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TOXICITY OF VARIOUS ENGINEERED NANOPARTICLES ON INSECTS: A REVIEW

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Abstract

Nanoparticles are very small particles that have at least one of their dimensions less than 100nm and have distinctive physical and chemical properties. Due to the fast development and widespread use of various engineered nanoparticles in different fields of science, there is a need for understanding their toxic effects on the growth, development, and physiology of non-targeted organisms. Nanoparticles are very commonly used in the field of pest management of insects. In insects, nanoparticles lead to DNA damage, cell death, oxidative strain, genotoxicity, and neurotoxicity. Oxidative strain is one of the most fundamental causes of nanoparticles persuaded toxicity in insects. Although the studies on the toxic effects of nanoparticles on insects are very few, there is a great need to evaluate their harmful effect on insect species as insects are a very diverse group of organisms and by evaluating the toxicity of nanoparticles on insects, provide a better understanding not only about invertebrate immune response but also about the human immune system as insect and human immune response exhibit several functional similarities. Moreover, as nanoparticles are very widely used in the field of pest management of insects, hence it is very important to determine their adverse effects on them. This review summarizes the current knowledge available on the toxic effects of nanoparticles on insects.

Keywords: *Nanoparticles, Oxidative strain, Toxicity, ROS, Cell death, DNA damage, Neurotoxicity, Genotoxicity.*

Introduction

Insects are the most essential organisms of our ecosystem because of their diversity, ecological role, and influence on human health, agriculture, and natural resources. Insects are an essential part of the food chain and are responsible for the pollination of about 70-80% of trees on the entire planet. Insects play a very crucial role in the decaying of animal and plant matter, which is essential for the release of nutrients that are later utilized for growing plants. Insects can be used as a part of comprehensive solutions to global challenges, including the provision of sustainable fuel, food production, and reducing environmental degradation. The proper care and handling of insects, the ecosystem, and their interactions in a feasible way is crucial for the survival of all organisms. Hence, insects because of their large number, diversity, and ecological position are one of the most essential groups of organisms in our environment. Therefore, any possible and recognized threat to any other form of life can be evaluated in this essential group of organisms as well. Further by investigating the toxicity of nanoparticles in insects provides a valuable understanding not only about invertebrate immune response but also about the human immune system as insect and human immune response exhibit a large number of functional similarities in several aspects e.g., they use similar receptors and effectors and also have a similar regulation of gene expression *(Baun et al., 2008).* It has also been demonstrated that the insect phagocytic cells, the granular cells and plasmatocytes, bear surface receptors that are quite similar to the human neutrophil receptors, and these cells, in insects as well as humans, engulf and kill pathogens and use similar proteins for the production of superoxide *(Kavanagh et al., 2004 and Renwick et al., 2007).*

With the worldwide utilization of various engineered nanoparticles, their increasing usage has now become a matter of public concern *(Huang et al., 2018).* Nanoparticles are very small in size, have unique structures, distinctive physical and chemical properties, and certain particular biological effects *(Chernousova et al., 2013).* The production of various engineered nanoparticles has increased enormously in the last 10 to 15 years and nowadays these nanoparticles are widely used in different fields. Due to their increased production and use, it is obvious that the exposure of the environment to these materials will certainly happen. The inevitable release of nanoparticles into the environment can cause toxic effects not only on humans but also on insect species. Insects are distributed worldwide in nature. However, only a few studies have demonstrated the toxic effects of nanoparticles on them *(Afrasiabi et al., 2016).*In the case of insects, it has been reported that exposure to various nanoparticles causes DNA damage, cell death, necrosis, oxidative strain, cytotoxicity, and genotoxicity. Several studies have reported that silver nanoparticles are responsible for causing oxidative strain and mortality in silkworms (*Pandiarajan et al., 2016 and Meng et al., 2017).* Silver nanoparticles affect adult development, reduce the ability of silkworms to withstand oxidative stress, disturb apoptosis and reduce the expression of detoxification proteins. Silver and graphene oxide nanoparticles also have a considerable impact on insect antioxidant and detoxifying enzymes, leading to oxidative strain and eventually cell death. Nanoparticles cause adverse effects on the reproduction, development, and survivorship of insects. They disturb their intestinal stability and oxidative strain is one of the most fundamental causes of nanoparticles persuaded toxicity in insects. Hence this review aims to present the current status of studies available regarding the toxicity of some of the engineered nanoparticles on insects.

