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SUSTAINABLE ALTERNATIVES TO SYNTHETIC INSECTICIDES: EVALUATING PHYTOCHEMICALS AGAINST *AEDES AEGYPTI:* A REVIEW OF EFFICACY AND MECHANISMS

[*1]Tahseen Javaid, [2]Muhammad Hasnain, [3]Muhammed Junaid, [4]Noor ul ain Khan

[*1]Department of Zoology, Wildlife and Fisheries, University of Agriculture Faisalabad, Pakistan
[2]Department of Entomology, University of Agriculture Faisalabad, Pakistan
[2]Department of Entomology, University of Agriculture Faisalabad, Pakistan
[3]Department of Zoology, Govt College Women University, Faisalabad

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Abstract

Aedes aegypti (A. aegypti) mosquitoes are vectors of most lethal diseases such as dengue, chikungunya, yellow fever, Zika, West Nile fever, and many others. So, their control is an important public health concern. Epidemiology is important for understanding the transmission dynamics of diseases caused by arboviruses. It clarifies the role played by environmental, social, and biological factors in the outbreak of arboviral diseases. The study aimed to review all ideas related to vector-borne diseases especially caused by A. aegypti. It focused mainly in searching of necessitating proactive and locally specific approaches to control this vector. This review also aimed highlighting drawbacks of synthetic insecticides and their impact on non target population. We studied several articles related to A. aegypti outbreaks, damage caused by the vector, epidemiological surveillance and predictive modeling that have helped us to report worldwide status and role of A. agypti. Phytochemicals are potential substitutes to synthetic insecticides because of their specificity, low costs, and environmental sustainability. These bioactive plant compounds (phytochemicals) along with their extraction and isolation methods can be used for controlling arbovirus vectors like A. aegypti. The use of phytochemicals against A. aegypti can be proved sustainable, ecofriendly and cost effective. If relevant solvent is used for exraction of phytochemicals to enhace their efficacy.

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Introduction

The mosquitos are prevalent in tropical and subtropical areas and they are vectors of some of the most devastating diseases that affect both the human beings as well as the animals. The major viruses of a variety of diseases such as dengue, chikungunya, yellow fever, Zika and West Nile viruses are mainly carried by *A. aegypti*. It is a very anthropophilic and opportunistic species that allows the transmission of pathogens efficiently and causes the disease outbreaks at the global level. Now it is estimated that there are 3.97 billion individuals at a risk of being infected by *A. aegypti* [1]. Therefore, proper management of this vector has been one of the central objectives in reducing the mosquito borne diseases overall in the world.

The outbreaks caused by the *A. aegypti* are more likely to occur in tropical and subtropical countries, specifically in overcrowded urban and peri-urban centres. The attrction of mosquito towards human blood also contributes immensely to the spread of diseases. In addition to that, there is also climate change, urbanization, globalization, and the growing international travels, led to the further geographical expansion of *A. aegypti* [2]. According to the recent estimates, over half of the world population is vulnerable to dengue infection alone, and about 390 million cases of dengue are reported each year [3]. All these make the process of controlling vectors more difficult and support the need to develop better and more sustainable methods for its control.

The key to control *A. aegypti* has always been chemical insecticides which attack both the adult and the immature stages of the mosquito. The most common examples of these insecticides are organophosphates, pyrethroids, organochlorines, and carbamates whose modes of action are mainly to disrupt neuronal signaling and interfere with regular physiological functions, whereas insect growth regulators influence developmental pathways [4]. Nevertheless, due to the over and inappropriate use of chemical insecticides, severe issues such as environmental contamination, the toxicity of the non-target organism, and the impact on human health have been caused [5, 6, 101]. Moreover, the extensive and ongoing emergence of insecticide resistance within mosquito populations has profoundly undermined the efficacy of conventional insecticides [7].

To address such shortcomings, more focus has been on substituting synthetic insecticides with alternatives that are sustainable and environmentally friendly. Phytochemicals and other plant derivatives have become potential agents to be used in controlling mosquitoes because of the factors including biodegradability, specificity in targeting, affordability, and less adverse environmental effects. Various plants in traditional medicine and human nutrition have bioactive compounds, such as secondary metabolites and essential oils, which disrupt mosquito life stages, including eggs, larvae, pupae and adults. The mosquitocidal action of botanical extracts against the vectors has been reported [8, 9]. Interestingly, Gope and Rawani [10] identified 344 botanical agents having potential mosquitocidal effects, whereas Pushpalatha et al. [11] also made a review of plant-based larvicides.

Phytochemicals have great importance as vectors control agents because of their complicated molecular structures and their variety of mechanisms of action, which minimize the chances of developing resistance in comparison to traditional insecticides [12, 13]. These compounds have larvicidal, ovicidal, pupicidal, and adulticidal effects as they interfere with all developmental stages of mosquitoes, impair the function of the

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nervous system, suppress feeding and reproduction [14, 102]. Moreover, phytochemicals play an essential role in the process of resistance control and contribute to the ability to control vectors in endemic areas [15].

This review thoroughly discusses plant-based extracts, phytochemicals, secondary metabolites and essential oils that have been used in *A. aegypti* control. It pays attention to their insecticidal effectiveness, modes of action, methods of application, and the existing restrictions, with the focus on the possibility of developing effective and environmental friendlier methods of mosquito control.

