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Review

Biosynthesis of gold nanoparticles via fungi: A review of their optimization, antibacterial action and applications

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Abstract: Gold nanoparticles (AuNPs) have been known to possess exceptional electric, biochemical, and optical characteristics and are 'the topic of discussion' these days, especially relating to the field of biomedicine. Several plants, bacteria, and fungi have been utilized for the generation of AuNPs, besides other physical and chemical methods. While some studies have been reported with gold nanoparticles, less are aimed at fungi and its optimization factors. These parameters can allow us to design AuNPs of our choice depending on the use. The present review focuses on and inspects AuNPs with green synthesis through fungus optimization parameters followed by applications, aiming specifically at their antibacterial activity. Their antibacterial characteristics can open new doors for the pharmaceutical industry in the future.

Keywords: gold nanoparticles; green synthesis; optimization; fungi; antibacterial activity

1. Introduction

Nano-biotechnology is the subdivision of nanotechnology that is expanding day by day and includes the development and fabrication of nanomaterials [1]. Nanoparticles (NPs) can be generated by utilizing several plants, bacteria, and fungi by using different approaches comprising of physical, chemical, and biological methods. Various microorganisms can be employed for both extracellular and intracellular nanoparticles owing to their incomparable characteristics; however, separation of intracellular NPs is laborious and requires extra processes [2].

The credit for discovering AuNPs in particular goes to Michael Faraday, who in 1857 observed these small particles (<100 nm) radiating a red colour. This phenomenon is also known as the Tyndall effect, which is in fact dispersion of the light as a ray of light passes through a colloid. Although these particles were not visible at that time, they gave a 'golden-coloured glow'. It is known that light's wavelength is more in contrast to the gold nanoparticles owing to their size. This is the basis of present-day nanotechnology, and it has allowed a lot of researchers to work in this field [3].

The nanoparticles can easily be characterized using multiple instruments; their varying size and morphology in particular can be identified by using Transmission Electron Microscope (TEM), Scanning Electron Microscope (SEM), zeta sizer, or Atomic Force Microscope (AFM). Moreover, their Surface Plasmon Resonance (SPR) band can be detected by using UV-Vis spectrophotometer whereas their functional groups can be exposed using Fourier transform infrared spectroscopy (FTIR). In order to find out the nature of a certain nanoparticle, X-ray diffraction (XRD) is also carried out [4,5].

Additionally, the process of nanoparticle formation can be enhanced by altering

a few factors like biomass weight of fungi, temperature, synthesis or incubation time, pH, and concentration of substrates, etc. Still further studies are necessary to regulate the size, assembly, conformation, and other physico-chemical characteristics of NPs developed by employing fungi [5,6].

2. Methods of nanoparticle development

There are three ways to generate nanoparticles: firstly, physical, then chemical, and finally biological. Physical techniques include ball milling, laser ablation, lithography, thermal evaporation, etc., which basically require the application of external force. These procedures are high maintenance and call for higher temperatures in addition to reaction time. On the other hand, chemical procedures are most commonly used to produce NPs but use and emit chemical and harmful gases along with contaminated end products. Additional steps like hydrolysis and reduction are also part of the chemical synthesis. Lastly, the biological technique has been gaining popularity these days and involves extracts from various plants, microbes like fungi, bacteria, algae, and viruses for its production.

Green synthesis of nanoparticles is not only harmless towards the environment and cost-effective but is known to have fewer inadequacies in contrast to the chemical and physical techniques discussed above; additionally, they are also excellent candidates for upscaling. Hence, fungi in particular have been selected for much research these days due to their easy availability, harmless nature, wide variety, and novel strains. Fungi are also known to produce natural metabolites and excrete enzymes and proteins that act as capping agents and support the reduction process during NP formation. Moreover, fungi itself have more surface area owing to their mycelial structure, releasing more proteins in return, forming NPs rapidly and effectively [7].

3. Attributes of gold nanoparticles

Many metals have been employed for the synthesis of NPs, but gold nanoparticles have amazed researchers due to their unmatched properties, which allow alterations on their surface. Gold nanoparticles, specifically, are known for their surface plasmon resonance (SPR) phenomenon and give out a range of colours, i.e., red, purple, and orange, as the size of NPs increases. Owing to this factor, the SPR band is formed between 500 and 550 nm, which is validated later by a UV-Vis spectrophotometer; moreover, highly charged particles have the ability to either be suspended or stay diffused in a solution, as Hammami and Alabdallah [5] described.

Gold NPs have enhanced adsorption capacity along with great biocompatibility, chemical, and opto-electronic capabilities, which also determine their morphology, permitting them to be used in various sectors, especially biomedical. Gold is a valuable metal known for its stability and for being inert henceforth allowing it to be used in many applications, specifically its role in antibacterial studies, which has gained popularity among researchers as microbe resistance towards antibiotics has become a dilemma these days [8].

