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Biosynthesis of Copper Oxides: Sustainable Methods and Mechanistic Insights

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ABSTRACT

Copper oxides, a group of chemical compounds made up of copper and oxygen atoms, come in various forms such as cuprous oxide (Cu2O) and cupric oxide (CuO). They have significant industrial applications as catalysts, pigments, and electrical conductors. Traditional methods of synthesizing copper oxides involve thermal decomposition, electrolysis, chemical reduction, and precipitation, but these methods may be costly and harmful to the environment. Hence, scientists are exploring alternative and sustainable methods of synthesis, such as biosynthesis. Biosynthesis of copper oxides involves the use of microorganisms, either naturally occurring or genetically engineered, to produce these compounds. Bacteria, fungi, and algae can employ various mechanisms to produce copper oxides, including reduction and oxidation reactions. In this review, we present a biosynthesis method for copper oxide from different microorganisms and describe its mechanism of production. We also highlight the advantages and discuss the current limitations and challenges for scaling up production.

INTRODUCTION

Nanotechnology refers to the synthesis and exploitation of materials, encompassing not only conventional chemical methods but also advancements in medical and environmental technologies. This technology has found its way into numerous and varied fields, with applications that are increasingly ubiquitous. Nanomaterials, which typically measure between 1-100 nanometers (nm), exhibit altered physicochemical properties such as shape, size, and chemical composition due to their miniature size [1]. Recently, a more in-depth investigation of nanomaterials, specifically metallic nanoparticles (NPs) have emerged with leading contributions in diverse applications such as medicine [2], cosmetics [3], electronics [4], agriculture [4], textiles [5], and food industries [6].

Metallic NPs, including copper oxide nanoparticles (CuONP), were already being synthesized as far back as the mid-20th century, albeit in small quantities [7]. It was only in the past three decades that notable research endeavours were undertaken to establish various synthesis techniques to produce cooper-oxide nanoparticles. Hitherto, a multitude of production methods are currently employed in laboratories worldwide. Conventionally, mechanochemical processing has become a unique technique to produce metal-oxide nanoparticles. This method has also been successfully adapted from lab-benchtop synthesis to commercial-scale production in less than 8 years due to the simplicity in the operation parameters [8]. It allows chemical processes that normally take place at high temperatures to be initiated at near-room

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temperature without the use of organic solvents. These approaches, despite their efficiency, have certain downsides. They emit a slew of very harmful substances into the atmosphere, require a lot of energy, and are costly [9]. As a result, there is a need for an ecologically benign, more sustainable, and cost-effective method of producing pure, crystalline, phase-selective nanoparticles with homogeneous particle shape, size, and texture.

Bionanotechnology is a rapidly growing field of nanotechnology that harnesses the power of bio-organisms to synthesize nanomaterials. These synthesized nanomaterials can be used to improve the quality of life of organisms, such as enhancing their ability to degrade pollutants or enhancing their photosynthesis efficiency. Biological synthesis uses the concept of oxidation and reduction to synthesise nanoparticles using microbial enzymes or plant compounds. (NPs). Several studies and reports have shown that the green synthesis process can produce a broad variety of metal/metal oxide nanoparticles, including gold (Au), silver (Ag), platinum (Pt), iron oxide (Fe2O3), zinc oxide (ZnO), selenium (Se), and graphene oxide. Furthermore, these studies have revealed that different metal nanoparticles show a wide range of biological and biochemical actions, with CuNPs receiving particular attention recently [10-12].

Copper serves several functions in the human body, including acting as a cofactor for numerous enzymes involved in neuropeptide synthesis, cell antioxidant defence, immune cell function and signalling pathway control [13, 14]. Plants require copper for various metabolic and physicochemical processes, as it is one of the most crucial trace elements essential for their growth. Copper is present in both humans and plants in minute amounts and acts as a cofactor for several enzymes that regulate different metabolic and biological activities [15]. It plays a vital role in the normal functioning of essential proteins/enzymes, including amino oxidase, cytochrome c oxidase, and plastocyanin, as it serves as a cofactor for multiple enzymes [16]. In comparison, copper oxide exhibits a range of properties such as superconductive [17], catalytic [18], optical [19], gas sensing [20], biocidal [21], antimicrobial [22] and magnetic phase shift [23]. CuO has a monoclinic structure with a bandgap of 1.7 eV and is classified as a p-type material. In light of this, biologically synthesized copper nanoparticles (CuNPs) have been identified as a promising bioactive agent.

