides in these sectors may contribute to the development of insecticide resistance in *A. aegypti* mosquitoes, which are the primary vectors for diseases such as DHF, chikungunya, and Zika [132]. Insecticides used in agriculture often contain the same or similar active ingredients as those employed in public health vector control [32]. For example, pyrethroids, a key class of insecticides used to manage mosquito populations, are also widely applied in agricultural practices to combat crop pests [133]. When *A. aegypti* mosquitoes are exposed to this insecticide in an agricultural setting, they may develop resistance to the same active ingredient, reducing the efficacy of the insecticide when used in public health vector control programs [134].

Research conducted in East Java revealed that mosquitoes found near agricultural land had higher resistance to pyrethroids compared to mosquitoes located farther from such areas [39]. This suggests that insecticide use in the agricultural sector imposes selective pressure that promotes the emergence of resistance in mosquito populations [32]. This phenomenon of cross-resistance means that resistance developed in agricultural contexts can undermine the effectiveness of insecticides in health-related vector control, complicating efforts to manage mosquito-borne diseases [135].

Cross-resistance occurs when resistance to one category of insecticide leads to resistance to another category with a similar mechanism of action [136]. In the context of insecticide application in non-health sectors, such cross-resistance may develop when *A. aegypti* mosquitoes are exposed to agricultural insecticides containing active ingredients identical to those used in vector control [137]. For example, research in North Sumatra demonstrated that mosquitoes exposed to organophosphate insecticides in agricultural settings had resistance to the same class of organophosphates used in dengue management programs [138]. This situation reduced the efficacy of insecticide applications in the region, contributing to an increase in dengue cases during the epidemic [139]. This phenomenon illustrates that insecticide use in agricultural and forestry sectors can significantly impact the effectiveness of vector control strategies in public health [135,138].

A major challenge in the non-health sector is the inadequate enforcement of strict regulations regarding insecticide use, while the health sector typically enforces stringent regulations with clear guidelines on dosage, application frequency, and active ingredient rotation to prevent resistance [140]. In agriculture and forestry, regulatory enforcement is often weak, leading to the improper application of insecticides at incorrect dosages or with excessive frequency. This accelerates the process of natural selection and promotes the development of resistance [140].

Research in West Kalimantan indicated that insecticide application on plantations often did not adhere to recommended standards, with farmers using higher doses than necessary to control crop pests [141]. This not only increased production costs but also accelerated the development of resistance in local mosquito populations, thereby reducing the efficacy of insecticides in health vector control programs [136]. The use of insecticides in the non-health sector has serious implications for the success of vector control programs in Indonesia [47]. The growing prevalence of cross-resistance in agriculture and forestry may diminish the effectiveness of insecticides used to control *A. aegypti* mosquito populations, subsequently increasing the risk of disease transmission, such as dengue [137]. An integrated strategy between the health and non-health sectors is essential to mitigate this adverse effect [46]. This strategy could involve refining regulatory policies and enhancing surveillance of insecticide use in the agricultural and forestry sectors, alongside increasing farmers' understanding of the importance of adhering to recognized insecticide application norms [124]. Additionally, promoting the adoption of environmentally sound pest management practices, such as biological controls or crop rotation, can reduce reliance on synthetic chemical insecticides [46,124].

The use of insecticides outside medical contexts, particularly in agriculture and forestry, has notably contributed to the rise of insecticide resistance in *A. aegypti* mosquitoes across Indonesia [31]. Cross-resistance in this context may undermine the effectiveness of insecticides in public health vector control programs, posing a significant challenge to disease control efforts such as those aimed at dengue [142]. To address these challenges, it is critical to implement strengthened regulatory frameworks, improved oversight mechanisms, and a more sustainable approach to pest management within the agricultural and forestry sectors [143].

Aedes aegypti resistance detection methods

Detection and surveillance of insecticide resistance in *A. aegypti* mosquitoes are essential in addressing mosquito-borne diseases such as DHF, chikungunya, and Zika [87]. A study demonstrated a reduction in mosquito susceptibility to various insecticides, indicating the emergence of resistance [144]. As a result, regular detection and monitoring of resistance are crucial [144]. The primary methodologies employed include biological assays (bioassays) and biochemical-molecular assays, which enable the prompt identification of resistance and contribute to the development of effective control strategies [145]. Timely monitoring facilitates early detection of resistance, enabling rapid intervention and mitigating the spread of resistance [145].

Biological test (bioassay)

The WHO developed a bioassay methodology to detect resistance in disease vector insects, particularly *A. aegypti* mosquitoes [145]. These bioassays can be categorized into two primary types based on the methods employed: dose-dependent and time-dependent [145]. In the dose-dependent bioassay, mosquitoes are exposed to varying concentrations of insecticides to determine the dosage that causes mortality in 50% or 90% of the population (LD_{50} or LD_{90}) [145]. This approach is effective for assessing resistance levels across a broad population, though it may demonstrate reduced specificity and requires a larger sample size of mosquitoes [88]. In contrast, time-dependent bioassays offer greater specificity and sensitivity in detecting resistance compared to dose-dependent methods [74]. This technique involves exposing mosquitoes to a constant insecticide concentration, with exposure time recorded to evaluate mortality rates. The development of this method has facilitated resistance testing by requiring fewer insect samples [146].

Biochemical and molecular tests

In conjunction with bioassays, biochemical and molecular analyses have been employed to identify insecticide resistance [91]. Both approaches offer notable advantages in terms of sensitivity and specificity, and they require fewer samples compared to bioassays [145]. The objective of biochemical evaluations is to identify resistance mechanisms at the enzyme level [91]. To illustrate, biochemical tests can detect elevated activity of detoxifying enzymes, such as esterase, GST, or monooxygenase, which are associated with insecticide resistance [91]. Although various biochemical tests exist to detect specific resistance mechanisms, none currently detect changes in resistance mechanisms involving sodium and gamma-aminobutyric acid (GABA) receptors [147]. Molecular assays serve as complementary tools for identifying resistance at the genetic level [148]. Using molecular methods, such as polymerase chain reaction (PCR), it becomes possible to identify specific organs that have undergone mutations, either within the insecticide receptor or the enzyme responsible for insecticide detoxification [149]. These tests provide valuable insights into the cross-resistance spectrum, resistance maps of insect populations, and which insecticides remain effective [150].

Identifying and monitoring insecticide resistance are critical to ensuring that insecticides used in vector management continue to function effectively [88]. Early resistance surveillance allows for the identification of resistance patterns and the selection of insecticides still effective against specific insects [151]. Given the declining susceptibility to insecticides, resistance detection and monitoring should be integral components of vector control programs [88]. This resistance surveillance is not only a national priority but also a global necessity, although its implementation remains incomplete [152].

Despite insecticide resistance becoming a global issue, the implementation of comprehensive resistance surveillance faces numerous challenges [153]. For instance, malaria vectors have developed resistance to all currently available insecticides [154], highlighting the urgent need for improved detection and monitoring. Addressing these challenges requires international collaboration and capacity building to perform resistance testing across regions, utilizing bioassays and biochemical-molecular methods to detect resistance in *A. aegypti*. This approach is a crucial step in combating insecticide resistance [87]. By employing appropriate methodologies, essential data can be gathered to develop effective control strategies, ensuring the long-term success of vector control efforts and enabling early detection and mitigation of insecticide resistance before it becomes a major public health threat [91].

Potential of Indonesia's local plants as biolarvicides

Indonesia, with its rich biodiversity, is home to numerous indigenous plants that offer potential as natural biolarvicides for controlling *A. aegypti* mosquito populations [155]. These mosquitoes are vectors of serious diseases, including DHF, chikungunya, and Zika [91]. The use of local plants as biolarvicides presents an environmentally friendly alternative to synthetic chemical insecticides, which often contribute to the development of mosquito resistance [91]. Several indigenous plant species in Indonesia have been recognized for their larvicidal properties and have also demonstrated anti-inflammatory, antibacterial, anti-anxiety, antioxidant, and anti-nephric effects [151]. This discussion explores the potential of various indigenous plants in Indonesia, drawing upon findings from previous research, including laboratory analyses and the identification of bioactive compounds within these species [91].

