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Industrial Applications of Nanomaterials Produced from *Aspergillus* Species

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Abstract

There is a great demand for green methods of synthesis of nanoparticles. Fungi play an important role in the synthesis of nanoparticles, of which *Aspergillus* spp. are known to secrete different enzymes responsible for the synthesis of nanoparticles. The process of biosynthesis of nanoparticles is simple, rapid, cost-effective, eco-friendly, and easy to synthesize at ambient temperature and pressure. Mostly, the metal nanoparticles such as silver, gold, lead and the oxides of titanium, zinc, and copper are synthesized from *Aspergillus* spp. These include mainly *Aspergillus fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, and *A. clavatus*. The fabrication of different nanoparticles is extracellular. In the present chapter, we have discussed the role of different species of *Aspergillus*, mechanism of biogenic synthesis particularly enzymes involved in the reduction of metal ions into nanoparticles. The biogenically synthesized nanoparticles have demonstrated several biomedical, agricultural, and engineering applications. The biogenic nanoparticles are mostly used as antimicrobial and cytotoxic agents. Their use as fungicidal agents is important for sustainable agriculture.

Keywords: *aspergillus* spp., nanomaterials, biogenic synthesis, industrial, biomedical, agriculture

1. Introduction

Nanomaterials (NMs) are the structures fabricated in the nanoscale, i.e. 1 to 100 nm and having at least one dimension in the nanoscale. The fabrication, study, and application of nanostructures are known as nanotechnology. The exhibition of novel physicochemical properties by the nanoscale materials has provided a unique opportunity for researchers to design and develop materials with applications in the diverse fields of science and technology. This has attracted attention towards nanoparticles (NPs) and their fabrication as compared to other sectors of NMs. Some of the nanomaterial productions have reached to the industrial scale due to the high demand for NMs in consumer products and their number is increasing at the moment with their developing applications. Ever-increasing demand for different NPs has generated the need for easy, safe, efficient, rapid, and eco-friendly procedures for their large-scale production.

Nanomaterials can be produced by two general approaches, i.e. top-down approach and bottom-up approach. Another classification includes different methods like physical, chemical, biological, and hybrid methods of nanoparticle production. The physical method requires an expensive setup, is high energy-consuming, and hazardous to health and the environment. Whereas chemical methods are highly efficient as compared to physical methods, but involve a toxic reducing agent, solvent, and stabilizing/capping agents. Recently, the biological method of nanoparticle production has attracted attention because of its ease, eco-friendly nature, high efficiency, and high yield. In this method, a biological agent or a biomolecule plays a significant role in the production of NMs [1]. Production of NMs by a biological method is a promising alternative for physical and chemical methods [2].

Among the different biological systems like bacteria, actinomycetes, fungi, plants, protozoa, and animals, fungi have shown great potential for the production of NPs on large scale. Bacteria normally produced NPs intracellularly, where large-scale production and purification of NPs is complicated and expensive. Unlike bacteria, fungi produce NPs extracellularly and are easy to use and purify NPs for large-scale production [3]. Fungi are easy to handle, versatile, tolerant, and economical biological systems for industrial production of biotechnology products and have been used extensively in large-scale production of different metabolites. The tremendous ability of fungi in the secretion of proteins up to 100 g/L, metabolic diversity, and high production capacity have made them a unique option for industrial biotechnology for decades. Hence, filamentous fungi are the first choice, since they are capable of secreting a large amount of proteins and other metabolites extracellularly. Moreover, the fabrication of NPs by a fungal system is a green process [4]. Among the fungal sources, *Aspergillus* is a very promising candidate for the production of NPs, this is because there are more than 350 species of this genus with enormous biochemical versatility in addition to the secretion of a large quantity of proteins [5]. Different *Aspergillus* species produce NPs of diverse sizes and shapes with interesting physicochemical properties like enhanced thermostability, stability over a wide pH range, greater solubility, and biocompatibility. Moreover, the compounds produced by *Aspergillus* are classified as generally regarded as safe (GRAS) status, which can be safely used in the industry [6]. NPs fabricated by fungi have been used for different applications such as in medicine, as an anti-cancer drug, antibiotic, antifungal, antimicrobial, and antiviral agents [7], in diagnostic, bioimaging, biosensor, agricultural, and other industrial applications [8]. A new term “Myconanotechnology”, was proposed by Rai and co-workers [9] to highlight the research on fungi in the production of NPs and their role in the nanotechnology research.

Industrial biotechnology processes demonstrate a significant reduction of greenhouse gas emissions using renewable resources. The process is environment friendly and do not result in the accumulation of toxic compounds in the ecosystem. In industrial biotechnology, biomass input is used under the process of biological agents like metabolites and biomolecules to create a wide spectrum of products. There is a worldwide interest to enable the production of different NPs on biotechnological lines because of their eco-friendly nature, less energy-intensive, ease of execution, and ability to modify biological agents, and products [10].