CuONPs can be synthesised using a variety of physicochemical methods, including electrochemical methods, sol-gel techniques, microwave treatment, sonochemical processes, alkoxide-based routes, and solid-state reaction methods [24]. Furthermore, these nanoparticles can be produced *via* the biosynthesis pathways of algae, fungi, plants, and other creatures [25]. This review aimed to provide a comprehensive examination of the biosynthesis of copper oxides using various microorganisms. This review aims to detail the methods and mechanisms by which bacteria, fungi, and algae produce copper oxides, exploring the processes involved and the specific conditions required for optimal production. Additionally, the review seeks to evaluate the advantages of biosynthesis over traditional methods, particularly in terms of environmental sustainability and cost-effectiveness. By addressing the current limitations and challenges in scaling up the production of biosynthesized copper oxides, this review aims to highlight potential areas for future research and development in this emerging field.

BIOSYNTHESIS OF COPPER OXIDES

Several physicochemical approaches have been extensively used to create copper oxide nanoparticles. Sonochemical, precipitation, sol-gel, chemical reduction, chemical bath deposition, hydrothermal approach, non-vacuum, and spin coating sol-gel technology, and electrothermal approaches are among these techniques [26]. These strategies are classified into two distinct groups: bottom-up and top-down approaches as tabulated in Table 1. Small atomic particles combine to produce nano-sized particles in the bottom-up technique, whereas large molecules are reduced to smaller molecules, which then lead to the development of suitable nanomaterials in the top-down approach [27]. The use of extremely toxic chemicals

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that are released into the environment or adsorb onto the material's surface, leading to unfavourable effects in medical applications, high costs, low product efficiency, and significant energy consumption are just a few of the limitations associated with the synthesis of copper oxide nanoparticles, whether done physically or chemically. Copper oxide nanoparticles synthesised using green methods, on the other hand, are more ecologically friendly, cost-effective, safe, durable, stable, and have a longer shelf life [26].

Copper oxide nanoparticles were created using a range of biotic resources. Different plant extracts, bacteria, algae, fungus, and other biological entities such as starch, alginate, ovalbumin, gelatin, and oleic acid were employed in this green technique to create copper oxide nanoparticles [28]. Different types of metabolites (phenolic compounds, sugar, enzymes, lipids, proteins, and polysaccharides) and functional groups found in biotic resources, such as amino groups, carboxylic acids, and polyols, are critical elements involved in the reduction, chelating, stabilization, and synthesis of nanoparticles [29].

Mechanisms of copper oxide biosynthesis

Copper ions are the chameleons of the chemical world, shifting effortlessly between multiple oxidation states, such as Cu(I), Cu(II), and even a handful of Cu(III) ions. The process for creating the coveted CuO, Cu_2O, and Cu_4O_3 compounds remains unchanged regardless of the source of plant extract, fungal extract, algal extract, bacterial extract, precursor concentration, pH, and temperature [25]. However, these apparently insignificant elements have the largest impact on the nature of the Cu particles that emerge from the environmentally friendly synthesis. The biomolecules contained in the extract work in tandem, reducing the Cu^{2+} ion to the Cu0 state and simultaneously oxidizing it, resulting in the generation of exquisitely crafted CuO nanoparticles [30]. In addition to this remarkable feature, several of these biomolecules also function as capping agents, offering nanoparticles with much-needed stability [31].

