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Review on plant-based bioinsecticides and repellents for mosquito control

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Abstract
Mosquito-borne illnesses continue to be a serious public health concern at global level, and growing resistance to synthetic pesticides has accelerated the hunt for safer substitutes. Because of their biodegradability, target specificity, low toxicity to non-target organisms, and decreased likelihood of resistance development, plant-based bioinsecticides have become attractive tools. This review highlights the insecticidal and mosquito-repelling properties of the main types of plant-derived bioinsecticides, such as Essential oils, neem compounds, pyrethrum, alkaloids, and other phytochemicals. They work by interfering with insects' neurological, endocrine, and respiratory systems. The limitations and commercial possibilities of plant-derived repellents are examined, as well as their traditional and contemporary uses. The report also highlights future plans that make use of synergistic formulations and integrated mosquito management strategies.

Keywords: Mosquito control, plant-based bioinsecticides, phytochemicals, mosquito repellents, essential oils

Introduction

Bioinsecticides are insecticides derived from natural products, such as plant extracted compounds, pheromones, and products derived from microorganisms such as virus, fungi, bacteria or protozoan.

Phytochemicals, microbiological pesticides, plant-incorporated protectants (PIPs), and pheromones are the four main categories of bioinsecticides according to their origin (Şengül Demirak & Canpolat, 2022) [48] (Fig 1).

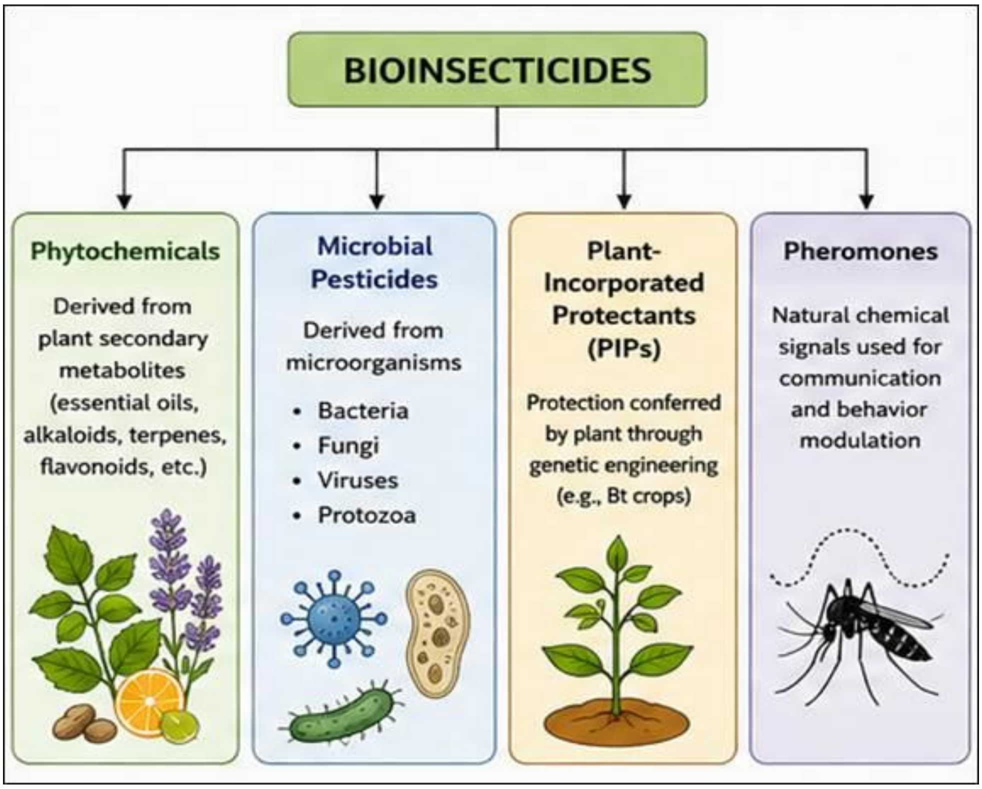


Fig 1: Types of bioinsecticides and their examples.

