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Ecological costs of botanical nano-insecticides

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Botanical nano-insecticides are a trend in pest control. The natural origin of the active substances, alongside with the methodological approach granted by nanotechnologies are a promising combination of innovation and eco-sustainability, hot topics in the context of ecological transition in agriculture. Nevertheless, their field application is still limited, due to production challenges and risk assessment concerns. Nanoformulations have some advantages over traditional bioinsecticides, including increased bioactivity and persistence, and slow-release rates. Recent research reported promising insecticidal activity of nano-emulsions, micro-emulsions, and nanoparticles loaded with different botanical extracts, oils, and essential oils. Though, despite their proven efficacy against insect pests and vectors, a limited number of studies investigated their safety towards nontarget organisms and fate in the environment. This mini-review provides an overview of the side-effects of botanical nano-insecticides and the main challenges to improve their sustainability in term of ecological and production cost.

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Introduction

In the last decades, ecofriendly pest control has become a key topic to safeguard crop production and ensure food security worldwide. The adverse consequences of the extensive use of synthetic insecticides, naming pesticide resistance, water and soil contamination, and the negative effects on human health and nontarget species, prompted stakeholders to explore innovative and more selective eco-friendly tools [1]. Combining nanotechnological approaches with botanical active substances is a leading trajectory for developing and commercializing innovative bioinsecticides [2]. Synthetic insecticides are usually preferred by farmers because of their superior effectiveness to control pests compared to botanical insecticides [3]. Nevertheless, nano-bioinsecticides often showed higher insecticidal activity, biodegradability, and controlled or targeted release, if compared to the synthetic counterparts [3].

Despite many studies on the efficacy of botanical extracts as insecticides, only a few commercial products are available because some disadvantages limit their use in field conditions [4]. Most bioactive botanicals are secondary metabolites synthesized by plants as a mixture of different molecules, called phytocomplex. Their natural origin secures biodegradability, although it also determines rapid degradation and low persistence, sometimes associated with flammability, poor solubility in water, and phytotoxicity [3,5].

Those negative characteristics are some of the challenges to overcome for the ecological transition in agriculture, which could be mitigated through the application of nanotechnology [6]. Granting improved persistence and efficacy on target pests, botanical nano-insecticides might also prove increased bioactivity toward nontarget organisms, as well as environmental concerns. Nevertheless, those aspects are usually neglected; besides, the selectivity of botanicals is commonly acknowledged, occasionally without a solid scientific ground [7].

In this scenario, the present mini-review explores the use of botanical nano-delivery systems in managing insect pests and vectors focusing on the associated ecological challenges. The primary objective is to define these systems and emphasize their environmental impact, including toxicity to nontarget organisms and

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long-term ecological effects. Nano-delivery systems, such as nanoparticles, nano-emulsions, and nanocapsules are described, and their respective characteristics are highlighted. The recent literature on side-effects of nanoformulations containing active substances obtained from plants or industrial botanical byproducts, rather than chemically-synthesized single molecules (e.g. terpenes) originally identified from botanical sources, is reviewed. Nanodelivery systems where botanicals were used as co-formulants or carriers were disregarded. Lastly, the sustainability of manufacturing processes leading to the production of botanical nano-systems and the future challenges for their development and commercialization are highlighted.

Botanical nanoinsecticides

Overall, nanotechnology refers to materials with dimensions ranging in the nanometric scale (between 1 and 100 nm). Instead, approaches for nanoinsecticidal design refer to nanodelivery systems with particle sizes lower than 1000 nm [8]. Nano-formulations applied to the development of botanical nanoinsecticides consist of two main groups: (i) nano-emulsions and micro-emulsions, and (ii) nanoparticles. Due to their ease of preparation and industrial scalability, both groups can work for innovative pest control formulations [9]. Nanodelivery systems offer several advantages over traditional botanical pesticides, improving surface coverage, dispersibility, controlled release kinetics, and enhancing penetration through the insect cuticles and the plant tissues. Overall, those features can reduce the amount of the active substance required in field conditions, meanwhile increasing pest control efficiency in crop protection [6]. Therefore, the efficacy of botanical nano-insecticides was well studied against different crop and stored product pests, as well as insect vectors [10,11].

