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Review

When Scent Becomes a Weapon—Plant Essential Oils as Potent Bioinsecticides

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Abstract: Crop protection still mostly relies on synthetic pesticides for crop pest control. However, the rationale for their continued use is shaded by the revealed adverse effects, such as relatively long environmental persistence that leads to water and soil contamination and retention of residues in food that brings high risks to human and animal health. As part of integrated pest management, biopesticides may provide crop protection, being eco-friendly and safe for humans and non-target organisms. Essential oils, complex mixtures of low-molecular-weight, highly volatile compounds, have been highlighted as major candidates for plant-derived bioinsecticides that are up to the sustainable biological standard. In this review, we screened the insecticidal activity of essential oils or their purified compounds, with focus given to their modes of action, along with the analyzed advantages and problems associated with their wider usage as plant-derived insecticides in agriculture.

Keywords: plant-based pesticides; integrated pest management; insecticidal mode of action; nanoformulations

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1. Introduction

"Finding enough to eat today so that you stay alive tomorrow is the mark of individual success. Finding so much today that you can afford to devote tomorrow to thinking is the start of civilization" [1].

From the collection of wild grain at least 105,000 years ago [2], through the domestication of crops starting from the Neolithic period around 9500 BC [3], to the implementation of intensively developed irrigation and crop rotation in the past 200 years, ending in the replacement of human labor by mechanization assisted by synthetic fertilizers, pesticides, and selective breeding, food production has been a challenge facing mankind. Despite huge efforts and great investments made, the inexorable growth of the human population, together with actual demands on food safety and quality, are still not enough to feed mankind. According to the United Nations (UN) Food and Agriculture Organization (FAO) for 2020 [4], about 800 million people do not have a safe food supply every day. Due to a shaken economy caused by COVID-19, around 118 million more people suffered from hunger in 2020 than in 2019, and a scenario will be further complicated by the enduring effects of the pandemic.

However, modern intensive agricultural food production, developed from highly selective breeding over the centuries, relies on monocultures that are extremely vulnerable to different challenges and frequently subjected to great losses due to different climate and/or biotic factors. The most adopted protective agricultural practices rely on the application of different chemicals, i.e., fertilizers and pesticides (including herbicides, fungicides, and insecticides), frequently in huge quantities. However, this is one of the most striking issues that seriously jeopardizes a sustainable approach to modern agriculture due to contamination of the produced food with synthetic chemicals used for the crop treatments. The over-used chemicals bring high risk to human and animal well-being, but also cause dramatic environmental footprints that lead to water and soil contamination. For instance, 4.17 million tons of different classes of pesticides were produced in 2019 (FAOSTAT, accessed on 10 April 2022), and about 385 million cases of unintentional acute pesticide poisoning (UAPP) occur annually worldwide, with around 11,000 fatalities [5]. Moreover, just 0.1% of the total pesticides used affect the target pests, and the remaining quantity contaminates water, air, and soil ecosystems [6]. Due to the phenomena of biomagnification, an enhanced amount of toxic pesticide residues increases at higher trophic levels [7,8]. Thus, there is an increasing demand to consider alternatives to widely used chemicals in agricultural food production systems and implement more diverse ecologically based practices. Although the prevalence of chemicals over natural pesticides (biopesticides) is continuing, legitimated by an increase in the agricultural output, there is an increasing call for food quality and safety.

As an effect of that call, the research and development of biopesticides in general (insecticides, nematicides, rodenticides, fungicides, bactericides, and others) are expanding, governments are offering supportive policies for biological control of pests, and global markets are aiming to increase the popularity of biopesticides. The concept of "green pesticides" refers to all types of nature-oriented and beneficial pest control materials that can contribute to reducing the pest population and increasing food production [9]. The current support of sustainable pest control strategies will be continued by encouraging farmers to implement biological pest control methods. For example, the EU Commission will act to reduce the use and risk of chemical pesticides by 50% by 2030.

This review aims to present the state of the art in bioinsecticide research and application and nominate the most promising trajectories (approaches, solutions, directions) for modern and efficient EO-based insecticide production. It points out all the advantages of plant-derived insecticides over chemical ones, along with an overview of their modes of action and new techniques for their efficient application, as well as the problems yet to be solved. Neurotoxic modes of action are highlighted as a promising mechanism of EO-based insecticides that do not cause high selective pressure on pest populations but act toward several target sites so it can be hard to develop resistance.

2. Insects as the Super-Pests of Modern Agriculture

The threat during all stages of agricultural production of food comes from insect pests that are continuously adapting to crop hosts [10]. Insect pests reduce agricultural yields by up to 30% before and after harvest, in similar proportions [11]. Interestingly, only about 20–30 insect species (from a total of about 6 million identified species) are considered important pests for major crops, making significant agricultural and economic impacts [12]. According to the Kew Royal Botanic Garden [13], some of the most harmful are the cotton bollworm (*Helicoverpa armigera* Hubner), tobacco whitefly (*Bemisia tabaci* Gennadius), Colorado potato beetle (*Leptinotarsa decemlineata* Say), diamondback moth (*Plutella xylostella* L.), and fall armyworm (*Spodoptera frugiperda* Smith). The populations of these pests are dominant in agricultural ecosystems. They can develop resistance to chemicals [14] and consequently have several generations annually, with the high fecundity of females increasing the probability of random mutation and rapid aggregation of resistant mutants [15].

