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Toxicity of nanoparticles on insects: A Review

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Abstract

The rapid development of nanomaterials in various fields of science results in being in need of understanding their toxic effects on development and physiology of non-target organisms and environment. Increased production and widespread use of these nanomaterials led to their release into the environment; nevertheless, the knowledge of their behaviour in organisms is scarce. Due to their physical and chemical characteristics, nanoparticles could be more toxic for the organisms than ion forms. Besides, they may enhance the enzymatic antioxidant defence systems, DNA damage, membrane permeability, cell death and also lead to genotoxicity and neurotoxicity in the organisms. Nanoparticles are also growing application in the field of pest management of insects. Therefore, it is necessary to evaluate the adverse effects of nanoparticles on insect species. Hence, in this study, it is summarized the current knowledge about the toxic effects of nanoparticles against insects.

Keywords: Antioxidant enzymes, DNA damage, Genotoxicity, Nanoparticles, Neurotoxicity

Nanopartiküllerin böcekler üzerine toksik etkileri: Derleme

Özet

Bilimde birçok alanda nanomateryallerin kullanımının hızlı bir şekilde artması sonucu bu partiküllerin hedef olmayan organizmaların gelişim ve fizyolojileri ile çevre üzerine toksik etkilerinin belirlenmesi büyük önem taşımaktadır. Nanomateryallerin üretimi ve yaygın kullanımları, çevreye salınımlarını artırmasına rağmen, canlı organizmalardaki davranışları tam olarak bilinmemektedir. Nanopartiküller fiziksel ve kimyasal özelliklerinden dolayı, canlı organizmalarda iyon formlarına göre daha toksik olabilmektedirler. Bunun yanı sıra, enzimatik antioksidan savunma sistemleri üzerinde olumsuz etkilere, DNA hasarına, membran geçirgenliğine, hücre ölümüne neden olmakla birlikte, genotoksik ve nörotoksik etkileri de bulunmaktadır. Son yıllarda, nanopartiküller tarımsal alanlarda zararlılarla mücadelede de kullanılmaya başlanmıştır. Bu yüzden nanopartiküllerin böcekler üzerine olumsuz etkilerinin belirlenmesi büyük önem taşımaktadır. Bu amaç kapsamında, nanopartiküllerin böcekler üzerine toksik etkileri hakkında güncel bilgiler özetlenmiştir.

Anahtar Kelimeler: Antioksidan enzimler, DNA hasarı, Genotoksisite, Nanopartiküller, Nörotoksisite.

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1. Introduction

Nanoparticles production massively increased in the last decade and nowadays these materials are used in a wide range of different areas such as electronics, biomedical, pharmaceutical, cosmetic, energy, environmental, catalytic and material applications [1]. The importance and potential of nanomaterials have catapulted nanotechnology as one of the most rentable and expanding technologies of the 21st century, with a worldwide increase in investment, research and development and with projections of nano-containing products to achieve sales in the order of trillions of dollars [2].

The development and increase in the production and use of nanoparticles predicted for the following years makes it likely that human and environmental exposure to these materials will inevitably occur. As a result, nanoparticles potential adverse effects are beginning to come to light and the discussion about their safety in terms of human health and the environment become a top priority for several governments, the private sector and the public all over the world [3-4].

The recent knowledge of nanotechnology materials and inevitable release into the environment may result in toxic effects not only on human and aquatic organisms but also on the insect species. Although there is much toxicity data on aquatic organisms, the studies on insects are rare. Therefore, it is needed to investigate the adverse effects of nanoparticles on insect species. For example, silica nanoparticles induced high mortality in *Sitophilus oryzae* [5]. Several questions such as the way by which the nanoparticle enter the cell and occur physiological events inside the cell is raised on the toxic effects of nanoparticles. Hence, the aim of this study is to present the studies regarding toxic effects of some kind of nanoparticles on insects.

