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The Effects of Neurotoxic Insecticides on Insect Antioxidant System Parameters: A Mini-Review

Kseniya Maslakova*, Elena Silivanova

Abstract

The resistance of insects to insecticides is one of the most pressing problems of our time. The study of resistance mechanisms is an important link in addressing a whole range of fundamental and practical problems of modern biology. The long-term and intensive use of insecticidal products was caused by the resistance development of different insect populations. Exposure to insecticides results in oxidative stress and changes in the antioxidant status of insects. The current review was aimed to accumulate the results of studies of neurotoxic insecticides in terms of their impacts on the parameters of the insect antioxidant system. Literature sources were searched by utilizing electronic databases. The gathered information was studied and structured. The review characterizes the insect antioxidant system, classifies insecticides by mechanism of action, and demonstrates the link between insecticide exposure and oxidative stress. The results show that insecticides with different active ingredients can have a significant effect on the antioxidant status of insects of different species. In some cases, this is manifested by an increase in activities of enzymes and in other cases – by a decrease. Thus, the stimulation of oxidative stress and the impairment of insect antioxidant capacity are the toxicity mechanisms of most insecticides.

Introduction

Insects, like any other living organisms, encounter a wide variety of environmental factors during their lives. Oxidative stress is an important consequence of external influences on the insect body [1]. It occurs specifically in response to the toxic effects of various chemical and biological compounds, including insecticides. Under intensive agricultural conditions, insects are intentionally or unintentionally exposed to a number of synthetic pesticides and other chemicals (e.g. fertilizers) [2]. Pesticides are chemical components applied against undesirable organisms such as insects, rodents, fungi, weeds, and other pests [3, 4]. Pesticides limit reproductive power, impair the survivability of the insect at various stages of its life cycle and cause its death [5-8]. They exercise a stimulating effect on lipid peroxygenation processes (LPO), oxidation processes of proteins, sugars and DNA [9]. The excessive use of insecticidal products has adverse effects on non-target organisms, leads to environmental pollution and disrupts the balance of ecosystems [10-13]. Specifically, chemicals can harm beneficial insects such as pollinators [14] and natural predators (entomophages) [15-17]. For example, the negative impact of insecticides on honeybees (important pollinators) is manifested, in addition to mortality, in disruption of behavior, learning, and other neurophysiological functions [18], the cause of which may lie in apoptosis in bee tissues caused by oxidative stress under the treatment of insecticides [17]. The additional example of damaging effects of insecticides on beneficial insects is an evaluation of exposure to insecticides of different chemical classes (neonicotinoids, pyrethroids, organophosphates) on biological parameters of parenteral and offspring generations of *Coccinella septempunctata* L. (Coleoptera: Coccinellidae), a natural predator that is a useful biological control agent. This study demonstrated that at sublethal doses all these insecticides significantly suppressed adult emergence, adult weight, fertility and fecundity [19]. Decreased fecundity after exposure to sublethal concentrations of imidacloprid was observed also in *Metopolophium dirhodum* Walk. (Hemiptera: Aphididae) [20]. It is known that insect development and reproduction are subjects of hormonal regulation (juvenile hormones, ecdysteroids, and regulator peptides). On the other hand, discussed the ability of the adipokinetic hormones (AKHs), one of main regulators of the insect metabolism, to impact on oogenesis and larval development via inhibition the synthesis of egg yolk protein, the mobilization of energetic substrates and the regulation of fat body dynamics [21]. There are studies demonstrating the increased change to titer of AKHs and the changes in AKH transcription regulation in insect bodies due to the oxidative stress including that caused by insecticides and bioinsecticides [22-23].

The oxidative stress is considered as a disbalance between the production of reactive oxygen species (ROS) and the organism's power to counteract the reactive molecules and the damage they cause [24-25]. Among ROS, superoxide radical anions ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) are prominent [26]. Hydroxyl radicals and hydrogen peroxide are able to form inside or enter the cell by diffusion [27-28]. Normally, ROS are produced by metabolic processes in cells; however, when their concentration exceeds their physiological limits, they begin to act as pro-oxidants and cause oxidative damage to biomolecules [29-31]. Radicals can modify and damage important biomolecules such as proteins, RNA, DNA, and membrane lipids [28, 32]. The imbalance of free radicals has a direct impact on LPO [33]. In insects, oxidative stress can be induced by different types of pesticides [27, 34-38]. The exposure to different classes of insecticides promotes the increased production of ROS and their reactive metabolites and therefore induces oxidative damage in insect tissues [27-28, 39-42]. According to Abdollahi M. et al., [43], the mechanisms of toxicity of most pesticides are: stimulation of free radical production; induction of LPO; and disruption of the body's overall antioxidant capacity. Lipid hydroperoxides, diene conjugates, Schiff base, and malonic dialdehyde (MDA) are the products of LPO that are used as an indicator of oxidative stress [44] along with other biomarkers such as adducts of ROS with DNA, ROS-induced protein modifications, and others [45].