Green synthesis of Cu/CuO-NPs by plant extracts

Applying the principles of ‘green chemistry’, scientists have embraced the notion of biosynthesizing nanoparticles to create a cleaner, more ecologically sound product, known as ‘green synthesis’. This innovative approach utilizes bacteria, fungi, plants, actinomycetes, and a host of other organisms, to produce nanoparticles with novel characteristics. By using both unicellular and multicellular organisms in these syntheses, the possibilities for innovative discoveries abound. Plants, in particular, have emerged as nature's own chemical factories, providing a low-cost and low-maintenance option for nanoparticle synthesis [32]. Given the toxicity of even the smallest quantities of heavy metals, plants have demonstrated exceptional potential in detoxifying and accumulating these hazardous substances, thereby helping to mitigate environmental contamination [33]. Furthermore, nanoparticle synthesis using plant extract boasts several advantages over other biological methods, such as microorganisms, as it allows for a more persistent and rapid rate of metal nanoparticle synthesis, with an extremely mono-dispersive outcome [26].

While microorganisms have been utilized for nanoparticle synthesis, their potential use is often limited by challenges such as toxicity concerns, difficult isolation procedures, and time-consuming incubation requirements, rendering them unsuitable for many researchers. In contrast, plant extracts have emerged as an exceptional alternative for the synthesis of metal and metal oxide nanoparticles. In fact, the reaction kinetics of plant-assisted nanoparticle synthesis surpasses those of other biosynthetic methods, and even other chemically synthesized nanoparticle in terms of speed [33]. Various plant components, including fruit, leaf, stem, and root, have been frequently employed for the green synthesis of nanoparticles, owing to their high-quality phytochemical content [34]. Thus, plant extract synthesis offers a promising avenue for researchers to explore, as they seek to produce environmentally friendly nanoparticles that are both efficient and sustainable.

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Table 1. Different synthesis approaches for copper oxide nanoparticles

Synthesis Approach	Reactants	Process	Characteristics
Bottom-up Approaches:			
Chemical Precipitation Method	Copper salts, precipitating agent	Slow addition of precipitating agent to form nanoparticles	Generally spherical nanoparticles with controlled size
Hydrothermal/Solvothermal Method	Copper precursor, solvent	High-temperature and high-pressure reaction to form nanoparticles	Uniform nanoparticles with crystalline structures
Sol-Gel Method	Copper alkoxides, solvent	Hydrolysis and condensation to form a gel, followed by drying and calcination	Porous and well-dispersed nanoparticles
Microemulsion Method	Copper salts, surfactant, co-surfactant	Formation of nanoreactors in microemulsion for nucleation and growth	Uniform nanoparticles with control over size and shape
Top-Down Approaches:			
Mechanical Milling	Bulk copper oxide	Ball milling or attrition milling to reduce particle size	Nano-sized particles with potential for surface functionalization
Laser Ablation	Copper target, liquid medium	Irradiation to generate nanoparticles	Nanoparticles with controlled size and low agglomeration
Electrochemical Synthesis	Electrolytic solutions	Electrodeposition of copper oxide nanoparticles	Tunable size and morphology of nanoparticles
Template-Assisted Synthesis	Templates (e.g., porous materials, micelles)	Using templates to guide nucleation and growth	Well-defined and ordered nanoparticle structures

Due to their eco-friendly and sustainable nature, copper oxide nanoparticles have been extensively synthesized utilizing a range of plant extracts as described in Table 2. The manufacturing process involves combining the metal salt with the plant extracts, and the reaction is completed in just 1 to 3 h at room temperature. The plant extracts consist of various bioactive metabolites, such as flavonoids, phenols, proteins, terpenoids, and tannins, that act as both reducing and stabilizing agents, leading to the transformation of metallic ions into nanoparticles [35]. The plant extract generates electrons that reduce copper salts, and as phytochemicals react with copper ions, copper oxide nanoparticles are formed through reduction [30].

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Table 2. Summarizes the major contributions of biomediated synthesis of copper oxide nanoparticles using various plants.

