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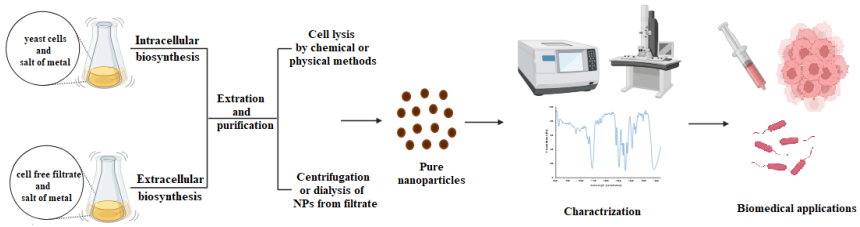
REVIEW ARTICLE

Today nanotechnology is widely spread and plays an important role in many fields, especially the medical field. Nanoparticles (NPs) have unique physicochemical properties giving them additional activities which encourage their use in many applications. Nanoparticles can be synthesized through three main methods: chemical, physical, and biological. The best method is biological synthesis that is considered green, sustainable, eco-friendly, and economic. It depends on living organisms or their extracts including plants, bacteria, algae, fungi, and yeasts instead of toxic chemicals. Yeasts are promising microorganisms that recently attract the attention of many researchers to discover their potential in biosynthesis of nanoparticles that can be applied in different fields. Many research studies proved the ability of various yeast species to synthesize various metal and metal oxide nanoparticles whether intracellularly or extracellularly. Such nanoparticles include silver, gold, selenium, selenium sulfide, zinc sulfide, palladium, manganese dioxide, and titanium dioxide nanoparticles. Yeast-mediated nanoparticles have biomedical activities such as anticancer, antioxidant, anti-inflammatory, and antimicrobial. Studies revealed that yeast-synthesized nanoparticles have safe and nontoxic properties. Compared to research on NPs biosynthesis using bacteria and fungi, there are fewer research that focused on using yeast in NPs biosynthesis which makes it a promising area for more scientific discoveries in biosynthesis and applications of NPs. This review outlines previous studies involving biosynthesis and biomedical applications of yeast-mediated nanoparticles.

Keywords: Yeast, Nanoparticles, Anticancer, Antioxidant, Anti-inflammatory, Antimicrobial, Biomedical applications



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INTRODUCTION

Nanotechnology is one of the highly progressed and developed technologies that aim to synthesize and use nanomaterials in many applications. It was found that nanoparticles have special and unique properties that are related to their large surface area to volume (Hussain et al., 2010). Nanoparticles are involved in several fields including biomedical, industrial, environmental, and agricultural (Khan et al., 2019; Abd El-Ghany et al., 2023a).

The synthesis of nanoparticles mainly depends on physical, chemical, or biological methods. Due to the disadvantage of physical methods (need more energy and consume more time) (Muddapur et al., 2022) and chemical methods (use toxic chemicals) (Shu et al., 2020), biological methods become an preferred alternative because they are green, eco-friendly, and low-cost methods that use living organisms and their extracts instead of toxic chemicals and also require simpler equipment (Wu et al., 2021; Abd El-Ghany et al., 2023b).

Plants, algae, bacteria, fungi, and yeasts or their extracts are used in biological methods for biosynthesis of NPs. They produce many bioactive molecules such as enzymes, proteins, and polysaccharides that act as reducing, capping, and stabilizing agents during the biosynthesis process (Muddapur et al., 2022). Bacteria and fungi are the most used microorganisms in intracellular and extracellular biosynthesis of many types of nanoparticles (NPs). Bacteria produce reductases to reduce ions and then convert them into NPs (Hulkoti and Taranath, 2014).

Compared with synthesis of NPs using bacteria, fungi can produce higher quantities of NPs because they could produce higher amounts of proteins as well as enzymes such as reductase (Jaidev and Narasimha, 2010). Also, they grow fast and are easily handled giving high biomass yield (Hulkoti and Taranath, 2014). They have the potential to produce NPs extracellularly or intracellularly (Sastry et al., 2003; El-Basiouny et al., 2024).

In the nanotechnology field, yeasts as unicellular fungi gained researchers' attention. Yeasts have the same properties as fungi; moreover, they grow faster than fungi. Therefore, they are better organisms for biofabrication of NPs with high yields within short time (Faramarzi et al., 2020). Yeasts have many advantages to be used in extracellular and intracellular biosynthesis of metal and metal oxide nanoparticles with high yield production (Karunakaran et al., 2023). NPs synthesis using yeast is mainly based on two suggested mechanisms: enzymatic catalytic (Wadhwani et al., 2018) and nonenzymatic catalytic (Saran et al., 2018). Several yeast species and strains are involved in biosynthesis of different nanoparticles with many biomedical applications including *Saccharomyces cerevisiae* (Shu et al., 2020), *Rhodotorula glutinis, Cryptococcus laurentii* (Fernández et al., 2016), *Rhodotorula mucilaginosa* (Ashengroph and Tozandehjani, 2022), *Geotrichum candidum* (Zahran et al., 2013), *Yarrowia lipolytica* (Apte et al., 2013), *Magnusiomyces ingens* (Zhang et al., 2016), *Nematospora coryli* (Rasouli, 2019), *Candida albicans* (Ahmad et al., 2013), *Hansenula anomala* (K et al., 2011), *Pichia jadinii* (Gericke and Pinches, 2006) Yeast HX-YS, Yeast LPP-12Y (Liu et al., 2021), yeast strain MKY3 (Kowshik et al., 2002), and extremophilic yeast strain (Mourato et al., 2011).

Yeast cells can tolerate toxicity of metal ions by reducing them and forming NPs with nontoxic properties (Gajbhiye et al., 2009). Stabilizers and capping molecules (Chen et al., 2008), besides size and shape of NPs (Woźniak et al., 2017), influence the toxicity of NPs. *S. cerevisiae*-synthesized silver nanoparticles (AgNPs) that exhibited negligible cytotoxicity so they can be applied as nontoxic antibacterial drug (Shu et al., 2020). Other *S. cerevisiae*-derived selenium nanoparticles (SeNPs) had an IC_{50} value more than 300 µg/mL; therefore, they can be used as antioxidant and anti-inflammatory drug with nontoxic effect, when used at much lower concentrations (Fath-Alla et al., 2024).

Several research studies proved the potential biomedical activities of nanoparticles that enable them to be used in health technologies and the medical field (Liu et al., 2021). Based on the previous research, yeast-mediated nanoparticles can act as anticancer, antioxidant, ant-inflammatory, and antimicrobial agents which will be discussed later in this review. Also, toxicity tests of yeast-mediated nanoparticles showed their safety and nontoxic properties (Shu et al., 2020; Fath-Alla et al., 2024).

Some studies tested the anticancer activity of yeast-mediated nanoparticles. It was found that HX-YS-mediated AgNPs and LPP-12Y-mediated AgNPs exhibited anticancer effects (Liu et al., 2021). Also, SeNPs biosynthesized by *S. cerevisiae*-fermented broth had anticancer activity against different cancer cells (Goud et al., 2016).

Antioxidant agents are important drugs that scavenge free radicals causing tissue damage leading to several diseases (Re et al., 1999). Nanoparticles are the promising antioxidant drugs because of their small size (Faramarzi et al., 2020). For example, *S. cerevisiae*-mediated SeNPs showed antioxidant activity at nontoxic concentrations with IC_{50} of 45.87 µg/mL (Fath-Alla et al., 2024).

Inflammation is activated in response to any irritant (Freire and Van Dyke, 2013). According to a previous study, nontoxic concentrations of *S. cerevisiae*-synthesized SeNPs exhibited anti-inflammatory action via inhibition of nitric oxide production (Fath-Alla et al., 2024).

In addition, yeast-synthesized nanoparticles are widely used as antimicrobial agents as proved in many studies. AgNPs had an antibacterial effect against *Escherichia coli, Shigella flexneri* (Sowbarnika et al., 2018), and *Pseudomonas aeruginosa* (Liu et al., 2021), in addition to their antifungal action against *Candida albicans* (Niknejad et al., 2015). Antibacterial activity of gold nanoparticles (AuNPs) was shown against *Bacillus cereus* and *Pseudomonas putida* (K et al., 2011). SeNPs can be used as antifungal drugs against *Candida albicans* (Rasouli, 2019).

Many previous studies reported the potential of various yeast species to synthesize both metallic and metallic oxide nanoparticles. However, still relatively much fewer research utilized yeasts compared to bacteria and fungi. Also, fewer studies tested the toxicity and biomedical activities of yeast-mediated nanoparticles. Therefore, using yeast in biosynthesis of NPs having biomedical applications is a promising research topic that needs more and more studies.

As there are very few review articles that present studies concerning the biosynthesis of NPs using yeast and their biomedical applications, the authors in the current work find that this topic is a riveting one to be presented. This review article offers more comprehensive elucidation of the topic by comprising more research studies compared to the few similar reviews.

Biosynthesis of Nanoparticles

Three methods can be used for synthesis of nanoparticles: physical, chemical, and biological. Physical methods consume time, need high energy, and form large-sized NPs with defected surface (Muddapur et al., 2022). Meanwhile, the chemical methods based on chemical reagents as reducing agents have cytotoxicity toward living tissue thus restricting their use in biomedical fields; in addition, those chemicals cause environmental pollution (Shu et al., 2020). Due to those drawbacks in physical and chemical methods, the biological method has become a better candidate for NPs synthesis. It is a nontoxic, green, sustainable, and economically effective method as it depends on living organisms or their extracted biomolecules in biosynthesis process (Wu et al., 2021). Plants and several microorganisms (algae, bacteria, fungi, and yeast) or their extracts are involved in biosynthesis of various NPs. They act as reducing, capping, and stabilizing agents (Muddapur et al., 2022).

Using a plant extract is one of the green methods for eco-friendly biosynthesis of nanoparticles (Zhang et al., 2020; Naikoo et al., 2021). Those extracts can be obtained from different plant parts including leaves stems, roots, flowers, vegetables, and fruits (Karunakaran et al., 2023). Plant extracts contain various bioactive compounds such as proteins, amino acids, polysaccharides, tannins, flavonoids, alkaloids, and polyphenols that can reduce and stabilize nanoparticles (Hano and Abbasi, 2021; Muddapur et al., 2022).

Several microorganisms and their extracts are used in biosynthesis of nanoparticles as they provide various bioactive molecules required for biosynthesis process. Algae and their extracts can be involved in bioreduction of NPs such as silver, gold, selenium, and other nanoparticles with antibacterial and antifungal activities (Singaravelu et al., 2007; Govindaraju et al., 2009; Rajesh et al., 2012). Bacteria and fungi are microorganisms that are commonly used in intracellular and extracellular biosynthesis of many types of nanoparticles. Bacteria can produce reductases as reducing enzymes during the formation of NPs (Hulkoti and Taranath, 2014). Metal and metal oxide nanoparticles with biomedical activities can be obtained from various bacterial species. For example, *Escherichia coli*, *Arthrobacter nitroguajacolicus*, and *Lactobacillus plantarum* are used in biosynthesis of gold (Dehnad et al., 2015), silver (Kathiresan et al., 2010), and zinc oxide (Selvarajan and Mohanasrinivasan, 2013) nanoparticles with biomedical properties.