The larvicidal activity of various Indonesian plants against *A. aegypti* larvae, the primary vector of dengue fever, varies significantly, as indicated by the LC_{50} and LC_{90}/LC_{95} values [156]. For example, *Chlorella* sp. demonstrated moderate larvicidal potential, with an LC_{50} of 132.76 ppm and an LC_{90} of 547.19 ppm [157]. In contrast, *Sonneratia alba* had lower efficacy, with an LC_{50} of 1,265 ppm, though the absence of LC_{90} data prevents a direct comparison with other plants that have complete records [158].

Syzygium aromaticum demonstrated a low LC_{50} value of 0.005%, indicating potent larvicidal potential [159]. This aligns with the presence of eugenol in the leaves, a compound known for its antimicrobial and insecticidal properties [159]. Eugenol, a significant component of clove oil, has shown strong insecticidal activity, with low concentrations already effective in causing larval mortality [156]. Similarly, *Tectona grandis* demonstrated promising larvicidal potential against *A. aegypti* mosquitoes [219]. Teak wood extract, containing the compound 2-methyl anthraquinone, demonstrated effectiveness as a larvicide, with an LC_{50} of 7.99 µg/mL and an LC_{90} of 11.87 µg/mL, indicating 50% and 90% larval mortality within 48 hours at these concentrations [156]. However, the direct application of teak wood powder was less effective, with an LC_{50} of 849.30 µg/mL and an LC_{90} of 1,051.10 µg/mL, requiring significantly higher concentrations to achieve comparable mortality rates [160]. Summary of the larvicidal potential of various Indonesian plants against *A. aegypti* is presented in **Table 3**.

Pinus merkusii demonstrated notable larvicidal activity, with an LC_{50} of 68.4 ppm and an LC_{90} of 125.7 ppm [179], although it was less effective than *S. aromaticum* [159]. This suggests that plants containing similar active compounds, such as flavonoids and saponins, do not always show uniform efficacy. Variations in the concentration of these compounds or the presence of additional synergistic substances may contribute to these differences in effectiveness [180].

The results of several studies also indicated that the solvent used in extraction could influence the outcomes. For instance, *Lavandula angustifolia* extracted with ethanol showed an LC_{50} of 87 ppm [175], demonstrating better effectiveness compared to other plants extracted with solvents such as water or methanol (**Table 3**). Overall, an analysis of select findings revealed that various plant species held potential as larvicides. However, the efficacy of these species was significantly influenced by factors such as the specific plant species, the plant parts utilized, the solvent used, and the concentration of active compounds. Further research is necessary to determine the optimal formulation and the most effective application techniques for controlling *A. aegypti* larvae using natural products derived from these botanical sources.

Despite promising laboratory findings, scaling up plant-based biolarvicides for large-scale mosquito control presents several challenges [181]. Ensuring a stable supply of raw plant materials requires dedicated cultivation or sustainable harvesting practices [182]. Standardizing extraction methods and active compound concentrations is essential to maintain consistent efficacy, as variations in solvent types, plant parts, and environmental factors can affect larvicidal potency [183]. Additionally, cost-effectiveness must be assessed, as higher production costs may hinder widespread adoption despite the potential for reduced environmental impact and resistance risks [17].

Field trials evaluating the efficacy and stability of plant-based biolarvicides under natural conditions remain limited [184]. Environmental factors such as UV degradation, biodegradation, and organic matter in breeding sites may influence their effectiveness [185]. Optimizing formulations with UV stabilizers or slow-release mechanisms could enhance field applicability [186]. Integrating plant-based biolarvicides into vector control strategies, such as integrated vector management, may improve effectiveness while reducing reliance on chemical insecticides [187]. Further research is needed on large-scale production, formulation standardization, cost analysis, and field efficacy to assess the feasibility of incorporating Indonesian plant-based biolarvicides into national mosquito control programs [188]. Multidisciplinary collaboration among botanists, entomologists, chemists, and public health experts is essential to address these challenges and optimize plant-based biolarvicides as sustainable alternatives to chemical insecticides [189].

Table 3. Larvicidal potential of various Indonesian plants against *Aedes aegypti*

Plant	Parts	Solvent	Active compounds	LC_{50}	LC_{90}/LC_{95}
Chlorella sp. [157]	Microalgae	Chloroform Methanol	Hexadecanoic acid, oleic acid, and sitosterol	132.76 ppm 523.02 ppm	547.19 ppm 5,683.1 ppm
Citrus sinensis [161]	Skin	Fresh extracts	Tanin and flavonoid	1.15%	2.45%
Citrus amblycarpa [162]	Skin	Aquades	-	0.29%	1.07%*
Teak wood [160]	Trunk	Ethanol: the most awning	2-metilantrakuinon	7.99 µg/mL	11.87 µg/mL
Citrus reticulata [163]	Leaf	n-Hexane	Flavonoid, saponin, steroid, and terpenoid	-	4,810 ppm

Plant	Parts	Solvent	Active compounds	LC$_{50}$	LC$_{90}$/LC$_{95}$
Pinus merkusii [164]	Tree bark	Ethanol	Alkaloids, flavonoids, saponins, tannins, and terpenoids	68.4 ppm	125.7 ppm
Citrus mitis, Citrus aurantifolia, and *Citrus maxima* [165]	Leaf	Methanol	Flavonoid, saponin, steroid, and terpenoid	1,547 ppm 2,197 ppm 2,938 ppm	3,328 ppm 3,660 ppm 6,369 ppm
Leuchaena leucocephala [166]	Leaf	Ethanol Methanol n-Hexane	Alkaloid, saponin, tannin, and flavonoids	1.07% 1.03% 0.30%	5.60% 1.62% 0.58%
Papaya sp. [167]	Leaf	Aquades	Alkaloids, flavonoid, saponin, steroid, and tannin	10.60%	18.3%
Vitex cofassus Reinw. [168]	Fruit	Methanol	-	0.51 µg/mL	1,921 µg/mL
Citrus aurantifolia [169]	Leaf	Stew	Phenolics, scopoletin, flavonoids, and limonin	-	6.60%
Euphorbia tirucalli L. [170]	Stem	Ethanol	Flavonoid, tannin, and steroid	171.48 ppm	2,363.9 ppm
Jasminum sambac and *Stenochlaena palustris* [171]	Flowers	Ethanol	-	0.49% 0.53%	0.63% 0.93%
Averrhoa bilimbi [172]	Fruit	Ethanol	Saponins, tannins, and terpenoids	977 ppm	1,380 ppm
Allium sativum L. [173]	Fruit	Aquades	-	0.24%	-
Melaleuca leucadendra [174]	Leaf	Ethanol	-	3.76%	6.59%
Lavandula angustifolia [175]	Leaf	Ethanol	-	87 ppm	-
Citrus aurantiifolia and *Alpinia galanga* [176]	Leaf rhizome	Ethanol	-	650 ppm 30 ppm	1,100 ppm 90 ppm
Artocarpus altilis [177]	Leaf and flower combination	Ethanol	-	1,871 ppm 2,531 ppm 903 ppm	-
Mangifera casturi [178]	Leaf	Methanol	-	241 ppm	1,964 ppm
Syzigium aromaticum [159]	Leaf	Distillation	Eugenol acetate, methyl eugenol, b-caryophyllene, methyl eugenol, saponins, flavonoids, and larvicidal tannins	0.005%	-
Sonneratia alba [158]	Root	Methanol	Metil 2-hidroksi-eikosanot; 4H-1-benzopiran-4-on, 3,5-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy	1,265 ppm	-

LC: lethal concentration

*LC$_{95}$ only; LC$_{90}$ value not determined or not available

Opportunities, challenges, and recommendations

Utilizing plants as biolarvicides in Indonesia to control dengue fever presents both opportunities and challenges [180]. One significant advantage is the natural and environmentally friendly nature of plant-based larvicides [190]. In contrast to synthetic insecticides, which may pose considerable risks to human health and ecological balance, plant-based solutions offer a safer alternative [17]. Indonesia's rich biodiversity provides a variety of plant species that have demonstrated larvicidal efficacy [188]. For example, *Nyctanthes arbor-tristis* (srigading) and *Centella asiatica* (brotowali) have been studied for their larvicidal properties, making them accessible for widespread use [191].

Another benefit is the local availability of these plant species, which reduces the reliance on imported materials and enhances accessibility for resource-constrained communities [190].