Insects have a complex and efficient system of enzymatic and nonenzymatic compounds for self-defense against ROS, which forms a complex response to exposure to various oxidants [46]. In insects, enzymes such as superoxide dismutase (SOD), catalase (CAT), peroxidases (POX) and glutathione S-transferases (GSTs) act as antioxidants [47-49]. SOD, CAT and POX are considered primary defenses against oxidative damage, and GST is an early marker of the detoxification system induction [27]. GSTs operate by conjugating the thiol group of glutathione with ROS and a wide range of xenobiotics (including insecticides and their secondary metabolites), leading to a larger number of polar compounds being eliminated from the body or subjected to further metabolism. Superoxide anion is the substrate of SOD, the enzyme operating in the cytoplasm, the mitochondrial matrix, the hemolymph and molting fluid of insects [50-51]. SOD neutralizes the superoxide radical anion to molecular oxygen and hydrogen peroxide via a dismutation reaction [45, 52-53]. Hydrogen peroxide, in turn, is catalyzed by CAT (reaction of H_2O_2 dismutation) or

POX (reaction of substrate oxidation) [54]. In addition, important component parts of antioxidant defenses are nonenzymatic compounds [47, 55]. In insects, this functionally heterogeneous group of antioxidants includes water-soluble (ascorbic acid, uric acid, glutathione, 3-hydroxykynurenine, trehalose, glucose, glycerol, ethylene glycol) and lipid-soluble (tocopherols, tocotrienols, and carotenoids) compounds as well as antioxidant proteins (transferrin, ferritin). For example, ascorbic acid and glutathione play an important role in neutralizing ROS via reacting with free radicals and damage to biological membranes by free radicals can be prevented by tocopherols. According to Felton and Summers (1995), trehalose, uric acid, ascorbic acid, and glutathione are supposed as main antioxidants in insect hemolymph [47]. The results of the study by Kolawole A.O. et al., [56] strongly confirm the hypothesis that antioxidant systems are activated in response to cytotoxicity mediated by oxidative stress caused by insecticides. The antioxidant mechanism is activated in insect tissue in response to stress and allows them to withstand chemically inappropriate environmental conditions [57].

Thus, insecticide toxicity is directly correlated with the formation of free radicals, induction of oxidative damage, enhancement of LPO and impairment of the overall antioxidant status of insects. The current review was aimed to accumulate the results of studies of neurotoxic insecticides in terms of their impacts on the parameters of the insect antioxidant system. This category of insecticides is chosen because it is quite common and widely used throughout the world.

Methods

Search strategy and selection criteria

Literature was sourced using Web of Science, Scopus, Google Scholar, PubMed. Electronic databases were searched for relevant articles including keywords and phrases such as: "insecticides"; ''insecticide exposure and oxidative stress''; ''insect antioxidant system''; ''free radicals''; ''insecticide classification''; ''lipid peroxidation''; etc. After the relevant information was gathered, the data was examined and structured. In this review, insecticides are discussed according to their ability to induce lipid peroxidation and/or alter the antioxidant status of insects.

Discussion

Classification of insecticide based on mode of action

One of the most common classifications of insecticides is based on the mechanism of action. Currently, the Insecticide Resistance Action Committee (IRAC) covers more than 29 groups of insecticides [58], combined into 4 categories: (1) insecticides affecting neurotoxic processes; (2) insecticides affecting growth and development; (3) insecticides affecting respiratory metabolism and energy metabolism; (4) insecticides affecting gut integrity. A separate category of compounds is also present, but they are not assigned to a particular group and are not classified [59]. Examples of neurotoxic insecticides and their effects on the antioxidant system in different insects are discussed below.

Acetylcholinesterase (AChE) inhibitors

Acetylcholinesterase (AChE, EC 3.1.1.7) hydrolysis the neurotransmitter acetylcholine at cholinergic synapses due to which synaptic transmission in the cholinergic nervous system blockade that is essential for normal function of nervous and neuromuscular systems [60]. Since AChE is a critical enzyme in the nervous system of insects and other animals [61], its inhibitors are used as pesticides in particular as insecticides. Organophosphates and carbamates phosphorylate or carbamoylate the serine of the active site of the enzyme and thereby inhibit AChE. This followed by the increasing of the acetylcholine content in the synaptic region that led to the permanent opening of acetylcholine receptors, and finally, to the insect mortality [62].