They have been successfully applied to the production of sustainable agricultural products and the control of pests (Thakore, 2006, Prabha *et al*., 2016) [44, 55]. They are good substitutes for synthetic substances because they are less toxic, target-specific, extremely effective in small quantities, and biodegradable. More significantly, in order to effectively control mosquito diseases, the problem of mosquitoes becoming resistant to synthetic substances must be addressed. Since biopesticides cause less insect resistance (Ohia & Ana, 2015 [37], Şengül Demirak & Canpolat, 2022 [48]), the majority of research now focuses on finding potential natural substances that may have an impact on mosquitoes in order to prevent the spread of diseases carried by mosquitoes (Fig 2).

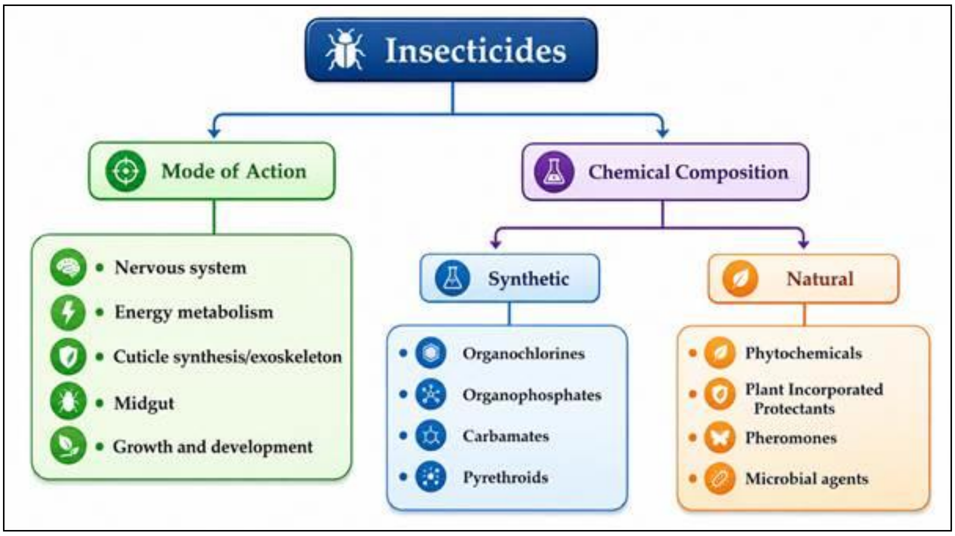


Fig 2: Mode of action and chemical composition of Insecticides.

Plants have developed a variety of chemical defenses against insects and harmful microbes. These physiologically active substances, known as "phytochemicals," work against insects as growth regulators, poisons, repellents, and feeding deterrents (Tyagi, 2016) [58].

An efficient plant-based pesticide can be made from a variety of higher plant parts (leaves, roots, stems, seeds, bark, fruits, fruit peels, and resin), the entire body of small herbs, or a combination of different plants. Depending on the type of plant, the age and section of the plant, the polarity of the solvents used in the extraction process, and the type of mosquito, a phytochemical's activity might vary dramatically (Shaalan *et al.*, 2005) [50].