In the present chapter, we are going to focus on the need for large-scale productions of NPs by biological methods in general and by *Aspergillus* spp. in particular. Different NPs fabricated by the *Aspergillus* spp., their advantages over the other methods, details of the mechanistic aspects of nanoparticle production, and various applications of fabricated NPs. Toxicity concerns of the large-scale production of NPs will also be discussed.

2. Diversity of *aspergillus* spp. for the synthesis of different nanomaterials

More than 6400 different biologically active substances have been reported from filamentous fungi which have potential bioactivities and different applications [11]. As these fungi have greater tolerance to high metal ion concentration and have the ability to internalize and bio accumulate metal ions they can be used for metal ion reduction and stabilization in nanomaterial synthesis [12–16]. A huge range of fungi is shown to have the ability to synthesize NPs. Out of which *Aspergillus* is one of the major contributors in the mycosynthesized (fungus mediated synthesis) NMs with various biological activities. A huge range of *Aspergillus* spp. have been reported to synthesize different NMs including metal and metal oxide NPs. The cell-free extracts, as well as supernatant of fermented medium, can also be used for the synthesis of NPs [14, 15, 17]. The following **Table 1**, summarizes the *Aspergillus* spp. and the respective NMs synthesized by them.

<i>Aspergillus</i> spp.	Nanomaterial synthesized	Reference
<i>Aspergillus tubingensis</i>	Silver	[18]
<i>Aspergillus niger</i> IPT856	Silver	[19]
<i>Aspergillus oryzae</i>	Silver	[20]
<i>Aspergillus flavus</i>	Silver	[21]
<i>Aspergillus versicolor</i>	Silver	[22]
<i>Aspergillus terreus</i>	Silver	[23]
<i>Aspergillus versicolor</i>	Silver	[24]
<i>Aspergillus oryzae</i> (MTCC no. 1846)	Silver	[25, 26]
<i>Aspergillus fumigatus</i> BTCB10	Silver	[27, 28]
<i>Aspergillus niger</i>	Silver	[14, 15]
<i>Aspergillus tamari</i> <i>Aspergillus niger</i>	Silver	[29]
<i>Aspergillus flavus</i>	Silver	[30]
<i>Aspergillus terreus</i>	Silver	[31, 32]
<i>Aspergillus flavus</i>	Silver	[33]
<i>Aspergillus fumigates</i>	Silver	[34]
<i>Aspergillus oryzae</i> var. <i>wiridis</i>	Silver	[35]
<i>Aspergillus flavus</i>	Silver	[36]
<i>Aspergillus fumigatus</i> DSM819	Silver	[37]
<i>Aspergillus niger</i>	Silver	[17]
<i>Aspergillus niger</i>	Silver	[38]
<i>Aspergillus niger</i>	Silver	[39]
<i>Aspergillus fumigatus</i>	Silver	[40]
<i>Aspergillus flavus</i>	Silver	[41]
<i>Aspergillus clavatus</i>	Silver	[42]
<i>Aspergillus flavus</i> NJP08	Silver	[43]
<i>Aspergillus terreus</i> CZR-1	Silver	[44]
<i>Aspergillus terreus</i>	Silver and Gold	[45]
<i>Aspergillus sydowii</i>	Gold	[46]
<i>Aspergillus niger</i>	Gold	[47]

<i>Aspergillus</i> spp.	Nanomaterial synthesized	Reference
<i>Aspergillus niger</i>	Gold	[48]
<i>Aspergillus terreus</i> IFO	Gold	[49]
<i>Aspergillus niger</i>	Gold	[50]
<i>Aspergillus clavatus</i>	Gold	[51]
<i>Aspergillus flavus</i>	TiO ₂	[52]
<i>Aspergillus flavus</i> TFR7	TiO ₂	[53]
<i>Aspergillus niger</i>	ZnO	[54]
<i>Aspergillus fumigatus</i>	ZnO	[55, 56]
<i>Aspergillus oryzae</i>	FeCl ₃	[57]
<i>Aspergillus tubingensis</i>	Ca ₃ P ₂ O ₈	[58]
<i>Aspergillus versicolor</i> mycelia	Hg	[59]
<i>Aspergillus aureoterreus</i> Samson et al. AUMC 13006	CuO	[60]
<i>Aspergillus carneus</i> Blochwitz AUMC 13007	CuO	[60]
<i>Aspergillus flavus</i> var. <i>columnaris</i> Raper and Fennell AUMC 13012	CuO	[60]
<i>Aspergillus fumigatus</i> Fresenius AUMC 13024	CuO	[60]
<i>Aspergillus sydowii</i> (Bainier and Sartory) Thom and Church	CuO	[60]
<i>Aspergillus terreus</i> Thom AUMC 13019	CuO	[60]

Table 1.
Various *aspergillus* spp. and respective nanomaterials synthesized by them.