Nano and microemulsions

Among all the nanodelivery systems, nanoemulsions (NEs) and microemulsions (MEs) have been the most common in the design of nano-insecticides from botanical extracts. NEs and MEs are dispersed systems composed of a mixture of immiscible liquids (e.g. oil and water) stabilized by an emulsifying agent. NEs and MEs can be mainly developed through bottom-up and top-down approaches [12]. Top-down methods, utilizing high-energy systems (i.e. sonication, high-pressure homogenization, or micro-fluidization) offer some advantages, such as precise control over physical properties and the scalability for large-scale production. Bottom-up approaches require low-energy (e.g. self-emulsification, phase inversion concentration or temperature, precipitation) and are advantageous in terms of versatility and the ability to develop materials with unique properties. The choice of the adequate method is a key issue to balance NE and ME characteristics and production's energy costs [13].

NEs and MEs can be applied to insecticidal formulations to make some lipophile botanical extracts miscible with water. This is the case of several vegetable oils, such as neem and castor oil, and essential oils (EOs). Some of those botanical extracts are quite common pests and vector control tools, although some drawbacks can impair their efficacy in field conditions [14].

Nanoparticles

Nanoparticles (NPs) refer to solid or liquid nanomaterials, such as nanospheres and nanocapsules, derived from substances capable of absorbing or encapsulating active substances. Various approaches can be used to develop NPs, including precipitation, solvent evaporation, and melt dispersion, utilizing materials like poly-ε-caprolactone (PCL), polyethylene glycol (PEG), silica, chitosan, and zein [15]. These nanoformulations can absorb, dissolve, encapsulate or entrap different botanical active substances, such as EOs, pyrethrins, rotenone, neem oil, and other plant extracts. Their insecticidal efficacy was proven against several crop and stored product pests, as well as on mosquito vectors [16]. The materials used to produce the nanocapsules or nanospheres can alter several physicochemical characteristics of the botanical extracts, influencing the release rate, the persistence and the bioavailability of the phytocompounds. However, the inclusion of active substances inside a protective shell can also assume undesired effects, like bioactivity reduction and residual presence on crops.

Are botanical nanoinsecticides ecofriendly and sustainable?

The impact of botanical nanoinsecticides for pest control on the biota of both natural and agroecosystems is still far to be clarified. However, nanoformulated substances could potentially impact several ecological components and processes. Recently, the environmental impact and fate of nanopesticides have been reviewed, dealing with different aspects of eco-sustainability [17–19]. Nevertheless, those studies mainly focused on metallic NPs or nanoformulations containing synthetic insecticides, highlighting the need of a focused revision of the literature on botanical nanoformulations. However, some of the considerations and concerns defined for synthetic and metallic nanomaterials cannot be extended to plant-based nano-insecticides since, for their nature, those are more prone to biodegradation.

Side effects on nontarget species

The potential adverse effects of botanical-based nano-insecticides towards nontarget organisms, including arthropods (such as natural enemies and pollinators), aquatic and soil organisms and microorganisms, plants, as well as humans, are still uncertain. Indeed, the undesirable effects of plant-based nanopesticides depend on several factors, including the particle number, concentration, size, distribution, and application rate [20].

However, the selectivity of bioinsecticides is commonly acknowledged and, thus, extended to nanobiopesticides. Nevertheless, current literature about the nontarget impact of botanical insecticides reported contrasting results [7], and the same may also be supposed for their nanoformulations. For example, pyrethrum-based nanopesticides did not significantly affect honeybee survival, whereas unformulated pyrethrum reduced bee longevity and caused morphological alterations in the midgut [21]. Natural enemies, such as insect predators and parasitoids, merit attention when considering the use of botanical nanoinsecticides for crop protection [22–24]. Among invertebrates, aquatic microcrustaceans, like *Daphnia magna* Straus, and earthworms, such as *Eisenia fetida* Savigny, are recognized model organisms for ecotoxicological study, which can help to understand the activity of xenobiotics on different organisms of the agroecosystem trophic chain [25–27]. Furthermore, botanicals may influence soil microorganisms, including soil nitrogen cycle microbiota [28], while their nanoformulation could be more selective [29]. Lastly, the safety of several EO-based NEs toward mammalian [30–32] and human cell lines has been reported [31–34]. The impact of botanical nanoinsecticides toward nontarget organisms is detailed in Table 1. To date, severe acute toxicity has not been reported for tested nanoinsecticides, although further research is required to safely apply botanical nanosubstances in the field.

