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Tendency towards the risky sides of nanoparticles

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Abstract:

Many questions and opinions often surround the development of science that can support it or arouse suspicion, either for fear of future consequences or to reinforce and expand knowledge. The study of nanoparticles and their effects has been the most critical area of scientific research in recent years, as their production and various applications have increased. This review highlights the multiple effects (negative and some positive) of nanoparticles on some genetic and immunological aspects, as these aspects are closely related to the health of the organism's bodily functions. This review also focuses on nanofertilizers as an example of the outcomes of nanotechnology. Moreover, it clarifies the reasons for concerns about the use of nanofertilizers in agriculture recently.

Keywords: Nanotechnology, Nanoparticles, Nanofertilizers, Genotoxicity, Risky sides, Immunotoxicity, Nanomaterials .

التوجه نحو الجوانب الخطرة للجسيمات النانوية

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مستخلص

ان تطور العلم غالباً ما تحيط به الكثير من الأسئلة والآراء الداعمة او المشككة، اما خوفا من عواقبه المستقبلية او لترسيخ المعرفة والارتقاء بها. أصبحت دراسة المواد النانوية وتأثيراها من أهم مجالات البحث العلمي في السنوات الأخيرة، مع تزايد إنتاجها وتطبيقاتها المختلفة. تسلط هذه المراجعة الضوء على التأثيرات المتعددة (السلبية وبعض الإيجابية) للجسيمات النانوية على بعض الجوانب الوراثية والمناعية، حيث ترتبط هذه الجوانب ارتباطاً وثيقاً بصحة وظائف الجسم. كما تركز هذه المراجعة على المخصبات النانوية كواحدة من نتاجات تكنلوجيا النانو. إضافة الى توضيح الأسباب التي أدت الى الخوف من استعمال المخصبات النانوية في الزراعة مؤخراً.

الكلمات المفتاحية: تكنلوجيا النانو، الجسيمات النانوية، المخصبات النانوية، السمية الوراثية، الجوانب الخطرة، السمية المناعية، المواد النانوية .

Introduction

Tokyo College science professor Norio Taniguchi coined the term "nanotechnology" for the first time in 1974 to describe a fast-evolving technology that could revolutionise many scientific and technological disciplines. This technology aims to transform large-scale materials into nano-sized (1-100) nm particles and gives the same materials new properties (Khan & Rizvi, 2014; Thamer, 2021; Hammud, 2023). The bulk material undergoes physical and chemical changes during miniaturisation, including its size, shape, agglomeration, surface, and structure. The tiny size of nanoparticles provides them with a high surface area and a powerful force for contact (León-Silva *et al*., 2018).

Nanoparticles can cause genotoxicity because of their composition. One interpretation is that they help produce reactive oxygen species (ROS), which cause oxidative stress and ruin DNA (Valko *et al*., 2005; Valko *et al*., 2006).

Nanoparticles activate or inhibit the innate and adaptive immune systems because of their comparable sizes to biological components, raising fears about the potential negative effects of nanoparticles on immune system function (Bonner & Brown, 2020).

Recently, some countries of the world have turned to producing special fertilizers which achieve sustainable agricultural development, increase crop productivity, reduce water consumption, and promote environmentally friendly practices. Scientists modified conventional fertilizers' chemical, biological, and physical characteristics to manufacture nanofertilizers and increase the number of crops to feed the world's expanding populations (León-Silva *et al*., 2018; Aljanabi, 2021).

Despite the benefits of nanofertilizers, the researchers must investigate their manufacturing and commercial marketing to evaluate the hazards to people and the environment. These procedures can keep society safe, and minimize harmful consequences (León-Silva *et al*., 2018). Our review aims to target the harmful effects of nanoparticles and mentions some positive effects.

1. The effect of nanoparticles on genetic material (DNA, RNA).

A. The mechanisms of genotoxicity to nanoparticles.

The main reason for the fear of nanoparticles and reluctance to use them, is their potential to cause genotoxicity (Kohl *et al*., 2020). Genotoxicity refers to the toxic effects on the genetic material of living organisms, which can lead to recoverable damage (temporary) or permanent changes (mutations). Mutations cause heritable changes when they occur in germ cells but can lead to cancer in somatic cells (Phillips & Arlt, 2009; Kohl *et al*., 2020).

The critical preservative role of cellular mechanisms such as replication, transcription, and translation involving DNA and RNA during the cell cycle, proliferation, and differentiation did not prevent the nanoparticles from entering the cells and interfering with the genetic material, leading to structural and functional changes because of their small size (Shukla *et al*., 2021).