The cell-free extracts of *Aspergillus* spp. are challenged against the precursor salt for direct synthesis of NPs. But *Aspergillus* extract fermented lupin was reported by Mosallam et al., [61], for the biological synthesis of selenium NPs in the presence of gamma radiation. Balakumaran et al. [45] reported the various strains of *Aspergillus* isolated from Kolli hills and Yercaud hills, South India, and identified their ability to synthesize extracellular gold and silver NPs. Out of all the screened isolates, *A. terreus* showed the most stable nanoparticle synthesis. Vala [46] reported the synthesis of gold NPs by marine-derived fungus *Aspergillus sydowii* [62]. The intracellular synthesis of gold NPs by *Ammophilus fumigatus* has been reported by Bathrinarayan et al., [63, 64]. In one of the studies on the experimental rat model have demonstrated the wound healing ability of *A. niger* mediated silver NPs [65]. Ghareib et al., [60] isolated *Aspergillus* strains from Egyptian soil and reported their biomass and culture supernatant mediated synthesis of copper oxide (CuO) NPs. Biogenic zinc oxide NPs are synthesized from the cell-free fungal filtrate of *A. niger*, which has antimicrobial and dye degradation ability [54].

All these various types of NPs synthesized using different isolates and strains of *Aspergillus* are shown to have distinguishing bioactivities, numerous functions, and applications in various fields [14, 15, 66]. These fungus-mediated metal and metal oxide NPs are synthesized intra or extracellularly and are reported to appear in various shapes and sizes [67].

3. Advantages of nanomaterial production by *aspergillus* spp

The green chemistry approach highlights the usage of microorganisms which offers a cheaper, lighter, reliable, nontoxic, and eco-friendly process [68, 69]. Fungi

secrete a higher amount of proteins owing to significantly higher productivity of NPs [70] which effectively proved a potential source for the extracellular synthesis of different NPs without using harmful toxic chemicals. The advantages made fungi more suitable for large-scale production and easy downstream processing, also economic [70, 71]. Besides, enzyme nitrate reductase is found to be responsible for the synthesis of NPs in fungi [68, 69]. Biofabrication of NPs using fungi (eukaryotic organism) has several advantages over the prokaryotic mediated approach for reproducibility of nanosized materials. Also include ease to multiplication, grow, handling, and rest of downstream process for this top-down approach of nanobiosynthesis through nano factories [72, 73]. Tarafdar et al., [74] observed rapid, low cost, and eco-friendly iron nanoparticle fabrication by using the fungi *Aspergillus oryzae* TFR9. This study evaluated the morphological and elemental characterization of the biosynthesized iron NPs [74].

Zielonka et al., [75] demonstrated fungi are almost ideal biocatalysts for NPs biosynthesis. In contrast to bacteria, as they are well-known for producing greater amounts of biologically active substances that make the fungus more appropriate for large-scale production [31, 32]. Moreover, fungal biomass can resist flow pressure, agitation, and harsh conditions in chambers such as bioreactors. Also, they exude extracellular reductive proteins which can be used in subsequent process steps. However, the fungal cell is deprived of unessential cellular components since NPs are accelerated outside the cell and can be immediately used in manifold ways without pre-treatment [76]. There are a large number of fungi, which can efficiently synthesize silver NPs, such as *Aspergillus clavatus*, and have many biomedical applications [77].

Here we highlighted the advantages of NMs produced by using *Aspergillus* spp. The high-scale production of NPs from fungi has wide applications in protein engineering, synthetic biology, and downstream processing (**Figure 1**). For large-scale production, fungi can be effectively employed. Gade et al., [14, 15] studied extracellular biosynthesis of AgNPs by *Aspergillus niger* isolated from soil. The nitrate-dependent reductase enzyme reduced the silver ions and a shuttle quinone extracellular process. The reduction of silver ions was an extracellular process.

AgNPs released silver ions in the fungal cell, which increased its antifungal function. AgNPs synthesized by using *A. terreus* HA1N sp. There is a large number of fungi, which can efficiently synthesize silver NPs, such as *Aspergillus clavatus* (*A. clavatus*) or ZnO NPs are produced by *Aspergillus terreus* [57]. The effect of prepared zinc oxide NPs on the growth and mycotoxin production by mycotoxigenic molds was evaluated which was concentration-dependent. The levels of produced mycotoxins were decreased when the concentration of ZnONPs increased [78]. Bathrinarayanan et al., [63, 64] produced gold NPs by *Aspergillus fumigatus*. It was found to be stable, spherical, and had irregular morphologies which were confirmed by SEM analysis.