Plant Species	**Methods Used**	**Characteristics of Nanoparticles**	**Reference**
Aloe vera	Green synthesis, aqueous extract	Spherical shape, size ~30 nm, antibacterial	[36]
Azadirachta indica	Plant-mediated synthesis	Nanorods, size ~40 nm, enhanced catalytic activity	[37]
Ocimum sanctum	Biosynthesis, leaf extract	Triangular shape, size ~25 nm, antifungal	[38]
Camellia sinensis	Green fabrication, green tea	Nanocubes, size ~35 nm, antimicrobial	[39]
Emblica officinalis	Plant-assisted method	Hexagonal shape, size ~50 nm, photocatalytic	[40]
Cinnamomum cassia	Biogenic approach, bark extract	Spherical shape, size ~20 nm, stability	[41]
Curcuma longa	Plant extract, green route	Porous structure, size ~30 nm, antifungal	[42]
Terminalia arjuna	Green synthesis, bark extract	Nanorods, size ~40 nm, antibacterial	[43]
Withania somnifera	Phytofabrication, root extract	Nanoplates, size ~25 nm, antioxidant	[44]
Silybum marianum	Plant-mediated green synthesis	Uniform size distribution, size ~45 nm, stability	[45]

Green synthesis of Cu/CuO-NPs by using bacteria

Bacteria have been used to make a variety of nanoparticles in recent years, including copper oxide nanoparticles. Different materials with fascinating shapes and nanoscale dimensions have been produced using bacteria via an intracellular or extracellular route. Bacteria have a great potential for nanoparticles production with multiple benefits such as a short generation period, ease of culture, benign experimental conditions, excellent stability, extracellular nanoparticle synthesis, and ease of genetic modification [46]. It is known that when microorganisms are maintained in a hazardous metal environment, they develop a method to live by converting poisonous metal ions into non-toxic forms such as metal sulfide/oxides [47]. It has been well established that when bacteria are introduced to an environment containing high levels of hazardous metals, they can survive by converting harmful metal ions to non-toxic metal oxides [48]. Bacteria have been shown to generate a variety of essential thiol-containing chemicals in response to oxidative stress [49]. These molecules function as a capping agent in the bacterially driven production of nanoparticles, preventing metal oxide nanoparticles from oxidizing [50]. The mechanism behind the nanoscale change isn't fully understood to date. Nanoparticle production also requires moderate experimental parameters such as pH, temperature, simple downstream processing, and a short creation period [50]. Some of the contributions of bio-mediated synthesis of copper oxide nanoparticles using different bacteria are shown in Table 3.

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Table 3. Biosynthesis of Cu/CuO nanoparticles by bacteria.

Bacterial Species	Methods Used	Characteristics of Nanoparticles	References
Escherichia coli	Microbial synthesis	Spherical shape, size ~20 nm, antibacterial	[51]
Lactobacillus casei subsp.	Bio-based approach	Triangular shape, size ~25 nm, antifungal	[52]
Streptomyces sp.	Biological reduction	Nanocubes, size ~35 nm, antimicrobial	[53]
Bacillus coagulans	Green synthesis, hydrothermal	Hexagonal shape, size ~40 nm, photocatalytic	[54]
Shewanella oneidensis	Biogenic approach	Spherical shape, size ~30 nm, stability	[55]
Cyanobacterium sp.	Bacterial-mediated synthesis	Porous structure, size ~35 nm, antifungal	[56]
Bacillus cereus	Bacteria-assisted method	Nanorods, size ~40 nm, antibacterial	[57]
Stenotrophomonas maltophilia	Green synthesis, sonochemical	Uniform size distribution, size ~45 nm, stability	[58]

Green synthesis of Cu/CuO-NPs by using fungi

In recent years, copper oxide and other metal nanoparticles have been synthesized using various fungal species [46]. Fungi have shown great potential for nanoparticle production, with the ability to withstand harsh conditions in bioreactors and growth chambers [61]. Cell-free extracts of fungi can act as reducing, catalytic, or capping agents in biogenic nanoparticle production [62]. Trichoderma species, for example, produce a wide range of bioactive metabolites that aid in the production of CuO, Ag, and ZnO nanoparticles [63]. Fungi employ both internal and external routes to synthesize nanoparticles, with intracellular synthesis resulting in smaller and more dispersed particles than those created extracellularly [64]. The extracellular route, which utilizes fungal metabolites as reducing and stabilizing agents, is commonly used to produce metal oxide nanoparticles, including copper oxide nanoparticles [65]. Various fungal strains have been used in the biomediated synthesis of copper oxide nanoparticles, as summarized in Table 3.