Different classes of nanoparticles and their applications

Based on chemical properties and composition, various engineered nanoparticles have been classified. Five main groups of engineered nanoparticles are:

Carbon-based nanoparticles, metal-containing nanoparticles (including metal oxides), quantum dots, and zero-valent metals and dendrimers 200*(Ju-Nam et al., 2008, Bhatt et al., 2011, Klaine et al., 2008)*. But nowadays toxicological research has focused mainly on the effects of carbon-based and metal oxide nanoparticles *(Oberdorster et al., 2004 and Smith et al., 2007).* These nanoparticles include Zinc oxide, Copper oxide, Cerium dioxide, Chromium dioxide, Titanium dioxide, and Indium tin oxide *(Bhatt et al., 2011 and Klaine et al., 2008).*

Nanoparticles	Applications
Carbon Nanoparticles	They are used as growth stimulators, water purifiers, fertilizers. They are also used for the removal of pollutants, tissue engineering, biosensing, delivery of biomolecules and drug delivery *(Zaytseva et al., 2016).*
Metal Nanoparticles	They are used for thermal excision, drug delivery, gene delivery, radiotherapy enhancement, and anticancer therapy. They are also used for bioremediation of diverse contaminants, water treatment and production of clean energy *(Ayodele et al., 2018).*
Silica Nanoparticles	They are used in the observation of single molecules, bioimaging, extraction of cells and cellular components and disease targeting *(Santra et al., 2004).*
Copper Oxide Nanoparticles	They are used for wound healing, targeted cancer therapy and are efficiently used for sensing and targeting in both vivo and vitro environments *(Ren et al., 2009).*
Zinc Oxide Nanoparticles	They exhibit good biomedical applications such as drug delivery, anti-inflammation, anti-cancer, antibacterial and anti-diabetics. They are also used for bioimaging, biosensing, gene delivery, and immunotherapy and wound healing *(Magrez et al., 2006).*
Cerium Oxide Nanoparticles	They are used for bioremediation, crop improvement, and stress tolerance. They are also used as anti-microbial and anti-oxidative agent, therapeutic agent and as biosensors *(Lorenzo et al., 2017).*
Silver Nanoparticles	They are used as anti-bacterial agents in the medical industry, used for food storage, wound dressings, textile coating and have many environmental applications as well *(Zhong et al., 2007).*
Gold Nanoparticles	They are exclusively used for the detection of microbial cells and their metabolites, bioimaging of tumor cells, detection of receptors on their surface and for the study of endocytosis *(Wang et al., 2010).*

Toxicity of various engineered nanoparticles on insects:

Various studies illustrated that nanoparticles enter inside the organism's body during ingestion or inspiration and can move within the body to various tissues and organs where the nanoparticles have the potential to exert toxic effects. Nanoparticles cause the degradation of enzymes and organelles by penetrating through the exoskeleton and then binding to sulfur or phosphorous from the DNA. This is the major pathway of nanoparticle exposure. Then they reduce the permeability of the membrane and affect the cellular function leading to cell death *(Benelli et al.,* *2016 and Benelli et al., 2018).* Nanoparticles are responsible for generating toxicity in insects by causing genotoxicity, disrupting the membranes, oxidation of proteins, interrupting the transduction of energy, formation of reactive oxygen species (ROS), and releasing the poisonous components. According to a study with titanium dioxide nanoparticles, it has been proved that these nanoparticles slowed down the growth, development, and molting duration of the silkworm *(Bombyx mori) (Wang et al., 2014)*. Nanoparticles affect the insect species by penetrating the exoskeleton *(Nowack et al., 2007)*; they enter into the intracellular space and lead to expeditious denaturation of enzymes and organelles. They slow down and reduce the permeability of the membrane which affects the functioning of cells and cell death can also take place *(Jiang et al., 2015 and Benelli et al., 2016).*

In the case of insect species, Zinc oxide nanoparticles caused 100% fatality in few species of mosquitoes *(Banumathi et al., 2017).* Besides, it was discovered by *(Mommaerts et al.,2012)* that in a few insect-like bees, Silicon dioxide nanoparticles are highly toxic specifically on worker bees, and induced midgut epithelial damage. Silicon dioxide nanoparticles also weaken and damage the membranes and affect the stability of mitochondrial membrane in the gut cells of *Drosophila melanogaster* along with the increased cell death and then the stimulation of caspases ultimately results in cell death *(Mao et al., 2018)*.