Organophosphates

Preparations based on organophosphorus compounds are used rather extensively, as evidenced by the presence of a considerable number of studies devoted to this group of insecticides. Organophosphates (or organophosphorus compounds) are chemical compounds formed by an esterification process involving phosphoric acid and alcohol. These chemicals serve as the main components of herbicides, pesticides, acaricides and insecticides [4, 63]. Organophosphates operate by inhibiting the activity of cholinesterase, an essential enzyme for the nervous system in insects [4]. Chronic or acute exposure to organophosphates can result in varying degrees of toxicity for insects, plants, as well as humans and animals [63]. Examples include malathion, chlorpyrifos and diazinon [64-65].

Chlorpyrifos

Chlorpyrifos is a broad-spectrum insecticide with low persistence in the external environment. The oxon form of the insecticide inhibits acetylcholinesterase in nerve tissues, which results in the accumulation of the acetylcholine neurotransmitter and cholinergic hyperstimulation [66]. Di Nica V. et al., [67] studied behavioral and biochemical changes induced by different concentrations of chlorpyrifos (1.1; 5.24; 11; 52.4; 110; 262; 524 and 1100 ng L^{-1}) in larvae of *Diamesa zernyi* E. (Diptera: Chironomidae). After 72 hours of exposure to high insecticide concentrations (⩾

110 ng L^{-1}), significant oxidative stress was detected, which was expressed as LPO (MDA level) and protein carbonylation (carbonyl level). The impact of this insecticide on the activity of antioxidant enzymes was investigated in *Nilaparvata lugens* S. (Hemiptera: Delphacidae) [68]. Brown planthoppers resistant to chlorpyrifos were selected over eight generations. The core result of the study was that the increase in the LD50 value of chlorpyrifos concurrently increased the activity of SOD, CAT and POX, which also increased gradually and from generation to generation. Using qRT-PCR, it was established that CAT is not directly involved in chlorpyrifos detoxification but insecticides can induce its transcription. The change in CAT activity correlated with chlorpyrifos toxicity, which may indicate that this enzyme performs a very important function in the antioxidant defense of *N. lugens* and may act as a biomarker of oxidative stress.

Methidathion

Methidathion is a non-systemic organophosphorus insecticide and acaricide with gastric and contact toxicity. This chemical is applied against insect and mite pests on different crops such as nuts, cotton and fruits. This insecticide is especially effective against scale insects [69]. Aslanturk A. et al., [70] evaluated the impact of methidathion LC50/48h on MDA levels and the activity of SOD, CAT and glutathione peroxidase (GPx) in midgut tissues of *Lymantria dispar* L. larvae (Lepidoptera: Erebidae). The treated larvae exhibited an increase in MDA level and activity of all the above enzymes in comparison with the control group. Therefore, methidathion causes an increase in oxidative stress, which induces antioxidant defense mechanisms in the insect.

Malathion

Malathion is a broad-spectrum insecticide for agricultural, industrial and household use. It has low stability in the environment. Oxidative desulfurization converts malathion to malaoxon, which inhibits acetylcholinesterase in nerve tissues. Malathion exhibits moderate or high toxicity to non-target organisms [71]. In their study, Mehdi M. et al., [35] cultivated a population of fruit flies *Drosophila melanogaster* Meigen (Diptera: Drosophilidae) under malathion exposure. After exposure to malathion, no significant difference in the levels of MDA lipid peroxidation biomarker was observed, when compared to the flies of the control group. Unaltered MDA levels in malathion-treated flies demonstrate decreased effects of insecticide-induced oxidative stress.

Dimethoate

Dimethoate is a systemic and contact acaricide/insecticide of indirect action that is used against a number of arthropods including mites, flies, aphids and cicadas. Omethoate is its primary metabolite; it has higher efficacy and effect than dimethoate. Qadri H.A. et al., [72] used *Bombyx mori* L. (Lepidoptera: Bombycidae) as a model organism to study the effect of dimethoate on the intestine, silk gland and fat tissues of the insect's body. Sublethal doses of dimethoate induced LPO in the silk glands, intestine and fat body of *B. mori*, damaging these tissues directly. In addition, a decrease in the level of reduced glutathione (GSH) and the activity of the following antioxidant enzymes was observed: CAT, SOD, GPx, and GST. This may indicate that dimethoate caused a shift in the ROS balance towards the formation of free radicals and, therefore, led to the overall damage to the insect organism.