PLANT SECONDARY METABOLITES

Plants do produce variety of metabolites, which are essential in defense against insect pests and diseases [16]. Phytochemicals comprise of both primary and secondary metabolites but secondary ones are more significant because of their broad spectrum of bioactive abilities that include insecticidal properties [17]. These compounds are usually concentrated in different plant tissues and they are widely used in flavor, fragrance, pharmaceutical and pesticides as biologically active agents [18].

Some of the major classes of plant secondary metabolites that have insecticidal significance are alkaloids, phenolics, terpenes, terpenoids, carotenoids, tocopherols, lipids, and carbohydrates. These compounds are present in various parts of plants (leaves, stems, roots, flowers, and seeds), and are usually accessed as crude extracts or purified metabolites [19]. Many studies have proved that plant extracts have large mosquito controlling properties, such as larvicidal, ovicidal, pupicidal, adulticidal, repellent and growth-regulating. Extraction of plants with fatty acids, glycolipid, aromatic phenols and saponins have been reported to increase insecticidal effects against mosquito vectors [20].

Essential oils (EOs) are volatile compounds that are derived out of aromatic plants and are characterized as a significant form of secondary metabolites. They are readily available and can be extracted by using renewable resources, these oils have selective toxicity with low adverse effects to non-target organisms, and have a limited number of adverse effects [21, 22, 23]. Some experiments have indicated that essential oils and other compounds found in plants interrupt the life cycle of mosquitoes by lowering the egg hatching rate, larval development, and adult survival [24].

The insecticidal effect of plant secondary metabolites is explained by the fact that they are able to disrupt several physiological processes in mosquitoes such as nerve axons, synaptic transmission, respiratory processes, and hormone regulation. These compounds are less prone to cause resistance than the traditional synthetic insecticides due to their complicated molecular structures and unique different modes of action. Plant-derived-secondary-metabolite-based natural insecticides are, as a result, getting a renewed interest as possible components of sustainable strategies in the control of vectors [25, 26]. Up to now, over 2,000 plant species have been documented to secrete metabolites with possible uses in mosquito control strategies [27]. Certain types of secondary metabolites such as ocimenone, rotenone, capillin, quassin, and thymol have been shown to be very effective in ovicidal, larvicidal, and pupicidal effects against mosquito species [28]. Specifically, the family Annonaceae comprises of diverse group of bioactive compounds known as acetogenins that have received significant attention due to their excellent mosquitocidal activity [29].

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In spite of these encouraging results, there are still few practical uses of plant secondary metabolites in large scale vectors control. And additional research should be conducted to determine their effectiveness, safety, stability of formulation and performance in the field. New plant-based secondary metabolites and the development of simple and cost-effective extraction methods that can be potentially scaled to community and household-level is needed. These methods offer safe, environmentally-sustainable and ecologically-effective mosquito control measures in the future [30, 11, 31].

Mechanism of action of phytochemicals against *A. aegypti*:

Generally, the insecticidal effects of the bioactive constituents of phytochemicals are achieved by interacting with a variety of molecular and cellular targets in the vector's mosquitoes, such as membrane-bound receptors, intracellular signaling cascades, structural proteins, ion channel complexes, nucleic acids and other essential cellular components [32]. Phytochemicals target the crucial insect tissues including proteins, genetic material, cell membranes and other cell structures. These compounds interfere with key enzymes required for nerve communication [33] alter receptor activity leading to weak or abnormal responses, and disturb neurotransmitter functions including their production, storage, release, binding, and breakdown. The phytochemicals also interact with metabolites exhibited severe physiological disruptions, as shown in fig. 1 [34]. In these, the key enzyme, AChE (which enhances resistance in mosquitoes to digest organophosphorus and carbamate insecticides), is responsible for terminating nerve impulse transmission through the insect synaptic pathway [35]. Hence, developing novel secondary metabolites to inhibit AChE and other key enzymes of vector mosquitoes may help control vector populations effectively. Phytochemicals and other natural compounds exert their insecticidal effects on insects, often through multiple and complex mechanisms. The mechanism of action of phytochemicals against A. *aegpti* is discussed below.