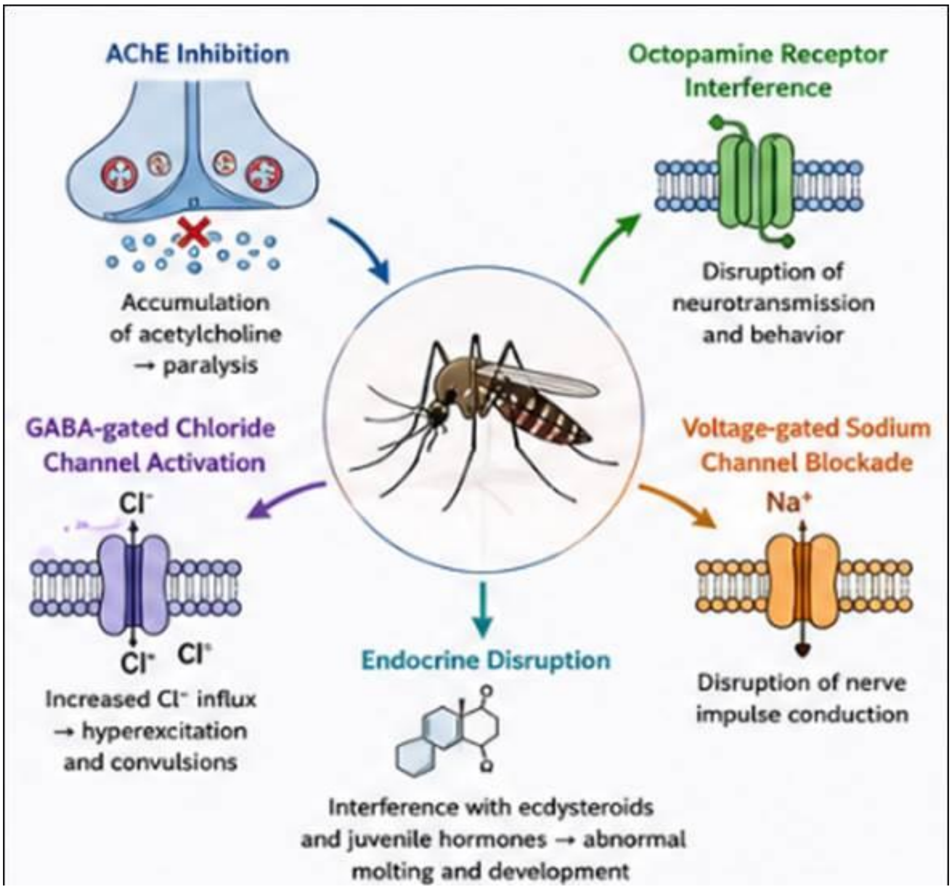


Fig 3: Major target sites and physiological effects of plant-derived bioinsecticides on mosquito nervous and endocrine systems.

By inhibiting AChE and Gamma-aminobutyric acid (GABA)-gated chloride channel activity, disrupting sodium-potassium ion exchange and nerve cell membrane action, blocking calcium channels, and activating nicotinic acetylcholine and octopamine receptors, phytochemicals exhibit their effects on insect physiology in various ways (Souto *et al.*, 2021) [53]. Furthermore, phytochemicals can impact metamorphosis and destroy mosquito midgut

epithelial cells (Sharma *et al*., 2006, Al-Mekhlafi, 2018) [2, 51] (Fig 3).
The mosquitocidal properties of a number of phytochemicals have been documented (Shaalan *et al*., 2005, Senthil-Nathan, 2020) [49, 50]. Essential oils, alkaloids, phenols, terpenoids, steroids, and phenolics from various plants are examples of secondary metabolites. Plant species include a wide variety of phytochemicals, and the identification of those with mosquitocidal properties-which are controlled by variations in the expression levels of detoxifying enzymes- is crucial for mosquito control.

Plant-Based compounds as insecticides and repellents
Many plant chemicals have been intensively researched for their ovicidal and larvicidal properties because mosquitoes are relatively vulnerable at these stages and can be effectively destroyed before emerging as adults (Fig 4). Human hosts can effectively prevent mosquito bites for a blood meal by using repellent chemicals. The development of effective repellents requires an understanding of the mosquito olfactory system. By altering or inhibiting the olfactory receptor neurons' response, insect repellents cause mosquitoes to either avoid or alter their host-seeking behaviour (Syed & Leal, 2008, Dickens & Bohbot, 2013) [11, 54]. Numerous plant chemicals possess repelling properties. When applied to human skin or sprayed inside, Essential oils, alkaloids, and aromatic chemicals from a variety of plants have been found to disrupt mosquito host-seeking behaviour (Maia & Moore, 2011, Pavela & Benelli, 2016) [32, 42].