4. Green technique by employing fungi

By using the green technique and choosing fungi over bacteria and plant extracts has more benefits, like they can withstand additional agitation along with pressure. Another important factor is temperature, which makes fungi a suitable candidate for biosynthesis; also, their scaling up is easy [8]. Quite a few inspections were aimed towards the biosynthesis of AuNPs by a variety of fungi giving off different sizes (**Figure 1),** such as *Candida albicans* (15 nm), *Aspergillus niger* (20 nm), *Fomes fomentarius* (50 nm), *Ganoderma lucidum* (30 nm), *Gliocladium roseum* (45 nm), *Lentinula edodes* (35 nm), *Myrothecium verrucaria* (40 nm), *Phanerochaete chrysosporium* (40 nm), *Pleurotus florida* (50 nm), *Schizophyllum commune* (45 nm), *Trichoderma harzianum* (40 nm), and *Tolypocladium ophioglossoides* (60 nm) [9]. After their generation, they were used in various applications like drug delivery, biosensors, preservation of paintings, effluent treatment and management, antifungal glazes, food preservation, optics, and environmental monitoring [8].

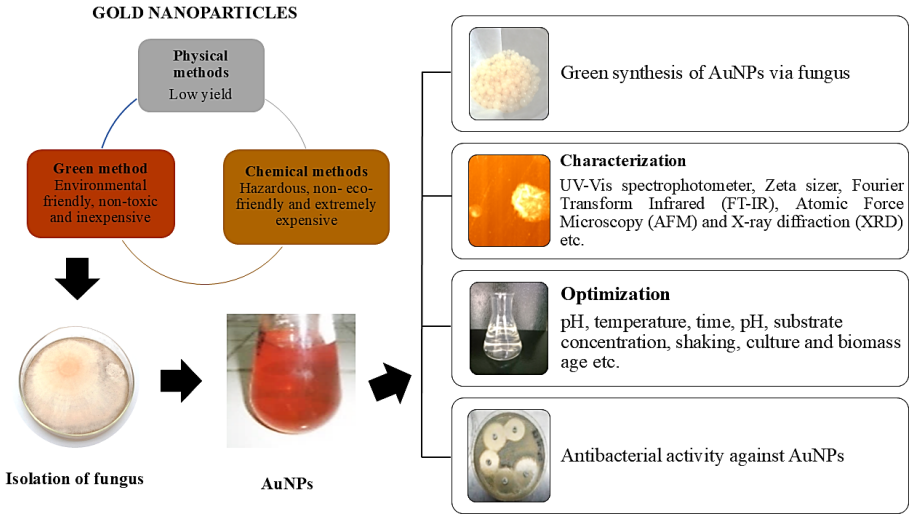

Figure 1. Overview of the fungi-mediated synthesis of gold nanoparticles.

Similarly, many more reports regarding AuNPs from fungi include *Pleurotus sajor-caju* [10], *Fusarium solani* [11], *Jahnula aquatica* [12], *Botryosphaeria rhodian* [13], *Aspergillus terreus* [14], *Pleurotus ostreatus* [15], *Aspergillus tamarii* [16], *Ganoderma neo-japonicum* [17], *Morchella esculenta* [18], *Cladosporium* sp. [19], and *Aspergillus flavus*, etc. [20]. Furthermore, AuNPs were also produced by employing some strains such as *Alternaria* sp. (9.5 nm), *Trichoderma viride* (24.7 nm), *Ganoderma sessile* (13.6 nm), *Trichoderma asperellum* (16.4 nm), and *Botrytis cinerea* (92.9 nm) [21]. Additionally, some more research on AuNPs was also conducted using *Helminthosporum solani, Neurospora crassa,* [22] *Penicillium citrinum*, *M. phaseolina,* [3] *Fusarium oxysporum, Colletotrichum* sp., *Fusarium semitectum, Phoma glomerata,* etc. with varying sizes and shapes. It was observed that AuNPs were generated both intracellularly and extracellularly by *Trichothecium* sp. with a variety of shapes consisting of triangular and spherical forms [23].

5. Mechanism of gold NPs

There are many benefits in the generation of gold NPs via fungi, such as little or no energy is required, additional supplements or agents are not needed, and they are highly functional. Furthermore, the process of production is quite simple, followed by purification. During research, several fungi have been utilized in the formation of gold NPs, as mentioned previously, and they can be both extracellular (outside the cell) and intracellular (inside the cell) with varying unique morphologies. It has been reported that phenols, peptides, and enzymes located on the outside of the fungal cell are mainly in charge of the extracellular production of gold NPs, whereas the intracellular process basically revolves around the concept of absorption through mostly proteins plus enzymes and reduction of gold ions occurring within the cytoplasm or in the cell wall through enzymes or proteins. We can attain NPs with varying sizes and forms along with unique characteristics by optimizing the parameters. In order to improve the function of NPs, we can also adjust substrate concentrations, pH, process time, temperature of incubation, biomass weight, etc. [24].