The extent of detrimental pest insects' impacts is even greater in the modern world, with intensive human movements, international trade, and goods transportation. Populations of pests are unintentionally dispersed beyond their native ranges, and these so-called invasive species, introduced to an area where they are not known to occur, spread explosively, causing disturbance of co-evolutionary, antagonistic interactions with predators, parasitoids, and pathogens present in invaded areas [16]. It is estimated that USD 76.9 billion are required annually to manage and mitigate the impacts of biological invasions worldwide [17]. It is more frightening that future costs are likely to increase as invasive insects expand their ranges in response to global warming [18], and both insects' population growth and metabolic rates will also increase [19].

Insect pests are frequently attributed as super-pests with continuously developing eco-physiological mechanisms and behavioral activities that allow them to overcome all obstacles to their successful spread [10]. As an example of the "indestructible" pest, the Colorado potato beetle is exhibiting a plethora of "responses" to agrotechnical control measures, but also co-evolutionary developed plants' "traps" [10,20]. This insect continually increases the number of new hosts (avoiding co-evolved plant defensive strategies) [21], expands the territory it inhabits (due to climatic change and human activity) [22], manages developmental dynamics in response to climatic conditions (by shortening larval stages in unfavorable conditions and digging deeper into the soil when it is cold) [23], and develops resistance to insecticidal agents (by detoxifying them, or by adapting its digestive process) [24]. In general, all major insect pests are exhibiting a similar "arsenal" of adopting strategies, giving them super-pest characteristics.

This extraordinary ability of insect pests to overcome agricultural practices employed to eliminate their populations (crop rotation, physical barricades, thermal or electromagnetic control, insect removal by machinery, etc.) constantly pushes the development of new strategies and new insecticide products, but with the imperative to be in line with Integrated Pest Management (IPM).

3. The Chemical Teeter: Plant-Based Alternatives for Insecticidal Chemicals

The overview of the current global insecticide market still shows the undoubted dominance of chemicals over bioinsecticidal products. In the period of 2017–2019, approximately 0.7 Mt of total insecticides were produced annually, and the value of the global market was about USD 14.5 billion [25]. Just about one fifth of the share in production value is devoted to the bioinsecticide market, but with an indication of growing from USD 2.2 billion in 2020 to USD 4.6 billion by 2025 [26]. This growing trend is expected to be even more intensive since chemical insecticides start to lose popularity mainly because of their extremely negative impact on the environment and non-target organisms, i.e., beneficial insects (pollinators, predators), domestic animals, or humans [27]. Bioinsecticides could derive from diverse natural sources, including animals, plants, microbes, and minerals [28].

One of the desirable biological means of insect pest regulation that is fast gaining popularity is the application of natural compounds isolated from plants. Due to their sessile way of life, plants have developed a full range of different strategies, including the synthesis of compounds that enable them to survive in the battle against pests and pathogens. Although only a small portion of known higher plant species has been screened for pesticide activity so far [29], an increase in the research of plant-derived compounds with pesticide potential during the last few decades has been noticed, judging by scientific publications.

Insecticidal plant-derived chemicals are considered to be safe in general, exposing low toxicity to non-target organisms (Figure 1).

In contrast to conventional insecticides as broad-spectrum products affecting different organisms, plant-based or botanical insecticides are more selective due to the high compatibility between active ingredients and targeted pest metabolic pathways [30]. On the other hand, they may directly kill pests [31,32], but the modes of action imply indirectly interfere with pest physiology and/or reproduction [33] or may simply repel pests by compounds they avoid [34]. This way, populations of pests are suppressed and can be managed over time. In addition, pest resistance is hard to achieve due to multiple component mixtures that cause toxicity by interfering with many aspects of insect physiology and biochemistry [35]. Botanical insecticides also tend to decompose quickly and leave fewer residues on food and the environment [36]. The renewable nature of plant material, together with all the above-mentioned advantages, as well as intensified attempts to reduce production costs, will drag market tendencies toward the plant-based insecticide industry.