Later, it was demonstrated by (*Kalimothu et al.,2017)* that Silver nanoparticles caused midgut epithelial cell injury in *Aedes aegypti* mosquito species and (*Sundarajan and Kumari et al.,2017)* reported that exposure of *Aedes aegypti* species to gold nanoparticles affected their cortex, midgut and epithelial cells. *(Armstrong et al., 2013)* reported that in *Drosophila melanogaster*, sliver nanoparticles damaged the melanin cuticular pigments and reduced their vertical flight capability. Later, (*Dziewiecki et al., 2016)* proclaimed that in some of the leaf worms like *Spodoptera litura*, being exposed to silver nanoparticles, reduced their amylase, protease, invertase, and lipase activities. Besides, *(Yasur and Usha et al.,2015)* demonstrated that silver nanoparticles are also responsible for increasing the antioxidant enzyme levels and inducing oxidative strain in the gut of moth larva, and also reduced the total protein concentration in mosquitoes (Aedes *albopictus) (Ga'al et al., 2018)*. *(Avalos et al., 2015)* determined that silver nanoparticles caused a reduction in the recombinogenic and mutagenic activity in *Drosophila melanogaster*. Silver nanoparticles are also responsible for causing cell death, oxidative strain, DNA damage, heat shock stress and affected the growth and development of insects *(Nowack et al., 2007 and Morones et al., 2005)*. Insects, specifically fruit flies when exposed to silver and cobalt nanoparticles had a compositional defect like abnormal patches on wings and abnormal growth of whiskers *(Buffet et al., 2011 and Singh et al., 2009)*. Flies treated with gold nanoparticles had abnormal development as it affected their fecundity and such flies showed DNA disintegration, oxidative stress, and early cell death *(Pompa PP et al., 2011 and Vecchio et al., 2012).*

Hydroxyapatite nanoparticles slow down the growth and development of insects, cause cellular damage, and also affected their behavior. Hydroxyapatite treated insects are less immune stress and thus die earlier *(Hoffmann et al., 2001).*

In insects when the toxicity of copper oxide nanoparticles was investigated, they were found to be highly toxic on their proper growth and development and also caused a reduction in the egg to adult survivorship. In the case of *Drosophila melanogaster,* copper oxide nanoparticles disturb their abdominal stability, because severe genetic mutations, damage the genes and also cause deterioration of neurons in the CNS *(Carmona et al., 2015)*. When *Drosophila* larva was exposed to higher amounts of copper oxide nanoparticles, their metabolism was disrupted due to which they stopped ingesting food and also slowed down their growth and maturation hence thereby resulting in a remarkable decrease in their population. Previous works have illustrated that copper oxide nanoparticles cause cellular damage and cell death in insects *(Alarifi et al., 2013)*.

After several experiments done by the researchers to evaluate the toxicity of nanoparticles on insects, it has been determined that excess amount of nanoparticles specifically silver nanoparticles resulted in expanding the goblet cells, destroying the basal lamina, deforming the columnar cells, and forming the abnormal cellular structures in insects. Nanoparticles cause toxic effects on the tissues and the primary target organs such as the digestive system of insects. In silkworm (*Bombyx mori*), the midgut not only secretes digestive enzymes but is also an essential organ for the digestion of food particles. Hence for the normal functioning of the silkworms, proper growth and development of the midgut is very important. Silver nanoparticles specifically damage the digestive organs and tissues of silkworms by affecting the activity of enzymes which are essential in protecting the cells from damage, therefore reducing the cellular apoptosis, hence thereby causing the oxidative strain *(Huang et al., 2018)*.