Environmental persistence

A further key issue about botanical nanoinsecticides is the environmental impact assessment, in particular their accumulation in soil, water, plants, and foods. In this context, the most common methodologies for studying the behavior and fate of nanoformulated pesticides in soil and water were discussed [48]. In aquatic and soil environments, the physicochemical properties of the botanical nanomaterials can alter some physicochemical characteristics and influence both the biotope and the biocenosis [45,49]. The European Food Safety Authority (EFSA) published a guideline on the food safety assessment of nanoformulations applied in agriculture [50]. Since the nanoinsecticides may not be environmentally safe, deeper knowledge about the fate of botanical nanosystems is required. Life cycle assessment (LCA) in soil, water, and plants could be an interesting approach to estimate the safety of botanical nanomaterials, since in open fields their fates depend on their physicochemical properties (e.g. particle size, surface chemistry, and charge) and bioactivity, alongside with field conditions (e.g. soil/water composition and climate), which can alter biodegradation and bioavailability processes [51], including soil enzymatic activity [24,52].

The possible bioaccumulation in the environment and the biomagnification through the trophic chain are the most concerning aspects related to the field application of botanical nanoinsecticides, although few studies have tried to investigate those aspects [53,54]. Nanoformulations could increase the soil half-life of some synthetic pesticides up to 2-fold, with recorded bioaccumulation in earthworms and plants [55]. On this basis, a similar persistence trend cannot be excluded also for botanical nanoformulations, which can stay active in organic substrates, such as soil and water, for quite a long period due to their controlled release rate and increased stability. In our opinion, long-term studies to fully understand the environmental persistence and potential bioaccumulation of botanical nanoinsecticides is a crucial issue deserving further research.

Sustainability and commercial challenges

Among the characteristic limitations of plant-based nanopesticides, the quantity of coformulants used to stabilize the nanoformulations is a key issue. Some of these substances are known to adversely affect plant growth and cell membrane permeability at high concentrations [56]. The use of natural *versus* synthetic emulsifiers and coformulants should be preferred to improve the complete biodegradation of the nanoformulation in open field conditions [57] (Table 2).

On the other hand, while reducing the use of synthetic coformulants, the botanical active substance included in the nanopesticidal formulation should be highly concentrated; otherwise, high volumes of nanoformulants would be needed for real-world use, causing issues during storage, transport, and application. There are only a few stable nanoinsecticides formulated with high ratios of botanical active substances (i.e. >15%) [e.g. 22,23], although this aspect needs to be further improved to match commercial requirements.

Lastly, the processes employed to produce botanical nanoformulations merit attention. Besides the promising physicochemical characteristics of nanoformulates, some of the proposed approaches require expensive external inputs, such as high energy costs, as well as expensive materials [57]. The environmental impact of the industrial production of nanoinsecticides involves land use for raw material production, carbon and water footprint, as well as waste management. Indeed, when accounting for the sustainability of those insecticides, all these aspects (i.e. from field to commercialization) should be considered. In this framework, the extraction methods of the botanical active substances, the

Table 1

Side effects of botanical nanoinsecticides on nontarget organisms.