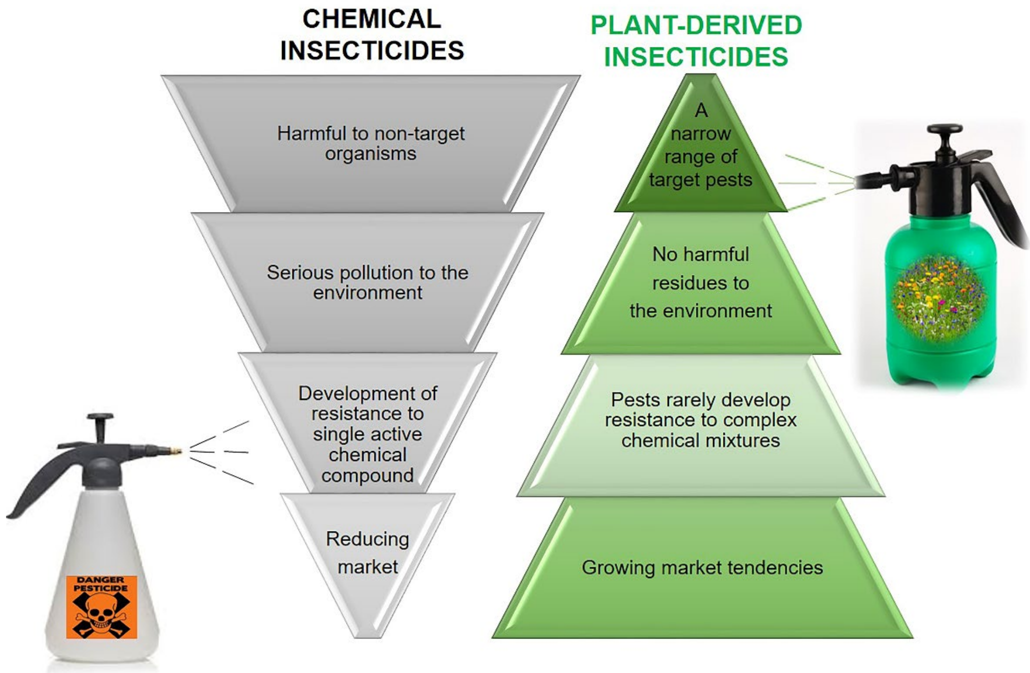

Figure 1. Advantages of plant-derived insecticides over chemical insecticides.

4. Scent That Can Hurt—Essential Oils as Insecticides

Recently, plant essential oils (EOs) have been brought into focus as major candidates for plant-derived bioinsecticides that are up to the sustainable biological standard of IPM. These complex mixtures are part of the plant's defensive arsenal against different enemies, with repellent, fumigant, feeding deterrent, and larvicidal activity [37–39]. Essential oil constituents are highly volatile organic compounds (VOCs) with low molecular weight, commonly with terpenoids as the dominant group [40]. They are mixtures of two to more than 100 active substances and are determined by up to three components present at relatively high concentrations compared to other EO compounds. The major components usually shape the biological properties of EO and can be divided into two main groups: (1) terpene hydro-carbons (monoterpenes and sesquiterpenes) and (2) oxygenated compounds (alcohols, phenols, aldehydes, and esters). Terpenes are dominant constituents of EOs related to aromatic and oxygenated compounds [41].

A plethora of published studies has confirmed that mixtures of EOs have insecticidal activity against diverse insects, mostly under in vitro conditions, and bioactivity is frequently related to their synergistic interactions. A literature survey of the potential use of EOs as bioinsecticides indicated that EOs obtained from several plant families, including Meliaceae, Asteraceae, Myrtaceae, Apiaceae, Lamiaceae, and Rutaceae, have very potent insecticidal activity. They act as a repellent or fumigant, expressing contact or digestive toxicity in larvae or adults of the Lepidoptera, Diptera, Coleopteran, Hemiptera, and Isopteran orders (Table 1).

Table 1. Essential oils and their major constituents with insecticidal activity.

Plant Species	Insects	Major EO Constituents	Lethal (LC_{50}) and Inhibition * (IC_{50} *) Concentrations	Ref. No
Cephalotaxus sinensis	*Megoura japonica* *Plutella xylostella* *Sitophilus zeamais*	α-Pinene β-Caryophyllene Germacrene D	8.82 mg/L 6.74 mg/L 7.35 mg/L 3.57 mg/L	[31]
Brassica nigra	*Sitophilus zeamais*	Allyl isothiocyanate	6.19 µL/L (larvae) 7.01 µL/L (adults)	[42]