In nanotechnology, fungi gained more attention in biosynthesis of nanoparticles as they have advantage over other microorganisms (Boroumand Moghaddam et al., 2015). Fungi can produce higher quantities of NPs than that produced by bacteria due to higher protein and enzyme production capacity (Jaidev and Narasimha, 2010). The most common enzymes involved in biosynthesis process are NAD(P)H-dependent reductases (Kitching et al., 2015). Furthermore, they are easily handled and grow fast with high biomass yield (Hulkoti and Taranath, 2014). They can produce NPs via extracellular and intracellular methods. Fungi have the potential to form metallic NPs because of their ability to tolerate and bioaccumulate metals and then reduce those toxic metals forming nontoxic NPs (Sastry et al., 2003).

Yeasts as a group of unicellular fungi gained the attention of researchers in the nanotechnology field. They have the same properties of fungi; in addition, they grow faster than fungi. So, they are a good choice for biosynthesis of NPs with high yield during short time (Faramarzi et al., 2020). Moreover, they produce many proteins and enzymes which increase the number of synthesized NPs (Castro-Longoria et al., 2012). Yeasts have many advantages to be used in the biosynthesis of metal and metal oxide nanoparticles (Figure 1). Many yeast species are used in biosynthesis of NPs having biomedical applications (Karunakaran et al., 2023).

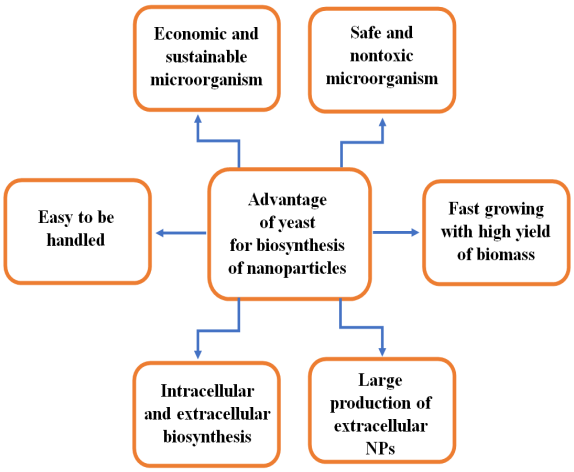

Figure 1. Advantages of yeast utilization in biosynthesis of nanoparticles.

Yeast Species Involved in Biosynthesis of NPs

Yeast is a eukaryotic and unicellular microorganism that belongs to the kingdom Fungi, phyla Ascomycota and Basidiomycota (Kurtzman and Boekhout, 2017). As it was reported in the previous studies, various yeast species and strains can be used in biosynthesis of metallic and metallic oxide nanoparticles. However, still relatively few research studies used yeasts in biosynthesis of NPs compared to bacteria and fungi. Different yeast species could synthesize NPs via intracellular and/or extracellular methods with several biomedical applications.

Saccharomyces cerevisiae

Saccharomyces cerevisiae (baker's yeast) is considered the most used species and best candidate involved in biosynthesis of NPs as it rapidly grows and is simply used (Korbekandi et al., 2016). It is also the best studied yeast species based on its genetics and physiology in addition to the high industrial impact (Parapouli et al., 2020). Since it is an edible and nontoxic yeast species, it is a promising species that can be used in NPs biosynthesis. Several research studies reported the potential of *S. cerevisiae* to synthesize different NPs whether intracellularly or extracellularly such as AgNPs (Jha and Prasad, 2008; Zahran et al., 2013; Niknejad et al., 2015; Roy et al., 2015; Korbekandi et al., 2016; Jafarov et al., 2017; Li et al., 2018; Sowbarnika et al., 2018; Olobayotan and Akin-Osanaiye, 2019; Shu et al., 2020), SeNPs (Hariharan et al., 2012; Faramarzi et al., 2020; Wu et al., 2021; Salem, 2022; Fath-Alla et al., 2024), selenium sulfide nanoparticles (SeSNPs) (Asghari-Paskiabi et al., 2019), palladium nanoparticles (PdNPs) (Li et al., 2018; Sriramulu and Sumathi, 2018), zinc sulfide nanoparticles (ZnSNPs) (Mala and Rose, 2014), manganese dioxide nanoparticles (MnO_2NPs) (Salunke et al., 2015) titanium dioxide nanoparticles (TiO_2NPs) (Peiris et al., 2018). *S. cerevisiae*-mediated NPs have a broad range of biomedical applications and can act as antimicrobial, antioxidant, anti-inflammatory, and anticancer agents.

Rhodotorula glutinis* and *Rhodotorula mucilaginosa

Most *Rhodotorula* species are widely spread and can be isolated from air, soil, and water. They can form orange or red colonies due to pigments they produce (El-Ziney et al., 2018). *Rhodotorula glutinis* is a yeast species that could produce a very large number of extracellular enzymes and metabolites that can be involved in biosynthesis of AgNPs. It was proved that *R. glutinis* could reduce silver salt into silver nanoparticles via both extracellular and intracellular methods (Zahran et al., 2013). A safe nontoxic epiphytic *R. glutinis* isolated from fruits showed the potential to synthesis AgNPs extracellularly and the formed AgNPs exhibited antifungal activity (Fernández et al., 2016). *Rhodotorula mucilaginosa* R-8441 is a novel yeast strain that was isolated, characterized as marine yeast, and then used in synthesis of SeNPs. The study results showed potency of *R. mucilaginosa* R-8441 to biosynthesize SeNPs extracellularly and intracellularly (Ashengroph and Tozandehjani, 2022).

Geotrichum candidum: Zahran et al. (2013) study proved that *Geotrichum candidum* can produce extracellular enzymes and metabolites with high quantity for bioreduction and stabilization of NPs. This yeast species can synthesize AgNPs intracellularly and extracellularly.

Cryptococcus laurentii: *Cryptococcus laurentii* is considered a safe nontoxic epiphytic yeast that can be isolated from fruits. This yeast species produced AgNPs via extracellular synthesis and the produced particles had antifungal action (Fernández et al., 2016).

***Yarrowia lipolytica*:** *Yarrowia lipolytica* is one of the most important microorganisms due to its biological and biotechnological significance (Nair et al., 2013). It has a promising biological activity allowing it to interact with metals (Strouhal et al., 2003) so it is used in various biotechnological applications (Barth and Gaillardin, 1997; Agnihotri et al., 2009). Two *Y. lipolytica* strains, *Y. lipolytica* NCIM 3589 (Agnihotri et al., 2009) and *Y. lipolytica* NCYC 789 (Nair et al., 2013), showed potential to synthesize AuNPs intracellularly. *Y. lipolytica* NCIM 3589 is a tropical marine yeast isolate that forms AuNPs inside its cells (Agnihotri et al., 2009). *Y. lipolytica* NCYC 789 biomass was able to form AuNPs inside the cells and its derived melanin can synthesize AuNPs extracellularly. Melanin-synthesized AuNPs exhibited antibacterial and antibiofilm activities (Nair et al., 2013). On the other hand, *Y. lipolytica* NCYC 789 and its extracted melanin-synthesized AgNPs intracellularly and extracellularly, respectively, as proved by Apte et al. (2013).

***Magnusiomyces ingens*:** *Magnusiomyces ingens* is a nonconventional yeast. Zhang et al. (2016) reported that *Magnusiomyces ingens* LH-F1 isolated from sea mud can biosynthesize AuNPs from $HAuCl_4$ extracellularly. They also reported that novel *M. ingens* LH-F1 isolate can extracellularly synthesize SeNPs that have antibacterial effect (Lian et al., 2019).

Nematospora coryli: In Rasouli (2019) study, *Nematospora coryli* was used to biosynthesize SeNPs. The intracellularly synthesized SeNPs had antioxidant and anticancer activities.

Candida albicans: Extract of *Candida albicans* cells had the ability to biosynthesize both silver and gold nanoparticles that showed antibacterial action (Ahmad et al., 2013).

Hansenula anomala: Extracellular biomolecules isolated from *H. anomala* showed their potential to reduce gold ions forming gold nanoparticles (K et al., 2011).

Pichia jadinii: This yeast species can form promising AuNPs when it is exposed to $HAuCl_4$ (Gericke and Pinches, 2006).

Other Yeast Strains: Yeast HX-YS and yeast LPP-12Y are two novel yeast strains that belong to the genus *Metschnikowia.* Both yeast strains were used in the extracellular biosynthesis of AgNPs that can be used as antibacterial and anticancer agents (Liu et al., 2021). Also, the silver-tolerant yeast strain MKY3 had the ability to form AgNPs extracellularly (Kowshik et al., 2002), in addition to the extremophilic yeast strain that had the potential to synthesize both silver and gold NPs intracellularly (Mourato et al., 2011).

Methods of Biosynthesis Used by Yeast Species

Yeast cells could synthesize metal and metal oxide nanoparticles inside (intracellular) and/or outside (extracellular) the cells. Both intracellular and extracellular synthesis have advantageous and disadvantageous properties, so it is recommended to use both methods (Korbekandi et al., 2016). Intracellular biosynthesis mainly depends on yeast cell biomass while the extracellular one is based on yeast cell extract. Steps included in the intracellular method are different than those in the extracellular one (Figure 2). During the intracellular method, salt of metal or metal oxide is added directly to yeast culture; then the mixture is incubated for specific period at certain temperature based on the type of yeast. After the incubation period, the color of mixture changed due to formation of NPs. The formed NPs are extracted and purified from yeast cells by cell lysis through chemical or physical method, while in the extracellular biosynthesis, salt of metal or metal oxide is added to the cell-free filtrate obtained from filtration of yeast biomass and incubated together. After a specific time, the color of solution changes indicating the formation of NPs that are then extracted and purified via centrifugation or dialysis of solution.