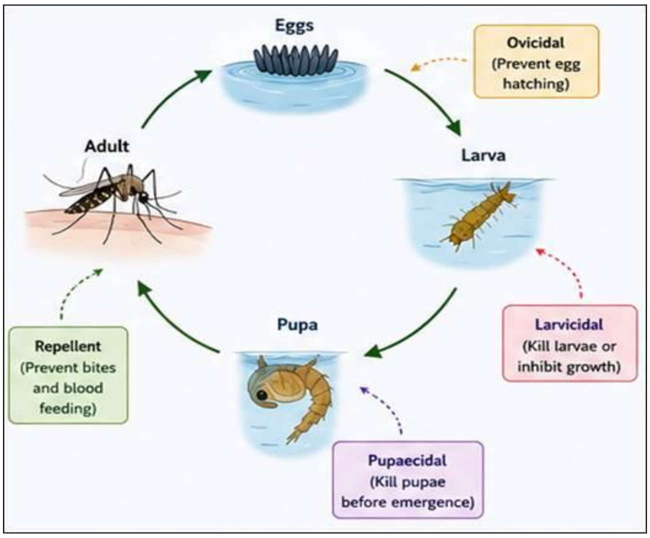
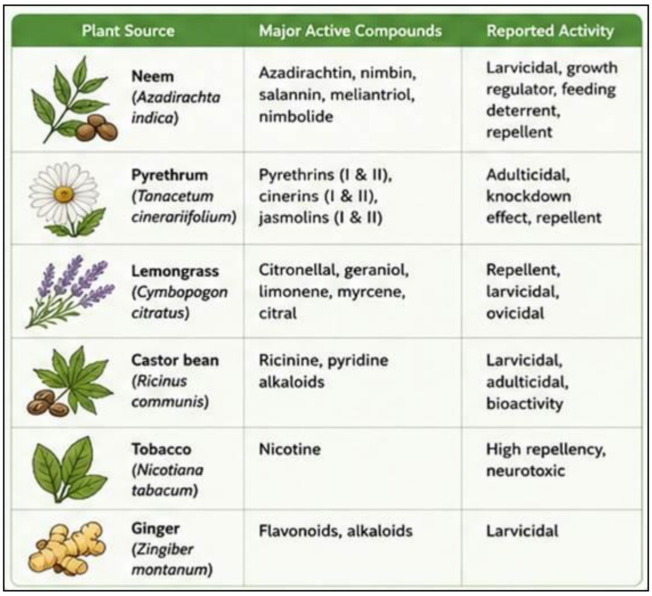


Fig 4: Mosquito life stages and the corresponding targets of plant-derived bioinsecticides.

For thousands of years, humans have taken use of the repellent properties of plant material, most commonly by hanging bruised plants in homes. This practice is still widely used in underdeveloped nations (Moore *et al*., 2006) [34]. For ages, ancient Greek (Herodotus, 2015) [23], Roman (Owen, 1806), and Indian scholars (Johnson, 2019) [28] wrote about the usage of plants as crude fumigants, in which plants were burned to repel bothersome mosquitoes, and later as oil formulations applied to the skin or clothing (Maia & Moore, 2011) [32].



Plant Source	Major Active Compounds	Reported Activity
Neem (*Azadirachta indica*)	Azadirachtin, nimbin, salannin, meliantriol, nimbolide	Larvicidal, growth regulator, feeding deterrent, repellent
Pyrethrum (*Tanacetum cinerariifolium*)	Pyrethrins (I & II), cinerins (I & II), jasmolins (I & II)	Adulticidal, knockdown effect, repellent
Lemongrass (*Cymbopogon citratus*)	Citronellal, geraniol, limonene, myrcene, citral	Repellent, larvicidal, ovicidal
Castor bean (*Ricinus communis*)	Ricinine, pyridine alkaloids	Larvicidal, adulticidal, bioactivity
Tobacco (*Nicotiana tabacum*)	Nicotine	High repellency, neurotoxic
Ginger (*Zingiber montanum*)	Flavonoids, alkaloids	Larvicidal

Fig 5: Important plant species, active compounds, and reported mosquitocidal activities.

In rural communities in the tropics, plant-based repellents are still widely used in this traditional manner because they are the only available protection against mosquito bites for many of the poorest communities (Moore *et al*., 2006) [34]. In fact, in some of these communities (Moore *et al*., 2007) [33], as in Europe and North America (Trumble, 2002) [57], "natural" smelling repellents are preferred because people believe that plants are a reliable and safe way to prevent mosquito bites.