Due to the significant importance of genotoxicity, scientists have divided the genotoxicity mechanisms into primary and secondary mechanisms (Fig. 1). The primary mechanisms of genotoxicity involve both direct and indirect impacts, resulting in genetic material destruction without inflammation. The direct interaction between genetic material and nanoparticles is the major genotoxicity mechanism. When the nanoparticles and the cellular system come into contact, the nanoparticles instantly diffuse through the nuclear membrane or interfere (physically or chemically) with the cell cycle, then react with the genetic material to produce ROS and reactive nitrogen species (RNS) (Gonzalez *et al*., 2008). The production of free radicals happens by ROS and RNS directly or indirectly through mitochondrial enzymes (nicotinamide adenine dinucleotide phosphate oxidases, NADPH). Free radicals attach to the cell membrane, induce oxidative stress, and damage DNA. Secondary genotoxicity correlates with inflammatory cells (macrophages, polymorphonuclear neutrophils PMNs) and results in these cells triggering the innate immune response and eventually producing free radicals that damage DNA (Azad *et al*., 2008).

Shukla *et al*. (2021) emphasised that there are three hypotheses about the mechanisms of genotoxicity of nanoparticles, namely:

1. The effects of the surface of the nanoparticle (direct effect).

2. The production of ROS and RNS, induced by nanoparticles (direct and indirect effects).

3. The activation of membrane receptors by nanoparticles (indirect effect).

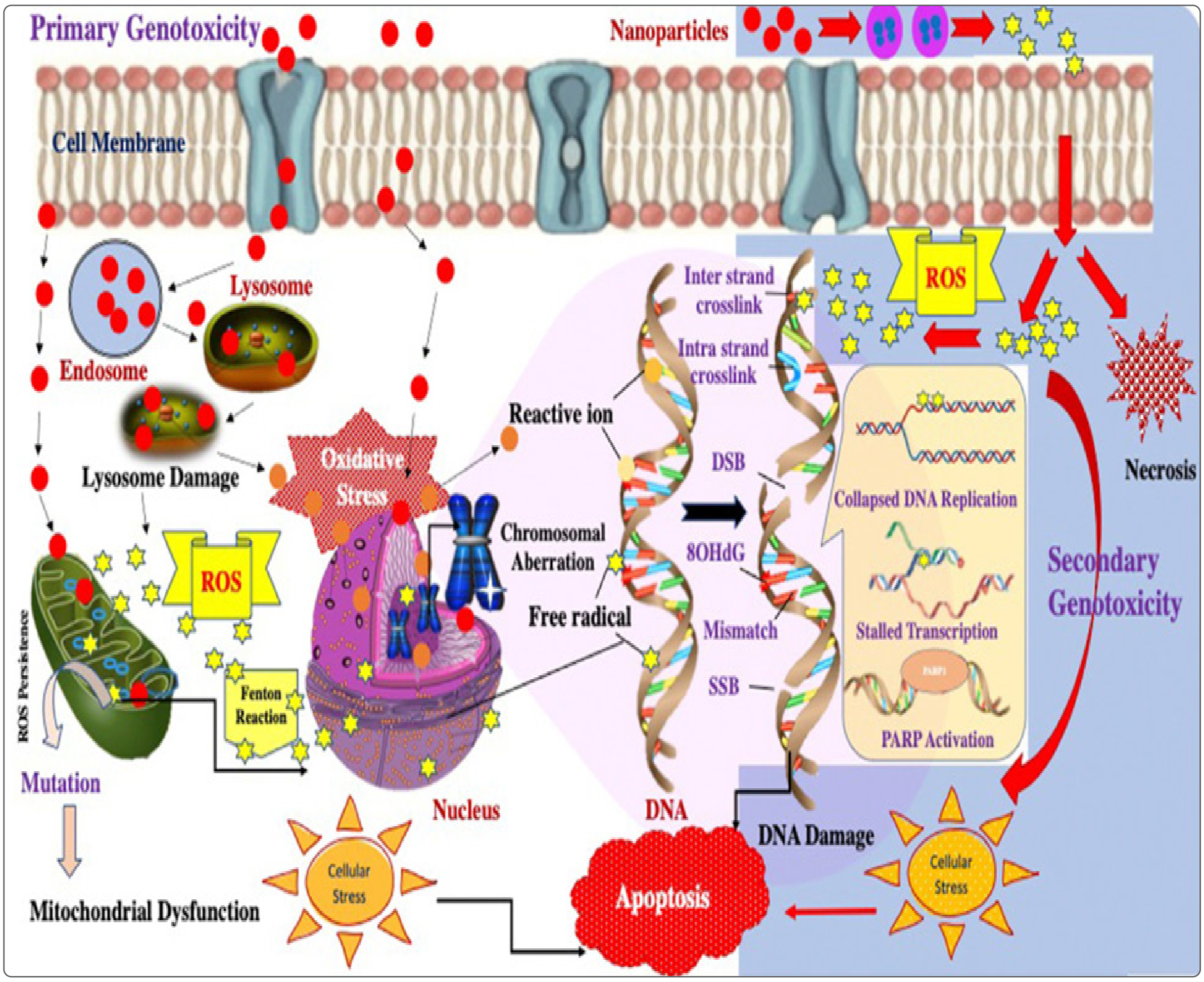

Fig. 1: Mechanisms of genotoxicity of nanoparticles (Shukla et al., 2021).