El-Desouky et al., [79] demonstrated the synthesis AgNPs by an eco-friendly and low-cost method using the fungi *Aspergillus terreus* HA1N. It is an alternative to chemical procedures which require drastic experimental conditions emitting toxic chemical byproducts. The AgNPs are widely used as a novel therapeutic agent as antibacterial, antifungal, antiviral, anti-inflammatory, and anti-cancer agents [80, 81]. The AgNPs synthesized by *Aspergillus* spp. present potential advantages such as fast growth rate, the rapid capacity of metallic ion reduction, nanoparticle stabilization, and facile and economical biomass handling. Moreover, these fungi have significantly higher productivity when used in nanoparticle biosynthesis due to their higher protein secretion [82]. Husain et al., [83] demonstrated the immobilization of *Aspergillus oryzae* β -galactosidase on native ZnO and zinc oxide NPs (ZnO-NP) by using a simple adsorption mechanism. The ZnO has wide

Figure 1.
Advantages of nanoparticles produced by *aspergillus* spp.

applications. In addition to this easy production, improved stability against various denaturants, and excellent reusability, ZnO-NP bound β galactosidase. There are many applications in constructing enzyme-based analytical devices for clinical, environmental, and food technology. *Aspergillus niger* showed effective fabrication of AgNPs [84]. The mycotoxin produced by mycotoxigenic fungi such as *Aspergillus* sp. Food toxin can be detected by nano-based biosensors. The functionalized NMs are used as catalytic tools, immobilization platforms, or optical or electroactive labels to improve the biosensing performance to obtain higher sensitivity, stability, and selectivity. Recently, these nano biosystems are also bringing advantages in terms of the design of novel food toxin detection strategies [85].

4. Mechanistic aspect of nanomaterial synthesis by *aspergillus* spp

It is well-identified that biological systems can fabricate the number of metallic and non-metallic nanoparticles. Synthesis of nanoparticles can be achieved at low cost by biological system especially from the fungal system at low pH, temperature, and salt concentration. Various studies have been proved that fungus-like *Fusarium* [7], *Phoma* [4], *Aspergillus* [86], and many more were found to be excellent factory for synthesis different types of nanoparticles. Every fungal species has unique biomolecule contents, which play a crucial role in the synthesis of nanoparticles. Due to this convolution still, an exact mechanism for nanoparticles synthesis from specific fungal species is yet to be revealed.

Even though, various studies have been initiated to understand the mechanism for the synthesis of nanoparticles from *Aspergillus* spp. Jain and co-workers [43] proposed two-step mechanism for silver nanoparticles synthesis from *Aspergillus flavus* NJP08. In the first step, 32 kDa reductase protein secreted by fungus might be responsible for the synthesis, and in the next step 35 kDa protein is responsible to provide stability to silver nanoparticles. In one of the study by Phanjom and Ahemad [86] proposed that the nitrate reductase enzyme secreted by *Aspergillus oryzae* (MTCC No. 1846) is responsible for the conversion of Ag^+ to Ag^0 . Selenium

Figure 2.
Possible mechanism for the biosynthesis of Co_3O_4 nanoparticles in *A. nidulans* [87].

nanoparticles are also proved to be synthesized by the aqueous extract of fermented Lupin using *Aspergillus oryzae* and nucleation by gamma-ray (30.0 kGy) [61]. The authors confirmed that due to unique characteristics and novel biosynthesis method, selenium nanoparticles could be a good green antimicrobial candidate in biomedicine, cosmetics, and pharmaceuticals. Endophytic fungi *Aspergillus nidulans* also produced cobalt oxide nanoparticles through the detoxification mechanism. In the synthesis, nitrate reductase along with electron shuttling compounds and other peptides are responsible for the reduction and synthesis [87]. Pavani et al. [88] reported the possible reductase or cytochrome base synthesis of lead nanoparticles from *Aspergillus* species. In the first step, the mechanism stated the trapping of lead ions on the fungal cell wall through electrostatic attraction. In the next step, these ions get entered into the cell and might get reduced by enzymes existing in the cell wall and inside the cell wall. In one of the study conducted by Li et al., [31, 32] reported the stabilized nanoparticles synthesis through reducing agent nicotinamide adenine dinucleotide (NADH) present in the *Aspergillus terreus* (Figure 2).

5. Applications of nanomaterials synthesized using *aspergillus* spp

The numerous NMs have been synthesized by *Aspergillus* spp. and applied in various fields, for instance, Ag, Cu, Fe, Fe_3O_4 , and ZnO NMs are some of them [55, 56, 72, 89–95]. Nanotechnology platform finds application of NMs in almost in each and every field such as agriculture, environmental science, health sciences, portable water treatment large/small scale plants, industrial separation, catalyst, electronics, energy storage, and energy regeneration [96–99]. The applications of NMs synthesized using *Aspergillus* spp. in various fields are shown in the graphical representation of Figure 3.