It was reported earlier that reduction within the AuNPs occurs within the cytoplasm or the surface of the cells due to the presence of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) or Nicotinamide Adenine Dinucleotide (NADH). Additionally, it was exposed that reduction occurs firstly with Au^{+3} which is further reduced to Au^{+} and finally into its elemental form, i.e., Au^{0}, but the enzymes or proteins involved are yet to be investigated [25]. Moreover, it was also reported that other metabolites, i.e., flavin adenine dinucleotide (FAD)-dependent glutathione reductase alongside NADH, have performed a major task in the generation of AuNPs via fungi. Other than that, quinine was also involved in the process of reduction along with phytochelatin when substrate concentration was increased to a certain level [26].

Mainly, the development of nanoparticles involves two processes occurring side by side: first, reduction, which transforms Au^{+3} into Au^{0}; and second, particles' growth and equilibrium amongst them are monitored by capping agents. The NPs are guarded by these ligands, which prevent any form of aggregates and additional development with the assistance of electrostatic charges. It is also reported that some amino acids or chemical metabolites are capable of working as both reducing and capping agents. Proteins and enzymes use Van der Waals forces and adhere to the surface of gold NPs or alternatively attach by bonds among sulfur along with nitrogen atoms within the protein. They are known to bind even at points of zero charge, but it decreases their bonding capability [27].

6. Optimization factors

The AuNPs can be acquired by altering several parameters one at a time of our choice with varying physical and chemical properties. Some of the important factors are discussed below in **Table 1**.

Table 1. Synthesis of gold nanoparticles by various fungi and their characterization.

Fungi	Incubation conditions	Size (nm)	Zeta potential (mV)	SPR band (nm)	Functional groups	Shape	Antibacterial studies	References
Cladosporium sp.	1 mM, ($HAuCl_4$) Fungal extract/ $HAuCl_4$ (70 mL: 30 mL) Temperature 37 ℃ Agitation rate 180 rpm Reaction time 24/h	5–10	-	524	O-H C=O	Spherical, irregular	-	[19]
Epicoccum nigrum	1 mM, ($HAuCl_4$) Temperature 28 ℃ Dark condition Agitation rate 180 rpm Reaction time 24/h	2–30	-	550	O-H C=O C-H	Quasi-spherical	*Bacillus subtilis* with 100, 200, 300 mg/L (AuNPs)	[28]
Fusarium chlamydosporum	0.1 mM, ($HAuCl_4$) CFF (10 mL) Temperature 25 ℃ Dark condition 120 rpm agitation rate Reaction time 24 h 25 g biomass weight	22.1	37.6	530	-	Spherical	*Escherichia coli* and *Pseudomonas aeruginosa*	[29]
Fusarium solani	Temperature 25 ℃ Dark condition Concentration 1 mM ($HAuCl_4$) pH 8.5 Fungal extract/ $HAuCl_4$ (1: 99) Incubation time 48 h	40–45	2.5	551	C-N C-H	Needle, flower	-	[11]
Jahnula aquatica	Reaction time 48 h Reaction temperature 70–90 ℃	8, 20, 60	−43.5	560	N-H O-H C=O C-H C-N C-C	Spherical	-	[12]
Aspergillus flavus	Filtrate concentration (10%) $HAuCl_4$ 1mM Tween 20 (0.1%) Incubation period 30 min with light Temperature (30 °C) Reaction time (15 min)	10–50	positive	530	C-O-O C=O C-N N-H O-H	Spherical, hexagonal, rectangular	*B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa* yeast, *C. albicans* No ZOI observed	[20]
Pleurotus ostreatus	pH 5 Salt concentration (5mM) Agitation 200 rpm Incubation time 48 h Temperature 30 ℃ Ratio of salt and ECF (5:1)	10–30	−24.0	550	N-H	Spherical	*B. subtilis* (30 mm), *E. coli* (30 mm), *S. aureus* (30 mm), *C. albicans* (13 mm)	[15]
Morchella esculenta	1mM $HAuCI_4$ Extract: gold chloride solution ratio (1:5)	16.51	-	511	O-H C=C C-H C=O	Cubic	*S. aureus* *P. aeruginosa* (10 mm)	[18]
Fusarium oxysporum	Temperature 37 ℃ and 80 ℃	50	−28	541	-	Spherical	-	[30]
Candida tropicalis	Temperature 37 ℃ CTAB	12.4	+57.5	482	-	Spherical	-	[31]

Table 1. (*Continued*).