Table 1. *Cont.*

Plant Species	Insects	Major EO Constituents	Lethal (LC_{50}) and Inhibition * (IC_{50} *) Concentrations	Ref. No
/	*Chilo partellus* *Spodoptera litura* *Helicoverpa armigera*	Thymol Linalool 1,8-Cineole trans-Anethole Carvacrol	189.7; 28.5; 290.8 µg/larva 462.4; 85.5; 431.5 µg/larva 412.1; 126.6; 406.8 µg/larva 409.7; 64.3; 378.6 µg/larva 550.3; 55.7; 414.7 µg/larva	[43]
/	*Ephestia kuehniella*	α-Pinene trans-Anethole Thymol	0.864 µL/mL * 0.490 µL/mL * 0.137 µL/mL *	[44]
Lippia sidoides	*Sitophilus zeamais*	EO mix Thymol p-Cymene	35.48 to 118.29 µL/L air 65.00 to 91.23 µL/L air 801.24 to 2188.83 µL/L air	[45]
Thymus vulgaris	*Aedes aegypti*	Thymol, p-Cymene	45.73 mg/mL	[32]
Salvia officinalis		1,8-Cineol, α-Thujone	76.43 mg/mL	
Lippia origanoides		Limonene, p-Cymene, α-Phellandrene	53.79 mg/mL	
Eucalyptus globulus		Thymol, p-Cymene	92.55 mg/mL	
Cymbopogon nardus		1,8-Cineol	75.85 mg/mL	
Cymbopogon martinii		Citronellal, Citronellol, Geraniol	114.65 mg/mL	
Lippia alba		Geraniol	72.34 mg/mL	
Pelargonium graveolens		Carrvone, Limonene, Citronellol	108.96 mg/mL	
Thymus alternans	*Spodoptera littoralis*, *Musca domestica*, *Culex quinquefasciatus*	(E)-Nerolidol, Linalool, Germacrene D	156.3 mg/L 103.7 mg/L 221.1 mg/L	[46]
Teucrium montanum subsp. *jailae*		Germacrene D, (E)-Caryophyllene	56.7 mg/L 154.9 mg/L 180.5 mg/L	
Allium sativum	*Sitophilus granaries*	Diallyl disulfide, Diallyl trisulfide	0.64%	[47]
Cumimum cyminum		Cuminaldehyde γ-Terpinene, p-Cymene	3.05%	
Eucalyptus citriodora		β-Pinene	2.98%	
Eucalyptus dives		Citronellal	2.03%	
Gaultheria procumbens		Piperitone, α-Phellandrene Methyl salicylate	1.59%	
Illicum verum		trans-Anethole	3.02%	
Lavandulla hybrida super		Linalool, Linalyl acetate	3.41%	
Melaleuca alternifolia		Terpinene-4-ol, γ-Terpinene	2.86%	
Mentha arvensis		Menthol	2.27%	
Myristica fragrans		α-Pinene, α-Thujene, Sabinene, β-Pinene	3.40%	

Table 1. *Cont.*

Plant Species	Insects	Major EO Constituents	Lethal (LC_{50}) and Inhibition * (IC_{50} *) Concentrations	Ref. No
Ocimum bassilicum spp. *basilicum*		Estragol, Linalool	3.14%	
Ocimum sanctum		Eugenol, β-Caryophyllene, Methyl eugenol	1.77%	
Origanum majorana		α-Pinene, 1,8-Cineole, Camphor, Camphene	3.04%	
Rosmarinus officinalis CT camphor		α-Pinene, 1,8-Cineole, Camphor, Camphene	3.72%	
Thymus vulgaris CT geraniol		Geraniol, Geranyl acetate	2.90%	
Carlina acaulis root	*Musca domestica*	Carlina oxide	2.74 µL (male) 5.96 µL (female)	[48]

The first promoted EO-based bioinsecticides were those obtained from the neem tree (*Azadirachta indica* A.Juss) and Dalmatian chrysanthemum (*Tanacetum cinerariaefolium* Sch.Bip.). The cores of both insecticides are terpenoid compounds, azadirachtin and pyrethrin. Azadirachtin is found in the seeds of the neem tree, and chemically it belongs to the group of triterpenes with a very complex molecular structure known as limonoids. It is a highly oxidized tetranortriterpenoid with a plethora of oxygen-bearing functional groups that ensure its biological functions. The first experiments showed it to be active as a feeding inhibitor towards the desert locust (*Schistocerca gregaria* Forsskal) [49], but subsequent formulations with neem oil have shown it to be antifeedant and a growth disruptor contact insecticide against about 200 insect species [50–52]. It is considered non-toxic to pollinators and fishes, having low mammalian toxicity (LD50 of >5000 mg/kg) [53]. Neem oil is also one of the least toxic bioinsecticides to humans. Thus, azadirachtin is still the active ingredient in many pesticides, including TreeAzin (BioForest Technologies, Inc., Sault Ste. Marie, ON, Canada), AzaMax (Hawthorne Gardening Co., Vancouver, WA, USA), BioNEEM (GroSafe Chemicals, Ltd., Mount Maunganui, New Zealand), AzaGuard (BioSafe Systems, LLC., East Hartford, CT, USA), AzaSol (Arbojet, Inc., Woburn, MA, USA), and Terramera (Terramera, Inc., Vancouver, BC, Canada). Due to its sensitivity to light and temperature and its low stability under field conditions, neem oil has a high rate of photodegradation [54]. Employment of modern technologies enables "trapping" of volatile azadirachtin, maintaining it as one of the most prominent biopesticides and tagging it as the most successful botanical pesticide in agricultural usage worldwide [55]. Similarly, pyrethrin as a natural insecticidal constituent of EO extracted from the dried flower buds of Dalmatian chrysanthemum also exhibits high photosensitivity, but exceptional insecticidal potential. The fact that pyrethrins degrade rapidly after application promotes the development of pyrethroids, synthetic pyrethrins. Therefore, through comprehensive chemical modifications, a total of 42 substances were placed in the fourth class of insecticides by the World Health Organization classification [56]. These so-called pyrethroids, characterized by decreased light-induced degradation in the field, are potent biopesticides that are about 2.250 times more toxic to insects than to higher animals [57]. Based on the toxicological and physical properties, pyrethroids are grouped into two classes, Type I and Type II, based on the presence of the cyano group in the molecule. However, all pyrethroids as synthetic chemical compounds are less degradable in the environment, but exhibit higher toxicity [58,59] than natural pyrethrin.