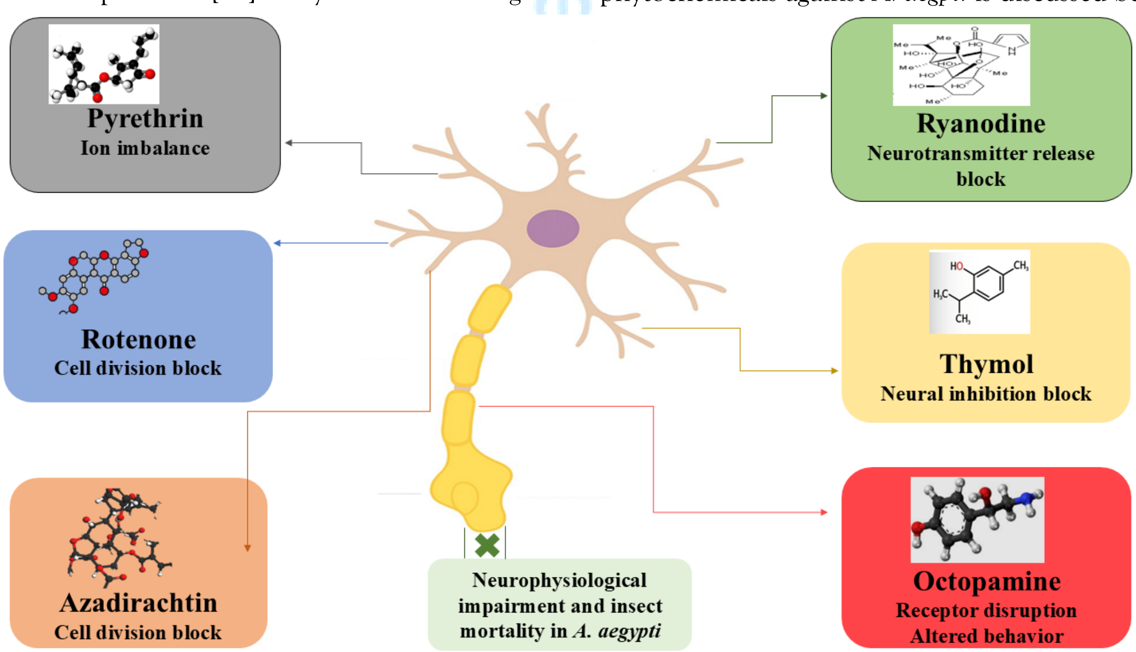

Fig.1 Phytochemicals effects on insects (www.biorender.com)

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Detoxification Enzyme Responses to Phytochemicals in *A. aegypti*

The antioxidant and detoxification enzymes of mosquito vectors are vital in detoxification of reactive oxygen species (ROS) synthesized by the toxic chemicals [36]. Esterase and phosphatase of the mosquito vectors play a key role in several physiological events. Excessive usage of toxic chemicals on mosquito control caused insecticide resistance through sodium channel mutations, activation of detoxification enzymes, and upregulation of key genes and other regulatory components like MicroRNAs (miRNAs) (Al Naggar et al., 2025) [4]. The CYP450s, GSTs, SOD, and esterase gene families are recognized as the foremost four enzymes accountable for the metabolic resistance of the insects [37]. Generally, detoxifying enzymes are involved in digestion, reproduction, juvenile hormone metabolism, neuronal conduction, moulting, and more importantly detoxification of toxic chemicals [38]. Phosphatases are involved in tissue development, cellular differentiation, carbohydrate metabolisms, and synthesis of ATP. Mainly these two major classes of detoxifying enzymes [39] are considered for evaluating the impact of toxic chemicals on physiological or biochemical events of arthropod vectors. Carboxyl-esterases (EC3.1.1.1) are non-specific omnipresent enzymes that are associated to the major "endogenous" functions in insects [40], which hydrolyze a different carboxylic-acid ester. Conventional chemical insecticides, particularly fourth-generation pyrethroids, act on voltage-sensitive sodium channels and disrupt the mosquito nervous system [41]. However, resistance in *A. aegypti* is often associated with the overexpression of detoxifying enzymes such as cytochrome P450s, esterases, and glutathione S-transferases, which metabolize these compounds [42]. In contrast, phytochemicals like essential oils exert their action by inhibiting or downregulating these detoxification pathways, thereby reducing the mosquito's ability to neutralize toxic molecules and enhancing their susceptibility to phytochemical toxicity [43, 103]. Generally, the metabolic pathway of these enzymes was targeted by the chemical pesticides, especially the fourth-generation class of Pyrethroids, which acts on the voltage sensitive sodium channels and blocks the mosquito nervous system [44]. Esterases can also target by sequestering the insecticide through rapid binding and slowly releasing the insecticide metabolites [45]. This latter type of resistance requires the presence of increased quantities of esterase due to the 1:1 stoichiometry of the reaction and decreases the metabolic breakdown time [46]. Plant extracts and their derivatives have been widely reported to decrease the levels of carboxylesterase (α- β-carboxylesterase) level in the *A. aegypti* larva [47]. Besides exhibiting larvicidal activity *Alangium salvifolium*, also substantially reduced the levels of α, β-carboxylesterase as well as superoxide dismutase (SOD) in *A. Aegypti* [48]. Higher rates of enzyme activities, such as SOD and physiological enzymes like esterase, phosphatases are recorded with increasing developmental stages and these are considered responsible for increased pyrethroid resistance [49]. The Mosquito vectors that established resistance to Temephos have been found to possess genes that insensitized ACHE on exposure to pesticides [50]. Insects were also characterized by the over expression of varied forms of detoxifying enzymes (GST, SOD, and esterases). Generally, Cytochrome P450s (CYP450) displayed upregulation when induced by plant secondary metabolites in diverse insect pests especially against the vectors of human diseases and have members which are considered as major

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elements conferring resistance against insecticides (i.e., CYP2, CYP4, and CYP6) [4, 51].