Essential oils
Essential oils are viable substitutes for synthetic insecticides used to control mosquitoes, and they have been effectively utilized worldwide to protect crops from a range of pests. Hydrocarbons (terpenes and sesquiterpenes), oxygenated hydrocarbons, and phenylpropenes are among the many volatile chemicals that make up Essential oils, which are extremely complex natural mixes. Mevalonic acid and 2-C-methyl-erythritol 4-phosphate (MEP) routes are used in the cytoplasm and plastids of plant cells, respectively, to produce Essential oils (Nagegowda, 2010) [35]. By blocking GABA-gated chloride channels, octopamine receptors, and AChE activity, Essential oils target the insect nervous system and produce neurotoxic effects (Isman & JunHyung, 2017, Jankowska *et al*., 2018) [25, 27]. Monoterpenes, which are found to be active components of possible plant-based larvicides that suppress insect AChE activity, make up about 90% of Essential oils (Pavela, 2015) [40]. Linalool, cuminaldehyde, 1,8-cineole, limonene, and fenchone are examples of monoterpenes that block AChE, accumulate acetylcholine in synapses, and induce a condition of persistent activation that leads to ataxia (Abdelgaleil *et al*., 2009, Houghton *et al*., 2006) [1, 24]. A combination of monoterpenoids works in concert to inhibit AChE more effectively than a single monoterpenoid treatment (Şengül Demirak & Canpolat, 2022) [48].
Essential oils that block octopamine receptors and have acute and sub-lethal behavioral impacts on insects also target the octopaminergic system of insects. A combination

of Essential oils (eugenol, γ-terpineol, and cinnamic alcohol) can prevent the rise in cyclic AMP levels that occurs when octopamine binds to octopamine receptors. Furthermore, low dosages of eugenol alone greatly decrease octopamine receptor binding (Enan, 2001 [18], Kostyukovsky *et al*., 2002 [30]). Ligand-gated chloride channels are another potential target for Essential oils. Monoterpenes found in Essential oils, such as linalool, methyl eugenol, estragole, and citronellal, inhibit GABA-gated chloride channels by binding at the receptor site and increase the influx of chloride anions into the neurons, causing convulsions, hyper-excitation of the central nervous system, and ultimately insect death (Bloomquist, 2003 [7]; Li *et al*., 2020). Numerous plant oils, some of which will be covered here, have ovicidal, larvicidal, pupicidal, and repellant properties against a variety of mosquito species. The repelling properties of Essential oils derived from plants belonging to the Lamiaceae, Poaceae, Rutaceae, and Myrtaceae families are widely recognized (Tyagi, 2016) [58]. In rural regions, several members of these families are hanged or burned within homes (Maia & Moore, 2011 [32]). Numerous plant Essential oils, such as peppermint, lemongrass, geraniol, pine oil, pennyroyal, cedar oil, thyme oil, and patchouli, are found in many commercial repellents, either for aroma or as repellents (Barnard, 1999; Rutledge & Gupta, 1995; Trongtokit *et al*., 2005 [3, 46, 56]). The majority of these Essential oils have a short shelf life as insect repellents due to their high volatility. However, by employing fixatives or carefully formulating them to increase their lifetime, this issue can be resolved.

The U.S. Environmental Protection Agency (US EPA) recommends commercial Essential oils derived from citronella, lemon, and eucalyptus as repellant ingredients for skin application due to their low toxicity. For instance, the lemon eucalyptus plant's active ingredient, P-menthane-3,8 diol (PMD), is what keeps mosquitoes away (Bekele, 2018) [6]. Despite being exempt from EPA registration requirements, Essential oils can cause skin irritation and have varying repelling effects depending on formulation and concentration.

