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EXPLORATIONS ON THE TOXICOLOGICAL POTENTIAL OF ZINC AND COPPER NANOCOMPOUNDS

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ABSTRACT
Nanoparticles (NPs) represent one of the most extensively studied topics today, as their increasing use across various fields of human activity necessitates an evaluation of their toxicological profile. Zinc (Zn) and copper (Cu) nanoparticles have gained significant attention due to their antimicrobial properties, role in plant nutrition and resilience, and potential applications in drug delivery. However, concerns persist regarding their environmental impact and biological toxicity, which depend on factors such as synthesis method, concentration, and exposure conditions. This study explores the toxicological potential of Zn and Cu NPs, their effects on plants and microorganisms, and their potential future applications, aiming to contribute to a deeper understanding of nanoparticle safety and sustainability.
KEY WORDS: *nanoparticles, zinc, copper, toxicity, environmental impact, nanotechnology*

INTRODUCTION

The literature defines the concept of nanomaterials in various ways, but among the most explicit is the general concept that they are materials smaller than 100 nm in size. Another definition, much more specific and restrictive, mentions that nanomaterials develop characteristics that depend on their size (Vollath, 2008).

Given their numerous and unique properties – including their role in energy conversion and storage, their catalytic properties and implications in surface treatments (Goesmann and Feldmann, 2010) – nanoparticles have begun to be used as antimicrobial agents or alternatives to conventional antibiotics. Moreover, some nanoparticles can be used as components of certain medical devices, due to their specific physical and biological properties (Datcu and Ciobanu, 2020).

An additional direction in which nanoparticles could be used is heritage preservation. A study done by Corbu et al. (2023) emphasized that gold, silver, copper and zinc oxide nanoparticles could be used as an alternative for heritage preservation as a result of their antimicrobial properties against biodeteriogenic strains. Moreover, nanoparticles, like magnesium diboride, could help preserve cultural heritage objects considering their antifungal properties, as demonstrated by Gheorghe et al. (2021).

There is extensive research on various materials, especially metals, such as silver (Bruna et al., 2021), gold (Azam et al., 2009), platinum (Aygun et al., 2020), zinc (Gordon et al., 2011), copper and their synthesis method, as well as antibacterial properties (Khandel et al., 2018). However, there is a prevalent need for extensive research regarding their potential toxicity on plants, animals and humans (Mathur et al., 2023; Xuan et al., 2023).

1. General aspects

1.1. Zinc nanoparticles

Zinc is one of the most important micronutrients required for plant growth, taken up by the roots in the form of Zn^{2+} ions or chelates of organic acids (Palmgren et al., 2008). Plants also absorb zinc through their leaves, although the underlying mechanism has not been described in detail. (Doolette et al., 2018).

Zinc plays a significant role in plant physiology by activating enzymes involved in carbohydrate metabolism, protein synthesis, auxin regulation, cell membrane integrity, and pollen formation (Umair Hassan et al., 2020). Zinc deficiency in soil and plants is a global problem due to its low solubility. In plant organisms, this leads to growth retardation, reduced leaf size, chlorosis, and also increases the sensitivity of vegetation to biotic and abiotic stresses, causing substantial losses in crop yield (Gondal, 2021).

Some approaches to overcome zinc deficiency include the use of chemical fertilizers, conventional breeding techniques, zinc-solubilizing bacteria, and others. However, the vast majority of farmers rely entirely on chemical supply to alleviate zinc deficiency, as similar alternatives are neither popular nor effective enough, according to the requirements of modern agriculture (Rani et al., 2020). Most of these agrochemicals applied to crops do not reach their target site due to processes that occur after distribution in the soil, such as leaching, hydrolysis, microbial degradation and so on. (Ortiz-Hernández et al., 2013).

Nanoparticles and nanocapsules have been shown to be an effective means of delivering pesticides and fertilizers in a more controlled manner with high specificity

(Pramanik et al., 2020). Plants are able to rapidly absorb nanoforms of micronutrients and also the concentration required is comparatively lower than their bulk form (Sabir et al., 2014).

In the field of agriculture, zinc nanoforms have made a significant contribution due to their antimicrobial potential, helping in targeted drug delivery and, respectively, alleviating zinc deficiency and stress tolerance of plants (Ansari et al., 2018). Among these, ZnO nanoparticles remain the most widely used type of nanoparticles due to its suitable properties, wide availability, low production costs, its stability at high temperatures and neutral pH (Sturikova et al., 2018).

1.2.Copper nanoparticles

Copper is one of the most abundant elements found on Earth. Over the centuries, it has played an important role in history, given its many properties, such as good electrical and thermal conductivity, high corrosion resistance, and high malleability (Vimbela et al., 2017).