Integrated Stress Responses to Phytochemicals in *A. aegypti*

With the insect midgut being the important site for synthesis of digestive enzymes, plant derived molecules primarily targets the gut epithelium layer (EL) [34]. This might be the significant cause for condensed metabolic rate in addition to a reduced enzyme activity [26]. The peritrophic membrane (pM) gaurds the EL from the surrounding the gut lumen (GL) [52]. Phyto-chemicals are proven to exert a serious impact on the digestive epithelial cells and further decrease the growth rate of arthropods. Panda et al. [53] stated that plant compounds flow into the gastric caeca and the malpighian tubules thereby affecting the midgut epithelium. Previous photomicrographic study on the midgut tissues of the dengue mosquito (Field and laboratory strains of *A. aegypti*) treated with the CVO of *P. betle* displayed severe injuries to the GL and EL [54]. Correspondingly, leaf extracts of *Aristolochia indica* L. (*Aristolochiaceae*) and their derivatives aristolochic acid I and II showed severe damage on the midgut vacuolated gut epithelial columnar cells (epi), GL, and pM [55]. Likewise, methanolic leaf extracts of *P. nigrum* severely affected the midgut cellular organelles of *A. aegypti* at the minimal dosage of 10 ppm [56]. Similarly, several phytochemicals exert insecticidal activity by interfering with the mosquito nervous system. Alkaloids and essential oils are well-known inhibitors of acetylcholinesterase (AChE), the enzyme responsible for breaking down acetylcholine at synaptic junctions [57]. Inhibition of AChE leads to excessive accumulation of acetylcholine, continuous stimulation of neurons, paralysis, and ultimately insect death [58]. In addition, certain terpenoids interact with octopamine receptors, which are insect-specific neuromodulators absent in vertebrates, thereby causing disruption of nerve signaling. These neurotoxic activities cause alkaloids and terpenoids promising selective insecticides with eco-friendly properties to insects [59]. Cellular membranes of *A. aegypti* can be harmed by saponins, phenolics and essential oil constituents. Saponin binds to membrane sterols and destabilizes the lipid bilayer, causing increased membrane permeability, which results in ion, protein and other cellular leakages [60]. In the same case, the phenolic compounds disrupt the membranes by oxidative reactions. Essential oils are known to contain terpenes and phenylpropanoids which can enter the cuticle of the mosquito, injure epidermal cells, and further weaken cell integrity [61]. This mechanism of action is a membrane-destabilizing one that compromises the insect defense mechanism, leading to quick death especially during the larval stages [62]. The other effect of phytochemicals is the production of oxidative stress within the mosquito tissues. Flavonoids, phenolics and terpenoids have the ability to trigger the production of reactive oxygen species (ROS), which increase and overwhelm the antioxidant defence system of the insect [63]. Increased levels of ROS cause oxidative stress to proteins lipids and DNA, resulting in dysfunction and programmed deaths of cell. Through causing oxidative stress, phytochemicals impair larval metabolism, hamper enzymatic activity [64] and lower survival rate, which make them an effective green approach to larvicidal action.

Developmental Toxicity of Phytochemicals in *A. aegypti*

Phytochemicals like glycosides and alkaloids disrupt hormonal control of insect development and in particular, the ecdysone signaling pathway

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which regulates molting and metamorphosis [65]. These compounds inhibit an insect from molting in one stage of development to the next by interfering with the production of ecdysone, its receptor or both. Consequently, larvae might not pupate successfully, pupae can be malformed or the adults emerged can be non-viable. Such a population control effect of phytochemicals is long term, which limits their use as *A. aegypti* populations control agents [66, 67]. Flavonoid, terpenoids and some alkaloids have been reported to eliminate the capacity of mosquitoes to reproduce. These toxins are potential oviposition deterrents, which is capable of altering the oviposition behavior of the female, and it does not allow eggs to be deposited in the breeding locations [68]. Also, flavonoids may damage ovarian development and disrupt vitellogenesis, reducing fecundity, and hatchability [69]. Phytochemicals are essential in mosquito control strategies because they reduce the reproduction in females, thereby decreasing their successive generations [63]. Owing to their lipophilic and volatile nature, some of these essential oils have fumigant activity on the larvae and pupae of mosquitoes. Once the oils are released into the breeding waters, they can be used to block or clog the spiracles (breathing holes) on the insect's cuticle resulting in suffocation [70, 100]. This is especially fatal in larvae and pupae which make heavy reliance on respiratory siphons. Therefore, respiratory toxicity offers a rapid-response and environmentally-safe system to attack aquatic stages of *A. aegypti* [71]. In addition to have direct toxicity, the behavior of mosquito is also modified by phytochemicals in a manner that decreases the spread of diseases. Citronella, eucalyptus, and neem compounds used as essential oils are very powerful repellents [72]. By occupying olfactory receptors, thus avoiding host-seeking behavior. Moreover, some terpenoids interfere with biting, decreasing blood feeding and, as a result, decreasing the capacity to transmit a pathogen carried by vectors [73]. Such behavioral changes provide additional key points about the positive aspects of phytochemicals and make them safe and useful constituents of integrated vectors management. Different doses of Phytochemicals extracted from different plants have shown different toxicity against different life stages of *A. aegypti* in Table 1.

Life Stage-Specific Efficacy of phytochemicals in *A. aegypti*

Egg Stage

Phytochemicals may lead to eggshell damage and abnormal embryonic development at the egg stage because of the limitations of chitinization process [74]. These compounds can also damage the egg exocorionic network, changing the structure of exocorionic cells and tubercles. Moreover, it has also been noted to have negative impact on the respiratory system and intestine of the embryo [75]. Possibly, the ovicidal action of plant extracts may be linked with the permeation of the phytotoxic compounds into the chorion that consequently interferes with embryogenesis [7].