Moreover, plant-derived larvicides can offer economic advantages compared to synthetic alternatives, particularly for populations with limited financial resources [190]. However, several challenges exist in using plants as biolarvicides [192]. A major challenge is the variability in efficacy [193]. For instance, a study on plants from the Asteraceae family found that only 47.05% of the reviewed studies indicated potential as *A. aegypti* larvicides, suggesting low to moderate efficacy [194]. This variability underscores the need for further research to standardize the extraction and preparation of plant extracts, ensuring consistent effectiveness [195].

Standardizing plant-based larvicides is challenging due to variations in plant quality and extraction methods. Scaling up production to meet the demands during dengue outbreaks requires substantial investment and a tailored regulatory framework [180]. A comprehensive framework should ensure the safety and effectiveness of plant-based larvicides, include proper registration and validation procedures, and emphasize public education on their benefits and correct usage to enhance the role of these solutions in controlling dengue fever [151]. Raising public awareness about the use of plant-based larvicides is essential for promoting widespread acceptance and utilization [190]. While utilizing plants as biolarvicides in Indonesia presents a promising approach to controlling dengue fever, several challenges must be addressed to realize the full potential. These challenges include variability in efficacy, the need for standardization, scalability issues, regulatory hurdles, and public awareness. Overcoming these barriers enables Indonesia to effectively employ herbal larvicides in the battle against dengue fever. Recommendations for overcoming these challenges are outlined in **Table 4**.

Table 4. Strategies to address challenges in the development of Indonesian plant-based biolarvicides

Recommendation	Key action	Expected outcome
Policy support and regulatory framework	• Develop clear regulatory guidelines for the production, evaluation, and commercialization of plant-based biolarvicides. • Implement policies for registration and certification based on standardized efficacy and safety assessments. • Harmonize regulatory frameworks with WHO standards to ensure compliance and effectiveness.	• Enhance standardization and safety assurance to ensure consistent efficacy and quality. • Facilitate broader acceptance and streamline regulatory approval processes.
Increased funding for research and development	• Obtain funding from governmental and private sectors to support research on extraction methods, bioactive compounds, and field trials. • Develop research grant programs for universities and research institutions to advance biolarvicide development. • Implement tax incentives and subsidies to encourage private sector investment in plant-based biolarvicides.	• Expedite research and development to advance biolarvicide efficacy and application. • Strengthen innovation and expand production capacity for large-scale implementation.
Interdisciplinary collaboration	• Foster collaboration among botanists, entomologists, chemists, public health experts, and policymakers to enhance interdisciplinary research. • Establish a national task force to integrate expertise and coordinate efforts in biolarvicide development. • Strengthen partnerships with international organizations to support knowledge exchange and capacity building.	• Integrated strategies for formulation, production, and regulatory compliance. • Strengthened technical expertise and collaborative resource utilization.

Implementing these recommendations enables Indonesia to utilize its biodiversity for developing sustainable plant-based biolarvicides while addressing challenges in standardization, regulatory approval, and large-scale application. Strengthening interdisciplinary collaboration and securing sufficient funding are essential for overcoming existing barriers and facilitating the integration of plant-based larvicides into national dengue control programs.

Conclusion

The rising resistance of *A. aegypti* to chemical insecticides poses a significant challenge in managing dengue fever in Indonesia. Resistance to insecticides such as permethrin, malathion, and temephos has been noted, especially in urban areas, highlighting the need for alternative vector control strategies. Local plants offer a promising solution as environmentally friendly biocides. Species like *S. aromaticum*, *T. grandis*, *P. merkusii*, *L. angustifolia*, and several *Citrus* types have shown larvicidal potential, influenced by bioactive compounds such as eugenol, flavonoids, and terpenoids. However, challenges persist, including variability in efficacy due to plant parts used, extraction methods, and compound concentrations. Standardization, scalability, and regulatory frameworks are essential for the widespread adoption of plant-based larvicides. Key strategies to address these challenges include policy reforms to establish clear regulatory guidelines, increased funding for research on extraction methods and field efficacy, and enhanced interdisciplinary collaboration among botanists, entomologists, chemists, and public health experts. Addressing these factors will optimize Indonesia's biodiversity for sustainable dengue vector control.

Ethics approval

Not required.

Acknowledgments

Acknowledgment is extended to the Indonesian Endowment Fund for Education (LPDP) and The Center for Education Financial Services (PUSLAPDIK) for their financial support for the Doctoral Program, which facilitated the funding of this research.

Competing interests

The authors declare that there are no conflicts of interest.

Funding

This research was funded by The Center for Education Financial Services (PUSLAPDIK), Higher Education Financing Center (BPPT) through the Indonesian Endowment Fund for Education (LPDP) with the Indonesian Educational Scholarship (BPI) (Grant number: 202101121173).

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tool and methodology of which AI-based language model, ChatGPT, was employed in the language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

How to cite

Kasman K, Ishak H, Alam G, *et al*. Resistance status of *Aedes* mosquitoes as dengue vectors and the potential of plant larvicides from Indonesia for biological control: A narrative review. Narra J 2025; 5 (1): e1819 - http://doi.org/10.52225/narra.v5i1.1819.

References

1. Liu Y, Wang M, Yu N, *et al*. Trends and insights in dengue virus research globally: A bibliometric analysis (1995–2023). J Transl Med 2024;22(1):818.
2. World Health Organization. Dengue and severe dengue. WHO fact sheet. Geneva: World Health Organization; 2021.

3. Souza-Neto JA, Powell JR, Bonizzoni M. *Aedes aegypti* vector competence studies: A review. Infect Genet Evol 2019;67:191-209.
4. Arsin AA. Epidemiologi demam berdarah dengue (DBD) di Indonesia. Vol. 24. Makassar: Masagena Press; 2013.
5. Mamenun, Koesmaryono Y, Sopaheluwakan A, *et al.* Spatiotemporal characterization of dengue incidence and its correlation to climate parameters in Indonesia. Insects 2024;15(5):366.
6. Erwin ASN, Noor NN, Wahiduddin, *et al.* Risk factors dengue fever in an endemic area in Sikka, Indonesia; A case-control study. Natl J Community Med 2024;15(8):676-684.
7. Ratnasari A, Jabal A ahman, Rahma N, *et al.* The ecology of *Aedes aegypti* and *Aedes albopictus* larvae habitat in coastal areas of South Sulawesi, Indonesia. Biodiversitas J Biol Divers. 2020 Sep 18;21(10):4648-4654.
8. Kementerian Kesehatan Republik Indonesia. Infografis dengue (DBD) tahun 2023. Jakarta: Kementerian Kesehatan Republik Indonesia; 2023.
9. Wilson AL, Courtenay O, Kelly-Hope LA, *et al.* The importance of vector control for the control and elimination of vector-borne diseases. PLoS Negl Trop Dis 2020;14(1):e0007831.
10. Putra RE, Ahmad I, Prasetyo DB, *et al.* Detection of insecticide resistance in the larvae of some *Aedes aegypti* (Diptera: Culicidae) strains from Java, Indonesia to temephos, malathion and permethrin. Int J Mosq Res 2016;3(3):2-28.
11. Hamid PH, Prastowo J, Ghiffari A, *et al.* *Aedes aegypti* resistance development to commonly used insecticides in Jakarta, Indonesia. PLoS One 2017;12(12):e0189680.
12. Amelia-Yap ZH, Chen CD, Sofian-Azirun M, Low VL. Pyrethroid resistance in the dengue vector *Aedes aegypti* in Southeast Asia: Present situation and prospects for management. Parasit Vectors 2018;11(1):332.
13. Ahmed M, Nath NS, Hugo LE, *et al.* Rapid detection of kdr mutation F1534C in *Aedes aegypti* using recombinase polymerase amplification and lateral flow dipsticks. Pestic Biochem Physiol 2022;187:105209.
14. Coleman M, Hemingway J, Gleave KA, *et al.* Developing global maps of insecticide resistance risk to improve vector control. Malar J 2017;16(1):86.
15. Silalahi CN, Tu WC, Chang NT, *et al.* Insecticide resistance profiles and synergism of field *Aedes aegypti* from Indonesia. PLoS Negl Trop Dis 2022;16(6):e0010501.
16. da Silva Sá GC, Bezerra PVV, da Silva MFA, *et al.* Arbovirus vectors insects: Are botanical insecticides an alternative for its management?. J Pest Sci 2023;96(1):1-20.
17. Şengül Demirak MŞ, Canpolat E. Plant-based bioinsecticides for mosquito control: Impact on insecticide resistance and disease transmission. Insects 2022;13(2):162.
18. Ridha MR, Mahdi N, Praristiya MRS, Setiawan D. Biolarvicide and inhibit egg hatching from Spondias dulcis leaf extract against *Aedes aegypti* (Diptera: Culicidae). AIP Conf Proc 2024;3095(1):020007.
19. Ridha MR, Marlinae L, Zubaidah T, *et al.* Control methods for invasive mosquitoes of *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) in Indonesia. Vet World 2023;16(9):1952-1963.
20. Santos VSV, Pereira BB. Properties, toxicity and current applications of the biolarvicide spinosad. J Toxicol Environ Health B Crit Rev 2020;23(1):13-26.
21. Priyono DS, Sofyantoro F, Putri WA, *et al.* A bibliometric analysis of Indonesia biodiversity identification through DNA barcoding research from 2004–2021. Nat Life Sci Commun 2023;22(1):e2023006.
22. Afrianto WF, Putra RP, Aini YS. Overview of the ethnobotany on the use of plants as potential botanical pesticides in Indonesia. J Biol Trop 2022;22(1):220-243.
23. Dua VK, Pandey AC, Raghavendra K, *et al.* Larvicidal activity of neem oil (*Azadirachta indica*) formulation against mosquitoes. Malar J 2009;8(1):124.
24. Perera SD, Jayawardena UA, Jayasinghe CD. Potential use of *Euphorbia hirta* for dengue: A systematic review of scientific evidence. J Trop Med 2018;2018(1):2048530.
25. Anees AM. Larvicidal activity of *Ocimum sanctum* Linn. (Labiatae) against *Aedes aegypti* (L.) and *Culex quinquefasciatus* (Say). Parasitol Res 2008;103(6):1451-1453.
26. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, *et al.* Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv 2015;33(8):1582-1614.
27. Moyes CL, Vontas J, Martins AJ, *et al.* Contemporary status of insecticide resistance in the major *Aedes* vectors of arboviruses infecting humans. PLoS Negl Trop Dis 2017;11(7):e0005625.
28. Parker-Crockett C, Lloyd A, Ramirez D, *et al.* Impacts of differential mosquito control treatment regimens on insecticide susceptibility status of *Aedes aegypti* (Diptera: Culicidae). SN Appl Sci 2022;4(9):249.