The generation of reactive oxygen species (ROS) is one of the most toxic cellular effects caused by subjection to nanoparticles. According to the previous studies, it has been determined that silver nanoparticles increase the antioxidant enzyme levels in certain insect species and hence causing oxidative strain *(Yasur et al., 2015)*. Later, *(Mao et al., 2018)* discovered that silver nanoparticles activate the agglomeration of ROS in *Drosophila melanogaster* hence leading to ROS- mediated cell death. They result in DNA damage, autophagy, therefore ultimately resulting in the death of the organism. Silver nanoparticles regulate the expression of heat shock proteins (hsps) in *Drosophila melanogaster* and hence causing oxidative stress *(Ahamed et al., 2008)*.

Due to the uncertain genotoxic properties of nanoparticles, they have the potential to induce DNA damage *(Ryter et al., 2007, Ahamed et al., 2008, Li et al., 2008)*. Their main genotoxicity comes from the production of reactive oxygen species. Nanoparticles enter inside the nucleus either directly through the membrane or get confined within the nucleus during mitosis, hence rupturing the nuclear membrane and inducing several DNA damages. *Mao et al., 2018*, reported that agglomeration of ROS in the tissues of *Drosophila melanogaster* caused by silver nanoparticles resulted in ROS-mediated cell death and DNA damage.

Nanoparticles cross the blood-brain barriers and therefore enter the central nervous system where they bind to acetylcholinesterase (an enzyme) and affect its activity. This enzyme is very important for the correct transmission of nerve impulses *(Hu et al., 2010, Long et al., 2006, Wang et al., 2009)* and is useful to analyze the toxicity of some of the engineered nanoparticles. According to a study by *(Milivojevic et al., 2015), it* was reported that zinc oxide nanoparticles increased the activity of this enzyme in worker bees.