Larval Stage

At the larval stage, phytochemicals disrupt the structure and functionality of the thoracic, abdominal, anal gills, and the external cuticle [76]. They also have the ability of preventing or altering the expression of acetylcholinesterase (AChE) and octopaminergic receptors which result in the disruption of digestive tract epithelium, decreases larval mobility, darkening, and partial extrusion of the midgut [77, 78]. Exposure to these compounds can cause endocrinological imbalances and deficiencies in essential proteins required for larval morphogenesis and development [79]. Specifically,

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treatment with ecboline-abundant fractions has been shown to severely damage midgut cells and the peritrophic matrix, resulting in leakage of endoperitrophic contents and disruption of intestinal homeostasis [80].

Pupal Stage

At the pupal stage, phytochemicals can impair external surfaces and the respiratory system, leading to abnormal swimming patterns, increased cephalothorax size, reduced pupal size, poorly formed wings, and abdominal darkening [81, 82]. Certain plant extracts contain chitin-binding proteins and protease inhibitors, which interact with the chitinous exoskeleton and modulate key processes involved in pupal metamorphosis and nutrition [83]. Such actions highlight the potential of phytochemicals as targeted agents for controlling the pupal stage of *A. aegypti*.

Adult Stage

Phytochemicals can disrupt hormone synthesis in adult mosquitoes, which may result in incomplete ecdysis, with tarsi, legs, wings, and the abdomen sometimes remaining attached to the pupal exoskeleton [84, 85]. Moreover, adult physiology and behavior can be adversely affected through dysfunction of olfactory receptors [86], disruption of feeding activity [87], and impairment of reproductive competence [88]. These effects Overall, phytochemicals including proteins, enzymes, carbohydrates, and phenolic compounds can interfere with key biological functions such as feeding behavior, oviposition, fertility, and lifespan of *A. aegypti* [69]. Extracts from *Acalypha alnifolia* (hexane, benzene, ethyl acetate, acetone, methanol) have demonstrated ovicidal, repellent, and adulticidal activities against *A. aegypti* [28]. Furthermore, disruption of larva-pupa and pupa-adult metamorphosis has been reported, emphasizing the stage-specific mosquitocidal potential of phytochemicals [80]. The use of phytochemicals against different stages of *A. aegypti* have been shown in fig. 2.

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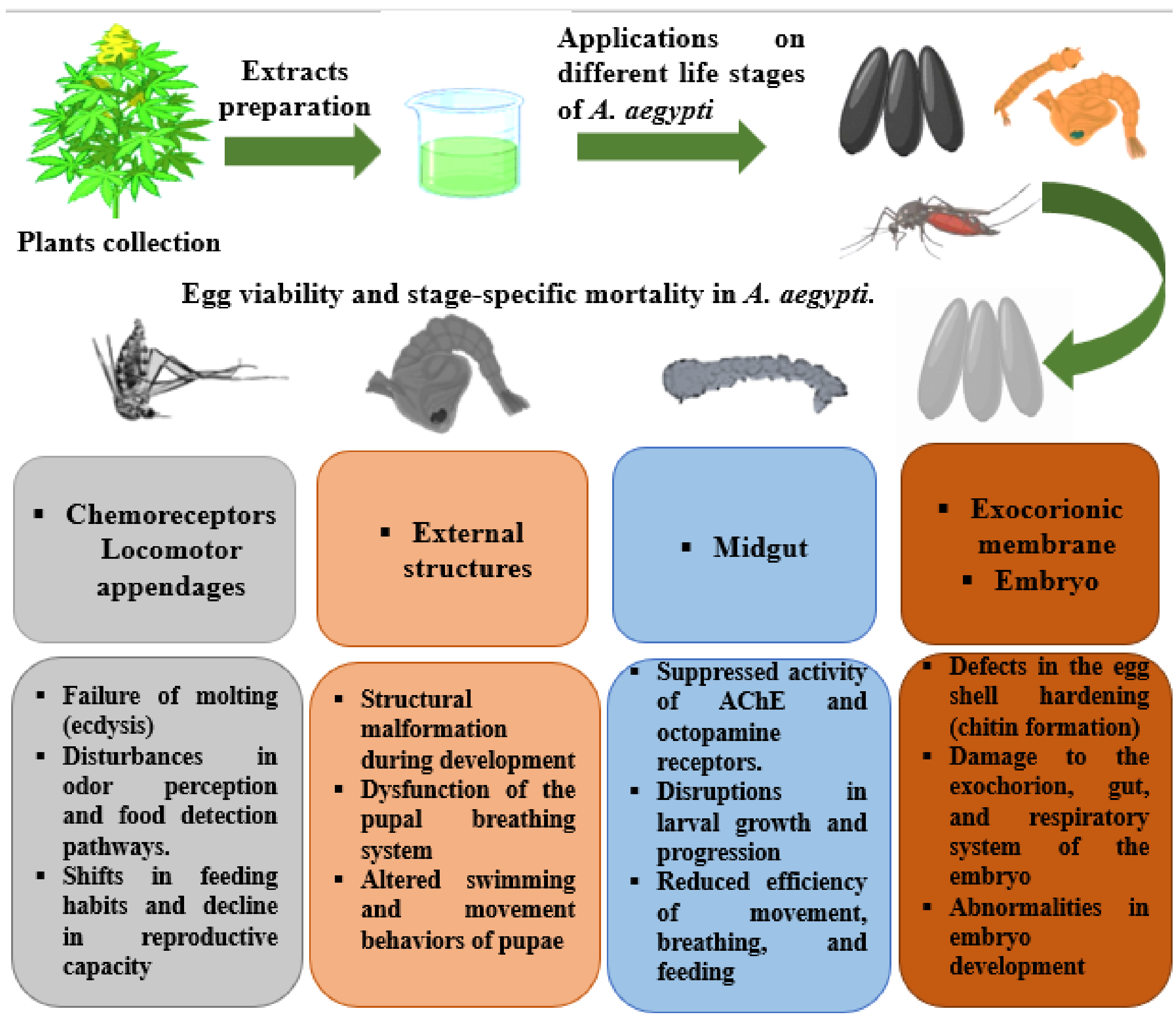