B. Effect of nanoparticles on the DNA repair system.

Measuring the concentration of repair proteins in the cell and/or estimating the expression of the gene encoded to proteins are methods used to detect nanoparticles' effects on DNA repair systems. Metallic nanoparticles such as zinc oxide nanoparticles (ZnO NPs) and silver nanoparticles (Ag NPs) can destroy DNA repair systems (Kruszewski *et al*., 2013; Demir *et al*., 2014).

Dissolving nanoparticles in cellular fluid causes the releasing of metal ions. Since some proteins require these ions as cofactors to activate, their interaction can lead to protein modification. Recent studies have shown that metal ions are the key to genotoxicity and DNA damage. The DNA repair system's damage depends on the type of metal that makes up nanoparticles.

Furthermore, nanoparticles can change essential cellular functions by interfering with the cell's metal homeostasis (Hartwig & Schwerdtle, 2002; Lebrun *et al*., 2014; Jawad *et al*., 2016; Abdalrazaq *et al*., 2022).

One explanation for how nanoparticles can interfere with the functions of proteins, including the DNA repair system, is that their charge density on their surface area increases as they get smaller, which greatly enhances their ability to bond and interact and forms a "corona" of nanoparticles, as scientists refer to them (Monopoli *et al*., 2011).

C. Epigenetics and nanoparticle-induced changes.

Epigenetics is the reaction between the genes of living organisms and their environment. Many mechanisms engage in epigenetics, including chromatin remodelling, histone modification, DNA methylation, and non-coding RNAs (Shukla *et al*., 2021; Aldal'in *et al*., 2023). (Fig. 2)

i. Nanoparticles' effect on DNA methylation.

DNA methylation is one of the key processes of epigenetics, which occurs when a methyl or hydroxymethyl group joins with fifth carbon atom of the cytosine nucleotides in the DNA sequence. This process is most seen in the dinucleotide cytosine-phosphate-guanine (CPG). However, it can also occur less often in cytosine-phosphate-adenine (CPA), cytosine-phosphate-thymine (CPT), and cytosine-phosphate-cytosine (CPC). The enzyme DNA methyltransferase starts this process. There is conflicting data about the impact of nanoparticles on DNA methylation. Some researchers discovered no impacts, while others show effects at the level of the genome or specific genes (Wang & Ibeagha-Awemu, 2021; Valente *et al*., 2023).

Several studies have shown that exposure to nanoparticles leads to hypomethylation (Shukla *et al*., 2021). Li *et al*. (2016) found that DNA exhibited hypermethylation. In the DNA of human white blood cells (WBCs), prolonged exposure to silica nanoparticles (SiO2 Nps) led to hypomethylation of CPG. At the same time, DNA methylation remained unaffected after short-term exposure (Rossnerova *et al*., 2020). Shukla *et al*. (2021) mentioned that there is considerable uncertainty about the functional effects of nanoparticles.

ii. Nanoparticles' effect on histone modification.

Many histone modification processes, such as methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation, influence the strength of DNA packing. These mechanisms change the histone at the terminal amino tail, thereby affecting the extent of DNA packaging. Tightly packed DNA suppresses gene expression, while loosely packed DNA enhances gene expression. Some studies have shown that the diffusion of nanoparticles into the nucleus alters many cellular processes, depending on which region of chromatin is affected (Bannister & Kouzarides, 2011; Jennifer & Maciej, 2013). Human cell lines treated with titanium dioxide nanoparticles (TiO2 NPs) had alterations in the H3 and H4 histones, resulting in the emergence of 70^{th} modifications (Pogribna *et al*., 2022).

iii. Nanoparticles' effect on chromatin remodelling.

Chromatin remodelling refers to the modification of protein structure. The driver of this mechanism is a protein complex that harnesses the energy from ATP hydrolysis to change the interaction between histones and DNA, hence regulating gene expression (Musolino *et al*., 2022). The precise mechanisms by which nanoparticles affect chromatin remodelling are not clear yet. However, they may entail oxidative stress and modifications in the enzymes responsible for regulating chromatin remodelling (Dubey *et al*., 2015). The effects of gold nanoparticles (Au NPs) in mice injected intraperitoneally appeared as chromatin instability and an elevated rate of DNA damage in their sperms (Nazari *et al*., 2016).

iv. Nanoparticles' effect on noncoding RNAs (ncRNAs).