Figure 3.
Graphical representation of different applications of NMs synthesized using *aspergillus* spp.

NMs synthesized by *Aspergillus* species have tremendous applications broadly in the areas like agriculture, food security and animal industry, environmental management, and medicine and pharmacy are some of them. The detailed description is given in the sections below.

5.1 Applications in agriculture

In recent years, the nanotechnological advances in the field of agriculture have been increasing as the application of various NMs in the development of nano-based products like nanofertilizers for increasing crop yield and soil improvement, for plant growth promotion, nanopesticides, nanofungicides, nanoencapsulation for slow release of agrochemicals, and more in which NMs plays a vital role. The application of NPs as agrochemicals has become more common as technological advances make their production more economical for employment in the agriculture sector. For the potential application of NPs in plant disease control primarily included the information about the antimicrobial activity of different nano-size compounds against phytopathogens and the development of better application strategies to enhance the efficacy of disease suppression [100]. The antimicrobial activity of *Aspergillus* spp. synthesized NMs have been reported by many researchers. Silver NPs have been reported as most effective against phytopathogenic fungi, *Magnaporthe grisea* and *Bipolaris sorokiniana*, *in-vitro* [101], *Alternaria solani* and *Erwinia cartovora* pv. *cartovora* [102], and *Alternaria* blight as well as *Phytophthora* blight [103]. Elgorban et al., [24] demonstrated the silver NPs synthesis using fungus *Aspergillus versicolor* and evaluate its antifungal activity against *S. sclerotiorum* and *Botrytis cinerea* in strawberry plants. The silver NPs showed the concentration-dependent activity towards both the tested organisms but showed the greatest effect against *B. cinerea*. In another study, Ismail et al., [104] evaluated the combined effect of silver and selenium NPs against fungus *A. solani* that causing

early blight disease of potato. The fungus isolated from leaf spot was identified by microscopy and treated with NPs suspension, which showed the formation of pits and pores. Therefore, the authors concluded that the myco-synthesized AgNPs were able to penetrate and distribute throughout the fungal cell area and interact with the components, and cause cell death. Silver/chitosan nanoformulations (NFs) were applied against various seed-borne plant pathogens, particularly seed-borne disease-causing fungi, isolated from chickpea seeds [105]. These studies reveal the possibilities of NPs application as an antifungal agent, alternative to the fungicide for controlling plant pathogens.

Nanoformulations of copper-chitosan (Cu/Ch) has been prepared as an anti-fungal agent against *A. solani* that causing early blight disease of tomato (*Solanum lycopersicum* Mill). These NPs caused mycelia growth inhibition and spore germination in *A. solani* and *F. oxysporum*, respectively, *in-vitro* model [106]. Recently, Shende et al., [94] synthesized the CuNPs using *Aspergillus flavus* and tested its activity against selected fungal plant pathogens namely *Aspergillus niger*, *Fusarium oxysporum*, and *Alternaria alternata*, which reveals significant antifungal activity. The study suggested the application of CuNPs as an effective fungicide for sustainable agriculture. ZnO NPs have also been investigated as an effective fungicidal agent against plant pathogens. ZnO NPs have many advantages over silver NPs for fungal pathogen control efforts [107]. He et al., [108] evaluated the antifungal effect of ZnO NPs and their mode of action against two post-harvest pathogenic fungi *viz.* *B. cinerea* and *Penicillium expansum*. Different concentrations of NPs, when applied to fungal hyphae demonstrated cell wall damage and collapse fungal hyphae. Raliya and Tarafdar [55, 56] reported the synthesis of ZnO NPs by *Aspergillus fumigatus* TFR-8, with the size range between 1.2 ~ 6.8 nm and Oblate spherical and hexagonal shape and evaluated its effect on phosphorous-mobilizing enzyme secretion and gum contents in cluster bean (*Cyamopsis tetragonoloba* L.). The antibacterial potential of photocatalytic nanoscale titanium dioxide (TiO₂), nanoscale TiO₂ doped with zinc (TiO₂/Zn; Agri-Titan), and nanoscale TiO₂ doped (incorporation of other materials into the structure of TiO₂) with a silver (TiO₂/Ag) has been evaluated against *Xanthomonas perforans*, bacteria causing bacterial spot disease in tomato [109]. Shenashen et al., [110] synthesized and characterized the mesoporous alumina sphere (MAS) NPs and evaluated their biological activity against *F. oxysporum*, that causing root rot disease in tomatoes, in comparison with the recommended fungicide tolclofomethyl, under laboratory and green house conditions. The authors reported cell death because of the entry of NPs in fungal cells due to disruption of the cell membrane and malformation of hyphae.