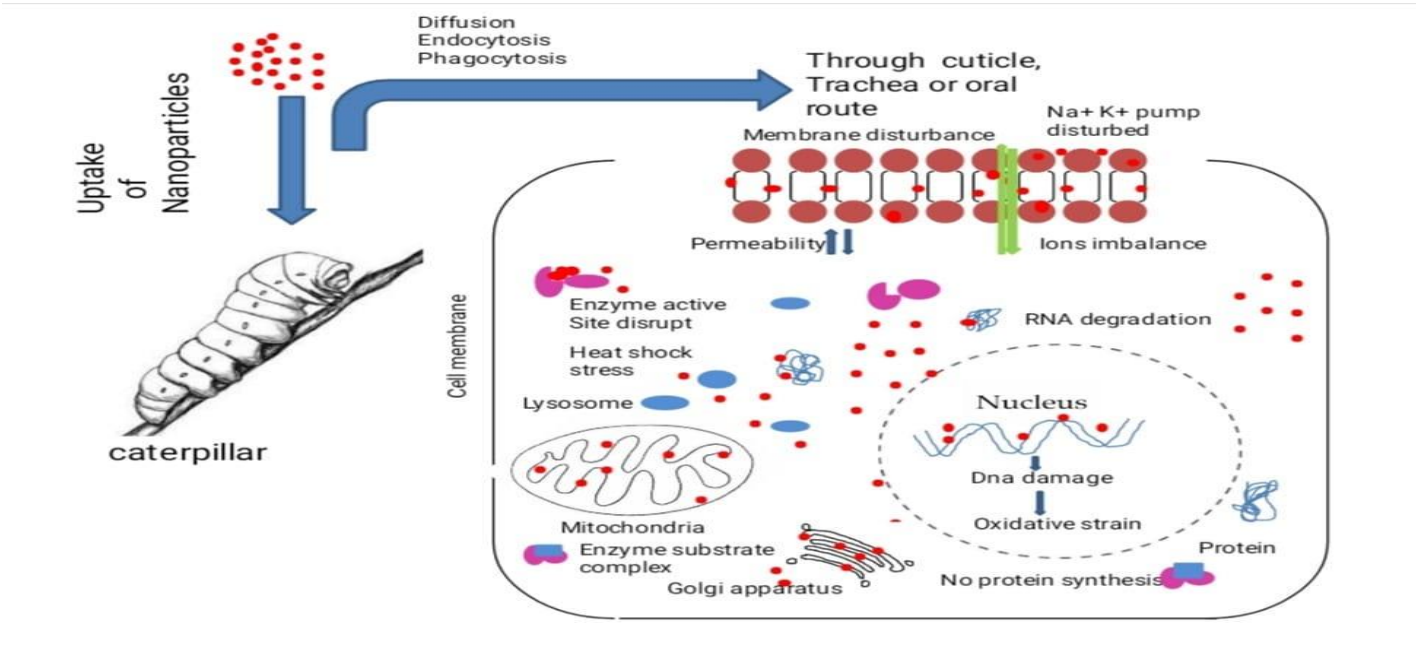

Figure 1: Mode of action of nanoparticles against insects.

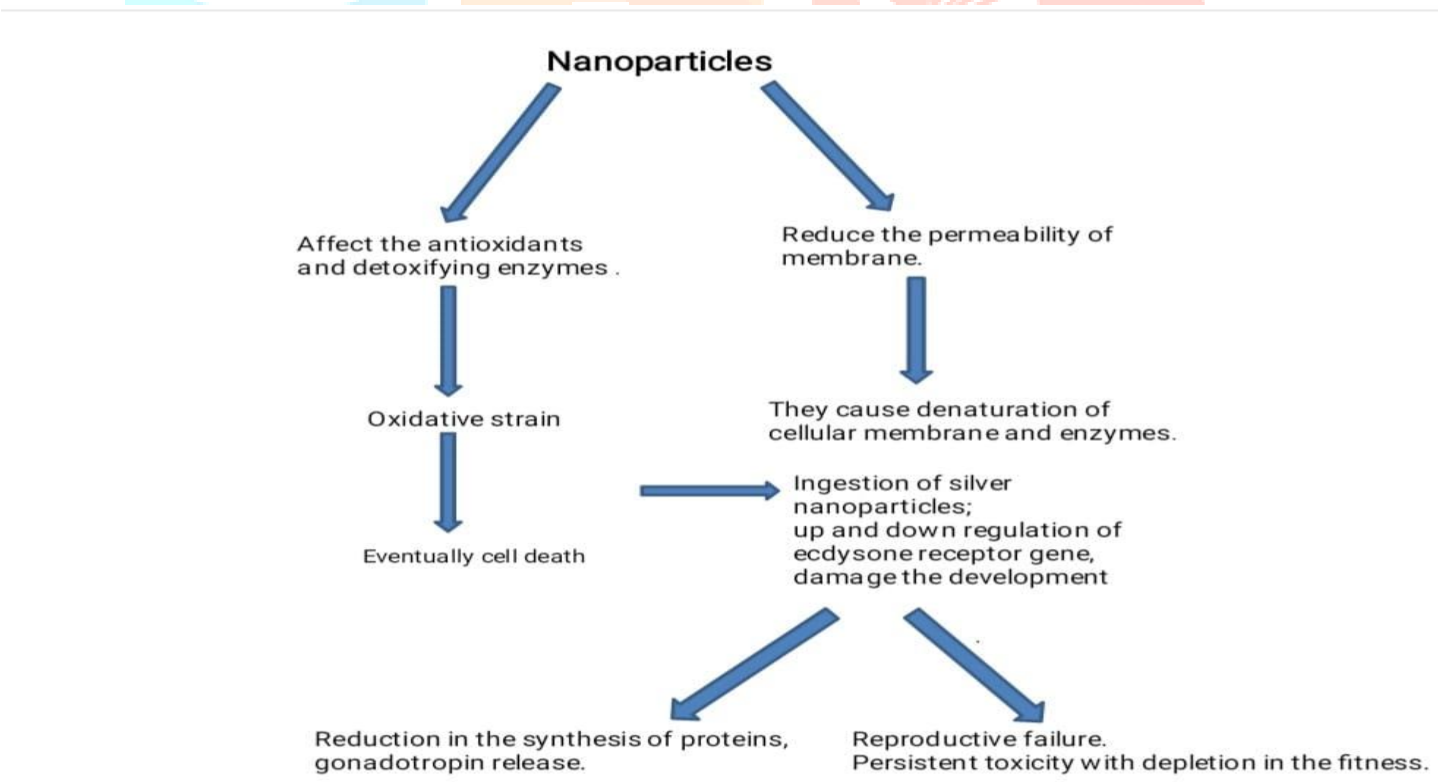

Figure 2: Toxic effects of nanoparticles on insects.