Fungi	Incubation conditions	Size (nm)	Zeta potential (mV)	SPR band (nm)	Functional groups	Shape	Antibacterial studies	References
Thermoascus thermophilus	pH (4.7) Temperature 35.0 ℃, 45.0℃ and 55.0 ℃ Reaction time 3–20 h Czapek-Dox medium	40	-	450–650	-	Spherical	-	[27]
Fusarium acuminatum	Acidic pH 1 mM (gold chloride) Temperature 37 ℃	8–28	-	520–550	-	Spherical	-	[32]
Aspergillus Trinidadensis	2–12 pH 48 and 72 h culture ages 1 mM substrate concentration Shaking (160 rpm) Biomass weight (80–240 mg/mL)	35		530–570	N-H C-N C=O	Spherical		[33]
Bipolaris tetramera	1 mM substrate concentration	58.4–261.7		570		Spherical, triangular, hexagonal	*B. subtilis,* *B. cereus,* *S. aureus,* *E. coli,* *E. aerogenes*	[34]
Agaricus bisporus	1 mM of $HAuCl_4$ solution (10 mL) 1 ml of mushroom extract	25	−45.8	510–570	N-H C-N C-O-C C-OH	Spherical	-	[35]
Aspergillus terreus	$HAuCl_4$ solution (1mM) pH (4–12) Temperature (25°C to 60 ℃) Fungal extract intensity (10–200 ppm) Shaking (150 rpm)	10–16	−28.2	536	O-H C-H C=O C-N	Spherical	*S. aureus,* *V. cholera,* *S.typhimurium*	[36]
	$HAuCl_4$ solution (1 mM) pH (5–10)	2–29	-	550	C-H, N-H −SH	elongated, triangular, rod	*Escherichia coli*	[37]
Candida rugopelliculosa	1 mM of $HAuCl_4$ solution Temperature (35 ℃), Shaking (120 rpm)	10–30	-	550	C-H C=O C-N $-NH_2$	-	-	[38]
Pycnoporus sanguineus	Substrate concentration (0.5–2.0 mM) Temperature (30 ℃), Shaking (165 rpm)	29.3–61.4	-	520–560	O-H C=O C-N C-H $-NH_2$	Spherical, pseudo-spherical, triangular, triangular, pentagonal hexagonal		[22]

6.1. Temperature and time of synthesis

NPs typically attain large-size to small-size during the synthesis at high temperatures. Usually, elevated temperatures favour bigger NPs as it is suitable for growth alongside the nucleation stage. In contrast to this, lower temperatures support ‘growth’ leading to an increase in the rate of reaction. Due to an alteration in temperature, NPs of many conformations are generated, and the number of substrates

secreted is also affected, which also shifts the equilibrium between growth and nucleation. In order to obtain small-sized NPs, higher temperatures are needed, which will trigger the reduction rate, use up the metal ions, and obstruct secondary reduction progress, which can still take place [39].

Many studies have evaluated the AuNPs with varying temperatures. In a study with *Pleurotus ostreatus*, AuNPs were optimized by employing varying temperatures such as 30 ℃, 37 ℃ and 40 ℃. It was seen that 30 ℃ gave the highest yield of AuNPs [13]. *Aspergillus terreus* was also utilized for the generation of gold NPs, and temperature was optimized at 30 ℃ within a period of twelve hours [14]. Moreover, *Verticillium luteoalbum* was also used for the formation of gold nanoparticles, and varying temperatures of 25 ℃, 35 ℃ and 50 ℃ were assessed. It was observed that rapid development of NPs occurred with rise of temperature in contrast to lower temperatures. Most of the growth and development was revealed in the first hour with a spherical shape and size of about 10 nm. At a temperature of 50 ℃ no further changes were detected [40]. In another study with *Fusarium oxysporum,* AuNPs were synthesized after incubation with two varying temperatures, one at 37 ℃ and subsequently at 80 ℃. AuNPs slightly above 50 nm were generated, but it was also seen that at higher temperatures they are more suitable, taking less time, and it was realized that this also allows the formation of smaller nanoparticles [31].

Similarly, in a study with *Aspergillus flavus*, various temperature ranges were applied and AuNPs were monitored; temperatures from 20 ℃ to 100 ℃ were analyzed. In this study, 30 to 40 ℃ proved to be the most suitable for monodispersed AuNPs, whereas after 60 ℃ a decline was observed, and later at 80 ℃ clumping of the nanoparticles was noticed. No AuNPs were formed at lower temperatures of 20 ℃ [20], whereas the time of synthesis was observed from 25 min to 55 mins. It was detected that the gold NPs started forming right after 15 mins of mixing CFF and gold chloride solution. It is known that time of reaction plays a significant role in molding the shapes and sizes of any nanoparticles, together with the yield of NPs [41].

In the recent studies, many shapes have been revealed with the changes in temperatures with AuNPs, such as spherical, triangular, hexagonal, etc. It was stated that generation of NPs can be boosted by raising the temperature up to 50 ℃ and substrate concentration up to 0.7 mM. Hammami and Alabdallah [3] found that the ideal temperature for the production of AuNPs was between 28–55 ℃ by maintaining the incubation temperature of the fungal cell-free extract [3].

6.2. pH

During the synthesis of nanoparticles, a change in pH can play a significant role. It is reported that at a low pH, the biomass itself clutches onto more positive charges and produces small-sized nanoparticles rapidly due to the weakened reduction power and binding site being nearby. Moreover, pH plays a vital role in the initial stages of AuNP generation with respect to size and shape. It was described that gold NPs specifically do not form at lower pH, but greater pH values help establish extracellular AuNPs. Furthermore, an increase in pH means a higher rate of reaction along with a reducing rate, thus producing a variety of shapes and sizes [42].