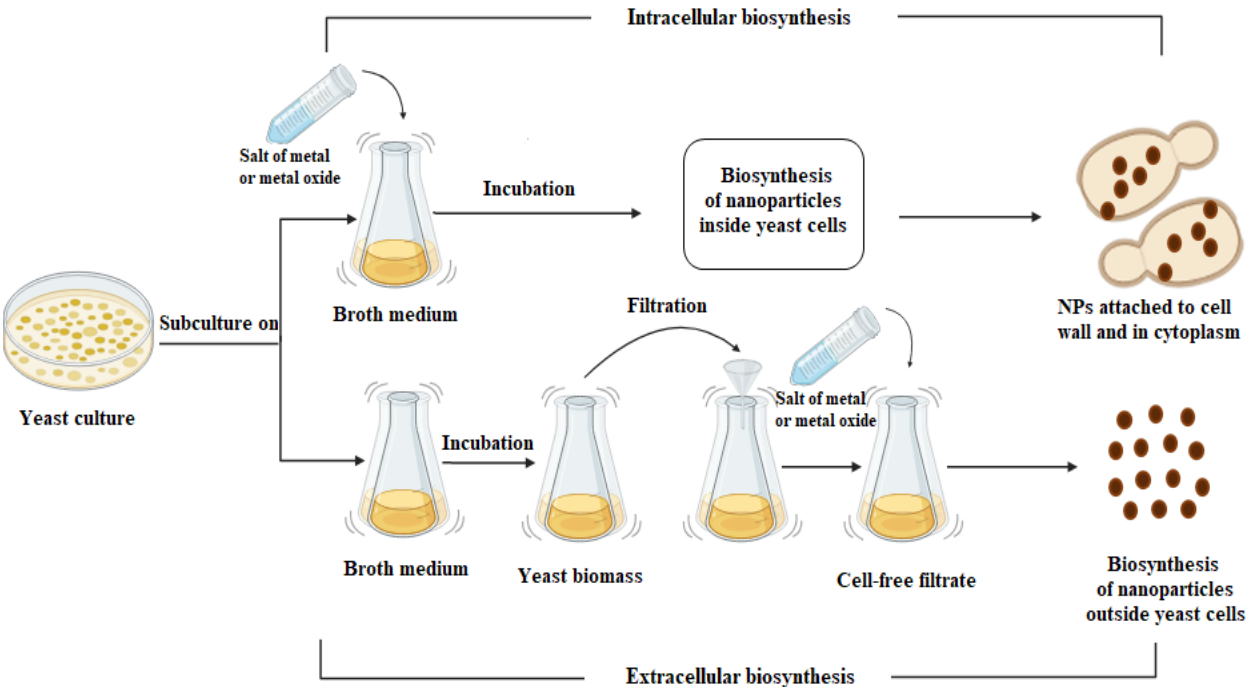

Figure 2. Procedures involved in intracellular and extracellular "cell-free filtrate" nanoparticles biosynthesis using yeast. Created in BioRender.com.

Intracellular Biosynthesis: Yeasts can form nanoparticles inside their cells as proved in many studies. It was reported that an extremophilic yeast strain can form AgNPs only via intracellular synthesis and cannot form them via extracellular synthesis. This indicates the critical role of cell wall in the biosynthesis of NPs (Mourato et al., 2011). A research study done by Wu et al. (2021) proved that SeNPs were fabricated and deposited in both culture medium and yeast cells. It was found that SeNPs were deposited around cell membrane or projected from cell surface. In addition, the SeNPs in medium were surrounded by an organic shell. The presence of SeNPs inside and outside yeast cells indicated the ejection of nanoparticles via vesicular mechanism. It was suggested that it is more useful to use cells in biosynthesis of NPs instead of discarding them, where this decreases the reduction potential required for biosynthesis process (Korbekandi et al., 2016). However, the one defect of intracellular biosynthesis process is that there is a loss in nanoparticles yield because NPs are attached to the wall of yeast cells (Zahran et al., 2013).

Extracellular Biosynthesis: Many yeast species have the potential to produce nanoparticles extracellularly depending on several biomolecules. Different metallic nanoparticles have been synthesized extracellularly. Extracellular production of NPs using yeast extract starts with self-assembly of biomolecules present in the extract, then reduction of ions of interest via biomolecules that act as reducing agents, and finally stabilization of formed nanoparticles also via biomolecules (Shu et al., 2020). It was suggested that the cell-free extract of yeast biomass contains enzymes and proteins responsible for reduction of metal ions into their neutral atoms which are then nucleated to form NPs (Ahmad et al., 2013). Different biomolecules produced by baker's yeast including carbohydrates, amino acids, and vitamins are involved in extracellular synthesis (Shu et al., 2020). Extracellular synthesis is more utilized than the intracellular one as it is a more rapid, simpler, and easier way allowing large-scale production of nanoparticles. It has also a great advantage over intracellular synthesis especially in the application term (Niknejad et al., 2015). It gives higher NPs yield than that of intracellular synthesis because the extracellular synthesis avoids the loss of NPs attached to wall of cells during the intracellular synthesis while extracellular synthesis needs several steps and longer time (Zahran et al., 2013).

Mechanisms of NPs Biosynthesis Used by Yeast Species

It is important to determine the yeast biosynthesis mechanism as this helps to control the conditions required for it which further simplify purification and applications of NPs (Liu et al., 2021). It was reported that metabolic and physiological advantage of Ascomycetes class, is the high transformation rate of metal ions into NPs (Jha and Prasad, 2008; Gajbhiye et al., 2009). The biosynthesis process mainly involves the main process including reduction, capping, and stabilization processes.

In the reduction process, positive metal ions are reduced by negative bioactive molecules (electron donors) that may be present inside or on the surface of cells or excreted outside the cells. The most detected biomolecules involved in the biosynthesis process are oxidoreductase enzymes. Reduction depends on enzymes produced from microorganisms such as reductase and protease (Durán et al., 2005) which are two main produced enzymes by which metals ions are reduced into an elemental form forming particles in nano size. There is a relation between enzyme activity and nanoparticles concentration, where NPs concentration is dependent on enzyme activity (Fernández et al., 2016). Yeasts form nanoparticles via its enzymes; for example, *Yarrowia lipolytica* produces reductase and protease enzymes during bioreduction process (Gonzalez-Lopez et al., 2002). It was reported that reductase and protease enzymes had a significant role in the reduction of the gold ions into AuNPs (Agnihotri et al., 2009). As the yeast extract powder is a rich source of functional organic molecules, it could reduce silver cations in the reacting solution (Roy et al., 2015). It was reported that NADH-dependent reductase (Wang et al., 2011) and nitrate reductase in microorganisms' extract had a significant role in the reduction process of AgNPs (Anil Kumar et al., 2007; Shu et al., 2020).

During biosynthesis of NPs, biomolecules of yeast extract also act as a capping agent and control the morphology, shape, and size of NPs. Fourier transform-infrared spectroscopy (FTIR) results suggested the involvement of proteins in capping of yeast-synthesized nanoparticles (Kaler et al., 2013 (Korbekandi et al., 2016; Shu et al., 2020). In addition, these yeast extract biomolecules act as stabilizers of NPs by stabilizing and preventing NPs from their aggregation and reaction together (Gudkov et al., 2020). Stability also depends on negative charge on the surface of NPs (Wu et al., 2021).

Yeast cells produce several bioactive molecules such as amino acids, proteins, and carbohydrates that are involved in reduction, capping, and stabilization (Nair et al., 2013). Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) revealed that there are two proteins on the surface of *Magnusiomyces ingens*-mediated SeNPs. They have a role in reduction, capping, and stabilization of NPs (Lian et al., 2019). This is also reported in Zhang et al. (2016) study that used both FTIR and SDS-PAGE to detect the bioactive molecules on the surface of *Magnusiomyces ingens*-synthesized AuNPs. It was suggested that proteins that contain carboxyl and amide groups are adsorbed on the AuNPs surface and involved in reduction of Au^{3+} and stabilization of formed AuNPs (Gangula et al., 2011; Zhang et al., 2016). Those proteins also act as a protective coat on the NPs surface (Kaler et al., 2013; Korbekandi et al., 2016), can regulate the size of NPs (Dobias et al., 2011), and facilitate their transfer outside the cells (Debieux et al., 2011). It was reported that both reduction and stabilization happened due to capping of NPs by specific proteins produced by cells (Gole et al., 2001). Types of biomolecules in yeast extract involved in extracellular biosynthesis were detected using high-speed amino acid analyzer. The results revealed that yeast extract contained twenty-two amino acids in addition to compounds containing $-NH_2$ including glutamine, ammonia, urea, and asparagine. The most abundant kinds of amino acids were alpha-linolenic acid, γ-aminobutyric acid, glutamic acid, and ornament. Carbohydrates, alpha-linolenic acid, and other amino acids are responsible for synthesis of AgNPs (Shu et al., 2020).

There are two suggested mechanisms by which nanomaterials are formed via the biological method. The first one is the enzymatic catalytic mechanism that depends on enzymes and suggests that enzymes (electron transporter) transfer electrons from the reducing substance to metal ions (Wadhwani et al., 2018). The nonenzymatic catalytic mechanism depends on substances other than enzymes that are produced by living cells such as quinine derivatives of naphthoquinones and anthraquinones. Those substances act as redox centers to reduce ions (Saran et al., 2018). As metal ions represent toxic substances to cells, they remove ions toxicity through transformation of metal ions into nanoparticles via the reduction process. In *S. cerevisiae*, metallothioneins are the only molecules that have a function to maintain the metallic ions homeostasis through binding with excess ions of heavy metals (Korbekandi et al., 2016).

It was suggested that the mechanism of intracellular biosynthesis involved several steps including (1) adsorption of metallic ions on the cell surface through electrostatic interaction (positive ions with negative biomolecules in cell wall) (Ul'berg et al., 2010), (2) reduction of metallic ions by enzymes produced by cells in cell wall, cell membrane, or within cytoplasm (after diffusion of ions into cytoplasm), (3) intracellular biosynthesis of NPs, (4) isolation of NPs from cell cytoplasm due to their toxicity effect on cells, and (5) excretion of NPs through cell membrane via exocytosis. Finally, NPs are found inside and outside the cells (Korbekandi et al., 2016). Mourato et al. (2011) discussed the mechanism of intracellular synthesis of AgNPs and AuNPs. Firstly, positive ions of silver or gold were trapped on the surface of cells and interacted with negative compounds. Then ions were reduced by cell enzymes. Meanwhile, several mechanisms described the role of enzymes in the biosynthesis of SeNPs. One suggested mechanism is that both membrane-bound and periplasmic nitrate reductases (Sabaty et al., 2001) or fumarate reductase (in anaerobic respiration conditions) are responsible for reduction of selenium ions (Li et al., 2014). The other one is that yeast cells can produce glutathione and oxidative stress enzymes such as glutathione reductase (Grant et al., 1996) that are responsible for reduction of selenium ion into selenium nanoparticles. That was also discussed in Rasouli (2019) study where *Nematospora coryli* cells were able to reduce selenite (Se(IV)) into selenium nanoparticles (Se(0)).

Extracellular biosynthesis mainly happened outside the cells and was based on several bioactive molecules present in the yeast extract. It was proved that the reduction process depends on reducing molecules present in yeast fermentation broth (Bhambure et al., 2009). It was suggested that reduction process in extracellular biosynthesis takes place as a result of one of the following mechanisms: (1) participation of nitrate or sulfate reductases that work in the presence of ATP and NADH or anthraquinone (Chaloupka et al., 2010), (2) activation of certain polypeptide chains that bind to positive metal ions forming complexes then those complexes degraded forming NPs (Cho et al., 2005), and (3) electrostatic interaction between positive metal ions and positive groups of bioactive molecules of cell wall (Sowbarnika et al., 2018). For example, interaction of Ag^{+} and negative carboxylate groups was present in

polypeptides, proteins, or enzymes (Jha and Prasad, 2008). It was also reported that positive silver ions have a high potential to bind with electron donor molecules that contain nitrogen, oxygen, and sulfur such as proteins (Kowshik et al., 2002).

Yeast Biosynthesized Nanoparticles

In the medical field, biosynthesized NPs are a good choice because they are nontoxic and biocompatible particles in addition to their anticancer, antioxidant, anti-inflammatory, and antimicrobial activities (McNamara and Tofail, 2017). As shown in Table 1, different types of metal and metal oxide NPs with specific size and shape exhibit various biomedical activities.