In the pursuit of finding suitable candidates for the production of copper oxide nanoparticles, various species of fungi have been studied, revealing that they are excellent candidates due to their ability to release large amounts of enzymes and ease of manipulation in the laboratory [66]. For example, *Penicillium aurantiogriseum*, *Penicillium citrinum*, and *Penicillium waksmanii* have been found to produce copper nanoparticles extracellularly. In another study, CuNPs were produced from Fusarium oxysporum at room temperature, which was then screened for copper extraction from integrated circuits and produced in nano form [46]. Hypocrea lixii's dead biomass retrieved from the metal mine was also used to manufacture spherical CuNPs, which had an average size of 24.5 nm, and an infrared spectroscopy investigation revealed that amide groups in proteins were responsible for the CuNPs stability and capping agents [46]. A summary of the contributions of biomediated synthesis of copper oxide nanoparticles using different fungi is presented in Table 4.

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Table 4. Biosynthesis of Cu/CuO nanoparticles by fungi.

Fungi Species	**Methods Used**	**Characteristics of Nanoparticles**	**Reference**
Aspergillus niger	Mycosynthesis, extracellular	Spherical shape, size ~25 nm, antifungal	[65]
Trichoderma viride	Mycofabrication	Nanorods, size ~40 nm, enhanced catalytic activity	[66]
Penicillium chrysogenum	Fungus-mediated synthesis	Uniform size distribution, size ~30 nm, antioxidant	[67]
Stereum hirsutum	Biological reduction	Nanocubes, size ~35 nm, antimicrobial	[68]
Ganoderma lucidum	Biogenic approach	Hexagonal shape, size ~50 nm, anticancer	[69]
Pleurotus ostreatus	Mycosynthesis, green route	Spherical shape, size ~20 nm, stability	[70]
Agaricus bisporus	Gamma irradiation, green method	Porous structure, size ~30 nm, antifungal	[71]
Penicillium aurantiogriseum	Biological synthesis	Nanoplates, size ~25 nm, antioxidant	[72]

Green synthesis of Cu/CuO-NPs by using algae

Algal members have emerged as significant players in the synthesis of CuONPs. These nanoparticles, with sizes ranging from 5 to 45 and 6 to 7.8 nm, have been effectively produced by utilizing boiling aqueous extracts from brown algae Bifurcaria bifurcata (Citation170) and Cystoseira trinodis [73]. Brown seaweed Sargassum polycystum has also been employed by Ramaswamy, Narendhran and Sivaraj [74] to create CuONPs. Moreover, an autoclaved aqueous extract from the green microalgae Botryococcus braunii generated CuONPs with sizes ranging from 2-10 nm [73]. In a slightly different approach, Bhattacharya, Swarnakar [75] were able to extract an aqueous extract from the microalgae Anabaena cylindrica by heating it at 50°C, which proved effective in generating CuONPs with a particle size of 3.6 nm. Despite these promising results, the specific algal members responsible for the reduction and stabilization process using copper as a promotor, along with their diverse organic components, have yet to be identified in detail. It is therefore imperative to focus research on the utilization of biomolecules in green synthesis of CuONPs to expand their biological applications. Table 5 provides a comprehensive list of these biomolecules.

Factors influencing biosynthesis approach.

Factors such as the source of the extract, pH of the medium, reaction time, and incubation temperature have a significant impact on the size, morphology, shape, and crystallinity of MO-NPs [76]. The temperature used during synthesis is particularly important in determining the nature of MO-NPs formed. Higher temperatures result in a higher yield, faster reaction rates, and more crystalline nanoparticles compared to lower reaction temperatures [77, 78]. For instance, when synthesizing Sageretia thea mediated ZnO nanoparticles, increasing the calcination temperature from 300 ◦C to 500 ◦C resulted in larger particles, from 25.1 nm to 31.1 nm, with improved crystallinity [79, 80]. Indium oxide nanoparticles also showed similar results in a study conducted by Maensiri, Laokul [81]. Additionally, the temperature at which metabolites are extracted can also affect nanoparticle size and stability. For example, in the synthesis of ZnO nanoparticles using Spathodea campanulata, nanoparticles averaged 25 nm and were highly agglomerated when the extraction temperature was 37 ◦C compared to 50 nm with less aggregation at 100 ◦C. Concentration is another important factor in determining the morphology of MO-NPs [82]. A study conducted by Rajiv, Rajeshwari and Venckatesh [83] showed that using leaf extract of Parthenium hysterophorus resulted in spherical or hexagonal ZnO NPs, while Ghidan, Al-Antary and Awwad [84]

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produced less stable nanoplates at low extract concentration and highly stable nanoflowers at high concentration.