Plant species (Family)	Active substance	Type of formulation	Target species	Major results	Nontarget species	Main effects	Reference
Schinus terebinthifolius (Anacardiaceae)	EO	NE	*Culex pipiens*	Larvae: LC_{50} = 6.8 µl/L, LC_{95} = 13.2 µl/L Adults: LC_{50} = 5.3 µl/L, LC_{95} = 11.3 µl/L	*Gambusia affinis*	LC_{50} = 3042.7 µl/ml LC_{95} = 5614.7 µl/ml	[35]
				Repellent at all tested doses (µg/cm^2).	*Eisenia fetida*	Not detected effects on mortality	
Allium sativum (Amaryllidaceae)	EO	NE	*Planococcus citri*	24h: LC_{50} = 0.76%; LC_{90} = 1.378% 48h: LC_{50} = 0.65%; LC_{90} = 1.1%	*Apis mellifera*	Survival: 100%	[13]
				Direct: LC_{50} 0.248%, LC_{90} = 0.967% Residual: LC_{50} = 0.782%, LC_{90} = 1.088%	*Cryptolaemus montrouzieri*	Survival = 90% ± 5.37 at LC_{90}; 84.44% ± 6.7 at 1.25%	[22]
			Tuta absoluta	Eggs: LC_{50} = 0.124%, LC_{90} = 0.772%	*Nesidiocoris tenuis*	Mortality: undetected	[23]
				Larvae: 100% mortality at 3%, 7.78 mortality at LC_{50} eggs		Reduced progeny in treated plants	
				Repellent	Tomato plants	Undetected	
Acmella oleracea (Asteraceae)	EO	NE	*Culex quinquefasciatus*	LC_{50} = 407.5 µL/L	Mammalian fibroblasts and microglia cells	Low level of cytotoxicity and anti inflammatory effect	[33]
Ageratina adenophora (Asteraceae)	4,7-dimethyl-1-(propan-2-ilidene)–1,4,4a,8a-tetrahydronaphthalene-2,6(1 H,7 H)-dione (DTD)	NE	*Spodoptera frugiperda*	*S. frugiperda*: 72h LC_{50} = 47.02 mg/L, 96h LC_{50} = 24.02 mg/L	Cell	Low toxicity	[36]
			Spodoptera litura	*S. litura*: 72h LC_{50} = 14.03 mg/L, 96h LC_{50} = 0.79 mg/L	Earthworms	7d LC_{50} = 40.46(mg/kg); 14d LC_{50} = 37.57 (mg/kg)	
			Ostrinia furnacalis	*O. furnacalis:* 72h LC_{50} = 33.89 mg/L, 96h LC_{50} = 2.19 mg/L	*Zea mais*	Undetected	
Carlina acaulis (Asteraceae)	EO & carlina oxide	NE	*Culex quinquefasciatus*	LC_{50} = 579.1 µL L^{-1}; LC_{90} = 791.3 µL L^{-1}	Human cells	Low toxicity	[31]
				Sublethal effects: LC_{16} (384.5 µL L^{-1}) = 100% mortality after 18 days	Wistar rats	Undetected toxicity (LC_{50} = 5000 mg/kg)	
Tanacetum cinerariifolium (Asteraceae)	Pyrethrins (commercial product)	solid lipid NP	-	–	*Apis mellifera*	Undetected on longevity and digestive cells	[21]
					Lithobates catesbeianus	Genotoxic	[37]
	Pyrethrins (commercial product)	ME	*Aphis gossypii*	Population reduction (%): 3.1 g a.i/hl after7d (90.68%); 1.86 g a.i/hl after 7d (77.66%)	*Coccinella septempunctata*	Undetected	[38]
					Macrolophus pygmaeus	Undetected	