AgNPs: Yeast cells can produce AgNPs via intracellular and/or extracellular biosynthesis process. Incubation of fresh *S. cerevisiae* biomass incubated with 1 mM $AgNO_3$ for 24 h produced a large amount of AgNPs inside yeast cells and some of them were released outside the cells. UV analysis showed an absorbance peak at 430 nm indicating formation of AgNPs. Transmission electron microscopy (TEM) image of intracellularly synthesized AgNPs showed that NPs have spherical shape with size of 2–20 nm and were formed inside the cells, then attached to the cell membrane, and secreted outside the cells. During monitoring of AgNPs using TEM, it was found that there was no notable change in their size, shape, and aggregation indicating that the formed AgNPs are stable until 72 h (Korbekandi et al., 2016). The yeast strain called *Saccharomyces* sp. BDU-XR1 showed the potential to form AgNPs intracellularly with circular shape and size ranges from 8 to 17 nm. The presence of absorption peak in the range of 410–420 nm in UV spectrum confirmed AgNPs formation (Jafarov et al., 2017). *S. cerevisiae* can reduce $AgNO_3$ forming intracellular AgNPs with crystalline nature. Scanning electron microscopy (SEM) and TEM analysis revealed the presence of AgNPs at cell wall and inside the cells. The average size of AgNPs formed covering yeast cells was 9 nm while that of AgNPs formed inside the cells was 4 nm. This study reported the role of glucans of cell wall as a reducing agent (Li et al., 2018).

Several studies reported that *Saccharomyces cerevisiae* has the potential to synthesize silver nanoparticles. Silver tolerating baker's yeast (*Saccharomyces cerevisiae*) had the ability to synthesize spherical AgNPs with a size of 6–20 nm and with a crystalline nature (Jha and Prasad, 2008). Shu et al. (2020) study proved that *S. cerevisiae* could extracellularly produce spherical AgNPs that were detected by a peak at 418 nm in UV spectrum. The particles' diameter ranged from 10.3 to 18.9 nm and the average size was 13.8 nm. X-ray diffraction (XRD) analysis revealed that AgNPs have a crystalline nature. Their zeta potential value changed by changing the pH value. At pH 3, the value of zeta potential was –3.2 mV, at pH 7, it was –12.1 mV, and at pH 11, it was –24.4 mV. This indicated that zeta potential decreases when pH value increases. Another work reported that cell-free filtrate of *S. cerevisiae* can produce spherical AgNPs with an average diameter equal to 10 nm and λ_{max} equal to 450 nm. XRD analysis revealed that the formed NPs were face-centered cubic and crystalline. Also, FTIR analysis showed the presence of amides, aldehydes, and phenols in baker's yeast extract that were used in the biosynthesis of AgNPs and suggested that those organic molecules are responsible for reduction, capping, and stabilization of AgNPs (Roy et al., 2015). Based on Niknejad et al. (2015) study, *S. cerevisiae* (PTCC 5052) can extracellularly synthesize AgNPs with λ_{max} of 410 nm, spherical uniform shape, size of 5–20 nm, and zeta potential of −25.0 mV. Another study reported that *S. cerevisiae*-mediated AgNPs were stable for 90 days. Characterization of those extracellularly formed NPs showed that they have maximum absorbance band at 429 nm, an average size equal to 16.07 nm, and oval shape. Their FTIR spectrum indicated that AgNPs bind to different bioactive compounds including phenols, alcohols, and aromatic amines (Olobayotan and Akin-Osanaiye, 2019). It was recorded that *S. cerevisiae*-fabricated AgNPs have λ_{max} at 440 nm, spherical shape, and particle size of 10 to 60 nm. Their FTIR results showed the presence of protein on the surface on AgNPs. It was proved that AgNPs bind to proteins through amide groups. Those proteins form a coat around NPs and have a significant role in formation and stabilization of AgNPs in aqueous solution (Sowbarnika et al., 2018). Niknejad et al. (2015) proved the extracellular biosynthesis of AgNPs that have absorbance band of 410 nm, uniform spherical shape, average size much less than 70 nm, and zeta potential of –25.0 mV. Extracellular biosynthesis of AgNPs with size ranging from 2 to 5 nm using silver tolerating yeast strain MKY3 was reported. The presence of peak at 420 nm ensured the formation of AgNPs (Kowshik et al., 2002).

The yeast species *Cryptococcus laurentii* and *Rhodotorula glutinis* were used for the biofabrication of AgNPs because of their ability to produce nitrate reductase. Cell-free filtrate of both yeast species was mixed with silver nitrate solution. Pale yellow color of

Table 1. Physicochemical properties and biomedical applications of various yeast-mediated nanoparticles.

NPs type	Yeast species or strains	Method of biosynthesis	Size	Shape	Applications	Ref.
AgNPs	*Saccharomyces cerevisiae*	Extracellular	10.3–18.9 nm	Spherical	Antibacterial activity	(Shu et al., 2020)
			10–60 nm	Spherical	Antimicrobial activity	(Sowbarnika et al., 2018)
			16.07 nm	Oval	Antibacterial activity	(Olobayotan and Akin-Osanaiye, 2019)
			10 nm.	Spherical	-	(Roy et al., 2015)
			5–20 nm	Spherical	Antifungal activity	(Niknejad et al., 2015)
			6–20 nm	Spherical	-	(Jha and Prasad, 2008)
		Intracellular	8–17 nm	Circular shape	-	(Jafarov et al., 2017)
			2–20 nm	Spherical	-	(Korbekandi et al., 2016)
	Yeast HX-YS	Extracellular	50–100 nm	Spherical	Anticancer and antibacterial activities	(Liu et al., 2021)
	Yeast LPP-12Y					
	Candida albicans	Extracellular	30 nm	Nonspherical	Antibacterial activity	(Ahmad et al., 2013)
	Cryptococcus laurentii	Extracellular	13% at 400 nm and 74% at 35 nm		Antifungal activity	(Fernández et al., 2016)
	Rhodotorula glutinis	Extracellular	65% at 15 nm, 17% at 160 nm, and 18% at 220 nm			
	Yarrowia lipolytica NCYC 789-derived melanin	Extracellular	15 nm		Antibacterial	(Apte et al., 2013)
	Extremophilic yeast strain	Intracellular	4–15 nm	Spherical	-	(Mourato et al., 2011)
AuNPs	Extremophilic yeast strain	Intracellular	30–100 nm	Spherical	-	
	Magnusiomyces ingens LH-F1.	Extracellular	80.1 ± 9.8 nm	Sphere, triangle, and hexagon	-	(Zhang et al., 2016)
	Candida albicans	Extracellular	5 nm	Spherical and nonspherical	Antibacterial activity	(Ahmad et al., 2013)
	Hansenula anomala	Extracellular	14 nm		Antibacterial activity	(K et al., 2011)
SeNPs	*Saccharomyces cerevisiae*	Intracellular	71 ± 18.17 nm	Spherical	Immune regulation and antioxidative activity in cyclophosphamide-induced rats	(Wu et al., 2021)
			34–125 nm	Spherical	Antioxidant and anti-inflammatory activities	(Fath-Alla et al., 2024)
			75–709 nm	Spherical	Antioxidant activity	(Faramarzi et al., 2020)
			30–100 nm		Antibacterial activity	(Hariharan et al., 2012)
		Extracellular	4–51 nm	Spherical	Antimicrobial activity	(Salem, 2022)
		Extracellular	170–240 nm	Rod	Anticancer, antioxidant, and antibacterial activities	(Goud et al., 2016)
	Nematospora coryli	Intracellular	50–250 nm	Spherical	Anticandidal and antioxidant activities	(Rasouli, 2019)
	Novel yeast *Magnusiomyces ingens* LH-F1.	Extracellular	87.82±2.71 nm	Spherical	Antibacterial activity	(Lian et al., 2019)
	Rhodotorula mucilaginosa R-8441	Intracellular and extracellular	83 nm (spherical) and 478 nm (rod)	Spherical and rod	-	(Ashengroph and Tozandehjani, 2022)
SeSNPs	*Saccharomyces cerevisiae*	Intracellular	6.0–153 nm	Spherical	Antifungal activity	(Asghari-Paskiabi et al., 2019)
ZnSNPs	*Saccharomyces* cerevisiae MTCC 2918	Intracellular	30–40 nm		-	(Mala and Rose, 2014)
MnO_2NPs	*Saccharomyces cerevisiae*	Extracellular	34.4 nm	Spherical and hexagonal	-	(Salunke et al., 2015)
TiO_2NPs	*Saccharomyces cerevisiae*	Intracellular	6.7 ± 2.2 nm	Spherical	Antimicrobial activity	(Peiris et al., 2018)

the mixture changed into dark brown color indicating formation of AgNPs. The size distribution of *C. laurentii*-mediated AgNPs was as follows: 13% at 400 nm and 74% at 35 nm and that of *R. glutinis*-mediated AgNPs was as follows: 65% at 15 nm, 17% at 160 nm, and 18% at 220 nm. Zeta potential of *C. laurentii*-mediated AgNPs and *R. glutinis*-mediated AgNPs were –24.9 ± 0.5 mV and –13.5 ± 0.8 mV, respectively. Also, FTIR spectra of both showed the presence of proteins and carbohydrates. and XRD profile of both showed their crystalline nature (Fernández et al., 2016). Supernatants of two yeast strains HX-YS and LPP-12Y were able to biosynthesize AgNPs within 4 days. Observation of absorbance peaks at 450 nm and 430

nm confirms the formation of AgNPs by HX-YS and LPP-12Y, respectively. SEM analysis of AgNPs synthesized by two yeast strains HX-YS and LPP-12Y showed that AgNPs have spherical shape and size ranging from 50 to 100 nm. The AgNPs synthesized by HX-YS were smaller in size and more uniform than those synthesized by LPP-12Y (Liu et al., 2021). Cell-free filtrate of *Candida albicans* contains enzymes and proteins that are responsible for the biosynthesis of AgNPs that was confirmed by the appearance of a peak at 450 nm. *C. albicans*-mediated AgNPs were nonspherical monodispersed with crystalline nature and an average size of 30 nm. They were surrounded by proteins, based on FTIR results (McNamara and Tofail, 2017).

It was proved that the three yeast species, namely, *Saccharomyces cerevisiae, Geotrichum candidum*, and *Rhodotorula glutinis*, could biosynthesize AgNPs intracellularly and extracellularly. The synthesized AgNPs were of small size ranging from 1.5–20 nm (Zahran et al., 2013). An extremophilic yeast strain has also the potential to biosynthesize AgNPs via an intracellular and extracellular method. The UV spectrum of intracellularly synthesized AgNPs showed a peak at 420 nm confirming the formation of AgNPs. They have a spherical shape and diameters that range from 4 to 15 nm with an average diameter of 7.5 nm. FTIR analysis of extracellularly biosynthesized particles showed the presence of carbonyl stretch in the amide linkages of the proteins which indicates the release of proteins from yeast cells in the supernatant and they are responsible for reduction, capping, and stabilization of AgNPs. Also, XRD profile showed that AgNPs have a polycrystalline nature (Mourato et al., 2011). AgNPs can be synthesized either intracellularly by the psychrotrophic yeast *Yarrowia lipolytica* NCYC 789 or extracellularly by melanin extracted from it. Yeast-mediated AgNPs showed a band at 410 nm of UV spectrum. They have face-centered cubic structures based on XRD data. Scanning electron microscopy image showed the accumulation of AgNPs on the surface of yeast cells at which silver ions were reduced into Ag^0. The presence of amino, hydroxyl, and phenolic groups were detected from peaks of FTIR spectrum. Those functional groups of bioactive compounds have a role in the biosynthesis process. Melanin-synthesized AgNPs also showed a peak at 410 nm and have an average size equal to 15 nm (Apte et al., 2013).