2. Classes of nanoparticles

There are several ways of classifying engineered nanoparticles being their chemical composition and properties the most commonly used. Other classifications and terminologies are also employed in the literature to refer to specific groups of nanoparticles, based on their dimension, morphology, composition, uniformity, and agglomeration [6-7]. Regardless of how these materials are classified, the extensive variety of nanoparticles even within a single chemical (size, specific surface area, shape) will result in different chemical reactivity, bioavailability and ecotoxicity [8]. Five main groups form the basis of the chemical composition of engineered nanoparticles, carbon-based nanoparticles, metal-containing nanoparticles (including metal oxides), quantum dots, zero-valent metals and dendrimers [7, 9-10]. Nowadays, toxicological research has mainly focused on the effects of three of the five classes of nanoparticles based on their composition: carbon-based nanoparticles (carbon nanotubes and fullerenes) [11-12] and metal or metal-oxide nanoparticles (Ag NPs, CuO NPs, TiO_2) [13-15].

2.1. Metal-containing nanoparticles

Metal-containing nanoparticles comprises the largest number of nanoparticles, which includes oxides such as zinc oxide (ZnO), titanium dioxide (TiO_2), cerium dioxide (CeO_2), copper oxide (CuO), chromium dioxide (CrO_2), molybdenum trioxide (MoO_3), bismuth trioxide (Bi_2O_3) and binary oxides such as barium titanate ($BaTiO_3$), lithium cobalt dioxide ($LiCoO_2$) or indium tin oxide (InSnO) [9-10]. The synthesis of these nanoparticles is very common and is achieved by hydrolysis of the transition metal ions (TiO_2 and ZnO) [16].

Metal oxide nanoparticles have received considerable attention and massively produced over the last years due to their extensive use in food, material, chemical and biological areas [17].

2.1.1. Biological uptake of metal nanoparticles

It is well known that due to a similar size to cellular proteins and components of nanoparticles, nanoparticles are able to cross some of the barriers of biological systems. The cell membrane is selectively permeable and controls the movement of small and large molecules in and out of the cell [18]. Though the cellular uptake mechanisms of nanoparticles are not fully understood, organisms living in environments containing nanoparticles incorporate them within their bodies, mainly by the gut and accumulate inside the cell [19-21]. This accumulation is dependent on their physicochemical properties such as chemical composition, size/geometry, surface charge, coating/ligands and aggregation status. It also relies on the exposed cell type (phagocytes, cancer cells), as well as the microenvironment (surfactant). Nanoparticles can enter cells by diffusing through cell membranes, endocytosis and pinocytosis [22]. As discussed by Moore [23], most internalization of nanoparticles will probably occur via endocytosis (particles up to 100 nm). Endocytosis is a complex mechanism that can occur through several pathways that can either lead to the endosomal and lysosomal compartments (clathrin- or non-clathrin-mediated endocytosis) or else via caveolae-mediated endocytosis (cell-surface lipid raft-associated domains) that avoids the degradation of material entering the endosomal/lysosomal system [24-25].

2.1.2. Toxicity of nanoparticles

Toxicity mechanisms include disruption of membranes, oxidation of proteins, genotoxicity, interruption of energy transduction, formation of reactive oxygen species, and release of toxic constituents. For example, silver nanoparticles (Ag NPs) may cause toxicity via multiple mechanisms such as adhering to the surface, altering the membrane properties, so it affects the permeability and the respiration of the cell [21]. They can also cause DNA damage and release toxic Ag^+ ions. Another study with titanium dioxide nanoparticles (TiO_2 NPs) showed that the development and molting duration of *Bombyx mori* (Lepidoptera: Bombycidae) were reduced by this type of nanoparticle [26].

Even though several evidences exist on the toxicity of nanoparticles, different experimental designs with diverse nanoparticle sizes, coatings, concentrations, times of exposure, measured endpoints and cell types make it difficult to compare results and determine the mode of action by which these particles inflict damage to organisms [27-29]. Generation of reactive oxygen species (ROS) and free radicals have been observed and implicated in the cause of oxidative stress, namely in the form of antioxidant defence system activation/inhibition such as depletion of glutathione, lipid peroxidation and DNA damage, decreased mitochondrial activity, inflammatory processes and apoptosis in a wide variety of cell types [19] [29-30; 32-33].