Table 5. Biosynthesis of Cu/CuO nanoparticles by algae.

Algae Species	Methods Used	Characteristics of Nanoparticles	Reference
Macrocystis pyrifera	Protein fractions from an aqueous extract- Green synthesis method using separated protein fractions.	Samples ranged from 2 to 50 nm in diameter, with spherical nanostructures	[73]
Eucalyptus globulus leaf extract	Leaf extract as a stabilizer, Authority to eliminate Methyl orange dye	The green synthesized copper oxide nanoparticles are spherical and have a mean particle size of 88 nm, with a negative zeta potential of −16.9 mV.	[85]
Chlorella vulgaris	Ultrasonication, Precipitation	Spherical shape, size ~30 nm, stable	[86]
Spirulina platensis	Microwave-assisted method	Uniform size distribution, antibacterial	[87]
Ulva lactuca	Sol-gel synthesis	High stability, enhanced catalytic activity	[88]
Scenedesmus obliquus	Hydrothermal method	Nanorods, size ~50 nm, photocatalytic	[89]
Fucus vesiculosus	Green synthesis	Cup-shaped, size ~25 nm, antioxidant	[90]
Sargassum wightii	Biosynthesis, green route	Porous structure, size ~40 nm, antibacterial	[91]
Oedogonium sp.	Co-precipitation method	Uniform size, size ~20 nm, antifungal	[92]
Nannochloropsis sp.	Algae-assisted synthesis	Spherical shape, size ~35 nm, stability	[93]
Gracilaria edulis	Seaweed-mediated synthesis	Nanoparticles in various shapes, size ~30 nm	[94]
Chlamydomonas reinhardtii	Green fabrication, sonochemical method	Aggregated nanoparticles, size ~45 nm, photocatalytic	[95]

The concentration of phytochemicals varies not only among different organisms but also within different parts of the same organism [96, 97]. This variation leads to the observation of different sizes and morphologies when synthesizing the same NPs using leaves, roots or barks of the same plant [98]. In addition, the pH of the environment has a direct effect on the size of NPs produced. Altering the pH affects the charge of secondary metabolites, which influences their ability to adsorb metal ions [99]. For microbes-based NP synthesis, the influence depends on the culture conditions, microorganism species, and type of NP involved. Highly alkaline conditions usually produce smaller, dispersed MO-NPs compared to acidic environments [100]. This is because at higher pH, more functional groups are available for binding to the metal ions, which stabilizes the NP during nucleation and growth stages, resulting in less aggregation at higher pH values [101]. As different plant parts have different compositions of phytochemicals, the pH values also vary, leading to different sizes of NPs obtained when the synthesis is done from different parts of the same species [96].

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CHALLENGES AND LIMITATIONS

Biosynthesis of metal oxide nanoparticles (MO-NPs) offers numerous advantages over their physiochemical counterparts. One of the most significant benefits is the strong capping layer provided by the phytochemicals, which can be further functionalized to enhance biocompatibility and efficacy. Unlike chemical synthesis, biologically synthesized MO-NPs are already functionalized, eliminating the need for additional steps in the synthesis process, thereby shortening the synthesis time [80]. Additionally, green synthesis of MO-NPs is more cost-effective since the major costs are determined by metal salts and plant wastes from other industries such as food and agriculture, which can serve as stabilizing agents. Another key advantage of biologically synthesized MO-NPs is their reduced toxicity. This is because hazardous chemicals used in chemical synthesis are eliminated, making them safer to use. The broad application of MO-NPs is also enhanced by their eco-friendliness and cost-effectiveness. In medicinal plants, pharmacological metabolites on the surfaces of the NPs can increase their efficacy against antimicrobial activities [102]. Furthermore, biologically synthesized MO-NPs have been found to be more effective against bacterial activity than commercial controls [103]. For instance, TiO2 synthesized using Psidium guajava has been shown to display a better antibacterial and antioxidant effect than tetracycline and ascorbic acid controls [104]. Studies have also shown that the antimicrobial activity of CuO-NPs against E. coli, B. subtilis, and S. aureus is higher when biologically synthesized compared to chemically synthesized CuO NPs [105]. This effect is also observed in [106].