5.2 Applications in food security and animal industry

The application of NMs in the food security and animal industry is attending the great interest of the scientific community in recent years. Food security is usually the preparation, treatment, and storage of food products in which the food-borne pathogens or illness will not going to cause any damage or spoilage to the product [96, 97, 111]. Food insecurity, like illegal additives, pathogens, pesticide residues, allergens, and other unsafe factors, those are not only seriously affects human health, but also limit the rapid development of food industries to a certain extent [112–114]. The identification and quantitative analysis of bacteria is a very important and crucial issue in food safety. Conventional practices require long culture time, highly skilled operators, or specific recognition elements of each type of bacteria [113]. For this purpose, the analytical methods or equipments that meet the requirement of modern detection of various hazardous substances present in the foods for example packaging materials, sensors, and food containers coated with

NPs are developed using NMs. The novel nano-based food packaging materials have the unique characteristics involving oxygen scavengers, antimicrobial potential, and barriers to gas or moisture, and many other. In view of these multiple benefits of nanopackaging, its application in the pathogens detection, antimicrobials, allergens and contaminants, UV-protecting activity, high gas barrier plastics, etc. are some important areas of research [115]. The use of such NMs in food packaging enhances the shelf life of food devoid of undesirable alteration in its quality.

The application of smart packaging systems has increased tremendously in animal industries the muscle-based food products such as meat, chicken, etc. that are prone to contamination. The packaging of meat and muscle products suppress the spoilage, enhance the tenderness by allowing enzymatic activity, avoid contamination, retain the cherry red color in red meats and reduce the loss in its weight [116]. Plastic food packaging is one of the most important areas of research that employ nanotechnology to make stronger and lighter packaging materials and also enhances its performance. Besides this, NMs with strong antimicrobial properties such as Ag and TiO₂ NPs could be used in the packaging of foods to prevent spoilage [117]. Additionally, the application of NPs of clay in food packaging helps to control the entry of carbon dioxide, oxygen, and moisture towards food materials, thus preventing food spoilage.

Nowadays, more researchers have been paying attention to the development of nanosensors, which are being added in plastic packaging to spot the gases released from spoiled food. In the food spoilage or contamination condition, the packaging material will alert the consumer by detecting toxins, microbial contamination, and pesticides in food products, based on flavor production and color changing [118]. Moreover, plastic films entrenched with silicate NPs are being developed to maintain food fresh for a longer period. In this case, NPs play a vital role in dropping the oxygen flow and also facilitate to impede the moisture seeping out from the package. In animal industries, *Aspergillus* spp. synthesized NMs such as ZnO NPs are used as antimicrobial agents. For instance, *Aspergillus fumigatus* JCF and *Aspergillus niger* synthesized ZnO NPs with 60 ~ 80 nm and 61 ± 0.65 nm size, respectively and Spherical shape demonstrated the antimicrobial potential [54, 93]. The antifungal activity was observed in the ZnO NPs, which were synthesized by *Aspergillus terreus* [90]. Recently, Mousa et al., [119] reported the mycosynthesis of various NMs viz. Co₃O₄, CuO, Fe₃O₄, NiO, and ZnO NPs by endophytic fungus *Aspergillus terreus*, and studied its antimicrobial and antioxidant activities, which leads to their application in different fields.

5.3 Applications in healthcare, medicine, and pharmacy

In medicine and pharmacy, NMs have been successfully applied due to their high surface area that is able to adsorb or conjugate with an extensive variety of therapeutic and diagnostic agents such as drugs, vaccines, genes, antibodies, and biosensors. In recent years, antibiotic resistance is an emerging major global health problem and novel antimicrobial formulations are essentially needed to fight against these drug-resistant microbes, therefore nano-based medicine as antimicrobial agents have gained considerable attention in the field of microbial drug resistance [119, 120]. Hence, the NPs synthesized by Mousa et al., [119] using the endophytic fungus *Aspergillus terreus* were studied to discover their efficacy against different multi-drug-resistant bacterial strains as well as some human and plant pathogenic fungi. The authors have reported the broad-spectrum antimicrobial action of all the mycosynthesized NPs, where the bacterial and fungal strains were inhibited. Furthermore, Co₃O₄ NPs among the five types of mycosynthesized NPs exhibited the strongest antimicrobial potential against the tested pathogens. There

are very few reports on the antimicrobial activity of Co_3O_4 NPs and only very less reported their antibacterial potential only [121]. Meanwhile, previous reports have observed the antimicrobial activity of CuO , Fe_3O_4 , NiO , and ZnO NPs [122–125].