In insects, nanoparticles damage the organism by penetrating through the exoskeleton [33], enter in the intracellular space, and then the nanoscale material binds to sulfur from proteins or to phosphorus from DNA which leads to the rapid denaturation of organelles and

enzymes. Due to the decrease in membrane permeability and disturbance in proton motive force, loss of cellular function and cell death occur [34-35].

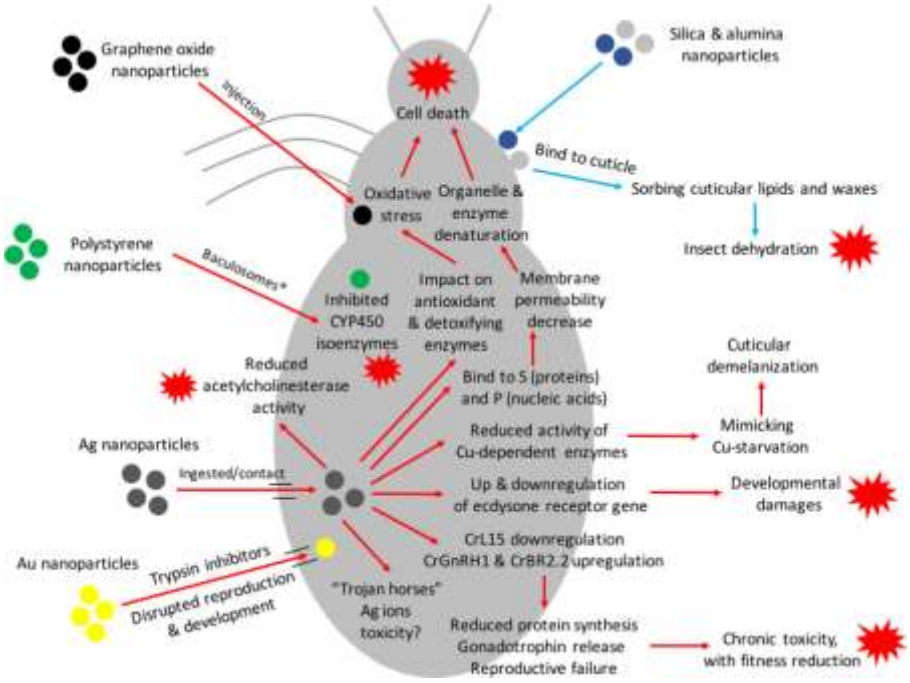

Figure 1. Toxicity mechanisms of nanoparticles against insects [36]

2.1.2.1. Oxidative stress

The generation of ROS is considered one of the most harmful cellular effects induced by exposure to NPs. From a mechanistic perspective, three main hypotheses have been proposed on how NPs can induce intra- and extracellular ROS in organisms: (i) NPs inherent redox-active properties or composition of surface properties, as well as of impurities present in particles preparation; (ii) physical interaction of NPs with cellular and sub-cellular components involved in the catalysis of redox processes; and (iii) NPs persistence in biological systems that can lead to continuous availability over time (by either disaggregate or dissolve) inducing site-specific ROS formation [25] [37].

It is known that several kinds of nanoparticles trigger oxidative stress in arthropod tissues [38-41]. Nair and Choi [38] showed the impact of the commercial silver nanoparticles on the expression of glutathione S-transferase (GST) genes, which are linked with the occurrence of oxidative stress in the aquatic midge *Chironomus riparius* (Meigen). Yasur and Usha-Rani [42] determined that nano silver induced oxidative stress in *Spodoptera litura* and *Achaea janata* larvae by enhancing antioxidant enzyme levels. Later, Mao et al. [41] detected that silver nanoparticles (Ag NPs) led to mortality and detrimental effects on the *Drosophila melanogaster* development and Ag NPs trigger the accumulation of ROS in the *D. melanogaster* fly tissues leading to ROS-mediated apoptosis, DNA damage, and autophagy at sublethal doses. Dziewięcka et al. [43] observed that graphene oxide nanoparticles triggered oxidative stress by increasing the enzymatic activity of catalase and glutathione peroxidases,

as well as heat shock protein (HSP 70) and total antioxidant capacity levels when the nanoparticle injected into the hemolymph of *Acheta domesticus* (L.) crickets. Ahamed et al. [30] also demonstrated that Ag NPs up-regulated the expression of heat shock protein 70 and induced oxidative stress in *D. melanogaster*.