Class of nanoparticles	Toxicity
1. Silica nanoparticles	Cause platelet aggregation and physiological toxicity *(Nemmar et al., 2015)*, reproductive toxicity *(Xu et al., 2014)*.
2. Ceramic nanoparticles	Cause oxidative strain and are responsible for cytotoxicity *(Singh et al., 2014)*.
3. Titanium dioxide	Cause toxicity to the CNS *(Younes et al., 2015 and Shrivastava et al., 2014)*.
4. Silver nanoparticles	Cause oxidative stress, cell death, Dna damage, heat shock stress and effect normal growth and development *(Huo et al., 2015)*. Flies exposed to silver and cobalt nanoparticles had compositional defects like abnormal patches on the wings and abnormal growth of whiskers *(Demir et al., 2011 and Vales et al., 2013)*.
5. Zinc oxide nanoparticles	Cross the gut barrier and reach the hemolymph where they interact with immune-competent cells resulting in various toxic responses like decline in the hemocyte viability, ROS generation, oxidative stress, morphological alterations and apoptotic cell death *(Magrez et al., 2006)*.
6. Molybdenum disulphide nanoparticles	They induce oxidative strain, cellular toxicity, and apoptotic activity, increase the level of ROS and act as an anti-proliferating agent in the insect immune cells and cause a drastic decrease in the hemocyte count *(Chacko et al., 2018)*.
7. Copper oxide nanoparticles	They resulted in a concentration dependent decrease in egg to adult survivorship and a hindrance in the growth and development of fruit flies and these NPs disturb the intestinal stability of insects, cause oxidative strain and cytotoxicity *(Alaraby et al., 2016)*.
8. Hydroxyapatite nanoparticles	They cause cellular damage and slow down the growth and maturation of insects in a dose dependent manner. Hydroxyapatite treated insects are less immune to stress *(Aurosman et al., 2017)*.
9. Gold nanoparticles	Insects treated with gold nanoparticles had abnormal development as gold NPs caused certain defective physical changes in their eyes, hairs and wings and also affected their fecundity and such flies showed Dna disintegration, oxidative strain and an early cell death *(Pompa et al., 2011 and Vecchio et al., 2012)*..
10. Silicon dioxide nanoparticles	They weaken and damage the membranes and also affect the stability of the mitochondrial membrane in the gut cells of insects along with the increased oxidative stress and then the stimulation of caspases ultimately results in

	cell death *(Pandey et al., 2013)*. SiO_2 and Al_2O_3 nanoparticles bind to the insect cuticle resulting in the physic-sorption of waxes and lipids, leading to insect dehydration.

Conclusion

Although the tiny-sized nanoparticles have always occurred in nature the latest development that has been done in the manufacturing and utilization of various engineered nanoparticles has raised concern over their capability, potential release, and side effects on various organisms and the environment. Insects are distributed worldwide, are very diverse, and have a unique ecological position. Although the studies on the toxic effects of nanoparticles on insects are limited, there is a great need to assess the hazardous effects caused by them on insect species. Further by investigating the toxicity of nanoparticles on insects provides a valuable understanding not only about the invertebrate immune system but also about the human immune system as insects and human immune response exhibit functional similarities in several aspects eg. They use similar receptors and effectors and also have a similar regulation of gene expression *(Baun et al., 2008)*. In insects, exposure to various nanoparticles causes DNA damage, apoptosis, necrosis, oxidative strain, cytotoxicity, and genotoxicity. This review summarizes the toxic effects of nanoparticles on insects. Nevertheless, further studies need to be done to confirm the stability of nanoparticles, their fate in the environment, and their toxic effects on the non-targeted organisms.

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