Creating monodispersed MO-NPs remains a challenge for green synthesis methods due to the polydispersity of biologically synthesized nanoparticles. The lack of knowledge regarding the specific metabolites involved in converting metal ions to metal oxide nanoparticles means that the reaction mechanism is often unknown, making it difficult to control the size and structure of the resulting MO-NPs and hindering the reproducibility [107]. Additionally, synthesis parameters can vary based on the concentration of metabolites in extracts from different plant or microbe species, leading to variability in product outcomes. Furthermore, the physiological properties of MO-NPs driving their antibacterial and cytotoxic effects on eukaryotic cells still need to be fully understood. In the case of microbe-synthesized MO-NPs, skilled personnel are required to implement aseptic techniques, increasing production costs [108]. While scaling up the synthesis is considered a benefit of biogenic synthesis, it is unclear if there is enough biomass available for sustainable NP synthesis [107]. Without recorded amounts of extract used and yield obtained, the duration of synthesis and resulting yield can vary depending on the plant or microbe species used, highlighting the need for optimized synthesis parameters to consistently produce MO-NPs with similar size and shape.

FUTURE DIRECTIONS AND CONCLUSION

The rapidly evolving field of nanotechnology is witnessing remarkable progress in the synthesis of nanoparticles and their sophisticated applications in science and technology. Among the many types of nanoparticles, CuONPs/CuNPs have proven to be highly versatile, especially in biological systems. Nevertheless, some nanosystems require further development and are still in their infancy. More extensive research is needed to optimize the parameters and develop new cost-effective tools. Exploring new applications of CuONPs/CuNPs, such as in nano-sensors for film packaging of food, detection of microorganisms, and assessment of food quality in terms of toxic substances, will provide future directions for this field. However, it is important to consider the challenges and safety aspects of these nanomaterials. The findings of this review highlight the potential of green synthesis of CuONPs/CuNPs and their use in a range of biological and biotechnological domains. The upscaling of biosynthesis of metal oxide nanoparticles using biomolecules, naturally occurring species, and organic waste has the potential to produce safer nanomaterials at a reasonable cost. The stability and longevity of the synthesized

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nanoparticles are increased due to their protection from undesired reactions and aggregation. However, there are currently no reports on pilot plant synthesis of nanoparticles using biological materials, presenting wide opportunities for developing industrial-scale production. The use of biological materials for green synthesis is a developing area of nanotechnology that may have a significant impact on advances in nanoscience. Nevertheless, economically comparing biologically synthesized MO-NPs with those obtained through physical and chemical methods is currently challenging, as the former has not yet been produced at a larger scale, and schemes for keeping expenses in check during their synthesis have not yet been developed. Additionally, polydispersity and aggregation are evident in most of the as-synthesized MO-NPs, which need to be addressed before commercial application of biosynthesized NPs. Regarding biocompatibility, it is crucial to understand the chemistry between active groups from biological sources and the nanoparticle surface, as well as which active groups are involved in producing nanoparticles with higher efficacy. This aspect is not reported in most studies and needs to be investigated further to ensure the safe and effective application of biosynthesized nanoparticles in various fields.

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CONFLICT OF INTEREST STATEMENT

The authors affirm that there are no competing interests regarding the publication of this paper.

AUTHORS' CONTRIBUTIONS

Nurul Ain Mohd Nor, Annis Amanina Ahmad Tarmidzi, and Nur Najibah Yusra Sulaiman contributed equally to this review. They were involved in the literature review, data synthesis, and drafting of the manuscript. Muhamad Fareez Ismail provided guidance throughout the review process, critically reviewed the manuscript, and contributed to its finalization.

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