Diazinon

Diazinon is a non-systemic insecticide used in agriculture to control insects on fruit, vegetable, nut and field crops [73]. The effects of diazinon were studied on *Pimpla turionellae* L. (Hymenoptera: Ichneumonidae) using a synthetic diet with different concentrations of the insecticide (from 0.01 to 0.75 ppm). Sublethal concentrations of diazinon were administered to *P. turionellae* over 24, 48, 72, and 96 h to determine the activity of antioxidant system enzymes. The researchers identified different antioxidant responses to insecticidal stress depending on the concentration and time of diazinon exposure. Compared to the control group, at high concentrations especially (0.50 and 0.75 ppm), diazinon boosted SOD activity. It also boosted CAT activity, but this increase was not consistent. CAT activity did not drop below control levels, while SOD activity, in this case, had more significance in defending against diazinon toxicity in this insect [74].

Carbamates

Carbamate insecticides are represented by a wide range of substances with different chemical and physical properties. Carbamates are N-methylcarbamates derived from carbamic acid [75]. Carbamates are used as herbicides, insecticides, nematicides and fungicides. Carbamate preparations are similar to organophosphorus preparations in mechanism of action, but they differ in their chemical structure. Carbamate insecticides, like organophosphorus insecticides, inhibit acetylcholinesterase, which leads to the retention of neurotransmitter in autonomic and certain central synapses, as well as in autonomic postganglionic and neurotoxic junctions [76]. The toxicity of carbamate compounds varies by molecular structure, but they generally have a shorter duration of action than the toxicity of organophosphates and organochlorine compounds [3]. Examples include

carbaryl, methomyl, formetanate, and propoxur [77-78].

Carbaryl

Carbaryl, a broad-spectrum insecticide, applied against agricultural pests, is a typical representative of this group. Its toxicity is based on an inhibition of the acetylcholinesterase enzyme in the nervous system, resulting in acetylcholine accumulation and cholinergic hyperstimulation. It exhibits high toxicity to non-target organisms, including honeybees [79]. The toxic effects of carbaryl were studied on larvae of *Spodoptera exigua* H. (Lepidoptera: Noctuidae) [80]. These insects were highly sensitive to this insecticide, and multiple malformations were observed. Carbaryl depleted crude body fat mass and altered (increased in most cases) the activity of antioxidant enzymes. All this implies serious metabolic abnormalities and also indicates that ROS may play an important role in the toxic action of carbaryl.

Formetanate

Staroň M. et al., [27] investigated the activity of antioxidant enzymes SOD, CAT and GST in homogenates of *Apis mellifera L.* larvae (Hymenoptera: Apidae) bred in vitro, after a single exposure to the formetanate insecticide. After exposure, a decrease in specific SOD activity and an increase in CAT and GST activity were observed. This suggests that an induction of oxidative stress occurred in response to insecticidal exposure. This is confirmed by higher levels of thiobarbituric acid reactive substances (TBARS), that allow to assess MDA content in the sample.

GABA-gated chloride channel blockers

Gamma-aminobutyric acid (GABA) is the major neurotransmitter of neuronal inhibition. Some of nowaday used insecticides (for example, lindane, endosulfan and fipronil) target the GABA receptor/chloride ionophore complex and operate as its antagonists by steading non-conducting conformations of the chloride channel. As a result of reduced neuronal inhibition due to blockade of the GABA-gated chloride channel, the nervous system becomes overexcited, leading to seizures and death [81].

Phenylpyrazoles (fiproles)

Fipronil

Fipronil is extensively used worldwide as a phenylpyrazole-based broad spectrum insecticide. This is an insecticide that affects the γ-aminobutyric acid (GABA) receptor and exhibits favorable selective toxicity to insects [82]. It is known about a high toxicity of fipronil to non-target insects, especially to pollinators. Farder-Gomes C.F. et al., [83] studied behavior, brain morphology, antioxidant activity and proteins associated with signaling pathways in the brain of worker stingless bees *Partamona helleri* F. (Hymenoptera: Apidae) under the acute fipronil exposure. According to the study, exposure to fipronil decreased CAT enzyme activity and increased GST activity but not affected SOD activity in insects.