DNA transcription results in producing important and vital molecules but not translated into proteins; these molecules called noncoding RNAs (ncRNAs). There are two divisions of ncRNAs. The first division has less than thirty nucleotides, so it is referred to as short noncoding RNAs (sncRNAs). The three main types of sncRNAs are called MicroRNAs (miRNAs), short-interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs). While the second division of ncRNAs is known as long noncoding RNAs (lncRNAs) because it has more than two hundred nucleotides. Noncoding RNAs have a role in controlling gene expression through facilitating the synthesis of heterochromatin, gene silencing, and targeted DNA methylation (Ohnishi *et al*., 2010). Halappanavar *et al*. (2011) illustrated the influence of surfaces coated with TiO2 NPs on mice through their studies, which revealed significant changes in the gene expression of the 16 microRNAs (16 miRNAs) in the mice's lungs. Additional research has also validated alteration in miRNAs in mice that were administered carbon nanoparticles (C NPs) (Balansky et al., 2013; Nagano *et al*., 2013). The hepatotoxicity mechanism in humans is affected by alterations in the expression profile of lncRNA generated by TiO2 NPs, suggesting the role of epigenetics (Shi *et al*., 2022).

Despite the negative aspects, Samanta & Medintz (2016) highlighted that the integration of DNA with various nanoparticles, including metal oxides, proteins, viral NPs, gold NPs, and others, contributes to the formation of composite nanomaterials characterised by exceptional characteristics and a wide range of applications in fields including drug delivery and disease diagnosis. As it combines the fields of engineering and biotechnology to develop novel systems and instruments for medical applications, this research area is widely recognised for its great potential (Verma *et al*., 2022).

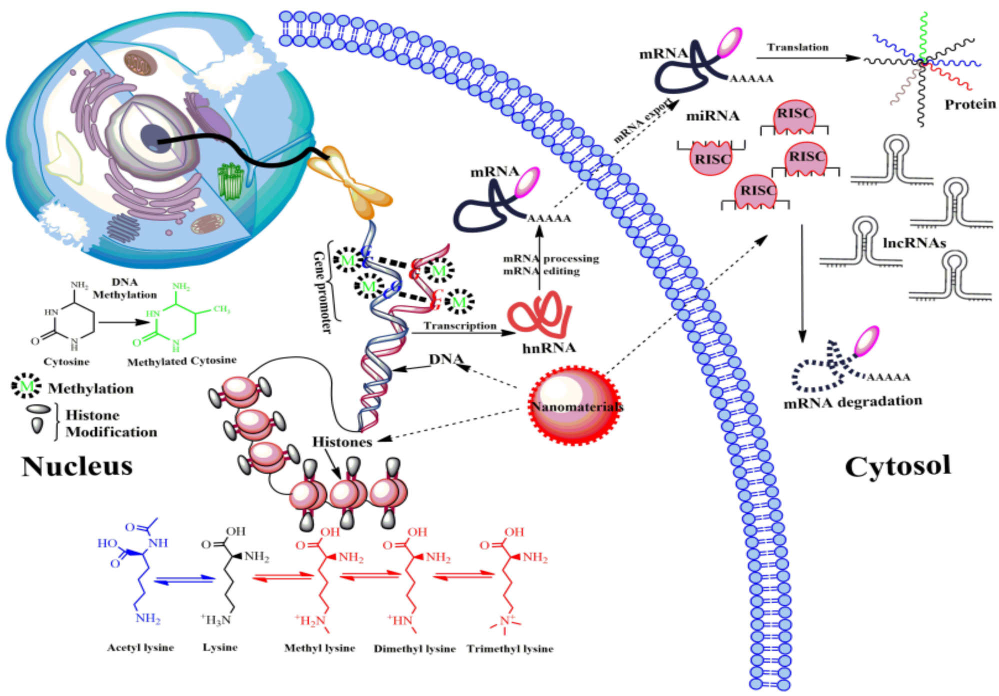

Fig. 2: The role of nanoparticles in the epigenetic modifications (Gedda *et al*., 2019)

2. The immune system's response to nanoparticles.

The innate and adaptive immune systems are essential components of the immune system. Elements of the innate immune system, such as phagocytic cells (macrophages (MΦ), dendritic cells (DCs), neutrophils, and mast cells), make it the first responder to foreign particles. Otherwise, T and B lymphocytes handle regulating the function of the adaptive immune system (Sompayrac, 2019).

There is an urgent need to understand the nanoparticles' mechanisms in amplifying or suppressing the immune system, so the scientists' efforts directed toward investigating this relationship (Aljabali *et al*., 2023). Nanoparticles trigger the immune response through their unique characteristics, such as their shape, size, crystalline structure, surface texture, and agglomeration (Schrand *et al*., 2010). The immune response to nanoparticles occurs at various levels, from tolerance to weak response, or it results in inflammation (Corbo *et al*., 2016; Puntes, 2016).

Phagocytic cells hold sialic acid on their surface, which carries a negative charge, so positively charged nanoparticles are more interactive with the immune system than negatively charged nanoparticles (Dobrovolskaia & McNeil, 2007; Dwivedi *et al*., 2009).

Macrophages are the first reactant against various intruders, including nanoparticles. They recognise them via their receptors (toll-like receptors TLRs) that bind to these intruders and trigger inflammation (Dwivedi *et al*., 2009; Aljabali *et al*., 2023).