29. Hamid PH, Ninditya VI, Prastowo J, *et al*. Current status of *Aedes aegypti* insecticide resistance development from Banjarmasin, Kalimantan, Indonesia. Biomed Res Int 2018;2018:1-7.
30. Kampango A, Hocke EF, Hansson H, *et al*. High DDT resistance without apparent association to kdr and Glutathione-S-transferase (GST) gene mutations in *Aedes aegypti* population at hotel compounds in Zanzibar. PLoS Negl Trop Dis 2022;16(5):e0010355.
31. Sayono S, Nurullita U, Handoyo W, *et al*. Bioassay and molecular detection of insecticides resistance of *Aedes aegypti*, vector of dengue in Central Java Province, Indonesia. Biodiversitas J Biol Divers 2023;24(1):300-307.
32. Porretta D, Mastrantonio V, Lucchesi V, *et al*. Historical samples reveal a combined role of agriculture and public-health applications in vector resistance to insecticides. Pest Manag Sci 2022;78(4):1567-1572.
33. Sucipto CD, Kuswandi K, Siswanto B. Uji resisten insektisida malathion terhadap nyamuk *Aedes aegypti* di Kota Tangerang. J Medikes 2015;2(1):1-12.
34. Mantolu Y, Kustiati K, Ambarningrum TB, *et al*. Status dan perkembangan resistensi *Aedes aegypti* (Linnaeus) (Diptera: Culicidae) strain Bandung, Bogor, Makassar, Palu, dan VCRU terhadap insektisida permetrin dengan seleksi lima generasi. J Entomol Indones 2016;13(1):1-8.
35. Amelia-Yap ZH. Pyrethroids use: Threats on metabolic-mediated resistance mechanisms in the primary dengue vector *Aedes aegypti* (Diptera: Culicidae). J Med Entomol 2019;56(3):811-816.
36. Brengues C, Hawkes NJ, Chandre F, *et al*. Pyrethroid and DDT cross-resistance in *Aedes aegypti* is correlated with novel mutations in the voltage-gated sodium channel gene. Med Vet Entomol 2003;17(1):87-94.
37. Ahmad I, Astari S, Tan M. Resistance of *Aedes aegypti* (Diptera: Culicidae) in 2006 to pyrethroid insecticides in Indonesia and its association with oxidase and esterase levels. Pakistan J Biol Sci 2007;10(20):3688-3692.
38. Purwanti OS, Sudaryanto A, Hartanto TD, *et al*. Dengue hemorrhagic fever incidence trend of the 2010-2016 period in Indonesia. Ann Trop Med Public Health 2019;22(11):294-300.
39. Silalahi CN, Tu WC, Chang NT, *et al*. Insecticide resistance profiles and synergism of field *Aedes aegypti* from Indonesia. PLoS Negl Trop Dis 2022;16(6):e0010501.
40. Wuliandari J, Lee S, White V, *et al*. Association between three mutations, F1565C, V1023G and S996P, in the voltage-sensitive sodium channel gene and knockdown resistance in *Aedes aegypti* from Yogyakarta, Indonesia. Insects 2015;6(3):658-685.
41. Sayono S, Hidayati APN, Fahri S, *et al*. Distribution of voltage-gated sodium channel (Nav) alleles among the *Aedes aegypti* populations in Central Java Province and its association with resistance to pyrethroid insecticides. PLoS One 2016;11(3):e0150577.
42. Hamid PH, Prastowo J, Widyasari A, *et al*. Knockdown resistance (kdr) of the voltage-gated sodium channel gene of *Aedes aegypti* population in Denpasar, Bali, Indonesia. Parasit Vectors 2017;10(1):283.
43. Ishak H, Ponno S. Resistance status in *Aedes aegypti* strain from North Toraja, Indonesia to malathion and temephos insecticides. Indian J Public Health Res Dev 2018;9(12):1345.
44. Hasmiwati H, Rusjdi SR, Nofita E. Detection of Ace-1 gene with insecticides resistance in *Aedes aegypti* populations from DHF-endemic areas in Padang, Indonesia. Biodiversitas J Biol Divers 2018;19(1):31-36.
45. Triana D, Umniyati SR, Mulyaningsih B. Resistance status of *Aedes aegypti* to malathion and cypermethrin in Bengkulu city, Indonesia. Southeast Asian J Trop Med Public Health 2019;50(3):461-468.
46. Haziqah-Rashid A, Chen CD, Lau KW, *et al*. Monitoring insecticide resistance profiles of *Aedes aegypti* (Diptera: Culicidae) in the Sunda Islands of Indonesia based on diagnostic doses of larvicides. J Med Entomol 2019;56(2):514-518.
47. Triana D. Entomological parameters and characterization of insecticide resistance in dengue vector *Aedes aegypti* larvae from Bengkulu City, Indonesia. Malaysian J Public Health Med 2021;21(1):96-102.
48. Lesmana SD, Maryanti E, Susanty E, *et al*. Organophosphate resistance in *Aedes aegypti*: Study from dengue hemorrhagic fever endemic subdistrict in Riau, Indonesia. Rep Biochem Mol Biol 2022;10(4):589-596.
49. Silalahi CN, Yasin A, Chen ME, *et al*. Behavioral responses and life history traits of Taiwanese and Indonesian populations of *Aedes aegypti* surviving deltamethrin–clothianidin treatment. Parasit Vectors 2024;17(1):117.
50. Mulyatno KC, Yamanaka A, Ngadino, *et al*. Resistance of *Aedes aegypti* (L.) larvae to temephos in Surabaya, Indonesia. Southeast Asian J Trop Med Public Health 2012;43(1):29-33.
51. Widjanarko B, Martini M, Hestiningsih R. Resistance status of *Aedes* sp strain from high land in central java, Indonesia, as an indicator of increasing vector's capacity of dengue hemorrhagic fever. Ann Trop Med Public Health 2017;10(1):71.