AuNPs: Several studies reported the intracellular and extracellular synthesis of gold nanoparticles (AuNPs) using different yeast species. Mourato et al. (2011) synthesized AuNPs intracellularly using extremophilic yeast strain which were detected by using the UV spectrum through observation of a peak at 550 nm which is a characteristic peak of AuNPs. The synthesized AuNPs were spherical in shape and their size ranged from 30 to 100 nm. XRD analysis revealed that the AuNPs have a polycrystalline nature with face-centered cubic unit cell. This study also detected the role of yeast cell wall in the biosynthesis of AuNPs, as the cell-free filtrate of the used yeast strain cannot form AuNPs. It was reported that tropical marine yeast *Yarrowia lipolytica* NCIM 3589 is able to reduce gold ions of $HAuCl_4$ intracellularly into AuNPs via its enzymes including reductase and protease. Formation of AuNPs was detected by color change into purple and this was confirmed by observation of the peak at 545 nm indicating the intracellular biosynthesis of AuNPs. Firstly, AuNPs were formed inside the cells and then released outside which was confirmed by a TEM micrograph in which the presence of AuNPs on the *Y. lipolytica* cell wall and outside the cells was observed. SEM image of AuNPs synthesized by yeast *Yarrowia lipolytica* NCIM 3589 showed nucleation sites at which gold ions of $HAuCl_4$ were reduced into Au and deposition of gold on the cell surface indicating intracellular biosynthesis. It was noticed that nucleation increased over a period (Agnihotri et al., 2009). It was noticed that the formed AuNPs inside *Y. lipolytica* yeast cells could be released outside the cells when the cells were incubated in cold conditions (Pimprikar et al., 2009).

Biosynthesis of AuNPs using *Magnusiomyces ingens* LH-F1 was reported by Zhang et al. (2016). Change of a mixture solution containing cell-free filtrate and gold salt from yellow to light purple and then to deep purple after 6 hours indicated the rapid biosynthesis of AuNPs. Also, the peak at 540 nm in UV spectrum confirmed the presence of AuNPs in cell-free filtrate. Based on the TEM image, the particles have an average size equal to 80.1 ± 9.8 nm while dynamic light scattering (DLS) results recorded that particles have an average size of 137.8 ± 4.6 nm. SEM and TEM results showed that AuNPs have different shapes including sphere, triangle, pentagon, and hexagon, and irregular shaped particles were detected. Biomolecules on the surface of AuNPs were detected by FTIR and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis. The results indicated the presence of carboxyl and amide groups referring to proteins that were involved in reduction of Au^{3+} and stabilization of AuNPs. In other research, cell-free extract of *Candida*

albicans was used in the biosynthesis of AuNPs that was confirmed by the observation of a peak at 540 nm. The formed monodispersed AuNPs have a crystalline nature, spherical and nonspherical shape, and an average size of 5 nm and were surrounded by proteins, according to FTIR results (Ahmad et al., 2013). Isolated bioreductants from *Hansenula anomala* yeast were used for reduction of gold ions into AuNPs. This was followed by the utilization of amine-terminated polyamidoamine dendrimer and cysteine as stabilizers. The broad band at 550 nm confirmed the formation of AuNPs that have an average size of 14 nm as was shown in TEM micrograph (K et al., 2011).

Nair et al. (2013) reported that both *Y. lipolytica* cells and *Y. lipolytica*-extracted melanin biomass has the potential to biosynthesize gold nanoparticles. Different amounts of yeast cells (10^9, 10^{10}, or 10^{11} cells mL^{-1}) were incubated with different concentrations of $HAuCl_4$ (0.5, 1.0, 2.0, 3.0, 4.0, or 5.0 mM) for intracellular production. Formation of AuNPs was seen only at 0.5 and 1.0 mM $HAuCl_4$ with 10^9 cells mL^{-1}). The used cell numbers could biosynthesize gold nanoparticles. UV spectrum of a mixture containing 0.5 mM $HAuCl_4$ showed a peak in the range of 520–580 nm referring to the presence of AuNPs. XRD analysis revealed that formed AuNPs were face-centered cubic metal structures. A SEM image of yeast cells (10^9 cells ml^{-1}) showed the presence of AuNPs inside the cells indicating intracellular synthesis. Also, triangular and hexagonal shaped crystals were seen referring to AuNPs. FTIR analysis revealed the presence of several functional groups including amino, carboxyl, hydroxyl, and phenolic groups that were involved in the reduction of AuNPs. It was proved that melanin pigment produced by *Y. lipolytica* had an important role in biosynthesis of AuNPs. After mixing gold salt with melanin extracted from yeast biomass, the color of the mixture changed into purple color referring to the formation of AuNPs extracellularly. As melanin concentration increased, the color of mixture increased indicating an increased AuNPs production. UV spectrum showed peaks ranging from 500 to 580 which are characteristic peaks of AuNPs. AuNPs were seen in SEM analysis of mixture containing melanin and AuNPs.

SeNPs: Several yeast species could synthesize SeNPs inside or outside cells. Many studies reported the ability of *S. cerevisiae* to synthesize SeNPs such as the Wu et al. (2021) study that produced spherical SeNPs with an average size of 71 ± 18.17 nm where 91.84% of the SeNPs have a diameter smaller than 100 nm which is considered as an acceptable size. The formed particles carried a negative charge equal to −34.00 mV and have an amorphous and crystalline structure. It was noticed that SeNPs were first formed inside yeast cells and then released into a medium. Comparing of FTIR spectra of both yeast-synthesized SeNPs and yeast cells, it was found that there is a similarity between them which indicated that SeNPs have some bioactive compounds of yeast cells. Detection of C–O and amide bond referred to the presence of protein. It was suggested that those proteins have a role to control size and maintain stability of SeNPs and help in transportation of SeNPs outside yeast cells. Also, a study done by Fath-Alla et al. (2024) and another one done by Faramarzi et al. (2020) used baker's yeast in the intracellular biosynthesis process. Fath-Alla et al. (2024) succeeded in synthesizing SeNPs by using sodium selenite at 25 µg concentration. The synthesis was confirmed by the presence of a peak of 360 nm in the UV spectrum. The formed SeNPs have a spherical shape, size range from 34 to 125 nm, and a negative surface charge equal to -22.4 mV. The presence of carboxyl groups, amines, and amines peaks in the FTIR spectrum refers to protein molecules. The XRD pattern showed their amorphous and crystalline nature. The Faramarzi et al. (2020) study used five different concentrations of sodium selenite (5.0, 10.0, 15.0, 20.0, and 25 µg) to synthesize SeNPs. The formed spherical particles have size ranges from 75 to 709 nm, zeta potential ranges from –7.06 to –10.3 mV, and a UV peak of 350 nm. It was observed that the smallest particle size (75 nm) and the highest zeta potential (–10.3 mV) were obtained by using the minimum amount of selenium salt (5 µg). In addition, sodium selenite treated with biomass of *S. cerevisiae* was reduced forming SeNPs with a size of 30–10 nm and crystalline nature (Hariharan et al., 2012). Another yeast species called *Nematospora coryli* could reduce the selenium ion of SeO_3^{2-} into spherical selenium nanoparticles Se^0 with a UV peak equal to 561 nm and a size of 50–250 nm. FTIR analysis of the particles surface biomolecules showed peaks of N–H, C=O, and C–H stretching referring to both amines (present in peptide chains and protein molecules) and amide groups. XRD results detected the absence of sharp peaks indicating the noncrystalline nature of particles (Rasouli, 2019).

Salem (2022) proved the potency of *S. cerevisiae* to reduce the Se ion of sodium selenite and transform it to SeNPs extracellularly. This was confirmed by the appearance of peak at 300 nm in UV spectrum. The produced SeNPs were with small size between 4 and

51 nm, spherical shape and negative charge –11.9 mV. Cell-free filtrate of *Magnusiomyces ingens* LH-F1 was able to reduce selenium ions of SeO_2 into spherical SeNPs with characteristic UV peak at 560 nm and average size of 87.82 ± 2.71 nm. It was suggested that amino, carboxyl and hydroxyl groups detected in FTIR spectrum of *Magnusiomyces ingens* cell-free filtrate have a role in SeNPs synthesis. According to XRD analysis, the prepared SeNPs were composed of hexagonal crystalline Se (Lian et al., 2019). Goud et al. (2016) tested the green production of SeNPs by mixing a solution of Na_2SeO_4 with agrowaste-based *S. cerevisiae*-fermented broth. A UV analysis showed the maximum peak at 540 nm indicating the formation of SeNPs. The particles had size ranges from 170 to 240 nm and rod shape and arranged as flower like crystalline aggregates. Both spherical and rod-shaped SeNPs had crystalline nature based on XRD analysis.

The aquatic yeast strain (*Rhodotorula mucilaginosa* R-8441) showed its ability to synthesize SeNPs not only intracellularly but also extracellularly using selenite oxyanion. The synthesized SeNPs were spherical in shape with an average size of 83 nm and rod shaped with an average size of 478 nm. The TEM image showed the presence and accumulation of SeNPs in the cell wall (Ashengroph and Tozandehjani, 2022).

SeSNPs: Selenium sulfide nanoparticles were successfully synthesized by *S. cerevisiae.* The intracellularly formed red colored SeSNPs had average size ranges from 6.0 and 153 nm, spherical shape, and crystalline nature. In addition, they were surrounded by proteins that were detected from peaks of FTIR analysis (Asghari-Paskiabi et al., 2019).

PdNPs: Palladium nanoparticles can be biosynthesized extracellularly using *S. cerevisiae*. Yeast extract was able to reduce Pd(II) to Pd(0) in the form of nanoparticles with dark brown color. SEM analysis showed a hexagonal shape of small PdNPs and XRD revealed that PdNPs have face-centered cubic structure. As proved from FTIR results, PdNPs are surrounded and stabilized by bioactive molecules present in the yeast extract as secondary metabolites that have an important role in PdNPs formation (Sriramulu and Sumathi, 2018). *Saccharomyces cerevisiae* can intracellularly synthesize PdNPs with a size of 11 nm and crystalline nature. SEM and TEM analyses showed the presence of PdNPs in every part of cells (Li et al., 2018).

ZnSNPs: Zinc sulfide nanoparticles were synthesized intracellularly using *S. cerevisiae* MTCC 2918. Formation of ZnSNPs was confirmed by observation of whitish yellow color and absorbance band at 302.57 nm. The formed particles had size ranges from 30 to 40 nm and are present in sphalerite phase based on XRD analysis. It was proved that the reduction process was based on oxidoreductase enzyme-mediated mechanism (Mala and Rose, 2014).