Besides bioinsecticidal formulations containing the two most popular, azadirachtin and pyrethrin, only one tenth of other EOs have passed comprehensive and strict regulations and commercialization procedures and can be found on global markets. Most of these insect repellents and pesticides contain mixtures of EOs from garlic, rosemary, clove, thyme, peppermint, and lemongrass, and/or purified essential oil compounds like carvacrol, thymol, geraniol, and eugenol (EcoSMART Technologies, Alpharetta, GA, USA).

5. Mechanisms of Neurotoxic Insecticidal Activity of the Essential Oils—How EOs Conquer the Battlefield in the Targeted Insect Pests

Essential oils exert their insecticidal effects through multiple modes of action such as reduced growth, affected molting and prolonged development, induced sterility, altered behavior, midgut membrane disruption, metabolic disorders, neuromuscular toxicity, and non-specific multi-site inhibitions [60–62].

It has been reported that common EOs with insecticidal activities can be inhaled, ingested or skin absorbed by insects. Once components of EOs have entered the insect body, due to their lipophilic chemical structure and good penetrance, they switch on different signaling pathways and insecticidal mechanisms, causing biochemical, physiological, developmental dysfunction, and eventually mortality [63]. They can also increase the bioavailability of co-administered products, which makes them good synergists [64]. The toxicity of EOs depends both on the chemical compounds that act as toxins, and many other factors affecting total toxicity. The key factors inducing EO toxicity are the point of toxin entry, molecular weights, and mechanisms of action.

Generally, mortality has been considered a desirable toxicological endpoint of conventional insecticides. However, not only are pests targeted and killed but also numerous non-target insect species that come into contact with lethal doses in the treated areas and surrounding environment [65]. Moreover, recent studies showed the tendency to fast resistance development in populations of insect pests treated with insecticides with high mortality effects [66]. The alternatives to these mechanisms that put high selective pressure on pest populations are neuroactive insecticides with several action sites defined so far in the most prevalent insect pests [67]. The advantages of neuroactive insecticides are (1) rapid activity that stops crop damage immediately, (2) the presence of many sites of action that are highly sensitive when even a small disruption may be lethal, (3) the lipophilic nature of insecticides that allows for easy penetrance through the lipoidal sheath, and (4) the lack of a detoxification mechanism in nerves, thus prolonging insecticidal activity. These advantages significantly shaped the modern insecticide industry, with the majority of synthetic insecticides today having a neurotoxic activity, most often by inhibiting acetylcholine esterases (carbamates) or disrupting the function of ion channels in the nerve cell membranes (pyrethroids) [67]. Being highly lipophilic, volatile constituents of EOs are therefore promising candidates for bioinsecticides with neuroactivity, and in vitro proofs have been numerous already. The complex nature of EO mixtures could potentially be an advantage in targeting even more sites of action at once.

5.1. Inhibitors of Acetylcholinesterase

Acetylcholinesterase (AChE), the enzyme found primarily in the synaptic cleft of insects, is responsible for the deactivation of the principal neurotransmitter acetylcholine (ACh) that transmits nerve impulses from one nerve cell to another or to involuntary muscles. This enzyme is the target site for most neurotoxic insecticides [68–72]. AChE of insects differs from that in the mammalian system, thus making AChE an insect selective marker for newly developing insecticides, which will be safer for non-target vertebrates, including humans. Approximately 70% of the world's insecticide market is based on synthetic AChE inhibitors (organophosphates, carbamates, and neonicotinoids). Gathered data suggest that the insecticidal action of EOs could be neurotoxic, leading to symptoms similar to those produced by organophosphates and carbamates [73]. Among various constituents of EOs, the evidence of anti-AChE activity was reported for 1,8 cineol, carvacrol, thymol, geraniol, α-pinene, and eugenol [74–77]. Fenchone, S-carvone, and linalool, followed by estragole, were also shown to efficiently inhibit the AChE of stored-product pests under in vitro conditions [70]. It should be noted that the activity of EO complex compounds and their mode of action may differ from the activity of their single component [78,79]. Some EO constituents function as competitive inhibitors, whereas others possess the opposite role (Figure 2).