In an interesting investigation with the fungus *Verticillium luteoalbum*, pH was adjusted several times using different levels, commencing from 3, 5, 7, and later 9. It was established that altering the pH greatly impacts the shape and size of NPs. A size of 10 nm AuNPs (spherical) was observed with a pH of 3, and a similar outcome was realized. Furthermore, a pH 5 exposed triangular-shaped or rod-shaped NPs as well after the synthesis. pH 7 and 9 revealed small-sized nanoparticles with spherical shapes [40]. A similar study with the fungus *Penicillium brevicompactum* was employed for the formation of gold NPs, and its pH was optimized by varying it between 5 and 8 [43].

Besides, *Aspergillus terreus* was also utilized for the formation of gold nanoparticles, and its pH was also optimized. No change was noted with pH 1 and 2, whereas at pH 3, pink to violet colour transformations were observed. Later, at pH 7, stable NPs were seen, and colour intensified at a pH of 10, with little or no synthesis at higher pH [14].

Likewise, in a study with *Aspergillus flavus*, various pHs commencing from 3 to 4 to 7, 9 and 12 were tested to enhance the functioning of gold NPs, but it was noted that alteration in pH did not influence the process of NP formation. Rapid synthesis was observed with the distilled water alone, and changes in pH only reduced the absorbance capacity, so it can be said that the reduction process was disturbed due to fluctuations in pH within the cell-free filtrate (CFF) [20]. Another experiment with *Pleurotus ostreatus* evaluated AuNPs; they were optimized by applying pH 5, 6, and 7. It was established that a pH of 5 gave a suitable outcome with AuNPs; however, little or no effect was felt on the nanoparticles themselves [15]. Moreover, another study with *Aspergillus trinidadensis* described the effect of pH on the stability of AuNPs. Varying pHs from 2 to 12 were applied to the AuNPs for a period of 12 h, and it was revealed that a pH of 7.4 enhanced the monodispersion and NPs were steady under all the tested pH ranges [33].

Another study states that the most optimum pH for AuNPs development is between 5 and 9 of the cell-free extract that can be easily maintained with the help of buffers. It was also stated that a change in pH can alter the conformation of AuNPs, like it was observed that a lower pH of 2 revealed rod-shaped (large) NPs, whereas a pH of 4 produced smaller rods. Likewise, it was noted that pH of 8 and 9 normally yielded spherical to oval-shaped NPs, while pH of 10 exposed rod-shaped morphology, though nanowires were exhibited at a pH of 11 [3].

In an examination of AuNPs with *Aspergillus terreus*, it was noted that NPs of varying sizes (20 to 29 nm) were developed with varying pH ranges. At a pH of 8, NPs were mostly polydispersed, establishing themselves with rod and spherical conformation, while at a pH of 5 to 7, NPs with triangular to rod-shaped shapes were attained along with broad SPR peaks. pH 9 and 10 showed monodispersed NPs, and size varied from 10 nm to 19 nm, and it can be stated that there was a reduction in size with the increasing pH towards alkalinity [37]. This also shows that the environment was ideal for the AuNPs and led towards small-sized nanoparticles.

6.3. Agitation rate

Optimizing the rate of agitation is important, as it plays a substantial part in the reduction of the nanoparticles. Static agitation will give low absorbance along with a low reaction rate during the process of the development of nanoparticles, resulting in low performance and efficiency in contrast to the experiment conducted with agitation [44].

However, in a study with *Pleurotus ostreatus,* AuNPs were optimized by using varying agitation rates, i.e., 100 rpm, 150 rpm, and 200 rpm; nevertheless, it was noted that the most suitable agitation rate was 200 rpm, which gave the greatest response [15]. Similarly, in a study with *Aspergillus flavus*, it was analyzed that the agitation speed of 120 rpm did not affect or boost the process of gold nanoparticle formation [20]. It was also noted in a study that *Trichothecium* sp. produced intracellular AuNPs quickly with a spherical shape with shaking. However, surprisingly, without agitation, it produced both intracellular and extracellular nanoparticles, giving rise to triangular and spherical NPs [23].

6.4. Substrate concentration

Metal salt concentration also leaves an impact on the size of the nanoparticles. It was described that nanoparticles may develop with very large sizes if the concentration is extremely high, as struggle between the capping agents and ions (metal) may possibly escalate to form NPs, and excess substrates may form aggregates [45]. Many studies were conducted to optimize the AuNPs with fungi, and interesting results were revealed in an investigation with *Aspergillus terreus.* 1 mM substrate concentration proved to be the most optimum even though $AuCl_3$ of many intensities was applied from 1 mM to 10 mM, but they simply failed to generate NPs [14]. Likewise, after investigation with *Penicillium brevicompactum*, it was seen that after 2 mM gold, NPs started to form aggregates and also increased in size, probably due to saturation of the environment [40]. In another study with *Pleurotus ostreatus*, AuNPs were optimized by using different substrate concentrations at 1 mM, 2.5 mM, and 5 mM. The most optimum substrate concentration was found to be 5 mM and showed a rapid reduction soon after its addition [15].