Pimpinella anisum	EO	ME	*Culex quinquefasciatus*	LC_{50} = ranging from 1.45 to 4.01 ml/L	*Daphnia magna*	Low toxicity	[39]
Trachyspermum ammi				LC_{90} = ranging from 1.81 to 6.48 ml/L	*Tubifex tubifex*	High toxicity	
Crithmum maritimum (Apiaceae)					*Eisenia fetida*	Undetected	
Smyrnium olusatrum (Apiaceae)	Isofuranodiene	ME	*Culex quinquefasciatus*	24h: LC_{50} = 17.7 ml/L, LC_{90} = 39.1 ml/L	*Daphnia magna*	Mortality: 18.7% (32 ml/L)	[40]
				7d: LC_{50} = 4.1 ml/L, LC_{90} = 11.3 ml/L	*Eisenia fetida*	Undetected mortality	
Cannabis sativa (Cannabaceae)	EO	NE	*Culex quinquefasciatus*	LC_{50} = 72.2 ppm; LC_{90} = 207.2 ppm	*Daphnia magna*	Mortality <16% at LC_{90}	[41]
Cupressus sempervirens (Cupressaceae)	EO	NE	*Culex quinquefasciatus*	Larvae: LC_{50} = 11.4 μg/ml, LC90 = 19.7 μg/ml	*Gambusia affinis*	LC_{50} = 1488.4 μg/ml	[42]
				Adults: LC_{50} = 7.2 μg/l, LC_{90} = 13.1 μg/l; Repellent at all tested doses (μg/cm^2).		LC_{90} = 2425.5 μg/ml	
Croton linearis (Euphorbiaceae)	EO	NE	*Aedes aegypti*	LC_{50} = 17.86 μg/mL	Human cells	Undetected effects (LC_{50} > 2000 mg/kg)	[32]
Aeollanthus suaveolens (Lamiaceae)	EO	NE	*Aedes aegypti*	24h: LC_{50} = 54.23 μg/mL, LC_{90} = 96.96 μg/mL 48h: LC_{50} = 46.06 μg/mL, LC_{90} = 75.31 μg/mL	*Mus musculus*	Undetected effects (LC_{50} > 2000 mg/kg)	[30]
Mentha piperita (Lamiaceae)	EO	Polymeric NP	*Sitophilus oryzae*	*S. oryzae:* LC_{50} = 130.5 μg/cm^2, LC_{90} = 327.61 μg/cm^2	*Artemia salina*	LC_{50} = 24.74 ppm, LC_{90} = 47.72 ppm	[43]
			Lasioderma serricorne	*L. serricorne:* LC_{50} = 162.04 μg/cm^2, LC_{90} = 348.86 μg/cm^2			
			Culex pipiens	*C. pipiens:* LC_{50} = 66.02 μg/cm^2, LC_{90} = 122.43 μg/cm^2			
Mentha spicata (Lamiaceae)	EO	Chitosan NP	*Callosobruchus maculatus*	*C. maculatus:* LC_{50} 56 μL/L	Vero cell line	Undetected effects	[34]
			Sitophilus granarius	*S. granaries:* LC_{50} 47 μL/L			
Persea venosa (Lauraceae)	EO	NE	*Dysdercus peruvianus*	LC_{50} = 28.73 μg/μL	*Apis mellifera*	Undetected mortality	[44]
					Partamona helleri	Undetected mortality	
Azadirachta indica (Meliaceae)	Neem oil	zein NP	-	–	*Allium cepa*	Decreased mitotic index	[28]
						Slightly increased damage index	
					Soil nitrogen cycle microbiota	Undetected	
					Caenorhabditis elegans	Undetected	
		PLC NP	-	–	Soil microbiota	Undetected until 300 days	[29]
					Zea mays	Dose-responsive phytotoxicity	
					Allium cepa		
	Neem gum	Nano-suspension	*Helicoverpa armigera*	LC_{50} = 10.20 ppm; LC_{90} = 32.68 ppm	*Eudrilus eugeniae*	Undetected mortality	[26]

(*continued on next page*)

Table 1. (*continued*)

				Antifeedant Pupal toxicity			
			Spodoptera litura	LC_{50} = 12.49 ppm; LC_{90} = 36.68 ppm; Antifeedant Pupal toxicity			
Myristica fragrans (Myristicaceae)	EO	chitosan NP	-	–	Rice	Reduced peroxidase activity	[45]
						Undetected phytotoxicity on seed germination	
					Mice	LC_{50} = 9231.89 μL/kg	
Syzygium aromaticum (Myristicaceae)	EO & Eugenol	zein NP	*Drosophila melanogaster*	Mortality after 14 days: 100% (Zn-EO) & >60% (Zn–Eu)	*Caenorhabditis elegans*	Low toxicity	[46]
Cymbopogon martinii (Poaceae)	EO	Polymeric NP	*Sitophilus oryzae*	*S. oryzae:* LC_{50} = 128.82 μg/cm^2, LC_{90} = 209.37 μg/cm^2	*Artemia salina*	LC_{50} = 30.74 ppm, LC_{90} = 69.97 ppm	[43]
			Lasioderma serricorne	*L. serricorne:* LC_{50} = 141.08 μg/cm^2, LC_{90} = 321.81 μg/cm^2			
			Culex pipiens	*C. pipiens:* LC_{50} = 53.12 μg/cm^2, LC_{90} = 105.55 μg/cm^2			
Citrus sinensis	EO	NE	-	–	*Nesidiocoris tenuis*	*C. reticula* causes lethal and sublethal effects	[24]
					Soil activity	Undetected	
Citrus reticulata					Tomato plant	Undetected	
		PEG NP			*Nesidiocoris tenuis*	*C. reticula* causes lethal and sublethal effects	
Citrus limon (Rutaceae)					Soil activity	Undetected	
					Tomato plant	Undetected	
Murraya koenigii (Rutaceae)	EO	NE	*Aedes aegypti*	LC_{50} = 11,8 μg/ml, LC_{90} = 22,6 μg/ml	*Allium cepa*	Antiproliferative	[47]
Siparuna guianensis (Siparunaceae)	EO	Chitosan NP	*Aedes aegypti*	Mortality 7d: 100%	*Poecilia reticulata*	Mortality 24h: <30% (0.83 mg/mL)	[27]
					Danio rerio	Mortality 24h: <30% (0.45 mg/mL)	

Table 2

Common coformulants used to produce nanoinsecticides.