Neem

Around the world, neem-based pesticides are widely used to defend against a variety of pests. Azadirachtin, meliantriol, salannin, desacetyl salannin, nimbin, desacetyl nimbin, nimbidin, and nimbolides are among the at least 100 active chemicals found in neem oil, which is the primary output of the plant (Campos *et al*., 2016) [8]. The main active ingredient of neem oil are limonoids, which impede the growth of insects. One of the most powerful active ingredients in neem extract, azadirachtin is a highly oxidized limonoid that is present in higher amounts (0.2–0.6%) in neem seeds than in other neem tree parts (Şengül Demirak & Canpolat, 2022) [48]. Neem-based solutions work well for insects in their juvenile stages. Azadirachtin shares structural similarities with ecdysones, which are insect hormones involved in metamorphosis. Azadirachtin primarily affects insect hormone homeostasis by disrupting the endocrine system (Fig 6).

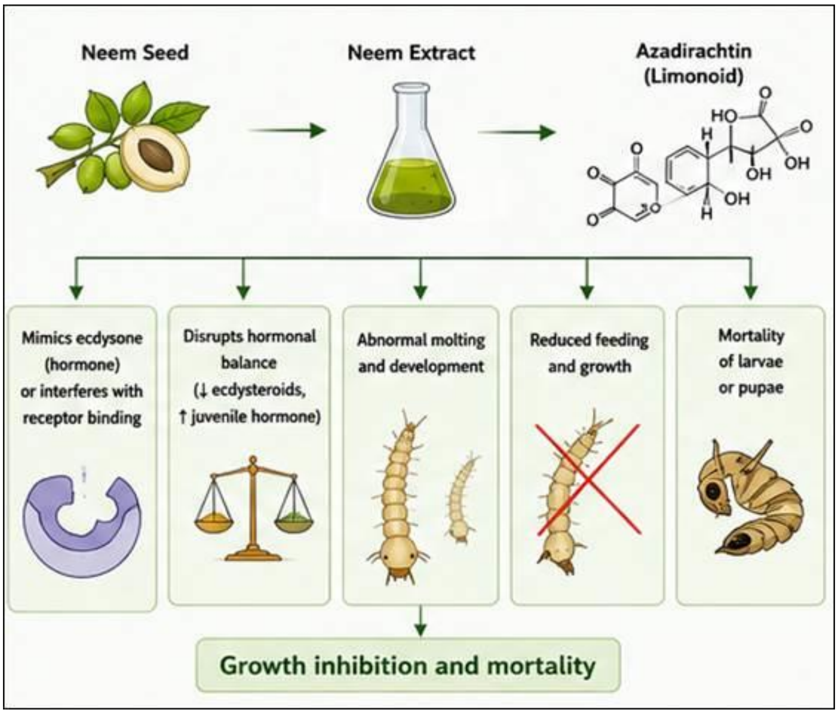


Fig 6: Mechanism of azadirachtin-mediated growth disruption and mortality in mosquitoes.

By altering ecdysteroid and juvenile hormone titers, azadirachtin functions as an ecdysone blocker and results in severe growth and molting abnormalities (Dwivedi, 2008) [15]. Azadirachtin's interaction with phagostimulants, which are crucial to mosquitoes' typical feeding behaviour, mediates its feeding deterrent action (Beckage *et al*., 2000) [5].

Neem has been widely marketed as a natural substitute for DEET (Maia & Moore, 2011 [32]) and has been tested for repellency against a number of medically significant arthropods in addition to its insecticidal and growth-regulating qualities. While some researches have shown relatively moderate levels of protection, several field tests carried out in India have indicated considerable repellency of neem-based treatments against mosquitoes (Maia & Moore, 2011 [32]). The solvents employed in repellent compositions and variations in testing techniques may be the cause of these discrepancies in efficacy. Dermatitis and other skin irritations can result from undiluted formulations of neem oil, despite its low dermal toxicity (Reutemann & Ehrlich, 2008) [45]. Despite offering some protection against bothersome mosquitoes, neem oil is typically not advised as a stand-alone repellent for travellers to disease-endemic areas due to the paucity of trustworthy studies (Goodyer *et al*. 2010) [20].

Pyrethrum

Tanacetum cinerariifolium flower heads are used to make pyrethrum, a plant-based insecticide. The six active components of pyrethrum extract are generated from esters of pyrethric acid (pyrethrin II, cinerin II, and jasmolin II) and chrysanthemic acid (pyrethrin I, cinerin I, and jasmolin I) (Grdiša & Gršić, 2013) [21].