Also, the toxic effect of fipronil was studied by Jameel M. et al., [84] on larvae of *Spodoptera litura* F. (Lepidoptera: Noctuidae). The insecticide was fed to larvae (stage 4) of *S. litura* over a 12-72-hour period. A variety of molecular, biochemical and organismal parameters were studied. Significant dose- and time-dependent changes were observed in biochemical parameters such as SOD, GST and CAT activity; levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) and TBARS in insecticide-exposed larvae.

The effects of fipronil, sulfluramid and metallic insecticide complex [Mg(hesp)2(phen)] on SOD and GSH activity, and the overall antioxidant capacity was studied in leafcutter ants *Atta sexdens* L. (Hymenoptera: Formicidae) workers. *A. sexdens* was exposed to insecticides for 24, 48, 72 and 96 hours. According to the results, sulfluramid may be a mainspring of ROS production, although its slow action in insects does not cause oxidative stress. A significant increase in SOD was a sign of oxidative stress activation in workers treated with fipronil, as opposed to the control group. [Mg(hesp)2(phen)]-complex suppressed both GSH and SOD [38].

Sodium channel modulators

Sodium channels play an important role in the initiation and propagation of action potentials along neurons. Modulators change the activity of sodium channels shifting their state to permanent open that leads to hyperexcitation or nerve block [85].

Pyrethroids, pyrethrins

Pyrethroids are widely used to protect plants, in veterinary science and medicine. This class of insecticides is capable of influencing voltage-gated sodium channels, which provokes an influx of sodium ions into nerve cells and stable depolarization [86]. The pyrethroid group is represented by both natural pyrethrins from pyrethrum flowers and their synthetic derivatives [4, 87].

Permethrin and fenvalerate

Fenvalerate and permethrin are synthetic pyrethroid insecticides widely used against pests even against resistant ones to other classes of insecticides (organochlorines, organophosphorus and carbamates). It is effective against insects and related organisms, molluscs and various invertebrates in agriculture [88]. Akbar S.M.D. et al., [89] studied the effect of fenvalerate and permethrin on oxidative stress in the

cotton bollworm *Helicoverpa armigera* H. (Lepidoptera: Noctuidae). The results indicate that both insecticides induce LPO, H_2O_2 and lactic dehydrogenase leakage; they alter the activity of antioxidant enzymes leading to oxidative stress in cells, contributing to the damage to the growth of *H. armigera* larvae by these insecticides. The decrease in glutathione reductase (GR) activity depended on the exposure time and dose of insecticides, whereas CAT activity was unaffected in insecticide-treated larvae. GR is a regulatory enzyme of the antioxidant system that ensures the maintenance of the reduced glutathione pool, which plays an important role in ROS control [90].

Lambda-cyhalothrin

Lambda-cyhalothrin is a pyrethroid insecticide that controls a wide range of pests such as aphids and Colorado potato beetle [91]. Motta J.V.O. et al., [92] assessed the extent of midgut cell damage and resulting oxidative stress induced by lambda-cyhalothrin in stingless bees *Partamona helleri* F. (Hymenoptera: Apidae). It is known that this compound can penetrate the intestinal barrier and circulate through the hemolymph, affecting various non-target organs of bees. Bees were administered lambda-cyhalothrin orally. The lethal concentration at which 50% of the bees died (LC50) was 0.043 mg a.i. L^{-1}. *P. helleri* workers were given this particular concentration of insecticide. The results demonstrated evidence of damage and lesions of the midgut.

In another study [93], the effects of chemical insecticides (cypermethrin and lambda-cyhalothrin) and bioinsecticides (ethanolic plant extracts of *Tithonia diversifolia*, *Cyperus rotundus*, *Hyptis suaveolens* leaves and *Jatropha curcas* seeds) were also studied on *Callosobruchus maculatus* F. (Coleoptera: Bruchidae). The increase in the contents of protein carbonyl and LPO processes in groups exposed to biological and chemical insecticides in comparison with the control demonstrates the degree of damage to the vital organs of the insect. GPx and glutathione synthetase levels were significantly elevated in response to insecticide exposure. Changes in the activity of glutathione-dependent antioxidant enzymes seem to reflect the presence of a functional defense mechanism against oxidative stress.

Nicotinic acetylcholine receptor (nAChR) competitive modulators

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels expressed in the central nervous system of insects. These include neonicotinoids, which are widely used throughout the world. The results Lu W. et al., [94] show that there are several nAChR subtypes with different subunit compositions that are responsible for the toxicity of different insecticides.