Fig. 2: Mechanisms of mosquito control using plant-based products highlighting ovicidal, larvicidal pupicidal and adult repellent effects against A. aegypti (www.biorender.com).

Table 1: *Phytochemicals for the control of A. aegypti by using various preparation methods of different plants with different doses.*

Source used	Specie name	solvent used	Preparation method	Mode of action	Time and concentration	Results: Mortality(%age)/ Lethality/LC_{50}/LC_{90}	Life stage of *A. aegypti*	References
Weed	*Cyathocline purpurae*	ethanol	Weed extract	Affect on mosquito's nervous system	At 48 h 0.05 mg/mL)	90%	Eggs	[89]
Weed	*C. purpurae*	ethanol	Weed extract	Affect on mosquito's nervous	At 48 h 0.1 (mg/mL)	85%	Eggs	[89]

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				system					
Weed	*C. purpurae*	ethanol	Weed extract	Affect on mosquito's nervous system	At 48 h 0.2 (mg/mL)	78%		Eggs	[89]
Weed	*C. purpurae*	ethanol	Weed extract	Affect on mosquito's nervous system	At 48 h 0.3 (mg/mL)	88%		Eggs	[89]
Weed	*Blumea lacera*	ethanol	Weed extract	disrupting enzymes and respiration.	At 48 h (0.05, mg/mL)	70%		Eggs	[89]
Weed	*B. lacera*	ethanol	Weed extract	disrupting enzymes and respiration	At 48 h 0.1 (mg/mL)	45%		Eggs	[89]
Weed	*B. lacera*	ethanol	Weed extract	disrupting enzymes and respiration	At 48 h 0.2 (mg/mL)	65%		Eggs	[89]
Weed	*B. lacera*	ethanol	Weed extract	disrupting enzymes and respiration	At 48 h 0.3 (mg/mL)	80%		Eggs	[89]
Weed	*Neanotis lancifolia*	ethanol	Weed extract	damage midgut cells and impair larval development.	At 48 h (0.05, mg/mL)	85%		Eggs	[89]
Weed	*N. lancifolia*	ethanol	Weed extract	damage midgut cells and impair larval development.	At 48 h 0.1 (mg/mL)	83%		Eggs	[89]
Weed	*N. lancifolia*	ethanol	Weed extract	damage midgut cells and impair larval development.	At 48 h 0.2 (mg/mL)	78%		Eggs	[89]
Weed	*N. lancifolia*	ethanol	Weed extract	damage midgut cells and impair larval development.	At 48 h 0.3 (mg/mL)	75%		Eggs	[89]

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Weed	*Neanotis montholonii*	ethanol	Weed extract	inhibition of egg hatching.	At 48 h (0.05, mg/mL)	95%	Eggs	[89]
Weed	*N. montholonii*	ethanol	Weed extract	inhibition of egg hatching.	At 48 h 0.1 (mg/mL)	90%	Eggs	[89]
Weed	*N. montholonii*	ethanol	Weed extract	inhibition of egg hatching.	At 48 h 0.2 (mg/mL)	85%	Eggs	[89]
Weed	*N. montholonii*	ethanol	Weed extract	inhibition of egg hatching.	At 48 h 0.3 (mg/mL)	87%	Eggs	[89]
Plant	*Ipomoea cairica*	ethanol	Plant extract	Damages larval digestive system	At 100 ppm, at 24h	40.0 ± 0.0	larvae	[90]
Plant	*I. cairica*	ethanol	Plant extract	Paralyzes and kills larvae quickly	At 100 ppm, at 24h	100.0 ± 0.0	larvae	[90]
Plant	*Piper umbellatum*	ethanol	Plant extract	Weak effect, may slow larval development	At 100 ppm, at 24h	9.2 ± 2.6	larvae	[90]
Plant	*P. umbellatum*	ethanol	Plant extract	Low toxicity, may affect feeding	At 100 ppm, at 24h	9.9 ± 0.2	larvae	[90]
Plant	*Zanthoxylum setulosum*	ethanol	Plant extract	Affects larval movement and energy	At 100 ppm, at 24h	9.8 ± 3.8	larvae	[90]
Plant	*Z. setulosum*	ethanol	Plant extract	Interferes with metabolism	At 100 ppm, at 24h	2.5 ± 5.0	larvae	[90]
Plant	*Erythroxylum macrophyllum*	ethanol	Plant extract	Very mild effect on larvae	At 100ppm, at 24h	1.3 ± 2.6	larvae	[90]
plant	*Rosmarinus officinalis*	ethanol	Plant extract	Affects nervous system, slow action	At 100ppm, at 24h	7.9 ± 3.0	larvae	[90]
Plant	*Argemone mexicana*	ethanol	Plant extract	Disrupts larval nervous control	At 100ppm, at 24h	5.3 ± 0.1	. larvae	[90]