Lucarelli *et al*. (2004) conducted an *in vitro* study using human phagocytic cells treated with various nanoparticles (SiO_2, TiO_2, ZrO_2, and cobalt Co) at nontoxic concentrations. The researchers noted an upregulation of cytokine production and the expression of macrophage receptors. Furthermore, specific nanoparticles induce inflammatory response (Szebeni *et al*., 2018).

Some nanoparticles have epitopes that bind to antibodies. However, their small size makes them a hapten, so they elicit a weak or no immune response. The immunisation of animals with nanoparticles does not generate specific antibodies even in the presence of Freund's adjuvant (Khalili Fard *et al*., 2015; Kononenko *et al*., 2015). However, the study by Chen *et al*. (1998) found that nanoparticles generate specific antibodies when they pair with protein carriers. To improve this effect mice immunized with a C60 fullerene nanoparticle linked with bovine thyroglobulin.

Some researchers used nanoparticles as vaccines or vaccine carriers to improve antigens' efficacy. Ag NPs administered to lab mice elevated the levels of macrophages, lymphocytes (B and T), cytokines (IL-4 and IL-6), and antibodies (Abd Al-Rhman *et al*., 2016).

The other usage of nanoparticles is treating autoimmune diseases through their ability to suppress the immune system. This process can weaken the immune system and develop infectious diseases and cancer (Muhammad *et al*., 2020; Perciani *et al*., 2020). Government should restrict the using of nanoparticles that correlate with human health because the excessive use of nanoparticles may lead to an undesired immune response and many consequences (Aljabali *et al*., 2023).

3. Application of nanoparticles in agriculture (Nanofertilizers).

Biocompatibility, non-toxicity, environmental safety, and efficacy are the most important properties of nanoparticles used in agriculture (Chokheli *et al*., 2021). The latest research has shown that nanoparticles have adverse and affirmative impacts on plants. Some nanoparticles hurt the cell structure of plants when used as fertilisers (El-Moneim *et al*., 2021). Lin & Xing (2008) pointed out that ZnO NPs cause changes in ryegrass plants, such as reduced vascular cylinders, altered root tip morphology, destroyed epidermis, and crumbled bladder cortex. Ag, ZnO, silver nitrate (AgNO3), and zinc sulphate (ZnSO4) nanoparticles cause damage to corn and cabbage (Pokhrel & Dubey, 2013). Tomatoes treated with nickel oxide nanoparticles (NiO NPs) suffer from the destruction of organelles and mitochondrial cristae in root cells, a high number of peroxisomes, and an agglomerated nucleus (Faisal *et al*., 2013). Different concentrations of ZnO caused significant toxicity and adverse effects on rice plants and inhibited root growth and biomass (Boonyanitipong *et al*., 2011). Applying copper oxide nanoparticles (CuO NPs) to dotted duck meat, English oak, and barley causes structural and cellular alterations (Rico *et al*., 2011; Lalau *et al*., 2014; Olchowik *et al*., 2017). The use of cobalt oxide nanoparticles (Co3O4 NPs) to treat eggplants can result in phytotoxicity and swelling of the mitochondria as negative effects. In contrast, cerium oxide nanoparticles (CeO NPs) effects on wheat appeared as microstructure changes in the cells of the leaf, abnormal nuclei, swollen chloroplasts, and disorganized thylakoids (Du *et al*., 2015; Faisal *et al*., 2016). CuO NPs at low concentrations do not affect the germination of *Echinacea purpurea*, but high concentrations decrease the photosynthesis rate (Ahmed &Omran, 2024).

Nanoparticles play a positive function by enhancing germination, vegetation, and plant tolerance to both biotic and abiotic stressors (Younes *et al*., 2019; Younes *et al.*, 2020; Jaafar & Abdullah, 2020). Chitosan-polyvinyl alcohol with copper nanoparticles (Cs-PVA+Cu NPs) enhanced the plants' tolerance to salinity stress, which augmented the activities of β-carotenes, phenols, lycopene, vitamin C, and antioxidant enzymes (Hernández-Hernández *et al*., 2018). The fertilization of bread and durum wheat by TiO2 NPs increases the growth rate in these plants (Dawood *et al*., 2019). Feng *et al*., 2016; Abbai *et al*., 2019; Cai *et al*., 2019; Hao *et al*., 2019; Adeel *et al*., 2021 are study nanoparticles' potency in protecting plants against viral, bacterial, and fungal infections.

Plants and nanoparticles share the responsibility for their interaction results with the help of unique characteristics such as species, organs, and organelles for plants and the structural characteristics of nanoparticles mentioned earlier (Rahman & Padavettan, 2012).