By obstructing voltage-gated sodium channels in nerv axons, they target the nervous system of insects and produce neurotoxic effects. This rapid knockdown effect results in hyperactivity and convulsions (Pavela, 2016) [41]. Pyrethrins work similarly to numerous synthetic organochlorine pesticides and DDT. Therefore, organophosphates and organochlorides can be substituted by pyrethrins. It is more hazardous to fish and aquatic invertebrates but less toxic to mammals. Their activity is enhanced and detrimental effects on non-target organisms are decreased when combined with a traditional synergist, like piperonyl butoxide (PBO) (Osimitz *et al*. 2009) [38]. The discovery that pyrethrum had a knock-down effect, repellency, and blood-feeding inhibition in pyrethroid-resistant strains of An. gambiae supports the use of natural pyrethrins in mosquito control (Duchon *et al*., 2014) [14].

Alkaloids

Alkaloids are naturally occurring substances that include nitrogen and are present in bacteria, fungi, plants, and mammals. Many members of the Berberidaceae, Fabaceae, Solanaceae, and Ranunculaceae families contain them in high numbers, and they are frequently isolated from plants. Conventional insect repellents make substantial use of the alkaloids derived from these plants (Secoy & Smith, 1983 [47], Gutiérrez-Grijalva *et al*., 2020, Ullah *et al*., 2022) [22, 59]. Alkaloids influence AChE receptors in the nervous system, control hormonal activity, and cause toxicity, all of which interfere with important cellular and physiological processes (Chowański *et al*., 2016 [9]). The mode of action of alkaloids differs depending on the kind of alkaloid. Unlike Essential oils, alkaloids are not volatile. However, by burning plants to produce an insecticidal smoke that both repels insects and directly causes toxicity, they could be utilized as mosquito repellents (Bekele, 2018) [6].

Table 1: Alkaloids, their sources and effect on mosquitoes.

No.	Alkaloid	Source Plant	Mosquito species	Activity	Reference
1.	Ricinine	Castor bean (*Ricinus communis*)	*An. arabiensis* Larvae	Larvicidal Effect	Elimam *et al*., 2009 [17]
2.	Pyridine	Castor bean (*Ricinus communis*)	*An. gambiense* larvae and adults	Bioactivity	Wachira *et al*., 2014 [61]
3.	Alkaloid	*Arachis hypogaea*	*An. stephensi* and *Ae. aegypti*	Larvicidal toxicity	Velu *et al*., 2015 [60]
4.	Nicotine	Tobacco plant (*Nicotiana tobacco*)	*Ae. aegypti*	High repellence	Jufri *et al*., 2016 [29]

Natural oils

Numerous oils have demonstrated mosquito repellency. They probably function in a number of ways: 1) by lowering short-range attractive cues like temperature, water vapor, and kairomones (Wright & Kellogg, 1962, Davis & Bowen, 1994, Eiras & Jepson, 1994) [10, 16, 62]; 2) by lowering the evaporation and absorption of repellent actives because of the presence of long-chained fatty molecules (Dremova *et al*., 1971) [12]; and 3) by containing fatty acids, which are known to repel mosquitoes at high concentrations (Skinner *et al*., 1970) [52]. In one study (Barnard & Xue, 2004) [4], Bite Blocker, a commercial preparation containing glycerin, lecithin, vanillin, oils of coconut, geranium, and 2% soybean oil, provided a mean protection time of 7.2 hours against a dengue vector and nuisance biting mosquitoes; in another study (Fradin & Day, 2002) [19], it provided protection for 1.5 hours, which is comparable to low concentration DEET.