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Plant	*A. mexicana*	ethanol	Plant extract	Slows down larval activity	At 100ppm, at 24h	2.6 ± 3.0	larvae	[90]
Plant	*Bocconia frutescens*	ethanol	Plant extract	Little to no toxic effect	At 100ppm, at 24h	1.3 ± 2.6	larvae	[90]
Plant	*Solanum mammosum*	ethanol	Plant extract	Likely neurotoxic to larvae	At 100ppm, at 24h	5.3 ± 0.1	larvae	[90]
Plant	*Kalanchoe sp.*	ethanol	Plant extract	Damage larval tissues	At 100ppm, at 24h	2.6 ± 3.0	larvae	[90]
Plant	*Citrus latifolia*	n-hexane	Plant extract	Affects larval skin and causes dehydration	At 30mg/ml 12h	10%	adults	[91]
Plant	*C. latifolia*	Ethanol	Plant extract	Disrupts larval nervous system	At 30mg/ml 12h	75-80%	adults	[91]
plant	*C. latifolia*	Chloroformm	Plant extract	Damages internal organs of larvae	At 30mg/ml 12h	75-80%	adults	[91]
Plant	*Citrus sinensis*	Ethanol	Plant extract	Disrupts larvae breathing and movement	At 30mg/ml 12h	≥50%	adults	[91]
Plant	*C. sinensis*	chloroform	Plant extract	Affects nervous system and metabolism	At 30mg/ml 12h	≥50%	adults	[91]
Plant	*C. sinensis*	hexane	Plant extract	Breaks down larval outer layer	At 30mg/ml 12h	80 %	adults	[91]
plant	*Steiractinia aspera*	water	EOs	Disrupts larval enzymes and breathing	At 42.4µg/mL 24h	50%	larvae	[92]
plant	*S. aspera*	water	EOs	Causes paralysis over time	At 42.2µg/mL 48h	50%	larvae	[92]
plant	*Turnera diffusa*	water	EOs	Interferes with larval nervous system	At 70.9 µg/mL 24 h	50%	larvae	[92]

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plant	*T. difusa*	water	EOs	Causes muscle failure and death	At 58.5µg/mL 48h	50%	larvae	[92]
plant	*Calycolpus moritzianus*	water	EOs	Destroys larval digestive tissues	At 55.8 µg/mL 24 h	50%	larvae	[92]
plant	*Piper aduncum*	water	EOs	Causes enzyme imbalance and death	At 61.9µg/mL 24 h	50%	larvae	[92]
plant	*P. aduncum*	water	EOs	Reduces larval oxygen intake	At 57.3µg/mL 48h	50%	larvae	[92]
plant	*Elaphandra quinquenervis*	water	EOs	Damages breathing and feeding system	At 59.8 µg/mL 24 h	50%	larvae	[92]
plant	*E. quinquenervis*	water	EOs	Disrupts nerve control	At 48.8µg/mL 48h	50%	larvae	[92]
Plant	*Hedychium coronarium*	water	aqueous extract	Damages cells in early larval stage	At 0.688% 24h	50%	Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	Strongly disrupts body systems	At 2.439% 24h	90%	Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	Weakens digestion in larvae	At 0.810% 24h	50%	Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	Causes death by gut rupture	At 2.170% 24h	90%	Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	Destroys tissue lining	At 0.952% 24h	50%	Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	Destroys tissue lining	At 0.952% 24h	50%	Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	High dose causes full body shut down	At 2.384% 24h	90%	Larvae	[93]

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Plant	*H. coronarium*	water	aqueous extract	Leads to nervous system failure	At 24h	1.051%	50%		Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	Rapid cell death at high dose	At 24h	2.414%	90%		Larvae	[93]
Plant	*H. coronarium*	water	aqueous extract	Kills pupae by affecting development	At 24h	1.882%	50%		Pupae	[93]

Limitations:

When used as adulticides, plant-derived extracts have been shown to disrupt mosquito growth, respiration, hormone balance, synaptic activity, nerve axons, and overall behavior [94]. However, the adulticidal activity of natural extracts that are primarily used as larvicides against *A. aegypti* remains underexplored, with only limited research available. A review study summarized the toxic effects of essential oils and their isolated compounds on nontarget organisms, showing that toxicological studies on fishes (mainly *Danio rerio*) are the most common, though research on water bugs (*Anisops bouvieri* and *Diplonychus indicus*) and microcrustaceans (*Artemia salina* and *Daphnia magna*) has also been reported. Most studies (76.5%) examining the toxic effects of essential oils on nontarget organisms focused on aquatic environments, particularly aquatic invertebrates (45.1%), whereas only 23.5% addressed terrestrial ecosystems.