Nanofertilizers are an essential product of nanotechnology, their production helps to enhance the quality and quantity of crops and ensure the continuous compatibility of nutrients with less use of fertilizers. They also reduce the adverse effects of excessive use of conventional fertilisers, such as soil degradation and water pollution. Nanofertilizers provide a hopeful approach to addressing the dual problem of rising food needs and minimising environmental consequences. Nevertheless, the extensive dispersion of nanofertilizers in the environment and their entry into the food chain pose potential risks to human and animal health (Solanki *et al*., 2015; Alkhader, 2022; Babu *et al*., 2022).

A. Methods of manufacturing nanofertilizers.

Nanofertilizers manufactured by using physical, chemical, and biological methods (Das & Beegum, 2022) (Fig. 3).

1. Physical methods (top-down): These are the most usual methods for nanofertilizer synthesis. Through these methods, the bulk material is converted into nano-size by breaking it over several hours, depending on many methods such as high energy ball mills, gas condensation, mechanical attrition, the aerosol synthesis method, thermolysis, and molecular beam epitaxy (Nayef & Khudhair, 2018; Imran *et al*., 2021; Das & Beegum, 2022).

2. Chemical methods (bottom-up): In these methods, nanofertilizers are made from atoms, molecules, and monomers. These include the sol-gel method, microemulsion, and electrochemical synthesis (Cele, 2020; Imran *et al*., 2021).

3. Biological methods: These methods depend on the biomineralization of bacteria, fungi, and plant extracts as reduction factors. These methods are characterised by their safety compared to chemical reduction methods that produce toxic materials (Bansal *et al*., 2005; Al-Abadi & Al-Abodi, 2023). Myrtle and tea are incorporated in biosynthesizing Cu NPs (Atiya *et al*., 2021; Al-Jubouri *et al*., 2022). Saleh (2020) cited the ability to use environmental bacteria as a cheap source in the biosynthesis of nanoparticles.

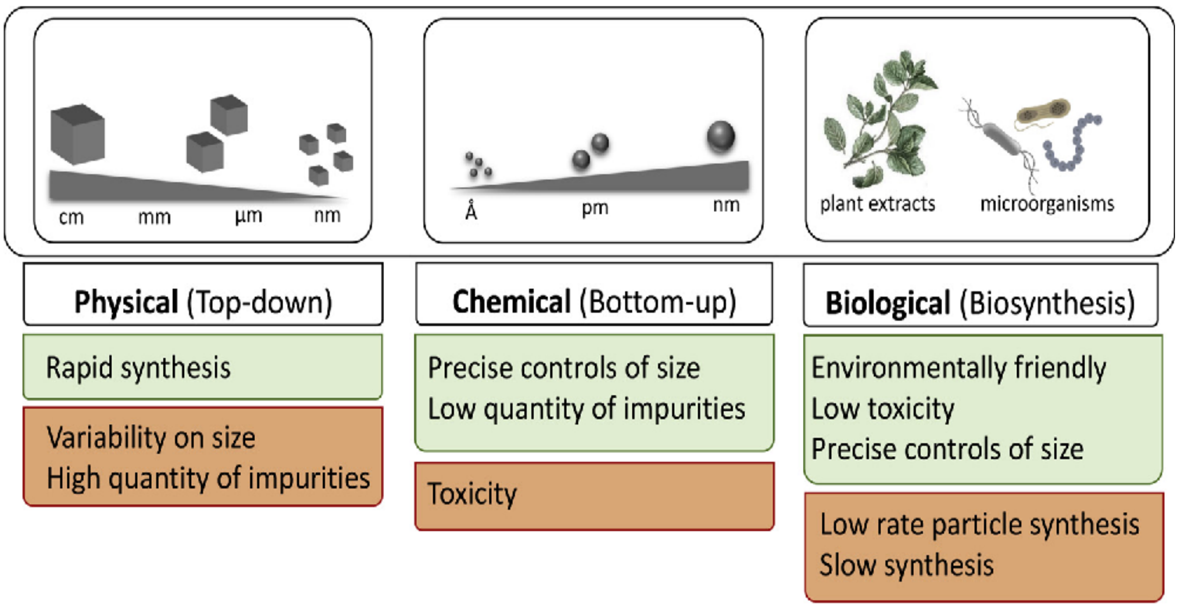

Fig. 3: Methods of nanofertilizers synthesis (Zulfiqar *et al*., 2019).

B. Some types of nanofertilizers.

The presence of many definitions of nanofertilizers is the reason for their classification by different methods. Some scientists classified them as a subgroup of nanotechnology; others classified them as a type of fertilizers, so the scientists rely on their action, nutrients, and consistency as classification criteria (Yadav *et al*., 2023a).

1. Action-based: classified into four groups as follows:

A. Controlled release nanofertilizers: nanoparticles used in controlling nutrient release (DeRosa *et al*., 2010). These include diverse types, as follows:

1) Carbon-based: such as biochar, which soaks up nutrients from the soil and rereleases them due to its porosity (Saxena *et al*., 2014).

2) Chitosan-based: a compound composed of nanofertilizers and positively charged polymers that ease nutrient delivery to plants (Corradini *et al*., 2010).