MnO_2NPs: Supernatant of *S. cerevisiae* was utilized to form manganese dioxide nanoparticles using potassium permanganate. The peak at 365 nm of UV-visible spectrum results confirmed the production of MnO_2NPs (dark brown color) that had uniform spherical and hexagonal shape with average size equal to 34.4 nm. FTIR revealed the presence of proteins and alcoholic compounds that have a role in synthesis of MnO_2NPs (Salunke et al., 2015).

TiO_2NPs: Peiris et al. (2018) investigated the capacity of *S. cerevisiae* to synthesize titanium dioxide nanoparticles (TiO_2NPs). The results indicated that *S. cerevisiae* had the ability to reduce $TiCl_3$ salt and form TiO_2NPs with brown color. Synthesized TiO_2NPs had spherical shape and their average size equals 6.7 ± 2.2 nm.

Extraction of Nanoparticles

Both intracellularly and extracellularly synthesized nanoparticles using yeast should be purified from yeast cells or their remains to be used as pure NPs in many applications. Extraction and purification of intracellularly synthesized NPs depend on lysis of yeast cells using chemical or physical methods. On the other hand, extracellularly synthesized NPs can be purified using centrifugation or dialysis (Besner et al., 2008). Extraction process should be standardized to obtain pure, stable, and effective NPs without degradation, aggregation, or even loss of their yield (Roychoudhury, 2020).

Characterization

After biosynthesis and extraction processes, NPs should be characterized to identify their physicochemical properties using different analyses including ultraviolet-visible spectroscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), Fourier transform-infrared spectroscopy (FTIR), and X-ray diffraction (XRD).

UV–Visible Spectroscopy: Ultraviolet-visible (UV-Vis) spectroscopy is an important analytical technique used to detect the optical properties of nanoparticles and confirm their formation (Kowshik et al., 2002). The reduction of metal and metal oxide ions into

nanoparticles was detected by color change that occurred as a result of the surface plasmon resonance phenomenon (SPR). Metal nanoparticles exhibit free electrons that are excited by light causing the SPR phenomenon (Zahran et al., 2013). For example, dark brown color of AgNPs (Korbekandi et al., 2016), purple color of AuNPs (Zhang et al., 2016), and red color of SeNPs (Salem 2022) appeared due to the surface plasmon resonance of them. Change in color is considered as the first indicator of NPs formation. UV spectrum of each type of NPs can be used to confirm their formation through the detection of the maximum absorbance band (λ_{max}).

TEM, SEM, and DLS: Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were used to study not only the size, shape, and morphology of nanoparticles but also the location of nanoparticles specially in intracellular synthesis (Roy et al., 2015). Different yeast-mediated NPs with different sizes and shapes are mentioned in Table 1. It is noticed that yeast-fabricated NPs have different sizes. This variation in the size of NPs may be due to several factors including formation of NPs at different times (Sowbarnika et al., 2018) and adhesion of nanoparticles to each other (Zhang, 2014). Dynamic light scattering (DLS) analysis is used to analyze the size distribution of NPs by using a nano-zeta sizer (Korbekandi et al., 2016). It was proved that the average size obtained from DLS is higher than that obtained from TEM or SEM analyses. This is because TEM and SEM measure only the core size of NPs while DLS measures the size of both metallic core and biomaterial deposited on NPs surface. DLS is said to measure hydrodynamic volume. It is the volume of nanoparticles that refers to the effective volume occupied by nanoparticles in a fluid and equals the whole diameter of nanoparticles core along with their surrounding biomolecules (Huang et al., 2007). Another study suggested that this difference may be due to overlapping of nanoparticles during DLS measurements (Malhotra et al., 2013). For example, the size of AuNPs detected by TEM was 80.1 ± 9.8 nm while the average size of DLS was 137.8 ± 4.6 nm (Zhang et al., 2016). TEM image showed that intracellular *S. cerevisiae*-synthesized SeNPs have a size ranging from 34 to 125 nm while DLS analysis revealed that the average size was 173.9 nm which indicated the difference in size obtained from TEM and DLS (Fath-Alla et al., 2024). Furthermore, size detection of extracellular yeast-prepared SeNPs proved the difference between TEM size (diameters of SeNPs range from 4 to 51 nm) and DLS size (83.3 nm) (Salem, 2022). DLS analysis also detected the zeta potential value of NPs that refers to the surface charge of NPs and is considered a main factor affecting the stability of NPs. As the negative charge on NPs surface increases, the repulsion of NPs increased and their aggregation decreased, thus increasing particle stability. Values close to ± 30 mV can inhibit agglomeration of NPs (Wu et al., 2021; Zhang et al., 2021).

FTIR: FTIR analysis is applied to identify the chemical nature of the biomolecules involved in the biosynthesis process and surrounding the biosynthesized nanoparticles. This analysis detects functional groups of biomolecules on the surface of NPs such as proteins, carbohydrates, and lipids that are produced by yeast cells during biosynthesis processes including reduction, capping, and stabilization (Bartosiak et al., 2019). FTIR results of several studies detected the presence of proteins in samples that act as reducing, capping, and stabilizing agents (Fernández et al., 2016; Sowbarnika et al., 2018; Wu et al., 2021).

XRD: XRD analysis is used to detect the nature and crystallinity of NPs that may have crystalline or noncrystalline nature (Khan et al., 2020). In XRD pattern, peaks of (111), (200), (220), and (311) at 2θ° values indicate the presence of silver element (Fernández et al., 2016; Shu et al., 2020). Gold element is indicated by observation of (111), (200), (220), and (311) peaks (Nair et al., 2013), while peaks of (100), (101), (111), (201), and (210) refer to the presence of selenium element (Lian et al., 2019; Salem, 2022).

Toxicity of Yeast-Synthesized Nanoparticles

Toxicity and biocompatibility of nanoparticles are important factors affecting their further biomedical application (Shu et al., 2020). Yeast cells can not only be viable in the presence of toxic metal ions but also reduce them and form NPs with nontoxic property. In yeast cells, metallothioneins, phytochelatins, and glutathione (GSH) are involved in detoxification mechanism (Gajbhiye et al., 2009). The method of nanoparticles synthesis and the type of biomolecules that act as stabilizer and capping agents are two factors that affect toxicity of NPs (Chen et al., 2008) in addition to size and shape of NPs (Woźniak et al., 2017).

***In Vitro* Cytotoxicity:** Cytotoxicity is an essential assay in which the biosynthesized NPs are tested against a variety of normal living cell lines. It aims to detect the

biocompatibility and safety of NPs before using them as therapeutic agents. MTS assay was applied to assess the cytotoxicity of AgNPs using Cos-7 cells. Different concentrations of *S. cerevisiae*-mediated AgNPs (13.3, 6.25, 12.5, 25, 50, 100, and 200 µg/mL) were incubated with the tested cells for 24 h. At concentrations as high as 200 µg/mL, there was no significant cytotoxicity detected. This indicated that AgNPs have good biocompatibility and negligible cytotoxicity. Moreover, those particles can be used as a nontoxic antibacterial drug (Shu et al., 2020). Cytotoxicity based on the MTT assay using normal human lung epithelial cell line Beas 2B was used to determine the cytotoxicity of AgNPs biosynthesized by two yeasts HX-YS and LPP-12Y. A weak inhibitory effect of AgNPs was detected against tested normal cells. At 0.25 µl/mL of LPP-12Y-synthesized AgNPs, there was a weak inhibitory action. It was proved that both HX-YS- and LPP-12Y-mediated AgNPs have low toxicity effect on normal lung cells. So, this study used both AgNPs as anticancer and antibacterial agent (Liu et al., 2021). Yeast could reduce toxic inorganic selenium salt converting it into nontoxic selenium nanoparticles (Wu et al., 2021). Fath-Alla et al. (2024) tested the cytotoxicity of *S. cerevisiae*-derived SeNPs against mouse normal liver cells using the SRB assay.

The results proved that SeNPs concentrations of 1, 3, 10, 30, 100, 150, 200, 250, and 300 µg/mL showed cell viability percentage of 102.66, 98.06, 94.24, 93.70, 90.06, 89.22, 88.14, 85.34, and 82.75%, respectively. The obtained IC_{50} value was above 300 µg/mL. Based on those results, the researchers used these safe SeNPs as antioxidant and anti-inflammatory drugs. When SeNPs synthesized by *S. cerevisiae*-fermented broth at a concentration of 100 µg/mL were tested against Chinese hamster ovary as a normal cell line, it was found that SeNPs exhibited very low cytotoxic effect; therefore, they can be applied as anticancer, antioxidant, and antibacterial agents (Goud et al., 2016). Cytotoxicity of *S. cerevisiae*-mediated SeNPs against normal mouse macrophage cell line (RAW264.7 cells) was tested. The cell viability percentages of 102.34, 99.98, 99.68, 97.36, and 88.88% were detected at SeNPs concentrations of 20, 30, 40, 50, and 100 µg/mL, respectively, with IC_{50} more than 100 µg/mL. This result allowed the use of SeNPs as an anti-inflammatory drug (Fath-Alla et al., 2024). Sun et al. (2023) found that there was no toxic effect of SeNPs stabilized by yeast glucan at concentrations range from 10 to 100 µg/mL on RAW264.7 cells, in addition to their cell division stimulatory action at 50 µg/mL. Cytotoxicity of *S. cerevisiae*-synthesized SeSNPs against A L929 murine fibroblast cell line was tested and compared with that of selenium sulfide powder via MTT assay. There was no cytotoxicity effect when different concentrations of SeSNPs (4, 3, 2, 1, 0.5, and 0.1 mg/mL) were used. In addition, more than 80% cell viability was observed at SeSNPs concentration equal to 2 mg/mL or more. Meanwhile, selenium sulfide powder at all concentrations showed cytotoxicity with detected cell viability of 35% (Asghari-Paskiabi et al., 2019).

***In Vivo* Toxicity:** After oral administration of 22 albino mice with whether HX-YS- or LPP-12Y-mediated AgNPs, there was a low toxicity effect on normal lung cells of mice. The LD_{50} was more than 5000 mg kg^{-1} body wight; therefore, those used nanoparticles were safe (Olobayotan and Akin-Osanaiye, 2019).

Biomedical Applications of Yeast-Synthesized NPs

Many studies reported that biosynthesized NPs have various biomedical activities, so they are highly recommended to be used in health technologies and modern medicine (Liu et al., 2021). As shown in Figure 3, yeast-mediated nanoparticles can be used as anticancer, antioxidant, anti-inflammatory, and antimicrobial agents.