52. Mulyaningsih B, Umniyati SR, Satoto TBT, *et al.* Detection of polymorphism on voltage-gated sodium channel gene of Indonesian *Aedes aegypti* associated with resistance to pyrethroids. Indones Biomed J 2018;10(3):250-255.
53. Satoto TBT, Satrisno H, Lazuardi L, *et al.* Insecticide resistance in *Aedes aegypti*: An impact from human urbanization?. PLoS One 2019;14(6):e0218079.
54. Rahayu R, Melta DH. Detection of Ace-1 mutation in temephos-resistant *Aedes aegypti* L. in West Sumatra, Indonesia. Pakistan J Biol Sci 2022;25(9):816-821.
55. Nurweni S, Kusnanto H, Widayani P, *et al.* Mapping and susceptibility of *Aedes aegypti* to alpha-cypermethrin and malathion in Magetan Regency, East Java, Indonesia. J Med Pharm Chem Res 2024;6(10):14851495.
56. Singh S, Mukherjee A, Jaiswal DK, *et al.* Advances and future prospects of pyrethroids: Toxicity and microbial degradation. Sci Total Environ 2022;829:154561.
57. Hołyńska-Iwan I, Szewczyk-Golec K. Pyrethroids: How they affect human and animal health?. Medicina 2020;56(11):582.
58. Fan Y, Scott JG. The F1534C voltage-sensitive sodium channel mutation confers 7- to 16-fold resistance to pyrethroid insecticides in *Aedes aegypti*. Pest Manag Sci 2020;76(6):2251-2259.
59. Schluep SM, Buckner EA. Metabolic resistance in permethrin-resistant Florida *Aedes aegypti* (Diptera: Culicidae). Insects 2021;12(10):866.
60. Ojianwuna CC, Omotayo AI, Enwemiwe VN, *et al.* Pyrethroid susceptibility in *Culex quinquefasciatus* Say. (Diptera: Culicidae) populations from Delta State, Niger-Delta Region, Nigeria. J Med Entomol 2022;59(2):758-763.
61. Ab Hamid N, Mohd Noor SN, Susubi J, *et al.* Semi-field evaluation of the bio-efficacy of two different deltamethrin formulations against *Aedes* species in an outdoor residual spraying study. Heliyon 2020;6(1):e03230.
62. Lees RS, Praulins G, Lissenden N, *et al.* The residual efficacy of SumiShield™ 50WG and K-Othrine® WG250 IRS formulations applied to different building materials against *Anopheles* and *Aedes* mosquitoes. Insects 2022;13(2):112.
63. Caroline F. Malathion. Reform J Pestic 2003;23(4):10-15.
64. Ishak H, Mappau Z, Wahid I. Uji kerentanan *Aedes aegypti* terhadap malathion dan efektivitas 3 jenis insektisida. J Med Nusant 2005;26(5):8-12.
65. Gafur A, Mahrina M, Hardiansyah H. Kerentanan larva *Aedes aegypti* dari Banjarmasin Utara terhadap temefos. Bioscientiae 2006;3(2):73-82.
66. Paeporn P, Komalamisra N, Deesin V, *et al.* Temephos resistance in two forms of *Aedes aegypti* and its significance for the resistance mechanism. Southeast Asian J Trop Med Public Health 2003;34(4):786-792.
67. Saelim V, Brogdon WG, Rojanapremsuk J, *et al.* Bottle and biochemical assays on temephos resistance in *Aedes aegypti* in Thailand. Southeast Asian J Trop Med Public Health 2005;36(2):417-425.
68. Hidajat MC, Dharmana E, Prihatin MT, *et al.* Molecular resistance status of *Aedes aegypti* to the organophosphate and pyrethroid insecticides in Central Sulawesi and East Nusa Tenggara Provinces, Indonesia. Proceedings of the 5th Universitas Ahmad Dahlan Public Health Conference (UPHEC 2019). Paris: Atlantis Press; 2020.
69. Ariati J, Perwitasari D, Marina R, *et al.* Status kerentanan *Aedes aegypti* terhadap insektisida golongan organofosfat dan piretroid di indonesia. J Ekol Kesehat 2019;17(3):135-145.
70. Putra RE, Ahmad I, Prasetyo DB, *et al.* Detection of insecticide resistance in the larvae of some *Aedes aegypti* (Diptera: Culicidae) strains from Java, Indonesia to temephos, malathion and permethrin. Int J Mosq Res 2016;3(3):23-28.
71. Wang L, Fontaine A, Gaborit P, *et al.* Relevance study of vector competence and insecticide resistance in *Aedes aegypti* laboratory lines. bioRxiv 2022:02.12.480187.
72. Wang Y, Wilson AE, Liu N. A new method to address the importance of detoxified enzyme in insecticide resistance – Meta-analysis. Front Physiol 2022;13:818531.
73. van den Berg H, Velayudhan R, Yadav RS. Management of insecticides for use in disease vector control: Lessons from six countries in Asia and the Middle East. PLoS Negl Trop Dis 2021;15(4):e0009358.
74. Brogdon W. Insecticide resistance and vector control. Emerg Infect Dis 1998;4(4):605-613.
75. Hobbs NP, Weetman D, Hastings IM. Insecticide resistance management strategies for public health control of mosquitoes exhibiting polygenic resistance: A comparison of sequences, rotations, and mixtures. Evol Appl 2023;16(4):936-959.
76. Kaura T, Sylvia Walter N, Kaur U, Sehgal R. Different strategies for mosquito control: Challenges and alternatives. In: Puerta-Guardo H, Manrique-Saide P, editors. Mosquito research - Recent advances in pathogen interactions, immunity, and vector control strategies. London: IntechOpen; 2023.
77. Hemingway J, Ranson H. Insecticide resistance in insect vectors of human disease. Annu Rev Entomol 2000;45(1):371-391.

78. Benelli G, Wilke ABB, Bloomquist JR, *et al.* Overexposing mosquitoes to insecticides under global warming: A public health concern?. Sci Total Environ 2021;762:143069.

79. Gong Y, Li T, Zhang L, *et al.* Permethrin induction of multiple cytochrome P450 genes in insecticide resistant mosquitoes, *Culex quinquefasciatus*. Int J Biol Sci 2013;9(9):863-871.

80. Gan SJ, Leong YQ, Barhanuddin MFH, *et al.* Dengue fever and insecticide resistance in *Aedes* mosquitoes in Southeast Asia: A review. Parasit Vectors 2021;14(1):315.

81. Aminu NR, Kristiana RD, Hartini S, Soetjipto H. Larvicidal potential of Lantana camara as bio larvicidal for *Aedes aegypti* 3rd instar larvae. AIP Conf Proc 2020;2237(1):020015.

82. Saavedra-Rodriguez K, Campbell CL, Lozano S, *et al.* Permethrin resistance in *Aedes aegypti*: Genomic variants that confer knockdown resistance, recovery, and death. PLoS Genet 2021;17(6):e1009606.

83. Chen TY, Smartt CT, Shin D. Permethrin resistance in *Aedes aegypti* affects aspects of vectorial capacity. Insects 2021;12(1):71.

84. Andreazza F, Oliveira EE, Martins GF. Implications of sublethal insecticide exposure and the development of resistance on mosquito physiology, behavior, and pathogen transmission. Insects 2021;12(10):917.

85. Hernandez HM, Martinez FA, Vitek CJ. Insecticide resistance in *Aedes aegypti* varies seasonally and geographically in Texas/Mexico border cities. J Am Mosq Control Assoc 2022;38(1):59-69.

86. Trefry SV, Aldridge RL, Sprague TR, *et al.* Gamma-irradiated female *Aedes aegypti* mosquitoes exhibit greater susceptibility to mayaro virus. Am J Trop Med Hyg 2024;111(2):421-428.

87. Sene NM, Mavridis K, Ndiaye EH, *et al.* Insecticide resistance status and mechanisms in *Aedes aegypti* populations from Senegal. PLoS Negl Trop Dis 2021;15(5):e0009393.

88. Kaura T, Sharma N, Mewara A. Insecticide resistance in vectors of medically important parasitic infections. In: Ranz RER, editor. Insecticides - Impact and benefits of its use for humanity. London: IntechOpen; 2022.