Neonicotinoids

Neonicotinoids are a type of insecticides that act by interacting with nicotinic receptors of acetylcholine in neurons [95]. They act as agonists of the Na^+/K^+ ionophore, an insect nicotinic acetylcholine receptor, affecting the initiation of electrical signals in the postsynaptic neuron [96]. Neonicotinoids, by acting on nicotinic acetylcholine receptors in insects, cause paralysis and death. Some examples include: imidacloprid, clothianidin, and thiamethoxam [97-98].

Imidacloprid

Imidacloprid is the most well-known utilized neonicotinoid insecticide. It is a broad-spectrum insecticide with excellent systemic and contact activity [99]. It is used to control insect pests of a wide range [100]. The results on the effects of imidacloprid on *D. melanogaster* in field conditions demonstrate that oxidative stress is a key factor in the effect of this insecticide at low doses. Imidacloprid induces a constant influx of Ca^{2+} into neurons and a rapid increase in ROS levels in the larval brain. It affects mitochondrial function, energy levels, lipid environment and transcriptomic profiles [101].

Kang Z.W. et al., [102] studied the short-term sublethal toxicity of imidacloprid in *Aphidius gifuensis* A. (Hymenoptera: Braconidae). Sublethal doses of the insecticide were found to have significant negative effects on the life cycle traits of *A. gifuensis* females, including reduced longevity. Exposure to sublethal doses of imidacloprid significantly increased carboxylesterase (CarEs) and POX activity, whereas no effect on the activity of CAT, GST and SOD was detected. Insect CarEs are enzymes that catalyze the hydrolysis of ester and amide moieties [103]. Enhanced expression of CarEs genes is an important mechanism of insecticide resistance in pests [104]. CarEs can hydrolyse pyrethroids [105], organophosphates [106], neonicotinoids [107].

Wang Y.Z. et al., [100] studied the effects of sublethal dose of imidacloprid on firefly *Pyrocoelia analis* F. (Coleoptera: Lampyridae). The activities of antioxidant enzymes SOD, CAT and POX changed depending on the time after imidacloprid exposure, namely, they increased at the beginning of the exposure and decreased at later stages. Similarly, the enzyme activities of polyphenol oxidase and acetylcholinesterase were increased after the imidacloprid treatment and then decreased at a later stage. In imidacloprid-treated insects, the authors observed a significant increase in MDA content after 12 hours of exposure to the insecticide. The authors suggested the antioxidant enzymes not neutralized overproduction of ROS that were consequences of

disruption in the tissue structure due to imidacloprid exposure at a sublethal dose.

Li W. et al., [108] studied sublethal effects of imidacloprid on biological parameters and enzyme activities, including antioxidant activities, in the Bird cherry-oat aphid *Rhopalosiphum padi* L. (Hemiptera: Aphididae). The LC10, LC20, and LC25 of imidacloprid for adult aphids were 0.0053, 0.0329, and 0.0659 mg L^{-1}, respectively. LC20 and LC25 values significantly inhibited SOD activity, but increased CAT activity. LC20 values increased the acetylcholinesterase activity as well. However, P450 and POX activities were not significantly different between the imidacloprid treated variant and the control.

Ammar H.A. et al., [109] assessed the effects of sublethal concentrations (LD50) of imidacloprid and other four insecticides on oxidative stress and antioxidant system in the cowpea weevil *C. maculatus* by exposing the insect adults to cowpea seeds treated with LC50 of each tested insecticide for 24 h. The authors observed a significant increase in the MDA and GSH content and a significant decrease in the SOD activity after exposure to imidacloprid than that of the control.

Glutamate-gated chloride channel (GluCl) allosteric modulators

The glutamate-gated chloride channels (GluCls) play essential roles in signal transduction by regulating fast inhibitory synaptic transmission in the nervous system of invertebrates [110-111]. The structural and functional diversity of GluCls is generated by the assembly of multiple subunits and through post-transcriptional alterations. Alternative splicing is the most common way to achieve this in insect GluCls, and splicing occurs primarily in exons 3 and 9 [110].

Avermectins

Emamectin benzoate and abamectin

Emamectin benzoate is an insecticide that is widely used to control Lepidoptera. Moustafa M.A.M. et al., [112] investigated the effects of four different formulations of emamectin benzoate (Absolute 5% microencapsulated emulsion (ME), Emi-Mainar 5.7% Water Dispersible granule (WG), Camaro 5% Emulsifiable concentrate (EC), and Proclaim 5% Water Soluble Granules (SG)) on second instar larvae of *Spodoptera littoralis* B. (Lepidoptera: Noctuidae) at sublethal concentrations (LC10 and LC50). The authors reported a significant increase in SOD activity in larvae after exposure to LC50 concentrations of the two formulations (Emi-Mainar and Camaro) and a decrease when exposed to LC50 of Absoluota, Proclaim and LC10 of Emi-Mainar, Camaro, and Absoluota formulations. For the CAT activity, there were no changes in this parameter in all tested larvae with LC10 and LC50 of all formulations.