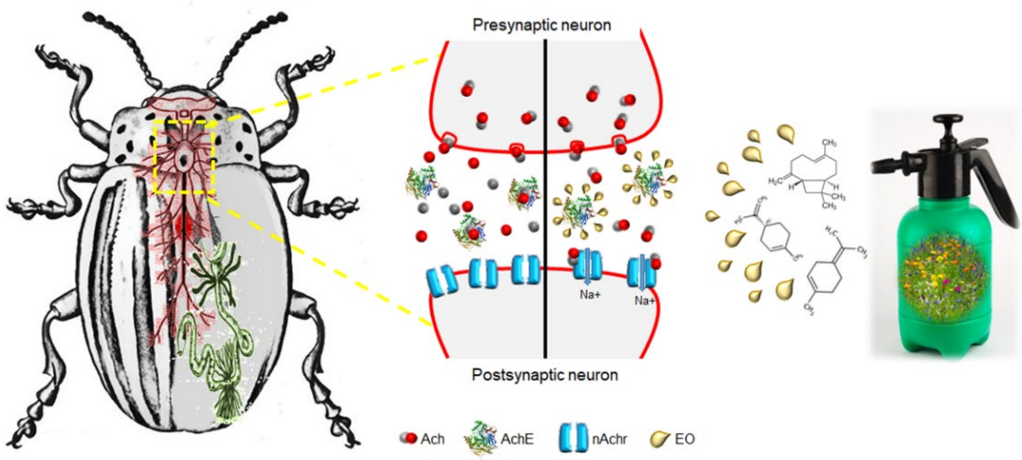

Figure 2. Neurotoxic mechanism of essential oil EO-based bioinsecticide by inhibiting the acetylcholinesterase (AChE) activity and preventing the hydrolysis of acetylcholine (Ach) molecules that bind to nicotinic acetylcholine receptors (nAChr).

As competitive inhibitors, EO or its constituents prevents the binding of AChE by attaching to its binding sites, thus maintaining the enzymes' activity unchanged. However, uncompetitive inhibitors prefer binding to the enzyme–substrate complex than to the enzyme alone, consequently altering the enzyme activity and formation of the product. Tea tree (*Melaleuca alternifolia* (Maiden & Betche) Cheel) EO acts as an uncompetitive inhibitor, whereas its single components may act as competitive inhibitors. As was shown in the study by Taylor and Radić [80], the AChE enzyme has two target sites. Accordingly, some EO components can act as dual binding site inhibitors and perform competitive and uncompetitive inhibition. Action toward AChE also depends on the interaction between different EO terpenoid constituents that can be synergistic or antagonistic [81]. Savalev et al. [82] proposed synergism between 1,8-cineole and α-pinene, whereas oppositely, an interaction between 1,8-cineole and camphor was antagonistic. Interestingly, Miyazawa and Yamafuji [74] revealed that EO exhibited less activity due to the oxygenated functional groups in the bicyclic terpene structure.

The inhibition of AChE is one of the most investigated mechanisms of action in EOs. However, the study on EOs as AChE inhibitors showed that EOs are rather weak inhibitors of AChE. The majority of EO constituents displayed anti-AChE activity in mM concentration. So far, only carvacrol has inhibited AChE in a μM concentration [83]. Thus, scientific literature suggests that AChE inhibition is most likely not the primary neurotoxic mechanism of EOs [84].

5.2. Alternant of GABA Receptors

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter in insects' nervous system and the muscles that binds to specific receptors (GABArs) associated with chloride (Cl^-) channels located on the post-synaptic plasma membrane of neurons and disrupts the functioning of the GABA synapse. The binding sites for the EO components in mammalian GABArs have been defined in numerous studies. Some of the EO components (e.g., menthol, borneol, and geraniol) show structural similarity to a known ligand of the GABArs anaesthetic site. The binding of GABA to GABArs causes the opening of Cl^- channels to allow the flow of chloride ions into the neurons and cause inhibition of the nervous system [85,86]. Pharmacologically, insect and mammalian ionotropic GABArs have different sensitivities to various chemicals; thus, GABArs can be used as a specific target for the development of new insecticides. Insect GABArs have three different subunits: RDL (resistant to dieldrin), GRD (GABA and glycine-like receptor of Drosophila), and LCCH3 (ligand-gated chloride channel homologue 3) [87]. However, the data regarding the effects of EOs on insect GABArs are still very limited. It was shown that monoterpenoid EO components are positive allosteric modulators of insect GABArs and increase the GABA-induced Cl^- uptake [88]. The research on RDL receptors has shown that thymol caused strong potentiation of the Cl^- current evoked by GABA. In addition, thymol, carvacrol, and pulegone intensified the binding of [3H]-TBOB to insects' neuron membranes. For example, some monoterpenes, such as thujone, can induce neurotoxic effects by acting GABA receptors in insects [89]. As a target for insecticidal activity, ion channels that include GABA-gated chloride channels and acetylcholine-gated cation channels contribute to the fast knock-down effects due to their presence in the peripheral nervous system of insects, especially in the neuromuscular junction. However, further research is necessary to elucidate the exact mechanism of EOs and their bioactive compounds on insect GABArs.