Other Plant compounds

Some other naturally occurring plant metabolites have insecticidal qualities in addition to the most widely used plant-based bioinsecticides. Among these, flavonoids block Acetylcholinesterase (AChE) in mosquito larvae to produce larvicidal action [182]. Additionally, they may disrupt the larval respiratory system by acting as respiratory inhibitors. Alkaloids can operate as stomach poisons, degrade cell membranes, and block the AChE enzyme, among other effects (Perumalsamy *et al*., 2015) [43]. It has been demonstrated that the alkaloid and flavonoid components of *Zingiber montanum* bangle rhizome extract have distinct effects on *Ae. aegypti* (Ningrum *et al*., 2019) [36]. Additionally, *Derris trifoliata* extract's flavonoids shown larvicidal action against *Ae. aegypti* (Yenesew *et al*., 2009) [63]. Derris (*Derris elliptica*, *Derris involute*), *Lonchocarpus* (*Lonchocarpus utilis*, *Lonchocarpus urucu*), and *Tephrosia virginiana* roots and stems are the sources of rotenone, an isoflavonoid (Dua *et al*., 2009) [13]. Because of its less detrimental effects on the environment, it has long been employed as a biopesticide. Rotenone interferes with insects' cellular respiration systems and stops them from producing energy, making it a possible larvicide for controlling mosquitoes (Zubairi *et al*., 2015) [64].

Potential future plans to improve plant-based bioinsecticide efficacy

Because plants naturally produce phytochemicals in response to their surroundings (such as in response to insect predators and microbial attacks), plants are in fact natural suppliers of insecticides. This makes phytochemicals produced from plant resources great targets for the search for bioactive molecules. When phytochemicals are used as a blend (such as a mixture of oils) against mosquitoes, their effectiveness can be increased since they have numerous modes of action and affect several target areas in insects. Furthermore, insects are more likely to become resistant to a single chemical ingredient than to a combination of compounds.

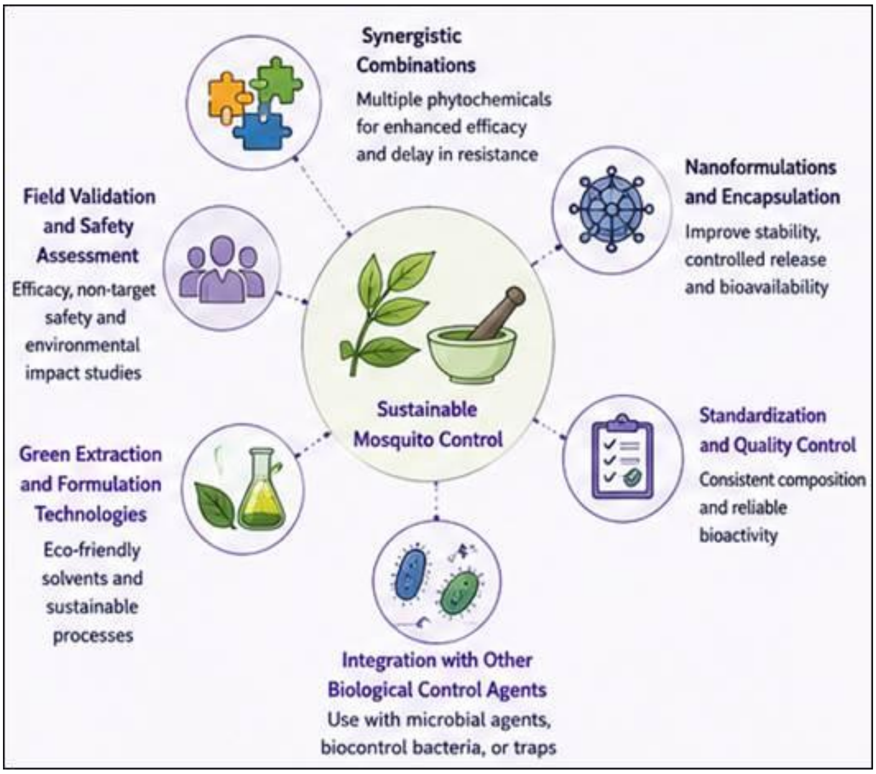


Fig 7: Emerging approaches for improving the efficacy, stability, and sustainability of plant-based bioinsecticides.

Therefore, using phytochemicals in combination would prevent mosquitoes from developing resistance. When combined with other biological control agents, phytochemicals' short residual half-life may be beneficial (Isman *et al*., 2011) [26].

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