There are several reports on the synthesis and antimicrobial applications of *Aspergillus* spp. synthesized NMs. Netala et al., [22] demonstrated the antibacterial activity of Ag NPs synthesized by *Aspergillus versicolor* against *Staphylococcus aureus*, *Streptococcus pneumonia*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* at concentration 1 mg/mL. In another study, *Aspergillus terreus*-mediated synthesis of Ag NPs, showed antibacterial activity against *Salmonella typhi*, *S. aureus*, and *Escherichia coli* [23]. The synergistic effect with Ag NPs synthesized by *Aspergillus flavus* and conventional antibiotics against multi-drug-resistant bacteria such as *Bacillus spp.*, *Micrococcus luteus*, *S. aureus*, *Enterococcus faecalis*, *E. coli*, *P. aeruginosa*, *Acinetobacter baumannii*, and *K. pneumoniae* at concentration 100 ppm [21]. Rodrigues et al., [18] reported the synthesis of Ag NPs using *Aspergillus tubingensis* and demonstrated the antimicrobial activity against *Candida* sp. and *P. aeruginosa* at concentrations 0.11–1.75 $\mu\text{g/mL}$ and 0.28 $\mu\text{g/mL}$ respectively. Ag NPs synthesized by *Aspergillus oryzae* revealed the antifungal effect against *Trichophyton rubrum* at concentration $> 7.5 \mu\text{g/mL}$ [20]. Another strain of *Aspergillus oryzae* (MTCC no. 1846) synthesized Ag NPs using 1 mM AgNO_3 , produced 7–27 nm-sized spherical particles, which showed the antibacterial effects [25, 26]. Ottoni et al., [19] reported the synthesis of Ag NPs by *Aspergillus niger* IPT856 and its antibacterial activity against *E. coli*, *S. aureus*, and *P. aeruginosa*. In another study, *Aspergillus fumigatus* BTCB10 synthesized Ag NPs with a spherical shape, which demonstrated the antibacterial and cytotoxic effects [27, 28]. The ZnO NPs as a dietary supplement in the animals gives health benefits, which improves the quality of egg in poultry, help in wound healing, act as an antioxidant, improve growth performance, hormone production, bone formation, immune system, a cofactor for enzymatic process, and reproduction system [126]. The antibacterial and antifungal potential improves the health of the livestock. In another study, Farrag et al., [92] reported the synthesis of Ag NPs by *Aspergillus niger* isolated from soil by treatment with silver nitrate. AgNPs exhibited significant inhibition of *Allovalkampiella spelaea* viability and growth of both trophozoites and cysts, with a reduction of amoebic cytotoxic activity in host cells that suggested the Ag NPs possibly will give a promising future for the treatment of *Allovalkampiella spelaea* infections in humans.

5.4 Applications in environmental management

NMs offer a unique platform for the purification of water contaminated with pollutants namely organics, metal ions, biological contaminants, and arsenic from the water because of the high surface area of nanosorbents and their ability of chemical modification as well as easier regeneration [127–130]. Chatterjee et al., [91] reported the synthesis of superparamagnetic iron oxide NPs (IONPs) (Fe_3O_4) of 20–40 nm size by manglicolous (mangrove) fungus *Aspergillus niger* BSC-1 and employed for the removal of hexavalent chromium from aqueous solution. Therefore, suggested the utilization of mycosynthesized IONPs could be employed for the heavy metal remediation from contaminated wastewater. The enzymatic bioremediation of textile industry wastewater containing direct green or reactive red azo dye by utilization of enzymes immobilized onto magnetic NPs for the improvement of industrial and environmental applications have been reported by Darwesh et al., [131]. Different types of magnetic NPs have been used to remove heavy metal ions from industrial wastewater [132].

In another study, the Au NPs was synthesized by *A. niger* that was found to be very effective against the mosquito larvae. The AuNPs were tested using the larvae

of three mosquito species viz. *Anopheles stephensi*, *Culex quinquefasciatus*, and *Aedes aegypti*. Among them, it has been observed that the effect of Au NPs was found to be significant against *C. quinquefasciatus* larvae than the *A. stephensi* and *A. aegypti* larvae. All larval instars of *C. quinquefasciatus* showed 100% mortality after 48 hours of exposure to the Au NPs synthesized by *A. niger* [50]. In conclusion, the authors suggest that the application of mycosynthesized Au NPs by *A. niger* could be the fast and environmentally friendly approach towards the control of mosquitoes than the currently available approaches. This may possibly lead to a novel potential strategy for vector control [50].

Other than this, nowadays NMs could be applied in antimicrobial surface coatings, environmental sensing, renewable energy, and many other environmental applications.