89. Rigby LM, Johnson BJ, Rašić G, *et al.* The presence of knockdown resistance mutations reduces male mating competitiveness in the major arbovirus vector, *Aedes aegypti*. PLoS Negl Trop Dis 2021;15(2):e0009121.

90. Madgwick PG, Kanitz R. What is the value of rotations to insecticide resistance management?. Pest Manag Sci 2024;80(4):1671-1680.

91. Khan S, Uddin M, Rizwan M, *et al.* Mechanism of insecticide resistance in insects/pests. Polish J Environ Stud 2020;29(3):2023-2030.

92. Indirawati SM, Salmah U, Chahaya I, *et al.* Relationship analysis of protection strategy and the number of containers with the existence of *Aedes aegypti* larvae at Tebing Tinggi city in 2022. Int J Community Med Public Health 2023;10(7):2343-2349.

93. Love RR, Sikder JR, Vivero RJ, *et al.* Strong positive selection in *Aedes aegypti* and the rapid evolution of insecticide resistance. Mol Biol Evol 2023;40(4):msad072.

94. Crawford JE, Balcazar D, Redmond S, *et al.* Sequencing 1206 genomes reveals origin and movement of *Aedes aegypti* driving increased dengue risk. bioRxiv 2024:07.23.604830.

95. Naw H, Võ TC, Lê HG, *et al.* Knockdown resistance mutations in the voltage-gated sodium channel of *Aedes aegypti* (Diptera: Culicidae) in Myanmar. Insects 2022;13(4):322.

96. Sankar M, Kumar S. A systematic review on the eco-safe management of mosquitoes with diflubenzuron: An effective growth regulatory agent. Acta Ecol Sin 2023;43(1):11-19.

97. Ablorde A, Ayettey J, Kroidl I, *et al.* Co-occurrence of multiple kdr mutations (F1534C, V1016I, V410L) in *Aedes aegypti* from coastal areas in Ghana and assessment of the role of mosquito coil in causing pyrethroid resistance. Acta Trop 2023;243:106937.

98. Ablorde A, Kroidl I, Wieser A, *et al.* Impact of the exposure of sublethal dose of mosquito coil on the development of insecticide resistance in *Aedes aegypti* (L.) (Diptera: Culicidae). Med Vet Entomol 2024;38(3):341-348.

99. Souza D, Jiménez AV, Sarath G, *et al.* Enhanced metabolism and selection of pyrethroid-resistant western corn rootworms (*Diabrotica virgifera virgifera* LeConte). Pestic Biochem Physiol 2020;164:165-172.

100. Major KM, Weston DP, Lydy MJ, *et al.* The G119S *ace*-1 mutation confers adaptive organophosphate resistance in a nontarget amphipod. Evol Appl 2020;13(4):620-635.

101. Akbar Panjinegara M, Basuki S, Husada D, *et al.* Distribution of voltage gated sodium channel (VGSC) gene mutational variation and acetylcholinesterase-1 (Ace-1) as a marker for insecticide resistance in *Culex* spp. mosquitoes in Surabaya. J Indones Sos Sains 2024;5(2):296-307.

102. Artana IGNB, Artini IGA, Rai IBN, *et al.* Hepatic injury and glutathione s-transferase deletion related to antituberculosis use: An observational study in Balinese population, Indonesia. Open Access Maced J Med Sci 2020;8(B):334-338.

103. Uesugi R, Jouraku A, Sukonthabhirom na Pattalung S, *et al.* Origin, selection, and spread of diamide insecticide resistance allele in field populations of diamondback moth in east and southeast Asia. Pest Manag Sci 2021;77(1):313-324.
104. Shen X, Cao L, Chen J, *et al.* A comprehensive assessment of insecticide resistance mutations in source and immigrant populations of the diamondback moth *Plutella xylostella* (L.). Pest Manag Sci 2023;79(2):569-583.
105. Schmidt TL, van Rooyen AR, Chung J, *et al.* Tracking genetic invasions: Genome-wide single nucleotide polymorphisms reveal the source of pyrethroid-resistant *Aedes aegypti* (yellow fever mosquito) incursions at international ports. Evol Appl 2019;12(6):1136-1146.
106. Yusra K, Lestari YB. Human mobility, sociolinguistic diversity, and social sustainability in rural areas: Insights from Indonesian transmigrant communities. Sustainability 2023;15(4):3615.
107. Namias A, Jobe NB, Paaijmans KP, Huijben S. The need for practical insecticide-resistance guidelines to effectively inform mosquito-borne disease control programs. Elife 2021;10:e65655.
108. Indriani C, Tanamas SK, Khasanah U, *et al.* Impact of randomised *wMel Wolbachia* deployments on notified dengue cases and insecticide fogging for dengue control in Yogyakarta City. Glob Health Action 2023;16(1):2166650.
109. Piovezan-Borges AC, Valente-Neto F, Urbieta GL, *et al.* Global trends in research on the effects of climate change on *Aedes aegypti*: International collaboration has increased, but some critical countries lag behind. Parasit Vectors 2022;15(1):346.
110. Chandra G, Mukherjee D. Effect of climate change on mosquito population and changing pattern of some diseases transmitted by them. In: Sobti RC, editor. Advances in animal experimentation and modeling: Understanding life phenomena. San Diego: Academic Press; 2022.
111. Prasad P, Gupta SK, Mahto KK, *et al.* Influence of climatic factors on the life stages of *Aedes* mosquitoes and vectorial transmission: A review. J Vector Borne Dis 2024;61(2):158-166.
112. Anee HK, Ferdous Z, Khandaker AM, *et al.* Effect of temperature on life cycle and behaviour of *Aedes aegypti* (Diptera: Culicidae). Bangladesh J Zool 2022;49(3):369-379.
113. Hawkins NJ, Bass C, Dixon A, *et al.* The evolutionary origins of pesticide resistance. Biol Rev 2019;94(1):135-155.
114. Díaz-Marín HG, Osuna O, Villavicencio-Pulido G. Modeling the effects of climate change on the population dynamics of mosquitoes that are vectors of infectious diseases. Proyecciones 2023;42(4):1031-1049.
115. Owusu-Asenso CM, Mingle JAA, Weetman D, *et al.* Spatiotemporal distribution and insecticide resistance status of *Aedes aegypti* in Ghana. Parasit Vectors 2022;15(1):61.
116. Novianto D, Hadi UK, Soviana S, *et al.* Comparison of diurnal biting activity, life table, and demographic attributes of *Aedes albopictus* (Asian tiger mosquito) from different urbanized settings in West Java, Indonesia. Acta Trop 2023;241:106771.
117. Yitbarek S, Chen K, Celestin M, McCary M. Urban mosquito distributions are modulated by socioeconomic status and environmental traits in the USA. Ecol Appl 2023;33(5):e2869.
118. Zoh MG, Tutagata J, Fodjo BK, *et al.* Exposure of *Anopheles gambiae* larvae to a sub-lethal dose of an agrochemical mixture induces tolerance to adulticides used in vector control management. Aquat Toxicol 2022;248:106181.
119. Rigby LM, Johnson BJ, Peatey CL, *et al.* The impact of sublethal permethrin exposure on susceptible and resistant genotypes of the urban disease vector *Aedes aegypti*. Pest Manag Sci 2021;77(7):3450-3457.
120. Shroff S, Mir S, Naik B, *et al.* Chemical methods for control of mosquito vector. In: Barik TK, editor. Molecular identification of mosquito vectors and their management. Singapore: Springer Singapore; 2020.
121. David MR, Dantas ES, Maciel-de-Freitas R, *et al.* Influence of larval habitat environmental characteristics on Culicidae immature abundance and body size of adult *Aedes aegypti*. Front Ecol Evol 2021;9:626757.
122. Li Y, Xu J, Zhong D, *et al.* Evidence for multiple-insecticide resistance in urban *Aedes albopictus* populations in southern China. Parasit Vectors 2018;11(1):4.
123. Bennett KL, McMillan WO, Loaiza JR. The genomic signal of local environmental adaptation in *Aedes aegypti* mosquitoes. Evol Appl 2021;14(5):1301-1313.
124. Sudo M, Takahashi D, Andow DA, *et al.* Optimal management strategy of insecticide resistance under various insect life histories: Heterogeneous timing of selection and interpatch dispersal. Evol Appl 2018;11(2):271-283.
125. Mendis BAN, Peiris V, Harshani WAK, *et al.* Fine-scale monitoring of insecticide resistance in *Aedes aegypti* (Diptera: Culicidae) from Sri Lanka and modeling the phenotypic resistance using rational approximation. Parasit Vectors 2024;17(1):18.
126. Parsons GJI, Lees RS, Balaska S, *et al.* A practical insecticide resistance monitoring bioassay for orally ingested dinotefuran in *Anopheles* malaria vectors. Insects 2022;13(4):311.