The effects of sublethal concentrations (LD50) of five different insecticides including abamectin and emamectin benzoate on oxidative stress and antioxidant system were investigated in the cowpea weevil *C. maculatus*. The 24 h- LC50 values of tested insecticides showed that emamectin benzoate was the most toxic insecticide; whereas abamectin was the least toxic insecticide. For the oxidative status assays, the insect adults were exposed to cowpea seeds treated with LC50 of each tested insecticide for 24 h. The results showed a significant increase in LPO, expressed as MDA content, after exposure to emamectin benzoate than that of the control. GSH and GPx were significantly elevated in all tested insecticide treatments in comparison with the control. However, SOD activity decreased significantly, especially when abamectin, indoxacarb and spinosad were administered [109].

Ryanodine receptor modulators

Ryanodine receptors are responsible for the release of calcium into the cytoplasm from intracellular stores and thus regulate insect muscle contraction [113-114]. Ryanodine receptor modulators such as highly active diamide insecticides [115] activate these receptors that result in muscle contraction and paralysis in insects.

Diamides

Plants contain alkaloids that are toxic to insects, for example, ryanodine from the flacourtiaceous plant *Ryania speciosa*. Researches of chemical structure and mode of action of ryanodine discovered it's a modulator activity towards calcium-release channels [116]. Chlorantraniliprole is the main representative of this group of insecticides.

Chlorantraniliprole

Insects exposed to chlorantraniliprole experience muscular paralysis, lethargy and death [117]. Chlorantraniliprole may influence biochemical and molecular parameters of insects. Thus, sublethal effects of chlorantraniliprole significantly reduced the activity of detoxifying enzymes (GST and carboxylesterase) in *Chironomus kiiensis* T. (Diptera: Chironomidae) and *Chironomus javanus* K. (Diptera: Chironomidae). Also, suppression of POX activity in *C. kiiensis* and POX and CAT in *C. javanus* was observed. As shown by gene expression levels, sublethal exposure to chlorantraniliprole affects detoxification and antioxidant capacities [118]. Chlorantraniliprole is widely used for control of *Pieris rapae* L. (Lepidoptera: Pieridae). It is not entirely clear whether chlorantraniliprole induces oxidative stress and whether the SOD enzyme is involved in ROS removal in

P. rapae. Li M.Y. et al., [42] identified and characterized the copper/zinc SOD gene (PrSOD1) in *P. rapae*. Insecticide-induced oxidative stress was indicated in *P. rapae* based on significantly increased MDA concentration in larvae exposed to three sublethal doses of chlorantraniliprole for 6, 12 or 24 hours. Upregulated PrSOD1 transcription levels and CuZnSOD activity in larvae after 6 and 12 h exposure to chlorantraniliprole allowed authors suggest an important role of PrSOD1 in antioxidant defense and possibly chlorantraniliprole tolerance in *P. rapae*.

Franeta F. et al., [119] evaluated effects of different insecticides on the antioxidative defense system of the European Corn Borer *Ostrinia nubilalis* Hbn. (Lepidoptera: Crambidae) larvae. *O. nubilalis* larvae were treated with indoxacarb (250 mL ha-1), or chlorantraniliprole (100 mL ha-1), or chlorantraniliprole+lambda cyhalothrin (200 mL ha-1) and were collected 20 days after exposure. The results obtained in this study showed significantly changed the activities of GST, GPx and the total number of free SH groups after indoxacarb treatment. The CAT and GST activities were significantly increased while the SOD activity and the total number of free SH groups were decreased in insects treated with chlorantraniliprole. And finally, significantly affected the activities of CAT, GST and the total number of free SH groups were observed after treatment with chlorantraniliprole+lambda cyhalothrin. Thus, exposure to these insecticides, especially chlorantraniliprole, significantly affects the antioxidant defense components of *O. nubilalis* larvae.

Octopamine receptor agonists

Octopamine receptor (OR) agonists cause reproductive toxicity through endocrine disruption in both animals and humans. Ahmed M.A.I. et al., [120] showed that sublethal concentrations of chlordimeform and amitraz delayed developmental time, including pupation and hatching in *D. melanogaster*. Thus, octopamine receptor agonists activate the OR in *D. melanogaster*, resulting in increased activity of the enzyme trehalase, resulting in impairment of the octopaminergic system and rapid energy exhaustion in insect.