2.1.2.2. DNA damage

DNA is another key cellular component highly susceptible to oxidative damage. Nanomaterials have unpredictable genotoxic properties with several mechanisms controlling their capacity to promote DNA damage. It is known that excessive free radical generation induce DNA damage and apoptosis [44-46]. The main genotoxic effect of nanoparticles comes from the production of ROS, either by the particles themselves, the induction of cellular responses or stimulation of target cells, presence of metallic contaminants or particle induced inflammatory processes. The presence and release or dissolution of transition metal ions such as cadmium, copper, iron, nickel, titanium, zinc from nanoparticles can enhance ROS production by metal-catalyzed Fenton and Haber-Weiss reactions and result in the formation of $OH^{\bullet}$, which are one of the primary DNA damaging species [47-49].

Direct nanoparticles genotoxicity can be caused either by a direct interaction of the particles with DNA or with cellular constituents associated with DNA integrity. Cellular internalization and accumulation of nanoparticles inside cells promote direct interaction with DNA inside the nucleus. NPs enter the nucleus either by direct passage across the membrane, transport through nuclear pore complexes or become trapped within the nucleus during mitosis when the nuclear membrane breaks down and they induce several DNA damages. Genotoxicity data for nanoparticles in insects are rare, they are especially concerning human and aquatic invertebrates. Gogne et al. [50] determined that high concentrations of Cd telluride quantum dots aggregate and accumulate in tissues of *Elliptio complanate* and caused DNA damage in gills and digestive gland. In Japanese medaka (*Oryzias latipes*) exposed to Ag NPs, expression of several stress-related genes showed cellular and DNA damage [51]. In a study with Zebrafish, it was determined that DNA damage such as induction of the p53 gene and double strand breaks was associated with Ag NPs treatments [52]. Later, Kadar et al. [53] also demonstrated that zero-volen Nano iron induce DNA damage in sperm of *Mytilus galloprovincialis* at higher concentrations. Besides, Gomes et al. [54] also showed that CuO NPs and Ag NPs induce DNA damage in hemolymph cells of *M. gallorovncialis* and a time response effect was evident when compared to unexposed mussels. Mao et al. [41] reported that accumulation of ROS in the fly tissues of *D. melanogaster* caused by Ag NPs lead to ROS mediated apoptosis, DNA damage and activation of the Nrf2-dependent antioxidant pathway.

2.1.2.3. Neurotoxicity

The brain is vulnerable to oxidative stress damage (high content of peroxidizable unsaturated fatty acids, high oxygen consumption rate and lack of antioxidant enzymes), and recent evidence suggests that different nanoparticles can cross the blood-brain barrier and gain access to the central nervous system. As an important enzyme in the nervous system, nanoparticles may bind to acetylcholinesterase (AChE) and affect its activity. This enzyme is

responsible for the correct transmission of nerve impulses, by hydrolyzing the neurotransmitter acetylcholine into choline and acetic acid in cholinergic synapses [55-57]. Although organophosphate and carbamate pesticides inhibit AChE activity in the marine environment, this enzyme can be also inhibited by a diverse range of metals [58-59]. Therefore, this enzyme could be useful to assess the potential neurotoxic capacity of some nanoparticles. Nanoparticles may subsequently influence the brain physiology and cause severe side effects. However, there are not many reports, which observed the neurotoxicity of them. Wang et al. [60] found that nasal instillation of TiO_2 NPs can lead to enhancing of AChE activity in brain tissues. Besides, Xie et al. [61] detected that TiO_2 NPs reduced the inhibition of AChE. Milivojevic et al. [62] found that AChE activity in bee workers increased when the bees exposed to zinc oxide nanomaterials (ZnO NMs) and zinc ions (Zn^{+2}). In *M. galloprovincialis*, Gomes et al. [63] demonstrated that AChE inhibition was only detected at the end of the exposure period.