5.3. Ligands of Octopamine Receptors

Several papers have demonstrated that EO constituents replicate the activity of octopamine. This molecule is a neuromodulator involved in the regulation of different forms of insect activity [90]. The octopamine receptor was not found in vertebrates. Therefore, EOs as bioinsecticides have selective toxicity to mammals. Octopamine exerts its effects through interaction with at least two classes of receptors that pharmacologically have been designated as octopamine-1 and octopamine-2 [91]. Roeder [92] demonstrated am existence of octopamine receptor class 3 in the locust nervous system. Many of the effects of octopamines binding to G-protein-coupled membrane octopamine-2 receptors might be mediated by cAMP [93] and linked to octopamine-sensitive adenylate cyclase, and agonists were shown to increase cAMP levels in the target tissue [93–95]. In addition, G protein induces the activation of phospholipase C, which elevates the calcium intracellular level and the activity of calcium-dependent protein kinase C. This results in the phosphorylation of many proteins, ultimately changing cell function. Studies have shown that α-terpineol, geraniol, citral, eugenol, cinnamyl alcohol, two natural terpenes (ZP-51 and SEM-76), and trans-anethole increased Ca^{2+} concentrations and cAMP levels in a similar way to octopamine [84,96–99]. Tripathi and Upadhyay [100] suggested insecticidal activity of *Hyptis suaveolens* EO against *Callosobruchus maculatus* Fabricius, *Rhyzopertha dominica* Fabricius, *Sitophilus oryzae* L., and *Tribolium castaneum* Herbst by octopamine receptor alteration. All these results provide strong arguments that the EO components interplay with octopamine, mainly as agonists of these receptors. The effects of EO components on octopamine receptors specific to insects lead to the conclusion that essential oils represent an insufficiently studied but promising pool of molecules with insecticidal activity.

6. The Future Is Here—New Technologies for EO-Based Insecticide Application

Based on reported investigations and available data in the literature, the usage of EOs has significant potential in IPM, but numerous limitations and constraints threaten to jeopardize this approach. Besides the arduous biopesticide registration process, which needs to be accelerated and adjusted to better accommodate these products, there are some "technical" issues concerning the safe and effective application of EO-based bioinsecticides.

Insecticides based on EOs or their constituents are commonly applied as fumigants, direct liquid sprays (in water or organic solvents), or granular formulations, mixed with various solid ingredients (talc, kaolin, clays, calcium carbonate, etc.), enabling the uniform spread of active compounds. The most-discussed constraint regards restraining the usage of these natural insecticides in common agricultural practices and is related to the volatility and limited persistence of EO under field conditions. This problem is enhanced by the lipophilic nature of most EO components and their inability to be fully dissolved in water to obtain a safe application. Due to high volatility, the efficacy of these substances falls short after EO application and pests reinvade the treated crop soon after the treatment, requiring frequent reapplication when used out of doors. This increases the plant material needed, which, together with high application rates (as high as 1% active ingredient), adds an additional challenge and elevates the production costs of this concept. Special attention should be given to the use of formulation ingredients that improve the stability and effectiveness of the biopesticide product, since it could be affected by air, light, and elevated temperatures [101]. These volatile substances are known to be susceptible to oxidative and polymerization reactions that can affect their properties and result in loss of activity. Therefore, nowadays, efforts are focused on the possibility of using innovative formulations for EO encapsulation that provide a controlled EO release, increasing the solubility, durability, bioavailability, and efficiency of EO, thus providing an optimal anti-insecticidal effect. In addition, reducing the dosage of pesticides and human exposure to them also represents a goal to be achieved. These innovative formulations include emulsions (nano- and microemulsion); nanoencapsulation technology, including inorganic nanomaterial (metal, metal oxide, nanoclays), lipid-based nanoformulations (liposomes, solid lipid nanoparticles); and polymer-based nanoformulations (nanocapsules, nanospheres, micelles, and nanogels).