The effectiveness of plant-derived insecticides depends on various factors, including insecticide type (active ingredients), formulation, application method, temperature, humidity, wind, insect attraction, respiration inhibition, abrasion of the insect cuticle, insect sensitivity, and biting density [95]. Insecticidal activities of plant extracts are also affected by different plant related factors including the species, geographic difference, part of the plant used, the age of the plant material, the extraction method and the polarity of the solvent [96]. Besides, chemical constituents of the extract, insect vulnerability, and variability of behavior are also important factors that influence the efficacy of bioinsecticides.

Plant-based insecticides possess diverse chemical compositions, multiple modes of action, and significant environmental effects. Though government regulate their use, it is poorly economical to commercialise due to expensive production process and long registration process [97]. In addition, some plants are endangered, geographically limited, or yield insufficient quantities of active compounds, mass isolation and production of commercial insecticides are difficult [98]. The residue duration of biologically prepared pesticides is usually less than synthetic agents, which is why they need to be applied repeatedly in order to be effective in controlling the pests [99]. There is a need to have high-quality products of herbs with sufficient safety information to be used widely. Although bioinsecticides are important in the process of managing vectors, they are not fully commercial and the combination of biological and eco-friendly approaches is yet not a viable practice.

Future Perspectives:

Controlling *A. aegypti* is subjected to a lot of difficulties, such as quick development of resistance to insecticides, scarcity of resources in the endemic areas and ecological complications of urban habitats. The problem of resistance has also

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forced many traditional chemicals to be ineffective and this has necessitated constant surveillance as well as adaptive management measures. Also, innovative interventions, including genetically modified mosquitoes and Wolbachia-based solutions, are rather expensive, which prevents their implementation in low-income nations. Climate change also makes vector control measures more challenging as it increases the geographical spread of *A. aegypti* and changes the patterns of transmission.

Nanoparticle-Based Biopesticides

Bio-pesticides based Nanoparticles have been shown to have great larvicidal and pupicidal activity against *A. aegypti*. The nanoparticles produced by green synthesis of silver, zinc oxide and titanium dioxide interfere with larval midgut epithelium, produce reactive oxygen species, and destroy the cuticle leading to high mortality at low concentrations. They are more efficient than crude phytochemical extracts because of their stability, eco-friendliness, and long residual activity.

Sterility-Inducing Technologies

Technologies are being developed that reduce the levels of sterility in order to control the population of mosquitoes. The sterile insect technique (SIT) involves the release of sterile males using irradiation or chemosterilants where the sterile male mates with the female and the unfertilized egg does not develop into a viable offspring. The novel CRISPR/Cas9 gene drive systems have the capability to propagate sterility or pathogen-resistance genes across wild populations in a short time. In combination with nanoparticle formulations, these measures can be viewed as the innovative methods of sustainable control of *A. aegypti*.

Integrated and Data-Driven Strategies

The application of nanotechnology, sterility-causing strategies, genomics, data science, and the development of the public health infrastructure should be combined in future mosquito control strategies. Sustainable control can further be improved by innovations like drone-based surveillance, AI-based risk prediction models and new next-generation insecticides with novel modes of action. Nevertheless, it will be impossible to achieve success without worldwide cooperation, effective policy, and involvement of communities to eliminate biological and socioeconomic barriers.

Toxicological Considerations

Acute toxicity trials will also be vital in monitoring the changes in phenotypes during short periods of exposure which will be important in future studies. Some of the possible routes of exposure that should be considered in toxicological studies are oral, dermal, and inhalation pathways. The research on pesticides, bio-control methods, and environmental management is still important for successful control of the mosquitoes.

Genetic and Molecular Approaches

Genetic engineering provides hopeful mean for controlling the number of mosquitoes and also restrict the spread of diseases. Integration of these strategies along with ecologically safe biopesticides and integrated management strategies is a comprehensive way to have sustainable *A. aegypti* management. This approach is not only for the security of the people but also an environmental friendliness.

Conclusion

A. aegypti, the major vector of dengue, Zika, West Nile, and chikungunya have been greatly controlled using synthetic insecticides. Nevertheless, their widespread application has resulted resistance in the vector against chemical insecticides.

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Environmental pollution, and unpleasant outcomes on non-target organisms, have made their replacement by sustainable alternatives. Phytochemicals have a high potential to serve as an environmentally friendly alternative, which can work by several different mechanisms including neurotoxicity, membrane disruption, induction of oxidative stress, hormonal interference, reproductive suppression, respiratory toxicity, and behavioral changes. This multitargeted activity does not only improve their efficacy but also decreases the chances of development of resistance. Also, phytochemicals are biodegradable, less harmful to the environment and less toxic to non-target organisms. Although the lack of uniform efficacy between species of plants, the variability in efficacy based on solvent polarity as well as the type of formulations used, and the fact that different solvent extracts from different plant components, all highlight the importance of standardization. In vivo studies, toxicity studies, and field trials must be used to optimize the safety of humans and the environment. The inclusion of phytochemicals in the integrated vector management systems will enhance sustainability. However, regulatory provisions and societal approval must be taken into account. The overall future of bioinsecticidal methods is that they will be useful in controlling *A. aegypti* in the future by offering an effective method of pest control as well as environmental friendliness in an era where the conventional insecticides are increasingly facing challenges of resistance.

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