6. Toxicity aspects of nanomaterials

Assessment of toxicity of synthesized NPs is the critical step for ensuring their safe and sustainable applications. Hence, toxicity evaluation of all the newly synthesized nanoparticle must be considered before their industrial applications. As far as the comparison of biosynthesized NPs with NMs synthesized by other methods especially the chemical method is concerned, the biosynthesized NPs seems to be biocompatible [133]. For instance, the green synthesized NPs were found to enhance the plant seedling growth, yield and quality, suggesting the biocompatibility of biosynthesized NPs as compared to the chemical synthesis NPs [134]. In contrast, few studies have shown the toxicity of biosynthesized or green synthesized NPs. Sulaiman et al., [135] have synthesized silver NPs (AgNPs) by using *Aspergillus flavus* and investigated its cytotoxic effect on HL-60, a human promyeloid leukemia cells. The study reported the dose-dependent toxicity of AgNPs at concentration of 5 and 10 µg/ml. The study claimed that although AgNPs have a toxic effect on normal cells but they also have the potential to act as a potential anticancer agent. However, the toxicity of AgNPs was found to be higher than silver nitrate solution. The said toxic effect was claimed to be due to the physicochemical interaction of silver atoms of AgNPs with the functional groups of intracellular proteins, nitrogen bases, and phosphate groups of DNA. The AgNPs may induce the accumulation of reactive oxygen species (ROS) leading to cellular apoptosis. Such effect will be helpful for the anti-cancer, antiproliferative, and antiangiogenic effects *in vitro*. Othman et al., [136] have synthesized AgNPs by using *A. terreus* and studied its antitumor activity against Human Caucasian breast adenocarcinoma (MCF7). It was found to inhibit the growth in dose-dependent manner with IC₅₀ value of 46.7 µg/ml. Similarly, ZnO NPs synthesized by using the culture filtrate of *A. terreus* have been reported to be cytotoxic to HeLa cells. It was shown to induce apoptosis by inhibiting the production of cellular superoxide dismutase, catalase, glutathione peroxidase levels and inducing the accumulation of ROS, and reduction in mitochondrial membrane potential. Moreover, further investigation found it to induce oxidative damage via down-regulating expression of p53, Bax, Caspase-3, Caspase-9, and up-regulating Cytochrome-C expression [137]. The nanoparticle when come in contact with the target cell membrane, gets accumulates at the cell surface and induces pore formation causing the leakage of cytoplasmic material outside the cell. The NPs entered in the cell can interact with intracellular protein and DNA and thus disturbing the cell regulation [138]. The discussed mechanism of nanoparticle toxicity, in general, is represented in **Figure 4**. In general, toxicity studies are performed on human and animal cell line and plants. But there is also a need to give attention to the toxicity studies on microbes that are directly

Figure 4.
 Mechanism of cytotoxicity of mycosynthesized nanoparticles.

or indirectly beneficial to humans. Gupta et al., [139] have explored the toxicity of AgNPs synthesized by different fungi. The study found the mycosynthesized AgNPs to show toxicity to soil beneficial bacteria *Pseudomonas putida* KT2440 at the concentration of 0.4 µg/ml. Mycosynthesized Selenium nanoparticles (Se-NPs) were found to alter Wi-38, a normal lung fibroblast cells. At the IC₅₀ value of 461 ppm, it exerted the loss of typical cell shape, granulation, loss of monolayer, and shrinking or rounding of cells [140].

Considering all of these observations from various studies it is suggested that before the actual application of any biosynthesized nanoparticle there is a need to undertake the toxicity studies and then make their use at biocompatible dose. For example, *A. terreus* strain AF-1 was exploited for the synthesis of CuO NPs which were integrated in cotton fabric. The said nanoparticle was used at a safe dose making it applicable for desired purpose [141]. Although mycosynthesized NPs are quite biocompatible as compared to NPs synthesized by other methods, it is recommended to verify the toxic effects of each type of NPs and choose their safe dose so as to make them safer for any kind of application.

7. Conclusion

Nanomaterials as the structures fabricated in the nanoscale have gained increasing attention for diagnostic and therapeutic purposes especially for those produced in a green safe approach by using fungi and other microorganisms. Among fungal species successfully used for this purpose, members of the genus *Aspergillus* are in the first line of investigation because of their huge diversity and capability to grow in abundance in laboratory conditions. Although there are many reports on the synthesis and biological activities of nanomaterials of different origins by fungi, little has been documented about important disciplines such as their mode of action and applications in medicine and industry. This chapter has highlighted the diversity of *Aspergillus* species and their advantages for nanomaterial production, mechanistic aspects of nanomaterial synthesis by selected *Aspergilli*, applications in healthcare, medicine, and pharmacy, role in environmental management as a unique platform for water decontamination, and finally, the cytotoxicity of introduced nanomaterials as a critical step for ensuring their safety and sustainability. Overall, these

results further substantiate the importance and priority of *Aspergillus* species for nanomaterial production at an industrial scale in a safe and cost-effective manner which enables researchers to use them for diagnostic, detoxifying, and therapeutic purposes in industry, medicine, and agriculture.

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