Microemulsions (droplet size 100 to 400 nm) and nanoemulsions (<100 nm) are isotropic dispersions of two immiscible liquids, oil and water [102]. These two systems are different in terms of thermodynamic stability. Microemulsions are thermodynamically stable system dispersions formed spontaneously, but a lot depends on thermodynamic variables such as temperature and composition. Each one of the phases can exhibit very different geometries, such as liquid crystalline, bicontinuous structures, hexagonal, or spherical micelles [103,104]. Nanoemulsions are formulated using specific devices (like ultrasound generators or high-pressure homogenizers) able to supply enough energy to increase the water/oil interfacial area for generating submicronic droplets or by spontaneous emulsification without requiring any device, just mixing a lipophilic phase, into which a hydrophilic surfactant is solubilized to form a homogeneous liquid, and an aqueous phase, which can be pure water [103]. For nanoemulsion formulation, the crucial point is to first mix surfactants with the oily phase. There are four types of surfactants: cationic, anionic, amphoteric, and nonionic, bur for the formation of nanoemulsions for pesticide applications, nonionic surfactants are usually used. The kinetics of the destabilization of nanoemulsions is so slow (∼months) that they are considered kinetically stable. Micro- and nanoemulsions result in a larger surface area for release, and compared to their counterparts, they exhibited more effective accumulation and uptake of the active ingredients with additional greater protection against photodegradation. Nanoemulsion against *Aedes aegypti* L. using copaiba (*Copaifera duckei* Dwyer) oleoresin has been developed and classified as a promising insecticidal agent against *Aedes aegypti* L. larvae [105]. Duarte et al. [106] presented the larvicidal effect of nanoemulsion prepared with *Rosmarinus officinalis* L. essential oil on also against *Aedes aegypti* L. larvae. Essential oil of *Eucalyptus globulus* was used for nanoemulsion formation that exhibited insecticidal activity against *Tribolium castaneum* Herbst and *Sitophilus oryzae* L. [107,108]. Nanoemulsions of eight commercial essential oils (anise *Pimpinella anisum* L., artemisia *Artemisia vulgaris* L., fennel *Foeniculum vulgare* Mill., garlic *Allium sativum* L., lavender *Lavandula angustifolia* Mill., mint *Mentha* x *piperita*, rosemary *Rosmarinus officinalis* L., and sage *Salvia officinalis* L.) was formulated and showed pesticidal activity against *Tribolium confusum* Jacquelin du Val, a key stored product pest [109]. *Citrus* x *sinensis* essential oil-based nanoemulsion was developed and applied as an aerosol, which was efficient at controlling and repelling *T. confusum* Jacquelin du Val and *Cryptolestes ferrugineus* Stephens [110].

By combining EOs with nonorganic materials such as hydroxyapatite (Hap), titanium dioxide, and zinc oxide, the highly stable inorganic nanoparticles can be designed with a wide variety of sizes, structures, and geometries [111,112]. However, some nonorganic nanoparticles, like titanium dioxide, showed strong negative impacts on soil microbial function [113]. Gold and silver in the form of oxide or salt in the presence of EO are employed for metal nanoparticle formation [114,115]. Fennel EO was encapsulated in silica nanoparticles and assayed against the crop pest *Spodoptera litura* Fabricius and the dengue vector *Aedes aegypti* L. [116]. Nanoparticles of cinnamon oil encapsulated with silica tested against the sixth instar larvae of the rice moth (*Corcyra cephalonica* Stainton) decreased the pupation percentage and prevented pupae from emerging [117].

Lipid-based formulations are most specifically spherical particles consisting of a lipid bilayer surrounding an inner aqueous compartment. The most-used lipids for the formulations include glyceryl monostearate, precirol, stearic acid, and acetyl palmitate [118]. Lipid nanoparticles have beneficial properties such as good physiochemical storage stability, a non-toxic nature, a high loading capacity, feasibility, and a target-oriented release profile [119–121].

Different polymers have been suggested for the encapsulation of EOs to polymeric nanoparticles consisting of solid colloidal particles that conserve and protect EOs from outside aggression by physical or chemical interaction with a matrix, but also allow their sustained or delayed release at an optimal threshold in the environment [122,123]. In order to maximize the utilization efficiency of pesticides, controlled-release formulations are highly desirable. Biodegradable polymeric nanoparticles are environmentally friendly and do not result in the production of any harmful by-products [124,125].

Before application, the minimum and the maximum release rate must be determined concerning the efficiency and phytotoxicity report of the EO or its active agent. The polymers serve to encapsulate EO or its active ingredient through the formation of different morphological nano-range forms [126]. Starch and its derivates (dextrins, maltodextrins, cyclodextrins), chitin, alginates, and polyesters (e.g., polyethylene glycol) are usually used for the synthesis of polymeric nanoparticles containing EO [123,127–130]. Thus, the essential oil of *Achillea millefolium* L. encapsulated with chitosan showed long-term acaricidal effects against adult *Tetranychus urticae* Koch due to the slow and persistent release of the essential oil used [131]. *Piper nigrum* L. essential oil has been encapsulated in chitosan nanoparticles, enhancing the fumigant toxicity and altering the neurotransmitter acetylcholine in *T. castaneum* and *S. oryzae* [132].

7. Conclusions

Increasing bioinsecticide adoption has arisen partially due to increasing global food demand, but also increased awareness of food quality, biodiversity, and environmental safety. Although a plethora of reported insecticidal properties have promoted many plant-derived essential oils as potent bioinsecticides, only a handful of them have been registered and are available on regional or global markets. According to a comprehensive research literature survey and analysis of current market offers, production pathways that will likely be considered in the future include the use of EO complexes with potent neurotoxic activity encapsulated to provide a controlled release, increased solubility, durability, bioavailability, and efficiency. The intensive investigation of the insecticidal potential of plant scents should be transferred from the laboratory to real field conditions, new plant species must be taken into consideration and extensive farming practices have to be developed, standard techniques for EO blend isolation have to be upgraded, and all of these steps have to be accomplished with adopted clear registration policies and market regulations.

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