3) Nanocapsule-based: they are organic or inorganic materials used to envelop and transport nutrients to plants as microscopic capsules (Petosa *et al*., 2017).

4) Nanogel-based: a mixture of polymer and liquid forms a spongy material that absorbs and releases nutrients over time (Krishnani *et al*., 2022).

5) Starch-based: water-soluble nanocrystals generated from starch that are conveniently applied to plants as a liquid or spray (Lin *et al*., 2011).

6) Zeolite-based: zeolite nanoparticles combined with various compounds (Jakkula & Wani, 2018; Sharma *et al*., 2022).

B. Targeted delivery nanofertilizers: these are oligonucleotides or peptides (nano-aptamers) that bind specifically to plant cells through special receptors and help the transfer of nutrients (Rameshaiah & Shabnam, 2015; Majeed *et al*., 2015; Kaushal & Wani, 2017; Naz *et al*., 2021).

C. Nanofertilizers that stimulate plant growth: include for example, carbon nanoparticles (C NPs) (Mondal *et al*., 2011).

D. Nanofertilizers that control water and nutrient loss: nano-beads and nano-emulsions that can bind water (Chand Mali *et al*., 2020; Sivarethinamohan & Sujatha, 2021).

2. Nutrient-based: classify into:

A. Inorganic nanofertilizers: these include macronutrient nanofertilizers (Ca, P, K, N, Mg, and S) and micronutrient nanofertilizers (B, Ti, Fe, Cu, Ni, and Zn) (Kalia & Sharma, 2019; Yadav *et al.*, 2023a).

B. Organic nanofertilizers: these are natural materials such as polysaccharides, chitosan, pectin, plant waste, and compost synthesised at the nanoscale (Fatima *et al.*, 2021).

C. Hybrid nanofertilizers: are fertilisers produced by mixing conventional fertilizers and nano-fertilizers (Tarafder *et al.*, 2020).

3. Consistency-based fertilizers: these include surface-coated nanofertilizers and nanocarrier-based nanofertilizers (Liu & Lal, 2015; Solanki *et al.*, 2015; Kah *et al.*, 2018).

C. Issues around the application of nanofertilizers

Despite the benefits of nanofertilizers, their risks should be kept in mind, as they have various negative effects due to the easy mobility of nanoparticles in the long food chain of many organisms. Fertilizers and pesticides have become indispensable in modern agriculture as they ensure the quantity and efficiency of agricultural products. However, these compounds have some negative consequences, including those on soil, water, food, and the environment, as well as adverse effects on human health (Kah, 2015; Singh *et al.*, 2021).

Soil is the first recipient of nanofertilizers; therefore, contamination with nanoparticles and the associated chemical reactions can alter soil structure and biota (Singh *et al.*, 2021). The toxicity level in plants is related to the characteristics and dimensions of nanoparticles (Du *et al.*, 2011). The incorrect use of nanofertilizers negatively affects the environment and living systems. The interactive nature of nanofertilizers also allows them to react with various environmental components, leading to changes in their physical and chemical properties. These altered nanofertilizers can cause poisoning, and when they accumulate in plants, generate ROS, inhibit growth, lead to cell death, and threaten human life. The accumulation of nanofertilizers in human food can be fatal. In the case of investigating the absorption and transportation of cerium dioxide nanoparticles (CeO2 NPs) in cucumbers, it was discovered that 15% of these nanoparticles underwent reduction to cerium trioxide (CeO3) and were then transferred into the plant's bark. This material may be a potential hazard to human health (Ma *et al*., 2017; Mohammed, 2021). There is considerable concern about the safety of farmers who handle nanomaterials due to their phytotoxicity, which is characterised by the variable responses of plants to different nanomaterials at varying concentrations (Nair, 2018; Bhojiya *et al*., 2023).

The aquatic and terrestrial organisms are affected If the water is contaminated with nanoparticles (Sharma, 2009). Portals of nanoparticles' entrance are skin contact, inhalation, and ingestion (Singh *et al*., 2021).

Random use of nanofertilizers and the unpredictability of their effects on plants, animals, and humans led to fear of their prospective adverse effects and safe disposal (Bernela *et al*., 2021; Rajput *et al*., 2021). So, the safety of nanofartilizers should be detected before use (Zulfiqar et al., 2019).

Despite the extensive and diverse applications of nanoparticles, their development should be approached with caution, as there are no laws regulating their use and limiting the potential risks. As with any modern technology, competition in the commercialization of nanofertilizers may discourage people from investigating their negative aspects. It is the responsibility of science to scrutinise any modern technology, especially in the context of human nutrition, and to learn from past experiences, such as genetically engineered foods (GE foods), which were not accepted by customers because they were dangerous. There is therefore an urgent need to assess the harmful effects of nanomaterials to ensure their safety. From this point of view, it is necessary to provide a comprehensive database and warning systems. In addition, international regulatory and legislative cooperation is important to ensure the best use of nanotechnology. (Prasad *et al*., 2017; León-Silva *et al*., 2018).