127. Bharati M, Saha D. Insecticide resistance status and biochemical mechanisms involved in *Aedes* mosquitoes: A scoping review. Asian Pac J Trop Med 2021;14(2):52.
128. Abobakr Y, Al-Hussein FI, Bayoumi AE, *et al*. Organophosphate insecticides resistance in field populations of house flies, *Musca domestica* L.: Levels of resistance and acetylcholinesterase activity. Insects 2022;13(2):192.
129. Burtis JC, Poggi JD, McMillan JR, *et al*. NEVBD pesticide resistance monitoring network: Establishing a centralized network to increase regional capacity for pesticide resistance detection and monitoring. J Med Entomol 2021;58(2):787-797.
130. Yainna S, Nègre N, Silvie PJ, *et al*. Geographic monitoring of insecticide resistance mutations in native and invasive populations of the fall armyworm. Insects 2021;12(5):468.
131. Andika IP, Martono E. Mapping of Indonesia's agricultural insecticide in 2021: Registered products, future research opportunities, and information dissemination. AGRIVITA J Agric Sci 2022;44(2):377-389.
132. Jangir PK, Prasad A. Spatial distribution of insecticide resistance and susceptibility in *Aedes aegypti* and *Aedes albopictus* in India. Int J Trop Insect Sci 2022;42(2):1019-1044.
133. Singh A, Singh A, Singh P, *et al*. Insecticidal activity, toxicity, resistance and metabolism of pyrethroids: A review. Sci Technol Indones 2022;7(2):238-250.
134. Wang Y, Wang X, Brown DJ, *et al*. Insecticide resistance: Status and potential mechanisms in *Aedes aegypti*. Pestic Biochem Physiol 2023;195:105577.
135. Rohaizat Hassan M, Atika Azit N, Mohd Fadzil S, *et al*. Insecticide resistance of dengue vectors in South East Asia: A systematic review. Afr Health Sci 2021;21(3):1124-1140.
136. Mariyono J, Kuntariningsih A, Kompas T. Pesticide use in Indonesian vegetable farming and its determinants. Manag Environ Qual An Int J 2018;29(2):305-323.
137. Silva JJ, Kouam CN, Scott JG. Levels of cross-resistance to pyrethroids conferred by the Vssc knockdown resistance allele 410L+1016I+1534C in *Aedes aegypti*. PLoS Negl Trop Dis 2021;15(7):e0009549.
138. Sofiana L, Rokhmayanti R, Martini M, *et al*. Insecticide resistance of *Aedes aegypti* in Indonesia: A systematic review. Int J Public Health Sci 2023;12(3):950.
139. Ninditya VI, Hamid PH, Nurcahyo RW, *et al*. The sensitivity status of *Aedes aegypti* from South Sumatra against several insecticides. IOP Conf Ser Earth Environ Sci 2022;1001(1):12042.
140. Karunaratne SHPP, Weeraratne TC, Perera MDB, *et al*. Insecticide resistance and, efficacy of space spraying and larviciding in the control of dengue vectors *Aedes aegypti* and *Aedes albopictus* in Sri Lanka. Pestic Biochem Physiol 2013;107(1):98-105.
141. Greenhill M, Walker I, Mendham D, Permadi D. West Kalimantan industrial plantation scheme: Twenty years on. For Trees Livelihoods 2017;26(4):215-228.
142. Bharati M, Saha D. Multiple insecticide resistance mechanisms in primary dengue vector, *Aedes aegypti* (Linn.) from dengue endemic districts of sub-Himalayan West Bengal, India. PLoS One 2018;13(9):e0203207.
143. Xia J, Latchininsky A, Hadi B, Elkahky M. Sustainable plant pest management through optimization and minimization. Front Agr Sci Eng 2022;9(1):161-166.
144. Mavridis K, Ilias A, Papapostolou KM, *et al*. Molecular diagnostics for monitoring insecticide resistance in the western flower thrips *Frankliniella occidentalis*. Pest Manag Sci 2023;79(4):1615-1622.
145. Liu N, Wang Y, Li T. Assays to measure insecticide toxicity and insecticide resistance in mosquitoes. Cold Spring Harb Protoc 2023;2023(7):pdb.top107705.
146. Jensen BM, Althoff RA, Rydberg SE, *et al*. Topical application bioassay to quantify insecticide toxicity for mosquitoes and fruit flies. J Vis Exp 2022;(179):10.3791/63391.
147. Buckingham SD, Ihara M, Sattelle DB, Matsuda K. Mechanisms of action, resistance and toxicity of insecticides targeting GABA receptors. Curr Med Chem 2017;24(27):2935-2945.
148. Yan R, Zhou Q, Xu Z, *et al*. Three sodium channel mutations from *Aedes albopictus* confer resistance to Type I, but not Type II pyrethroids. Insect Biochem Mol Biol 2020;123:103411.
149. Mavridis K, Papapostolou KM, Ilias A, *et al*. Next-generation molecular diagnostics (TaqMan qPCR and ddPCR) for monitoring insecticide resistance in Bemisia tabaci. Pest Manag Sci 2022;78(11):4994-5001.
150. Grossman MK, Oliver SV, Brooke BD, *et al*. Use of alternative bioassays to explore the impact of pyrethroid resistance on LLIN efficacy. Parasit Vectors 2020;13(1):179.
151. Priya SS, Vasantha-Srinivasan P, Altemimi AB, *et al*. Bioactive molecules derived from plants in managing dengue vector *Aedes aegypti* (Linn.). Molecules 2023;28(5):2386.