Similarly, in a study, *Aspergillus flavus* gold chloride solutions of varying molarities starting from 0.5 mM to 2 mM were applied to control the functionality of AuNPs. Results displayed that at 1 mM some synthesis took place, whereas at 0.5 mM a broad SPR band was revealed, while 2 mM exposed reduced absorbance [20]. It was also stated in an investigation that lower intensities of substrates along with reduced weight of biomass give rise to AuNPs with a smaller size, but on the other hand, their yield becomes restricted if upscaled [8].

6.5. Fungal filtrate

Fungal filtrate concentration clearly effects the formation of nanoparticles. In order to analyze fungal filtrates and the functionality of AuNPs, varying concentrations of 5% to 40% were applied in a study with *Aspergillus flavus*. It was seen that at a higher percentage of fungal filtrate, a broad SPR band was obtained in contrast to a reduced concentration of 5 to 10%, which probably occurred due to the

presence of exceedingly reducing agents [20]. In a study with *Agaricus bisporus*, it was seen that fungal filtrate of '1 mL' generated AuNPs of approximately 25 nm with great stability of −45.8 mV by Zeta sizer [35].

6.6. Biomass weight

Biomass weight is another important factor that must be kept in mind while optimizing nanoparticles. It was reported that if the biomass quantity is increased during the synthesis of NPs, its size begins to modify, and if the enzymes become saturated while the process is taking place, researchers may have to deal with large-sized NPs as the enzymes are secreted in excess, which might lead to aggregation later [46]. Another study was conducted using *Aspergillus terreus* to produce NPs with varying biomass weights, such as 10 g/100 mL to 30 g/100 mL. It was noted that the increase in the biomass weight did not work for the biosynthesis of gold NPs, probably due to the occurrence of additional reducing agents; however, at a weight of 10 g/100 mL, NP formation was observed as the environment must be in equilibrium and not saturated with enzymes [14].

Furthermore, *Aspergillus Trinidadensis* was also studied with varying biomass intensities until optimization was achieved. Initially, experiments were conducted with biomass of 160 mg/mL; later, more ranges were introduced, starting from 40–240 mg/mL with 1 mM of $HAuCl_4$ solution. Finally, 4 g (160 mg/mL) of biomass was found to be ideal along with the rest of the optimization variables like culture, temperature of incubation, pH, etc. [33].

6.7. Fungal culture age

In an inspection with the fungus *Verticillium luteoalbum*, different time periods, i.e., 24 h, 48 h, and 72 h, were applied and AuNPs were monitored. Initially it was observed the fungal culture age did not seem to affect the AuNPs, but it was perceived that as the reaction time progressed and culture grew old, generation of the NPs was reduced, which probably means the rapid development occurred in the exponential phase, reducing the gold ions right away. The older culture hence has a low rate of reduction and reaction and is less active, declining the production of NPs. At low reaction rates, spherical particles were formed in contrast to high rates, which yielded rods and a platelet-like appearance [40]. Furthermore, in an investigation with *Aspergillus trinidadensis*, the effect of different fungal cultures was examined with gold nanoparticles. Cultures of 36 h, 48 h, 72 h, and 96 h were employed with 160 mg/mL intensity, and it was observed that 72 h produced the best results and was optimized using these conditions [33].

6.8. Supplementation with surfactants

Microbes such as bacteria, fungi, and yeast are known to produce extracellular bio-surfactants comprising both hydrophobic and hydrophilic elements. Stabilization of the nanoparticles is usually established by the addition of surfactants during the generation of NPs that consist of mostly fats and sugar. Due to the addition of surfactants, an even distribution occurs with the NPs colloidal solution; moreover, it

is eco-friendly and non-hazardous. They are also utilized for designing NPs with varying shapes and sizes [47].

Likewise, in a study with *Aspergillus flavus*, surfactants were added to enhance the performance of gold NPs. Various surfactants such as sodium dodecyl sulphate (SDS) 0.1% along with Tween 20, 0.1% were used in the experiment with AuNPs. It was observed that Tween 20 stabilized the AuNPs, and the SPR band persisted and remained unaffected for approximately three months, whereas others were able to keep them steady for less. It was also reported earlier that surfactants like Tween 20 are biocompatible; moreover, they are utilized for surface modifications [20].

7. Antimicrobial activity

Antimicrobial resistance has become a major problem all over the globe these days. It is basically the capability of the microbes to resist a variety of antibiotics, hence making the medicine ineffective [48]. The entire concept of antimicrobial activity of gold nanoparticles revolves around the gram-negative and gram-positive bacteria occurring on the surface of the membrane. It was previously described that the reduction of adenosine triphosphate (ATP) is perceived, along with obstruction of ribosomal structures and an increase in oxidative stress, in the presence of AuNPs; hence, they are successful antimicrobial agents. After interaction between microbes and NPs, an increase is felt in the production of ROS, which initiates degeneration together with degradation in the cell membrane and overall cell structure, proving their antibacterial nature (**Figure 2**) [41]. It was reported earlier that small nanoparticles approximately 20 nm are able to penetrate the cell wall of bacteria and cause degradation in organelles, hence leading towards death, which makes AuNPs a good contender for antibiotics [49].