Anticancer Activity: Today cancer is considered as one of the common diseases that causes death. Recently several nanoparticles are used in cancer treatment as it was proved in many research studies (Karunakaran et al., 2023). MTT assay was used to detect anticancer activities of AgNPs synthesized by both yeasts HX-YS and LPP-12Y against two human lung cancer cell lines A549 and H1975. Different amounts of AgNPs were incubated with cancer cells (0.1 µL, 0.25 µL, 0.5 µL, 1.0 µL, and 2.0 µL). Both HX-YS- and LPP-12Y-mediated AgNPs at 0.5 µL exhibited a significant inhibition of the growth of A549 and H1975 cells with reduction in cell viability below 20%. HX-YS-mediated AgNPs had antitumor activity but at a higher concentration than LPP-12Y-mediated AgNPs. Therefore, these yeast-synthesized AgNPs may have a powerful action for cancer treatment (Liu et al., 2021). SeNPs synthesized by *S. cerevisiae*-fermented broth fulfilled significant antiproliferative activity against various cancer cell lines: adenocarcinomic human alveolar basal epithelial cells (A549), human breast cancer (MCF7), and human ovarian cancer (SKOV3) and no cytotoxicity effect on normal cell line of Chinese hamster ovary (CHO). SeNPs at 100 µg/mL showed high cytotoxic action against all tested

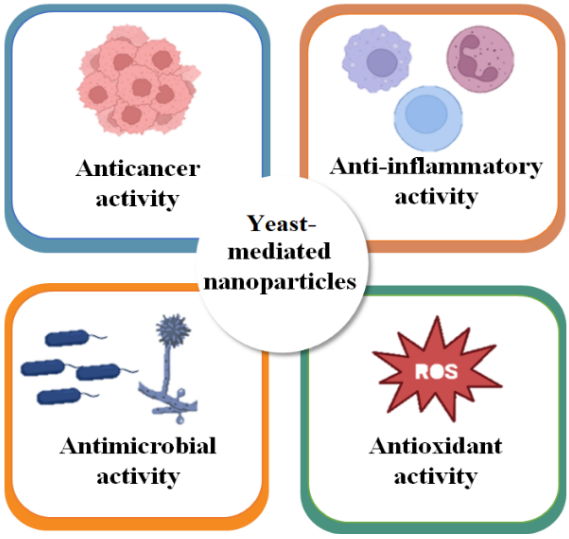

Figure 3. Biomedical applications of yeast-mediated nanoparticles. Created in BioRender.com.

cancerous cell lines. It was suggested that differential interaction of SeNPs with both cancer and normal cell lines may be attributed to distribution and differential expression of cell membrane receptors (Goud et al., 2016).

Antioxidant Activity: Free radicals cause tissue damage and imbalance between antioxidant protection activity and oxidative stress (Re et al., 1999). NPs have a promising antioxidant action and can scavenge free radicals especially due to their small size (Faramarzi et al., 2020). SeNPs improve antioxidation through Se-containing molecules such as glutathione peroxidases and selenoproteins having protection effect against free radicals (Wu et al., 2021). Antioxidant activity of SeNPs may be related to surface charge, hydrogen transferring capacity, and capping molecules containing hydroxyl (OH^-) group (Zhang et al., 2019). In addition, their large surface area improves the antioxidant capacity by increasing reactive sites at which free radicals are eliminated (Yang et al., 2023). Several studies recorded the powerful antioxidant capability of biosynthesized SeNPs. *S. cerevisiae*-mediated SeNPs showed antioxidant activity at nontoxic concentrations. The results of DPPH free radical scavenging assay revealed that the free radical scavenging percentages were 54.24, 60.35, 63.26, 50.27, and 52.90% at 50, 100, 150, 200, and 250 µg/mL of SeNPs, respectively. The highest antioxidant activity (63.26%) was observed at SeNPs concentration of 150 µg/mL. Meanwhile, the concentration that is needed to inhibit 50% of free radicals (IC_{50}) was 45.87 µg/mL (Fath-Alla et al., 2024).

In addition, the antioxidant action of *S. cerevisiae*-synthesized SeNPs was reported in Faramarzi et al. (2020) study. SeNPs have free radical inhibition percentage dependent on the amount of sodium selenite salt that was used for SeNPs production. The percentages of free radicals were 48.5, 35.4, 26.1, 20.8, and 21.7% at 5, 10, 15, 20, and 25 µg of selenium salt. Results indicated that antioxidant activity decreased when selenium salt concentration increased. The maximum antioxidant percentage of SeNPs was 48.5% at the lowest selenium salt amount (5 µg). Goud et al. (2016) proved that SeNPs biofabricated by *S. cerevisiae*-fermented broth exhibited the highest inhibition activity (79%) at 500 µg/mL SeNPs and the detected IC_{50} value was 236 µg/mL. It was found that the antioxidant activity of SeNPs increases when their concentration increases. This is also proved in Rasouli (2019) study that when *Nematospora coryli*-mediated SeNPs concentration increases, DPPH free radicals scavenging potency increases. Antioxidant activity of yeast-synthesized SeNPs was assessed not only through in vitro studies but also at the in vivo level. Wu et al. (2021) detected the antioxidant activity of *S. cerevisiae*-synthesized SeNPs in rat models by measuring malondialdehyde (MDA), glutathione peroxidase (GSH-Px), total superoxide dismutase (T-SOD), and total antioxidant capacity (T-AOC). MDA is a product of lipid peroxidation, and its increase refers to oxidative stress. On the other hand, increases in GSH-Px, SOD and AOC levels indicate an antioxidant status. Se-NP significantly decreased MDA by 31.52% and increased GSH-Px, SOD, and AOC by 38.39%, 13.52%, and 12.70%, respectively. Accordingly, it can be concluded that SeNPs protect rats from free radicals and reactive oxygen species via decreasing lipid oxidation and increasing the activity of antioxidant enzymes present in the test organism.

Anti-Inflammatory Activity: Inflammation is a localized protective immune response that is activated in response to any irritants such as pathogens, chemical agents, mechanical effect, and toxins (Freire and Van Dyke, 2013). The anti-inflammatory activity of *S. cerevisiae*-synthesized SeNPs was detected by measuring the inhibitory percentage of nitric oxide production. NO inhibitory percentages were 12.05, 13.43, 23.24, 27.20, and 41.34% at different SeNPs concentrations of 20, 30, 40, 50, and 100 µg/mL. At the highest nontoxic SeNPs concentration (100 µg/mL), the maximum activity was observed. Therefore, the pretreatment of RAW264.7 macrophage cells with SeNPs inhibited the

production of nitric oxide by cells because of inflammatory induction with lipopolysaccharides (LPS) (Fath-Alla et al., 2024). It was also found that SeNPs stabilized by aminated yeast glucan exhibit anti-inflammatory effect where several concentrations of SeNPs (10–100 µg/mL) showed an inhibitory action on NO production by macrophage cells (Sun et al., 2023). Selenium can affect signaling pathways of macrophage cells showing anti-inflammatory activity (Javdani and Barzegar, 2023). It was reported that the anti-inflammatory action of SeNPs is attributed to several suggested mechanisms. SeNPs may downregulate PI3K/Akt/NF-κB pathways (Mi et al., 2022) or decrease iNOS transcription and therefore inhibit NO production (Sun et al., 2023).

Antimicrobial Activity: Recently, antibiotic resistance of microbes became a serious problem that threatens people's lives, so it is necessary to find new alternative antimicrobial agents (Frieri et al., 2017). Previous research studies proved the antibacterial and antifungal potency of yeast metal nanoparticles, as shown in Table 2. Usually, the antimicrobial assay aims to measure the diameter of zone of inhibition (ZOI) and/or minimum inhibitory concentration (MIC) that refers to the minimum concentration required to inhibit microbial growth (Lambert and Pearson, 2000). Results of antimicrobial activity of various NPs against different bacterial and fungal species in addition to their minimum inhibitory concentration and/or ZOI values are shown in Table 2.

Antibacterial Activity

Shu et al. (2020) evaluated the antibacterial activity of *S. cerevisiae*-mediated AgNPs against both *E. coli* and ampicillin-resistant *E. coli*. Results revealed that AgNPs concentrations of more than 20.0 µg/mL completely inhibited *E. coli* growth while 10.0 µg/mL AgNPs partially inhibited the growth. The concentration of 13.4 µg/mL of AgNPs was half inhibitory concentration (EC_{50}). Combination between ordinary used antibiotics and metal nanoparticles is a strategy to overcome antibiotic resistance of many bacterial species. It was reported that combination between ampicillin and AgNPs showed superior antibacterial action against ampicillin-resistant *E. coli* while there was no inhibitory effect with sole ampicillin treatment. Both methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* were exposed to different concentrations of *S. cerevisiae* AgNPs (5, 10, 25, 50, 75, and 100 µg/mL). At a concentration of 75 µg/mL, AgNPs had significant antibacterial action while concentrations equal to or less than 50 µg/mL had no effect on bacterial growth. It was noticed that AgNPs exhibited higher inhibitory effect against methicillin-resistant *S. aureus* than *P. aeruginosa* (Olobayotan and Akin-Osanaiye, 2019). Antibacterial activities of both yeasts LPP-12Y- and HX-YS-mediated AgNPs against five pathogenic bacteria were assessed by Liu et al. (2021). *Staphylococcus aureus* ATCC6538, *Monilia albicans* ATCC10231, *Bacillus subtilis* ATCC6051, *Escherichia coli* ATCC8099, and *Pseudomonas aeruginosa* were used as tested bacteria and the antibacterial activity of AgNPs was detected by measuring of ZOI. Results indicated that both AgNPs had antibacterial action against all tested bacteria. Values of ZOI are mentioned in Table 2. The highest inhibitory effect was noticed against *P. aeruginosa* with ZOI 21.8 and 21.4 cm after treatment with LPP-12Y-mediated AgNPs and HX-YS-mediated AgNPs, respectively. Also, it was noticed that the inhibitory effect of LPP-12Y-synthesized AgNPs against *S. aureus* ATCC6538, *B. subtilis* ATCC6051, *E. coli* ATCC8099, and *P. aeruginosa* was higher than that of HX-YS-synthesized AgNPs. However, the latter AgNPs had inhibitory action against *M. albicans* ATCC10231 higher than that exhibited by LPP-12Y-synthesized AgNPs.

Antibacterial and antibiofilm activities of both melanin-synthesized AgNPs (Apte et al., 2013) and AuNPs (Nair et al., 2013) were evaluated. Growth of bacteria with biofilm mode makes it more resistant to antibacterial agents. AgNPs synthesized by melanin extracted from *Yarrowia lipolytica* showed antibacterial and antibiofilm activities against *Salmonella paratyphi* MTCC 735. It was proved that AgNPs can inhibit the *S. paratyphi* biofilm proliferation, where after treatment time of 24 h and 48 h the inhibitory percentage was 37% and 67%, respectively (Apte et al., 2013). Melanin-synthesized AuNPs showed antibacterial and antibiofilm activities against *Salmonella paratyphi*, *Shigella soneii,* and *Pseudomonas aeruginosa* (Nair et al., 2013). Ahmad et al. (2013) evaluated the antibacterial activity of both AgNPs and AuNPs synthesized by *C. albicans* against one type of Gram-positive bacteria (*Staphylococcus aureus*) and one type of Gram-negative bacteria (*Escherichia coli*). The obtained values of ZOI and MIC_{80} indicated the promising antibacterial effect of both NPs on the two tested pathogens. MIC_{80} refers to the minimum inhibitory concentration that inhibits 80% of bacterial growth. With AgNPs treatment, the ZOI values were 19 mm and 24 mm and MIC_{80} values were 32 µg/mL and 8

µg/mL against *S. aureus* and *E. coli*, respectively. After treatment with AuNPs, ZOI values were 11 mm and 16 mm and MIC_{80} values were 512 µg/mL and 128 µg/mL against *S. aureus* and *E. coli*, respectively. Based on the obtained values, AgNPs had higher antibacterial activity than that of AuNPs against both bacterial species. This may be attributed to the fact that AgNPs have higher surface activity than AuNPs. Also, *E. coli* was more susceptible to both NPs than *S. aureus* which may be related to difference in cell wall structure between Gram-positive and Gram- negative bacteria. Gram-positive bacteria have thick layer of peptidoglycan in cell wall while Gram-negative have thin layer; therefore, the thick layer of peptidoglycan may resist the attack of the NPs (Taglietti et al., 2012; Ahmad et al., 2013).