Amitraz

Toxicity of amitraz was studied on the life cycle and biochemical processes in *Chironomus riparius* M. (Diptera: Chironomidae) [121]. Chronic exposure to amitraz accompanied by the disturbance of developmental parameters (reduced larval growth, emergence, delayed development time). Acute amitraz influence induced changes in the activities of antioxidant enzymes (GPx and CAT), lactate dehydrogenase and electron transport system and in the content of compounds reflecting energetic metabolism. In addition, amitraz exposure led to increased LPO. The oxidation of amitraz is accompanied by ROS production and the consequences of an increase in the ROS content can be oxidative damage, including the increase of LPO [122-123]. Amitraz exposure induced LPO in *C. riparius* larvae, indicating oxidative imbalance and damage. The inhibition of CAT activity and possible accumulation of H_2O_2 could have led to an increase in GPx activity, which has a higher affinity for H_2O_2 compared to CAT. However, the increase in GPx activity was not sufficient to prevent oxidative damage.

Bioinsecticides with acetylcholinesterase (AChE) inhibitory activity

Biological insecticides are derived from natural materials such as microbes, plants (e.g., essential oils, extracts from roots and leaves), animals, nanoparticles, and minerals (e.g., gold/silver nanoparticles) [124-125]. They are used to eliminate agricultural and household insect pests [126].

Essential oils

Essential oils are natural phytochemicals formed in plants as secondary metabolites. They are complex mixtures of volatile compounds, typically containing twenty to sixty individual compounds in varying concentrations [127]. Essential oils are being used more and more as bioinsecticides because they are renewable, natural, biodegradable, non-permanent in the environment and safe for humans and animals [128]. Essential oils derived from various plant species are considered eco-friendly and have been suggested by many researchers for pest control [129]. It was established that essential oils have repellent, ovicidal, larvicidal and insecticidal properties against various pest species, but they also have some disadvantages associated with high volatility and low solubility in water [128]. The results of study Georgiev B. et al., [130] show that alkaloid-rich plant extracts and essential oils have the most intense AChE inhibitory activity, in this regard, they can be recommended for studying insecticidal activity.

Lemongrass and tea tree

In the study by Chintalchere J.M. et al., [36], it was observed that lemongrass and tea tree essential oils exerted a significant effect on AChE activity. Among the above-mentioned oils, lemongrass affected neurotransmission by inhibiting AChE to a greater extent. In the same study, antioxidant responses of *Musca domestica* L. larvae (Diptera: Muscidae) to lemongrass and tea tree essential oils were examined during short-term exposure (24 h). After treatment, larvae exhibited an increase in MDA concentrations, indicating an enhancement of LPO processes. Tea tree

essential oil caused a significant growth in SOD and GPx activity in comparison to lemongrass essential oil. Also, lemongrass essential oil influenced CAT activity significantly.

Lavender

Talić S. et al., [131] showed that *Lavandula angustifolia* Mill showed good inhibitory against AChE. The contact toxicity of the essential oil extracted from *L. angustifolia* and its effects on the biochemical composition and activities of CAT, GPx and SOD in adults of *Rhyzopertha dominica* F. (Coleoptera: Bostrichidae) has been reported [132]. It is shown that the essential oil exhibits contact toxicity to *R. dominica* in a dose-effect relationship. Adults treated with LC25 and LC50 showed an increase in CAT and SOD activity, but did not affect GPx activity. Thus, *L. angustifolia* essential oil can be considered as an alternative to chemical insecticides for controlling *R. dominica* and other pests.

Conclusion

In accordance with the above mentioned, proper optimization of essential oil concentration together with the exposure time to the insect can be a prerequisite for the development of bioinsecticides against house fly populations and other insect pests.

The presented research results clearly show that insecticides of neurotoxic action of different groups promote elevated production of ROS, thereby causing oxidative stress and affecting the antioxidant status of insects by changing the enzymatic activity and the amount of lipid oxidation products. As studies show, this may be manifested by an imbalance of the antioxidant system depending on dose and time of exposure and in an increase in the concentration of lipid peroxidation products as a general rule.

By studying the antioxidant enzyme activity and the quantitative content of free-radical oxidation products in the insect body, it is possible to assess its ability to cope with a given level of insecticidal load. The understanding of insect antioxidant defense responses will allow a targeted approach to the problem of insect population management in the future.

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Author Contributions

Kseniya Maslakova: searching the literature, writing the manuscript; Elena Silivanova: revising the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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