Copper can be found in over 30 types of proteins and plays an important role in the metabolism of living organisms. Numerous copper-containing enzymes contribute to various physiological functions, such as oxygen transport and iron homeostasis (Vimbela et al., 2017), and it is also found in the skin, bones, and various organs (Al-Hakkani, 2020).

In the case of plant organisms, copper plays essential roles in developmental processes, helping to regulate proteins, photosynthetic electron transportation, mitochondrial respiration, and cell wall metabolism. When plants present a copper deficiency, their leaves are curled, the petioles are downward-pointing, and the turgor of young leaves is permanently absent. Otherwise, a high concentration of copper leads to toxicity, growth inhibition, interference with the photosynthesis process, and oxidative stress (Shobha et al., 2014).

Copper nanoparticles have gained public interest due to their mechanical, electrical, magnetic, and thermal properties, being used in water treatment, heat transfer systems, and antimicrobial coatings for surgical instruments (Mohamed, 2020).

2. Synthesis of nanoparticles

A number of factors involved in the synthesis of zinc nanoparticles vary, from the type of microbial species, the biosynthetic pathway, the metal ion precursor, the incubation time for microbial growth, and the physical conditions, such as pH, temperature, or reaction time. These factors lead to considerable variations in the quantity and quality of the nanoparticles, reflected in their characteristics, such as size, shape, and stability (Patra and Baek, 2015). Their distinctive features are responsible for determining the unique properties of nanoparticles. The main synthesis pathways and their characterization is presented in table 1.

TABLE 1. The main synthesis pathways of zinc and copper NPs

Method	Pathway	Characterization	References
Conventional	physical	- through ultrasonication, laser ablation, electromagnetic wave irradiation. -requires highly sophisticated instrumentation. -involves high costs. - NPs obtained by physical synthesis are free from solvent contamination and have a uniform distribution, which is an improvement over chemical synthesis.	Jameel et al., 2020; Patel et al., 2015; Iravani et al., 2014.
	chemical	-through pyrolysis, solvothermal synthesis, chemical reduction, photochemical reduction, hydrothermal synthesis, etc. -requires high number of steps. -involves issues regarding the non-biodegradable nature and toxicity of chemicals used in the process.	Salem and Fouda, 2021; Khandel et al., 2018; Giannousi et al., 2014.
Biogenic	plant-mediated	- the atoms obtained aggregate and form small clusters that further grow into particles. - there are no reduction factors required since they are already present in the plant extract used for NPs synthesis. -could help address agricultural waste issues since these materials can be processed to synthesize NPs -is cost-effective. -environmentally friendly.	Bankar et al., 2010; Ishak et al., 2021: Asghar and Asghar, 2020; Thiruvengadam et al., 2019.
	microorganism-mediated	-NPs are formed due to the oxidation/reduction (O/R) of metal ions by enzymes, proteins, and sugars. -it can be done using intracellular pathways or extracellular pathways. -it is possible to control and manipulate the size and shape of NPs so as to produce the desired ones, suitable for a specific application.	Zhang et al., 2011; Makarov et al., 2014; Salem and Fouda, 2021;

3. Effects of zinc and copper NPs on organisms

Plants

Drought stress has a negative impact on plant growth and productivity, negatively affecting seed germination percentage, transpiration rate, net photosynthetic rate, relative leaf water content, overproduction of reactive oxygen species, nutrient translocation, and so on (Rani et al., 2020). A sufficient number of studies have reported the amelioration of drought stress in flora by applying ZnO NPs in optimized concentration and in different delivery modes. It is known that different methods of nanoparticle delivery have varied results, although there is no clarity on the most appropriate method of application (Rani et al., 2021). Overall, NPs used in agriculture have the potential to provide a higher plant biomass and mitigate soil requirements (Ciobanu, 2019).

Soil improvement with nanoparticles is one of the most widely used methods of their application in agriculture, the biofortification of many essential nutrients such as N, Zn, K, P and Fe being observed after ZnO NP application (Dimkpa et al., 2019). Another potential use of NPs is represented by foliar application, being quite convenient for use in agricultural crops as they can be fed to plants in a more controlled manner compared to solid fertilizers, thus reducing toxicity symptoms compared to soil application (Kah et al., 2018). ZnO NPs have also been applied as seed priming agents in many crops to date, resulting in a significant positive influence on plant growth. A particular advantage of nanopriming is the requirement of a reduced amount of NPs, which thus reduces the production cost as well as environmental degradation, compared to foliar and soil application (Khalid et al., 2021).

Bacteria

Specialized research has focused on several metal nanoparticles that have antimicrobial activity, such as silver, copper, and gold nanoparticles (Ramazanzadeh et al., 2015).