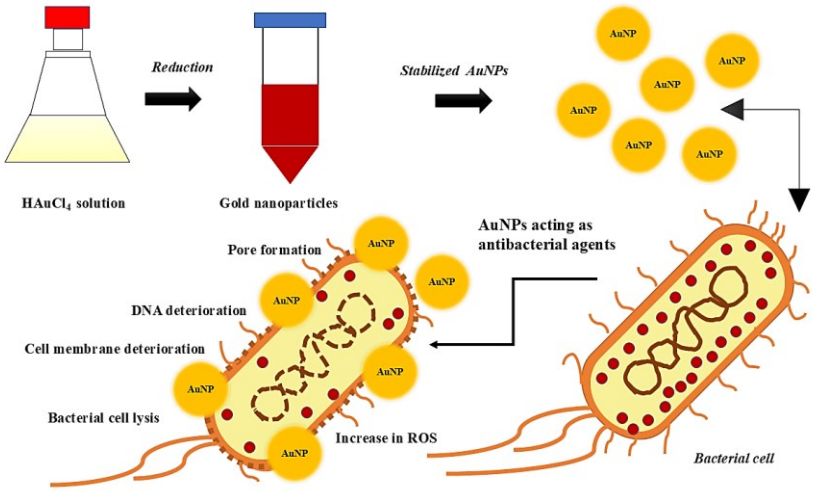

Figure 2. Antibacterial activity of gold nanoparticles.

Size and dimensions both play a significant role in determining the efficiency of the antibacterial properties of nanoparticles. Consequently, gold nanoparticles with smaller sizes usually demonstrate a substantial amount of antibacterial activity [50]. Thus, a study with *Inonotus obliquus* showed antibacterial properties of gold NPs against various stains like *S. aureus*, *E. coli*, and *B. subtilis*. After analysis, ZOI were

noted down for the afore mentioned strains. A zone of 14 nm was observed with *E. coli*, whereas *S. aureus* displayed 16 mm while *B. subtilis* established a ZOI at 12 mm.

In earlier studies, it was reported that the positive charge occurring within the gold ion directs the antimicrobial activity of any microbe. The cell membrane supporting a negative charge along with NPs carrying a positive charge makes the whole mechanism work. It was also proposed that cell death occurs when the NPs creates perforations within the cell walls elevating its penetrability, forcing the cellular environment to change and contents to leak, hence another idea towards mechanism [18].

Likewise, in another recent investigation with *Aspergillus terreus*, antibacterial activities were revealed, showing maximum ZOI against *Vibrio cholerae* (9.31 ± 0.14) and *Staphylococcus aureus* (8.58 ± 0.28) with AuNPs at 400 µg/mL. The antibacterial activities are again thought to be using processes affiliated with ROS or deterioration of enzymes or cell membranes to kill bacteria [43].

Similarly, in another evaluation with *Bipolaris tetramera*, antibacterial activity was also assessed. The bacterial pathogens like *B. subtilis*, *B. cereus*, *S. aureus*, *E. coli*, and *E. aerogenes* were tested against AuNPs with varying concentrations from 10 µM to 150 µM. The highest ZOI of 1.3 cm was formed against *S. aureus* at a concentration of 100 µM, whereas the lowest was observed with *E. coli* at 0.5 cm with 100 µM intensity. Overall, 10 µM formed the lowest ZOI of less than 0.5 cm with all the pathogens, and it was noted that as the intensities of the AuNPs were increased, the antibacterial activities also increased, which could be due to its small size [34].

Another study with *Aspergillus terreus* exposed the antibacterial abilities of gold NPs against some stains like *S. aureus*, *V. cholera*, and *S. typhimurium* with concentrations ranging from 100 to 400 µg/mL. After investigation, it was revealed that maximum ZOI appeared at 400 µg/mL with *S. aureus* and *V. cholera*, i.e., 8.58 ± 0.28 mm and 9.31 ± 0.14 mm, respectively. Other concentrations did not reveal any significant results [36].

8. Applications

AuNPs are known to have many applications in different fields of life as they occur in their natural form (**Figure 3**). Firstly, as the gold NPs are biology compatible and less harmless, they are utilized in drug deliveries and are used in early detection for various ailments related to cancer and heart along with gene therapies [42] and photoacoustic imaging [48]. The anti-tumor activities with the AuNPs are being carried out by employing varying categories of NPs, which include nanoshells, nanotubes, nanostars [51], nanocages, etc. These are inserted in the body, which then incorporate themselves into the tumor; later, they are subjected to infrared followed by heat, which destroys the cancerous cells after raising the temperature, avoiding the healthy cells. It is an efficient tool for the treatment of cancer without comprising any more healthy cells. Two of these successful methods include thermo-chemotherapy (TCT) and gene therapy (GT), which are worth mentioning. AuNPs have also proved themselves in immunotherapy, where these small-sized NPs can pass through and penetrate various tissues, such as lymphoid tissue, and harm the immune cells [3].