152. Utami PD. Pengendalian nyamuk *Aedes aegepty* sebagai vektor demam berdarah dengue dengan insektisida malathion dan temephos. Hang Tuah Med J 2020;5(2):43-52.
153. Dusfour I, Vontas J, David JP, *et al.* Management of insecticide resistance in the major *Aedes* vectors of arboviruses: Advances and challenges. PLoS Negl Trop Dis 2019;13(10):e0007615.
154. Mohammed-Awel J, Iboi EA, Gumel AB. Insecticide resistance and malaria control: A genetics-epidemiology modeling approach. Math Biosci 2020;325:108368.
155. Campos-Ruiz JA, Granados-Echegoyen C, Hinojosa-Garro D, *et al. Agave angustifolia* extracts as natural larvicides and growth inhibitors against *Aedes aegypti* and *Culex quinquefasciatus* mosquitoes. Southwest Entomol 2024;49(1):133-154.
156. Hussaini S, Alhassan AB, Panda SM, *et al.* Larvicidal activity of *Ageratum conyzoides* L. extracts on *Anopheles gambiae* complex. GSC Biol Pharm Sci 2018;3(3):001-005.
157. Sigamani S, Chinnasamy R, Dharmaraj RK, *et al.* Larvicidal potency of the extracts from *Chlorella* sp. against *Aedes aegypti*. Biocatal Agric Biotechnol 2020;27:101663.
158. Wijaya MD, Indraningrat AAG, Kirtanayasa IGYA. Phytochemicals and larvicidal activity of *Sonneratia alba* root extracts from Ngurah Rai mangrove forest, Denpasar-Bali. Biol Med Nat Prod Chem 2023;12(2):499-505.
159. Budiman B, Ishak H, Stang S, *et al.* Effectiveness of clove oil (*Syzigium aromaticum*) as biolarvacide of *Aedes aegypti*. Biomed Pharmacol J 2022;15(4):2287-2292.
160. Nawawi DS, Carolina A, Werdiningsih C. Larvicide activity of teak wood powder and its extract to dengue fever mosquito. JITKT 2014;12(2):101-107.
161. Manyullei S, Ishak H, Ekasari R. Perbandingan efektivitas air perasan kulit jeruk manis dan temephos terhadap kematian larva *Aedes aegypti* comparative efficiency of the juice of sweet orange peel and temephos on *Aedes aegypti* larvae efficacy. J MKMI 2015;11(1):23-31.
162. Kasman K, Ishak NI, Octaviana ESL, *et al.* Larvicidal efficacy of *Citrus amblycarpa* peel extract against the larvae of *Aedes albopictus*. Divers Dis Prev Res Integr 2022;2(2):51-59.
163. Ansori ANM, Kusala MKJ, Irawan H, *et al. Citrus reticulata* extract as biocides to control *Aedes aegypti*, the vector of dengue. Biosci Res 2018;15(3):1661-1665.
164. Setiawan S, Koerniasari K, Ngadino N, Sudjarwo SA. Bioinsecticide effect of *Pinus merkusii* tree bark extract on *Aedes aegypti* larvae. J Young Pharm 2017;9(1):127-130.
165. Hamidah H, Adrianto H. Toxicity of *Citrus mitis*, *Citrus aurantifolia*, and *Citrus maxima* leaf extract toward mortality of *Aedes aegypti* larvae (Diptera: Culicidae). KnE Life Sci 2017;3(6):41.
166. Lusiyana N, Citraningrum N, Aqidah F, *et al.* Larvicidal activity of different solvent extracts of *Leucaena leucocephala* againts *Aedes aegypti*. J Entomol Zool Stud 2018;6(3):589-593.
167. Cahyati WH, Asmara W, Umniyati SR, Mulyaningsih B. Biolarvicidal effects of papaya leaves juice against *Aedes aegypti* Linn larvae. J Int Dent Med Res 2019;12(2):780-786.
168. Muslimin L, Burhan A, Khairuddin K, *et al.* Chemical composition and bioactivity of *Vitex cofassus* Reinw. extracts on the larval and pupal stages of *Aedes aegypti*. J Pharm Bioallied Sci 2020;12(1):77.
169. Muniandy PD, Riswari SF, Ruchiatan K. Larvicidal activity of *Citrus aurantifolia* decoction against *Aedes aegypti* larvae. Althea Med J 2020;7(1):35-39.
170. Yusuf Y, Efendi K, Diantasari S. Larvicidal activity test of ethanolic extract of (*Euphorbia tirucalli* Linn) stem on *Aedes aegypti* larvae. Syst Rev Pharm 2020;11(3):388-392.
171. Hidayah N, Suhartono E, Hakim AR, *et al.* Bio-larvicidal effectiveness of *Jasminum sambac* (L.) ait (Oleaceae) and *Stenochlaena palustris* (Blechnaceae) against dengue vector, *Aedes aegypti* (Linn.). Eurasian J 2020;14(2):7205-7210.
172. Rohmah EA, Subekti S, Rudyanto M. Larvicidal activity and histopathological effect of *Averrhoa bilimbi* fruit extract on *Aedes aegypti* from Surabaya, Indonesia. J Parasitol Res 2020;2020(1):1-5.
173. Yearsi SEN, Munawaroh SD. Effectiveness of garlic extract (*Allium sativum* L) as larvicide of *Aedes aegypti*. Insights Public Health J 2021;2(1).
174. Porusia M, Septiyana D. Larvicidal activity of *Melaleuca leucadendra* leaves extract against *Aedes aegypti*. Casp J Environ 2021;19(2):277-285.
175. Komansilan A, Suriani NW, Komansilan R. Toxic test of lavender leaf (*Lavandula angustifolia*) ethanol extract as biolarvicide for *Aedes aegypti* mosquitoes vectors of dengue hemorrhagic fever. Int J Environ Agric Biotechnol 2021;6(6):291-295.
176. Muntasir, Abanit YM, Weraman P, *et al.* Natural larvicide mixed lime leaf extract and *Galangal rhizome* to mortality *Aedes aegypti* larvae. Biocatal Agric Biotechnol 2022;39(1):102274.

177. Nindiastuti R, Wahyuni D, Ma'rufi I. New bioinsecticides from combination extract of leaf and flower of breadfruit (*Artocarpus altilis*) on mortality of *Aedes aegypti* larvae. J Health Sains 2022;3(2):279-288.
178. Mahdi N, Ridha MR, Setiawan D, *et al*. Bio-efficacy of *Mangifera* leaf extracts on mortality of *Aedes aegypti* and inhibition of egg hatching. Vet World 2022;15:1753-1758.
179. Romanello M, Napoli C di, Green C, *et al*. The 2023 report of the Lancet Countdown on health and climate change: The imperative for a health-centred response in a world facing irreversible harms. Lancet 2023;402(10419):2346-2394.
180. Fadana Y, Dinana IA, Srihardyastutie A, *et al*. Screening Indonesian pine (*Pinus merkusii* Jungh. de Vriese) compound as an antibacterial agent: In vitro and in silico study. Trop J Nat Prod Res 2023;7(3):2586-2595.
181. Kumar D, Kumar P, Singh H, Agrawal V. Biocontrol of mosquito vectors through herbal-derived silver nanoparticles: Prospects and challenges. Environ Sci Pollut Res Int 2020;27(21):25987-26024.
182. Onen H, Luzala MM, Kigozi S, *et al*. Mosquito-borne diseases and their control strategies: An overview focused on green synthesized plant-based metallic nanoparticles. Insects 2023;14(3):221.
183. Pavela R, Maggi F, Iannarelli R, *et al*. Plant extracts for developing mosquito larvicides: From laboratory to the field, with insights on the modes of action. Acta Trop 2019;193:236-271.
184. Dutta U, Dey S. Bioassay of larvicidal efficacy of selected plant extracts against mosquito larvae *Anopheles culicifacies* and *Aedes aegypti* L. Bull Pure Appl Sci Zool 2023;42(1):170-189.
185. Oliveira SR de, Caleffe RRT, Conte H. Chemical control of *Aedes aegypti*: A review on effects on the environment and human health. Rev Eletrônica Gestão Educ Tecnol Ambient 2017;21(3):240.
186. de Jesus Santos A, Macêdo NA, de Holanda Cavalcanti SC, *et al*. Larvicidal formulation containing N-tosylindole: A viable alternative to chemical control of *Aedes aegypti*. Colloids Surf B Biointerfaces 2022;213:112380.
187. World Health Organization. Global strategic framework for integrated vector management. Geneva: World Health Organization; 2004.
188. Manuahe C, Semuel M, Adil E, *et al*. Mosquito larvicides of partial and combinations extract of ethnobotanical plant from North Sulawesi, Indonesia. Pakistan J Biol Sci 2022;25(10):911-921.
189. Ernawan B, Sasmita HI, Sadar M, *et al*. Current status and recent achievements of the sterile insect technique program against dengue vector, *Aedes aegypti*, in Indonesia. Atom Indones 2019;45(2):115.
190. Sadino A, Nuari DA, Masturoji DEA, *et al*. Larvicide activity and anti-mosquito activity of several plants in Indonesia against *Aedes aegypti*: Review articles. Bul Farmatera 2023;8(2):26-34.
191. Permana TI, Sasmitasari NID, Susetyarini E, *et al*. Bintaro leaves (*Cerbera manghas*): Toxicity to *Aedes aegypti* instar III larvas. J Kesehat Masy 2022;17(4):509-516.
192. Kaura T, Pervaiz N, Mewara A. Larvicides: Plant oils and Zika control. In: Martin CR, Martin CJH, Preedy VR, Rajendram R, editors. Zika virus impact, diagnosis, control, and models. San Diego: Academic Press; 2021.
193. Asrianto A, Samai S, Sahidin M, *et al*. Literatur review: Plant efficacy as biolarvicide for anopheles mosquito vector control. J Sains Kes 2023;5(2).
194. Matos RLF dos R, Souza NN de, Santos SM dos, *et al*. Larvicidal activity of leaf extract from *Mauritiella armata* (Aceraceae) on *Aedes aegypti* and *Culex quinquefasciatus* (Culicidae). J Agric Sci 2022;14(2):63.
195. Widodo MNPS, Augustina I, Trinovita E, *et al*. Studi literatur: Potensi daya bunuh tanaman keluarga Asteraceae terhadap larva *Aedes aegypti*. J Surya Med 2023;9(2):243-256.