Nanoparticles can reduce or stop the evolution of resistant bacteria, as they target multiple biomolecules simultaneously (Slavin et al., 2017). The literature mentions that Gram-positive bacteria have a greater resistance to the mechanism of action of nanoparticles, based on the assumption that the difference in cell walls affects the resistance of bacteria (Crisan et al., 2021). The outer extra layer of Gram-negative bacteria is covered with lipopolysaccharides, creating a negative surface charge, with high affinity for the positively charged ions released by nanoparticles, leading to their accumulation and uptake, ultimately producing intracellular damage (Slavin et al., 2017).

Most often, copper and silver nanoparticles can be compared due to their low cost, their physical and chemical stability, and their ease of fusion with polymers (Bruna et al., 2021). The US Environmental Protection Agency recognized copper as the first solid antimicrobial element due to its antibacterial activity. It was first used to sterilize wounds and water, and it was later discovered that workers in copper processing plants developed immunity to cholera (Sistemática et al., 2016).

Other studies have also shown the effects of copper and zinc nanoparticles as bactericidal agents such as *S. mutans*, obtaining excellent results at a lower toxicity rate (Ramazanzadeh et al., 2015).

Fungi

For many years, copper has been used as a raw material in the manufacturing process of pesticides, fungicides and fertilizers. Recent technological developments suggest that copper nanoparticles are effective fungicides against a wide range of plant pathogenic fungi, such as *Fusarium sp., Phoma destructiva, Curvularia lunata, Alternaria alternate, Fusarium oxysporum, Penicillium italicum, Penicillium digitatum* and *Rhizoctonia solani* (Pariona et al., 2019).

4. Nanoparticles toxicity

There is an extensive literature base regarding both zinc and copper nanoparticles, in relation to the potential toxic effects that their use may have on the organisms themselves and/or on the environment. For example ZnO NPs were found to influence some bacterial lineages in the rhizosphere bacterial community to a greater extent than the bulk form (Xu et al., 2018). In a review study from 2020, it has been highlighted the importance of phytotoxicity tests application in order to establish the degree of NPs toxicity (Alexan, 2020). Several studies indicate that ZnO nanoparticles and their conventional forms exhibit similar toxicity levels. There is an obvious need to undertake targeted studies to obtain clear toxicity statistics (Rani et al., 2022). Reactive oxygen species (ROS) formation and oxidative stress are common toxicological mechanisms for nanoparticle-induced cellular damage (Yang et al., 2009). For instance, small amounts of CuO nanoparticles are capable of generating large amounts of ROS, such as O2−, OH and H2O2, triggering their production and the disruption of the cell membrane once they enter the mitochondria (Xia et al., 2007).

5. Future prospects for the use of nanoparticles

Toxicity studies conducted on the two substances presented confirmed their beneficial character, with adverse effects being correlated with the NP synthesis method, concentration, method and environment of exposure of organisms. Both Zn and Cu nanoparticles have proven to be more harmful than their conventional form due to their high concentration and high solubility potential, organisms showing adverse effects when the optimal application concentrations are exceeded, depending on the method used and their solubility in the environment (Rani et al., 2022; Crisan et al., 2021). Regarding the method of synthesis of nanoparticles, due to the production costs and resources involved, chemical synthesis is still the most used in this regard, the use of chemical precursors, toxic to organisms and the environment, showing its negative impact (Patel et al., 2015; Lee et al., 2013).

Zinc nanoparticles

The current information available regarding the process of bacterial-mediated synthesis of NPs, both through extracellular and intracellular mechanisms, as well as the reducing and stabilizing agents involved in bioreduction and stabilization, respectively, is still scarce (Rani et al., 2022). NPs derived from microorganisms are not applicable for large-scale production due to the requirement of a completely aseptic environment and special maintenance (Dhuper et al., 2012). Scaling up production requires detailed optimization studies to minimize the influence of various factors (Salem and Fouda, 2021).

The complete biomass filtrate with metabolites involved in ZnO NP synthesis needs to be analyzed to reveal the biochemical and molecular aspects associated with bacteria-mediated synthesis. A constant search is needed to explore and screen new microorganisms for nanoparticle synthesis (Yusof et al., 2019). A more critical evaluation of nano-agrochemicals against their conventional analogues is needed to assess the benefits and risks associated with their use (Kah et al., 2018).

Copper nanoparticles

Cu nanoparticles have been shown to be effective in combating a wide range of pathogens and in stopping and preventing infections. The number of potential applications is enormous and allows for further development of this field of study (Kalińska et al., 2019). Further studies are needed to assess the safe use of copper nanoparticles, given their potential toxicity.

In addition, copper nanoparticles can also be considered for agricultural purposes, such as growing wheat crops, to meet the high demand due to population growth. However, extensive research is needed to determine the best concentration, application method and appropriate exposure time (Hafeez et al., 2015).

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