A study investigated the antibacterial action of *S. cerevisiae*-derived AgNPs against two bacterial species (*Esherichia coli* and *Shigella flaxneri*). Antibacterial activity was detected by measuring values of ZOI and MIC (Table 2). AgNPs had significant antibacterial effect against *Esherichia coli* with ZOI equal to 2.1 cm and MIC equal to 40 µg/mL; yet they exhibited low effect against *Shigella flaxneri* (Sowbarnika et al., 2018).

It was proved that AuNPs had antibacterial action against *Bacillus cereus* (12 mm ZOI) and *Pseudomonas putida* with (8 mm ZOI) (K et al., 2011). It was found that SeNPs synthesized by *S. cerevisiae* possessed significant antibacterial property against both Gram-positive (*S. aureus* and *B. subtilis*) and Gram-negative

Table 2. Antimicrobial potential of various yeast-mediated nanoparticles.

Yeast source of nanoparticles	Type of nanoparticles	Susceptible microorganism	Inhibitory effect (ZOI or MIC)	References
		Bacteria		
Saccharomyces cerevisiae	AgNPs	*Escherichia coli*	2.1 cm/40 µg/mL	(Sowbarnika et al., 2018)
		Shigella flexneri	1.5 cm/220 µg/mL	
		Escherichia coli	> 20.0 µg/mL	(Shu et al., 2020)
Yeast HX-YS	AgNPs	*Escherichia coli* ATCC8099	14.8 cm	(Liu et al., 2021)
		Pseudomonas aeruginosa	21.4 cm	
		Bacillus subtilis ATCC6051	15.3 cm	
		Staphylococcus aureus ATCC6538	14.6 cm	
		Monilia albicans ATCC10231	18.5 cm	
Yeast LPP-12Y	AgNPs	*Escherichia coli* ATCC8099	15.2 cm	
		Pseudomonas aeruginosa	21.8 cm	
		Bacillus subtilis ATCC6051	16.2 cm	
		Staphylococcus aureus ATCC6538	15.0 cm	
		Monilia albicans ATCC10231	17.8 cm	
Candida albicans	AgNPs	*Escherichia coli*	24 mm/8 µg/mL	(Ahmad et al., 2013)
		Staphylococcus aureus	19 mm/32 µg/mL	
	AuNPs	*Escherichia coli*	16 mm/128 µg/mL	(Ahmad et al., 2013)
		Staphylococcus aureus	11 mm/512 µg/mL	
Hansenula anomala	AuNPs	*Bacillus cereus*	12 mm	(K et al., 2011)
		Pseudomonas putida	8 mm	
Saccharomyces cerevisiae	SeNPs	*Escherichia coli*	31.25 µg/mL	(Hariharan et al., 2012)
		Pseudomonas aeruginosa	125 µg/mL	
		Klebsiella pneumonia	250 µg/mL	
		Salmonella typhimurium	62.5 µg/mL	
		Staphylococcus aureus	31.25 µg/mL	
		Bacillus subtilis	250 µg/mL	
		Staphylococcus aureus	250 µg/mL	(Goud et al., 2016)
		Fungi		
Saccharomyces cerevisiae	AgNPs	Fluconazole-susceptible *Candida albicans*	2–4 µg/mL	(Niknejad et al., 2015)
		Fluconazole-resistant *Candida albicans*	2–4 µg/mL	
		Cryptococcus gastricus	1.8 cm/120 µg/mL	(Sowbarnika et al., 2018)
		Fusarium oxysporum	1.0 cm/140 µg/mL	
		Trichophyton rubrum	0.8 cm/180 µg/mL	
Nematospora coryli	SeNPs	*Candida albicans*	80 µg/mL	(Rasouli, 2019)
Saccharomyces cerevisiae	SeSNPs	*Candida albicans*	1.25 µg/mL	(Asghari-Paskiabi et al., 2019)

Zone of inhibition: ZOI, minimum inhibitory concentration: MIC.

bacteria (*P. aeruginosa*, *E. coli*, *Salmonella typhimurium*, and *Klebsiella pneumonia*) that cause nosocomial infection. The highest values of ZOI were shown against *S. aureus*, *P. aeruginosa*, *E. coli*, and *S. typhimurium* (Hariharan et al., 2012). MIC values are mentioned in Table 2. Antibacterial activity of *S. cerevisiae's* fermented broth-synthesized SeNPs against *S. aureus* was also proved by Goud et al. (2016). At 250 µg/mL, SeNPs inhibited the growth of bacteria completely. Peiris et al. (2018) tested the antibacterial activity of *S. cerevisiae* TiO_2NPs in the presence and absence of sunlight against Gram-positive bacteria (*S. aureus* ATCC 25923 and methicillin-resistant *S. aureus* (MRSA)) and Gram-negative bacteria (*Acinetobacter baumannii*, *E. coli* ATCC 25922, and *P. aeruginosa* ATCC 27853). All bacteria were exposed to TiO_2NPs in the presence or absence of light. The percentage of decrease in microbial growth was 77% for *S. aureus*, 97% for MRSA, 58% for *P. aeruginosa*, 46% for *E. coli*, and 50% for *A. baumannii*, after 30 min light exposure. Without exposure to light, the inhibitory percentage decreased and became 20% for *S. aureus*, 25% for MRSA, 30% for *P. aeruginosa*, 26% for *E. coli*, and 23% for *A. baumannii*. This result indicated that TiO_2NPs exhibited higher inhibitory effect against Gram-positive bacteria than Gram-negative bacteria. The presence of light enhanced antibacterial action due to the photocatalytic effect of TiO_2.

Antifungal Activity

S. cerevisiae-mediated AgNPs exhibited the antifungal activity against 10 fluconazole-susceptible *C. albicans* isolates and 10 fluconazole-resistant *C. albicans* isolates. MIC values ranged from 2 to 4 µg/mL against both fluconazole-susceptible and resistant isolates, respectively. It was noticed that there was no significant difference in values of MIC for both tested fluconazole-susceptible and resistant *C. albicans* (Niknejad et al., 2015). The antibacterial and antifungal activities of *S. cerevisiae*-derived AgNPs against three fungal species (*Trichophyton rubrum*, *Cryptococcus gastricus*, and *Fusarium oxysporum*) were investigated. Antifungal activity was determined by measuring values of ZOI and MIC (Table 2). AgNPs exhibited a low effect against tested fungi (Sowbarnika et al., 2018).

Different concentrations of *Nematospora coryli*-mediated SeNPs (40, 60, and 80 ppm) were tested against a clinical isolate of *C. albicans*. The results revealed that SeNPs exhibited anticandidal activity with MIC value of 80 ppm. Antifungal activity is affected by nanoparticles' size and shape; therefore, small-sized SeNPs can highly inhibit the growth of *C. albicans* (Rasouli, 2019). Asghari-Paskiabi et al. (2019) proved that *S. cerevisiae*-mediated SeSNPs at noncytotoxic concentrations had antifungal activity against several fungal species. SeSNPs were tested against *Candida albicans* (ATCC 10231), *Candida glabrata* (ATCC 90030), *Candida krusei* (PTCC 5295), *Fusarium oxysporum* (PFCC 38e115), *Alternaria alternata* (PFCC 116), *Aspergillus flavus* (PTCC 5004), *Aspergillus fumigatus* (Af239), *Trichophyton rubrum* (PFCC 1762), and *Microsporum canis* (PTCC 5069). Peiris et al. (2018) tested the antifungal activity of *S. cerevisiae* TiO_2NPs in the presence and absence of sunlight against *C. albicans* ATCC 10231.

The fungal strain was exposed to TiO_2NPs in the presence or absence of light. The percentage of decrease in *C. albicans* growth was 95%, after 30 min light exposure. Without exposure to light, the inhibitory percentage decreased and became 74%. This result indicated the strong antifungal activity of TiO_2NPs against *C. albicans* in the presence and absence of light. The presence of light enhanced antifungal action due to the photocatalytic effect of TiO_2.

Antimicrobial Mechanism of NPs

There is no clear antimicrobial mechanism reported. Only few studies explained proposed mechanisms to understand the antimicrobial activity of NPs. In this regard, there are multiple antibacterial mechanisms by which NPs lead to cell death. This can be summarized in the following points, formation of holes in bacterial cell wall, increase in membrane permeability, formation of reactive species, inhibition of respiration, denaturation and dysfunction of cell proteins, and inhibition of DNA duplication (Ahmad et al., 2013; Shu et al., 2020; Liu et al., 2021). AgNPs interact with bacterial cell wall forming holes. Then they accumulate in cell membrane and bind with peptidoglycan increasing its permeability leading to death (Shu et al., 2020; Liu et al., 2021). AuNPs can bind with thiol groups found in enzymes required for respiration process such as NADH dehydrogenases resulting in blocking of the respiration chain and release of ROS causing oxidative stress, and finally, cell damage and death happens (Feng et al., 2000; Ahmad et al., 2013). Respiration inhibition may happen because of binding of AgNPs and oxygen with sulfhydryl (SH) groups present on the cell wall and

finally leads to cell death (Ahmad et al., 2013). Cells contain many proteins and enzymes in cell wall or cytoplasm and have an important role in cell function. Binding of those proteins with NPs causes denaturation of proteins, therefore loss of their function and cell death. Meanwhile, AuNPs have the potential to bind with sulfur- or phosphorus-containing compounds such as sulfur-containing proteins and phosphorus-containing DNA molecules. Subsequently AuNPs cause damage in protein and DNA that leads to cell damage (K et al., 2011; Ahmad et al., 2013). Many factors can influence the antimicrobial activity of nanoparticles including size, shape, surface area, dispersity, and biocompatibility of NPs (Niknejad et al., 2015; Shu et al., 2020; Liu et al., 2021). Small and large surface area of NPs enhance their interaction with membrane of bacterial cell.

CONCLUSION

Yeast is considered as a rich source of many bioactive compounds and a safe source for green biosynthesis of many nanoparticles as well. Various species and strains of yeast could be used in biosynthesis of metal and metal oxide nanoparticles. *Saccharomyces cerevisiae* is the species frequently used and the most valuable candidate involved in biosynthesis of NPs as it rapidly grows and is used simply. Yeast cells have unique features as they can remain viable in the presence of toxic metal ions and form nanoparticles by production of reducing enzymes in a nontoxic matter. The metallothioneins, phytochelatins, and glutathione (GSH) are involved in a detoxification mechanism for yeast cells. The produced nanoparticles have many biomedical applications including antimicrobial, anticancer, antioxidant, and anti-inflammatory. Types of yeast-mediated NPs are still limited; so many different NPs need to be synthesized using yeasts. Yeast-mediated NPs and their biomedical applications are considered as promising tools for many scientific discoveries and developments in many fields.

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