Yadav *et al*. (2023b) highlight many impediments to the commercialization of nanofertilizers, such as:

1. Higher costs: Nanotechnology needs more requirements, equipment, and training.
2. Lack of standardisation: due to the need for uniform protocols for their production and evaluation.
3. Limited public understanding.
4. There are knowledge gaps in their development, limiting their adoption in many countries.

There are several commercial nanofertilizers, but studies on their side effects on living organisms (especially laboratory animals) have yet to be conducted. The next table details the adverse effects of a selection of nanoparticles that could be used to fabricate nanofertilizers, using laboratory animals as an experimental model.

Types of Nanoparticles	Study outcomes	References
Hexagonal boron nitride nanoparticles (hBN NPs)	Rats exposed to high concentrations of hBN NPs develop oxidative stress	(Kar *et al*., 2021)
Erythrocyte Membrane-Coated Boron Nitride Nanoparticles	BNRBCM has low toxicity in mice (LD50 258.94 mg/kg)	(He *et al*., 2023)
Mo NPs	Decrease body weight, number of fetuses, and DNA damage occur to pregnant female mice administrated Mo NPs orally	(Mohamed *et al*., 2020)
(MoO3 NPs)	Pulmonary toxicity and molecular mechanisms after exposure to MoO3 NPs in golden Syrian hamsters	(Huber & Cerreta, 2022)
MoO3-NPs	High doses of MoO3-NPs induced more adverse effects in rats than low doses	(Shaban *et al*., 2022)
MoO3-NPs	Higher concentrations of MoO3-NPs have toxic effects on blood parameters and organ degradation in male Wister rats	(Akhondipour *et al*., 2018)
MoO3-NPs	Exposure to MoO3 NPs can induce the risk of thyroid dysfunction in female rats	(Assadi *et al*., 2016)
CuO NPs	Rats exposed to copper oxides showed disorders at various levels of organization	(Sutunkova *et al*., 2023)
CuO NPs	The levels of reproductive hormones and sperm morphology changed in males of albino mice exposed to CuO NPs (25 and 35 mg/kg)	(AL-Musawi *et al*., 2022)

Types of Nanoparticles	Study outcomes	References
CuO NPs	CuO NPs reduce glutathione (GSH) levels and increase ROS	(Tulinska *et al.*, 2022)
FeOx NPs	Environmentally relevant FeOx NPs, at realistic exposure levels, produce finite acute pulmonary effects in Sprague-Dawley rats	(Guo *et al.*, 2021)
ZnO NPs	Zn NPs (300, 2000 mg/kg body weight) administrated orally to Swiss mice affected by increasing ROS level, reducing sperm count and motility, and decreasing genomic stability	Srivastav *et al.*, 2017
ZnO and FeO NPs	Variations in luteinizing hormone (LH), estrogen, and progesterone levels are statistically significant between groups administered low and high concentrations of ZnO NPs and FeO NPs, However, no significant differences were seen in FSH levels when compared to the control group	(Ibraheem & Ibrahim, 2017)
ZnO NPs	ZnO NPs induced hepatic and renal toxicity in male mice	(Salman, 2018)
ZnO NPs	In male Wistar rats, the effects of ZnO NPs at 20 and 40 ppm on haematological parameters were minimal; however, the liver and kidney functions were adversely affected by the 40-ppm concentration	(Shaban *et al.*, 2021)
MnO2 NPs	Wistar rats administered subcutaneous injection of Manganese dioxide nanoparticles (MnO2 NPs) showed reduced spermatozoa, spermatogonia, spermatocytes, vas deferens diameter, and sperms motility	(Yousefalizadegan *et al.*, 2019)
MgO NPs	Sprague-Dawley adult female rats injected with MgO NPs suffer from a significant reduction in T3 and T4 hormones and a significant increase in TSH	(Obaid *et al.*, 2022)

Conclusions

Notwithstanding the large amount of research that has proved the critical significance of nanoparticles (generally) across diverse domains of human life and nanofertilizers (specifically) in augmenting the growth and quality of crops, it is imperative to show the adverse effects that these substances may cause.

Genetic material and the immune system are the main targets for nanoparticles, which enter the body through entry ports (digestive system, respiratory system, and skin) and then penetrate the cells, reaching the genetic material and causing direct or indirect destruction. Immunostimulation or immunosuppression are intrinsic phenomena resulting from the confrontation of the immune system with nanoparticles.

Nanofertilizers can indirectly threaten unrelated organisms (animals, humans, and invertebrates) through transfer via the food chain or directly during production and application. Due to the dearth of comprehensive research on the adverse effects of commercial nanofertilizers and the absence of uniform legislation governing the industry and the evaluation of nanofertilizers, the use of nanofertilizers is still fraught with fears and caution about long-term effects.

Future research must focus on investigating the light and dark sides of nanotechnology products to achieve the desired result.

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