2.1.3. Nanoparticles uptake and toxic effects in insects

Penetration of nanoparticles by the exoskeleton [34], binding the nanoscale material to sulfur from proteins or to phosphorus from DNA in the intracellular space, leading to the rapid denaturation of organelles and enzymes are the main routes of nanoparticles exposure. Then the decrease in membrane permeability and disturbance in in proton motive force may cause loss of cellular function and cell death [35-36].

In the case of insect species, only a few studies exist on nanoparticles uptake, accumulation and toxic effects. Bonumathi et al. [64] reported that ZnO nanoparticles induced 100% mortality when tested at 100 mg/L, the LC_{50} was extremely low, 1,57 mg/L in *Aedes aegypti*. Besides, Mommaerts et al. [65] demonstrated that SiO_2 NPs caused midgut epithelial injury in intoxicated workers of *Bombus terrestris*. Later, Kalimothu et al. [66] detected that Ag NPs induced midgut epithelial cell damage in *A. aegypti*. Sundararajan and Kumari [67] also showed that histopathology of *A. aegypti* with Au NPs after 24h exposure at the highest mortality concentration caused damage in midgut, epithelial cells and cortex.

Fröhlich et al. [68] determined that polystyrene nanoparticles inhibited the enzymatic activity of CYP 450 isoenzymes in Baculosomes®. Armstrong et al. [69] also showed that Ag NPs caused loss of melanin cuticular pigments, reduced vertical flight ability and Cu-dependent enzymes in *D. melanogaster*. Later, Dziewiecka et al. [43] conducted a study regarding increasing of enzymatic activities of catalase and glutathione peroxidase, as well as heat shock protein (HSP70) and total antioxidant capacity levels of *A. domesticus* when exposed to graphene oxide. In *S. litura*, amylase, protease, lipase and invertase activities decreased when exposed to Ag NPs. Moreover, gut microflora, the extracellular enzyme production also diminished as well as weight, pH, and total heterotrophic bacterial population [70]. Besides, Yasur and Usha-Rani [42] determined that Ag NPs induced antioxidant enzyme levels and caused oxidative stress in moth larval guts. As recently pointed out by Fouad et al. [71] total protein levels, AChE, α and β carboxylesterase activities decreased in *Aedes albopictus* and *Culex pipiens* pallens when exposed to Ag nanoparticles. In addition, it is also showed that Ag NPs induced a decrease in total proteins, esterase, acetylcholine esterase, and phosphatase enzymes in 4^{th} instar larvae of *A. albapictus* [72]. Concerning effects of

nanoparticles on genes, Nair and Choi [38] found that GST genes up or down regulated in *Chironomus riparius* according to tested concentration and exposure period. Later, Li et al. [73] showed that upregulation of *pi3k* and *P70S6K* [rapamycin (TOR) signaling pathway], 4 cytochrome P450 genes (20-hydroxyecdysone biosynthesis), were up-regulated and 20-hydroxyecdysone biosynthesis was stimulated when *B. mori* exposed to TiO_2 NPs. Avalos et al. [74] also demonstrated that Ag NPs caused lack of mutagenic and recombinogenic activity in *D. melanogaster*. However, both nanoAg 4,7, and 42 nm evoked pigmentation defects and locomotor ability decreased in adult flies.

3. Conclusion

Overall, although nano-sized particles have always occurred in nature, the latest developments in the use and production of engineered nanoparticles have raised concern over their potential release and side effects not only in human health but also in the environment. In order to determine the fate and behaviour of nanoparticles in the environment, it is necessary to understand their potential risks. The present studies show that due to the abundance of reports on the toxicity of nanoparticles against insects, nanomaterials currently being used in toxicological research still need to be investigated. Further studies need to validate the stability of nanoparticles, their fate in the environment, and sublethal effects on non-target organisms.

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