Also, they are being used as reliable antimicrobial agents against various infections [52].

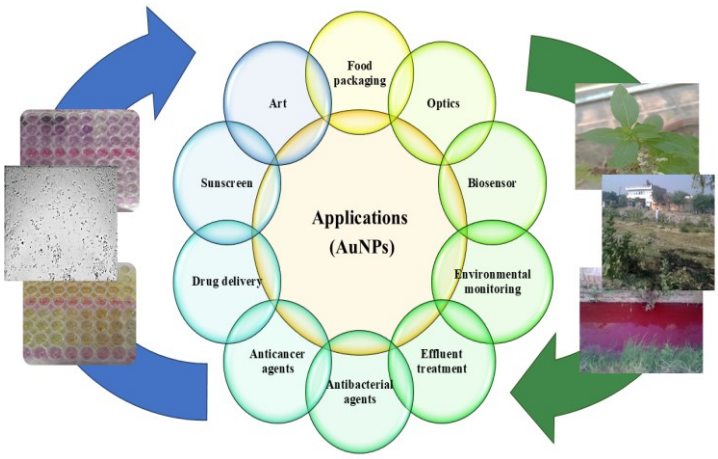

Figure 3. Some applications of gold nanoparticles.

Gold nanoparticles have also been used in drug delivery in which they were coupled up with the medicine or antibiotics using simple covalent or ionic bonds or by absorption approach. For instance, an anti-cancer treatment involved the coupling of folic acid with 13 nm AuNPs to interrupt the cancer cells during folate metabolism [53]. AuNPs have also been applied in the treatment of various skin diseases like psoriasis, pemphigus, hives, etc., and illnesses related to joints such as Lupus, etc.

Secondly, AuNPs have good chemical and thermal properties, which enable them to act as sensors. They have also been utilized in cleaning of the air, like removing carbon monoxide or any odour from an enclosed space [3]. Thirdly, gold nanoparticles can be controlled, their size and shapes can be varied according to your requirements, permitting them to be used in various processes, like food preservation. Additionally, they are consumed in some food items as 'nano-capsules that transfer varying nutrients without comprising the taste or its presence [3].

Other applications include optics, conservation of paintings, environmental assessment, waste water treatment, and control. When fungal extract is revealed to metals, they usually generate nanoparticles from it, and it overpowers the toxic elements present within the wastewater by reducing it; hence, it develops into a less harmful form and persists the metal toxicity. In this way, the metal toxicity is reduced from varying sources, ensuring a better and cleaner environment through the use of gold nanoparticles. Some species of fungi have developed high tolerance towards heavy metal pollution, like *Penicillium* sp. and *Aspergillus* sp. [54], but their mechanisms still need to be studied further to develop new techniques [55–58].

Moreover, during the production of AuNPs via green synthesis, no external agent is required, so no capping agents are added, which stabilizes the NPs by themselves, allowing researchers to alter their form easily [41]. Besides, they can also be used as an insecticide [39] and in agriculture too [48,59]. The agriculture sector is also suffering due to depletion of nutrients and increasing human population; thus, new techniques must be developed for increasing the productivity of the crops. Hence, NPs are employed as agro-chemical 'agents' and have been introduced to eradicate

pesticides. Moreover, they are designed to enhance crop productivity and are being utilized as fertilizers as well. Some biosensors have also been introduced to protect the crops and detect various diseases occurring in a specific crop. Additionally, they are also being employed as growth regulators for the plants and help improve the overall yield of the crops [60].

9. Future perspectives and challenges

Even though the gold nanoparticles have proven to be non-toxic and have great potential as antibiotics, further research is required, and doses need to be administered before they can actually be used in the biomedicine field on a larger scale. Experiments are essential to make sure that they are safe and can be used as drugs alone. We need to indulge in this notion a bit more, as the antimicrobial resistance and its overuse are growing day by day, and it is becoming challenging for the pharmaceutical companies to come up with novel strains for this purpose; therefore, we need to find treatments that are innovative [49].

10. Conclusion

The green technique of synthesizing gold nanoparticles is an interesting approach as it is simple, safe, economical, stable, and biocompatible in contrast to old methods. After synthesis, unique shapes and sizes can be expected and controlled, which can be utilized in many applications, specifically biomedical. These intriguing AuNPs can be optimized according to the need by altering various parameters like temperature, pH, amount of biomass, agitation rate, surfactants or enhancers, metal concentration, etc. The gold NPs are unique due to their antimicrobial properties, and their small size and large surface area are another plus, which makes them excellent candidates for future antibiotic investigations.

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