Substance	Description	Advantages	Disadvantages
Polysorbates (Tween)	Ethoxylated sorbitan esterified with fatty acids Amphiphilic, synthetic nonionic surfactants	Biodegradable in soil Used as wetter on agricultural crops	Phytotoxicity (high concentrations) High amount required Expensive
Sorbitan esters (Span)	Sorbitan esterified with fatty acids Amphiphilic, synthetic nonionic surfactants	Biodegradable in soil	Phytotoxicity (high concentrations) High amount required Expensive
Polyethylene glycol (PEG)	Linear polyether Synthetic coating	Biocompatible Soluble in water and most organic solvents	Dry formulations Moisture degradation
Polycaprolactone (PCL)	Linear aliphatic polyester Synthetic adsorbent, coating	Biocompatible Long term persistence	Hydrophobic Residual problems
Polyvinyl alcohols	Vinyl polymer Synthetic thinner, emulsifier	Biocompatible Water-soluble	Low persistence High degradability
Silica	Amorphous mineral, natural or synthetic Adsorbent	Biostimulant on several crops Natural or synthetic	High temperature ROS generation Limited water solubility
Alginates	Linear anionic polysaccharide Adsorbent, coating, emulsifier	Natural product Water soluble	Intrinsically variable structure Not degradable by mammals
Chitosan	Linear polysaccharide Emulsifier, coating	Natural product Biostimulant on several crops	Insoluble in water and organic solvents Variable molecular weight and deacetylation degree
Zein	Plant protein isolated Adsorbent, coating, emulsifier	Natural product Soluble in organic solution	Expensive Low stability, enzymatic degradation
Pectin	Linear polysaccharide Emulsifier, coating	Natural product Soluble in water	Intrinsically variable structure Strong retention

production technologies, byproduct disposal, but also the storage requirements (i.e. refrigeration), could greatly impact on the sustainability of botanical nanoinsecticides [5,58]. Researchers are beginning to face these challenges, as for the bioproduct management, proposing alternative and more sustainable methods (i.e. solvent-free extraction) [59].

Conclusions

Although the potential of botanical biopesticides has been recognized by a growing body of literature, to date only a few biopesticides are commercialized and used by stakeholders [4]. This could be explained by the limited effectiveness of botanical insecticides in the field. Nevertheless, the dangers associated with synthetic insecticides became clear once residuals accumulated in soil, water, and plants and contaminated the environment, highlighting that in several cases the risks have outweighed their benefits [58].

A similar misconnection between research and market is apparently occurring also for botanical nanoinsecticides. Undoubtfully, their widespread adoption and commercial development hinge on addressing ecological concerns, optimizing formulation processes, and ensuring compatibility with environmental and human health standards. Therefore, risk assessment of nanomaterials has become a trend challenge to face in the next future. However, common methodologies and frameworks for risk assessment of botanical nanoinsecticides are still lacking, posing difficulties to assess and compare their side effects on nontarget species, as well as their impact and risks on aquatic and terrestrial ecosystems, biodiversity, and food webs.

Overall, besides the encouraging results available from the literature on their ecotoxicology, the risk assessment and the sustainability of botanical nanoinsecticides need further investigation to validate both industrial scalability and environmental safety.

Author's contributions

Antonino Modafferi Visualization, Writing- Original draft preparation. **Giulia Giunti** Conceptualization, Visualization, Writing- Original draft preparation. **Giovanni Benelli** Validation, Writing- Reviewing and Editing. **Orlando Campolo** Conceptualization, Writing- Reviewing and Editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Giovanni Benelli is a Guest Editor of the Special Issue "*Environmental Toxicology 2025: Non-target effects of Bio-insecticides*". Giovanni Benelli has not been involved in decisions about the present article, peer review of the present submission has been handled independently of the guest editor and his research group. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data were used for the research described in the article.

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** of outstanding interest

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