Chapter 11
Applications of Fungal Nanobiotechnology in Drug Development

Kanti Bhooshan Pandey and Brahm Kumar Tiwari

Abstract Nanotechnology is gradually being incorporated into drug industry sector. This technology is used to overcome the problem of drug delivery through existing approaches; however the cost factors and implementation issues have restricted this field and increased the need for basic as well technological innovations. There is an increasing interest in the use of fungi in these processes since they have potential to generate eco-friendly and relatively rapid and clean metallic nanoparticles. Fungal nanobiotechnology (FNBT) has resulted in development of nanodrugs and novel diagnostic/analytical tools for therapy and prevention of many chronic diseases such as cancer, HIV infections, and kidney diseases. In present chapter applications of FNBT in targeted drug delivery, bio-sensing, and development of drugs with enhanced efficiency and efficacy having lesser side effects have been discussed.

Keywords Nanobiotechnology · Nanoparticles · Drug delivery · Anticancer · Antibacterial · Antifungal · Biosensor

11.1 Introduction

The term coined by Prof. Norio Taniguchi "nanotechnology" in 1974 to illustrate the synthesis of materials at the nanometer level has now become one of the most fascinating technologies to design the products with several folds smaller but many folds higher effects (Taniguchi 1974). In recent years, almost all the areas connected directly or indirectly to the humans from food to environment have reflected positive influence of this innovative technology (Prasad et al. 2014; Mi et al. 2016; Eleftheriadou et al. 2016; Formoso et al. 2016; Scheinberg et al. 2017). To put the nanoscale into context of human biology, a typical hair is 80,000 nm wide,

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R. Prasad et al. (eds.), *Fungal Nanobionics: Principles and Applications*,
https://doi.org/10.1007/978-981-10-8666-3_11

erythrocyte (red blood cell) 7000 nm, and key of life DNA is 2.5 nm wide (Alghuthaymi et al. 2015). Various nanoparticles are being successfully utilized as catalysts, biosensors, and semiconductors; however metal nanoparticles like gold (Au), silver (Ag), titanium (Ti), iron (Fe), etc. have gained much attention in recent years due to their fundamental and technological interests in biomedical applications especially in nanodrug/medicine development (Formoso et al. 2016; Rudramurthy et al. 2016; Prasad et al. 2017). Using nanoscale structures for biomedical applications is preferred due to increase in functional surface area to optimize the operational abilities with comparatively reduced size. In addition to this desired stability, resistance and support mobility are other important characteristics which make nanoparticles an ideal candidate for health preventive measures (Prasad et al. 2014; Saglam et al. 2016).

Nanobiotechnology is a new branch of nanotechnology, combining biology with physical and chemical means to generate nanoscale particles with specific functions and structures. The correlation of nanomedicine and public health has accelerated each other in number of ways. Nanodrug identifies cells/receptors of the concern disease, reaches to the target, and releases the medicine in sustainable way (Panchangam and Dutta 2015). This innovative way is used to overcome the problem of drug delivery through existing approaches; however the cost effectivity and implementation issues have restricted this field and have increased the need for basic as well as technological innovations. The conventional methods including chemical and physical techniques employed for synthesis of nanoparticles are much costly. Besides this, application of hazardous and poisonous chemicals in these techniques causes biological mischief (Boroumand Moghaddam et al. 2015). All these serious concerns raise the need to develop environment-friendly procedure or green synthesis of nanoparticles using biological means. Implementation of microorganisms such as bacteria, fungi, etc. with nanotechnology is the latest trend to synthesize nanoparticles with least hazard (Pantidos and Horsfall 2014; Boroumand Moghaddam et al. 2015; Prasad et al. 2016).

Among many microorganisms available for green synthesis, use of fungi in nanotechnology is considered as important due to their toleration and metal bioaccumulation capability (Sastry et al. 2003). Besides this, easiness in their scale-up, economic liability, and facility of employing biomass are other merits for utilization of green approach mediated by fungi to biosynthesize nanoparticles. Many species of fungi grow fast, and therefore their culture in laboratory is very simple (Castro-Longoria et al. 2011; Prasad 2016, 2017; Prasad et al. 2016).

Fungi are frequently used source of industrial enzymes due to their good capacity of protein production extracellularly. These fungi-derived industrial useful enzymes are mainly utilized in chemical and biomedical products, food, drinks, detergents, and baking (Saglam et al. 2016). The integration of nanotechnology with fungi to biosynthesize nanomaterials is known as fungal nanobiotechnology (FNBT) which has resulted in development of novel diagnostic and analytical tools and nanodrugs for therapy and prevention of many chronic diseases such as cancer, kidney diseases, multiple sclerosis, microbial infections, and chronic pain (Fig. 11.1) (Nithya and Ragunathan 2014; Gupta et al. 2012; Panchangam and Dutta 2015).

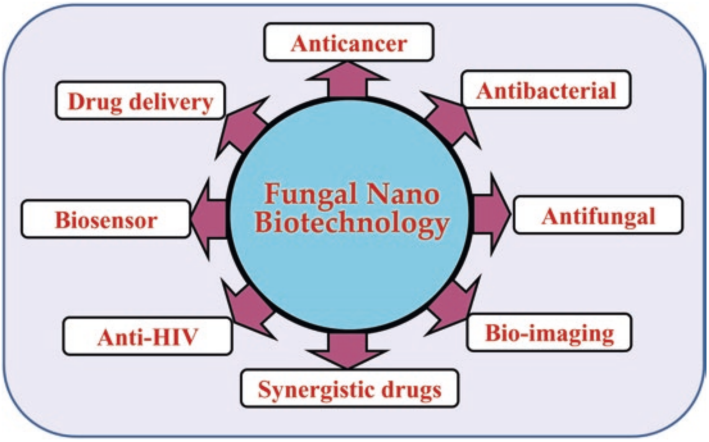

Fig. 11.1 Use of fungal nanobiotechnology in therapeutic applications

The successful and promising studies in these areas have provided a better understanding of fungi in nanobiotechnological applications (Prasad 2016, 2017). The present chapter deals with applications of FNBT in precise drug delivery and development of targeted drugs with enhanced efficiency and efficacy.

11.2 Advantages of FNBT and Applications in Drug Delivery

There is wide-spectrum application of FNBT in pharmaceutics to promote human health including development of analytical tools, nano-imaging, flourishing of nano-devices, improved drug delivery systems, and regulation of many toxicological issues (Bouwmeester et al. 2009; Castro-Longoria et al. 2011; Nithya and Ragunathan 2014). In the area of drug development especially drug delivery and therapy applications, FNBT has a great impact. Different types of metallic nanoparticles of dynamic medicinal effects can be biosynthesized by using many fungal species (Table 11.1). Silver nanoparticles (AgNPs) are one of the most studied metal nanomaterials; its wide-spectrum usage in health-protecting applications including against cancer and infections makes them very preferable and attainable particularly in biomedical field (Saglam et al. 2016). Nano-therapeutics obtained through FNBT is able to provide targeted drug delivery, improved drug solubility, extended drug half-life, and improved drug therapeutic drug index. Another most important property of these developed drugs is their reduced immunogenicity which has resulted in the potential to positively transform the treatment of many life-threating human diseases including cancer (Aliosmanoglu and Basaran 2012; Smith and Lodder 2013; Toffoli and Rizzolio 2013).

The unique properties of nanomaterials regardless of their sizes have been utilized in a wide range of applications. To synthesize metallic nanoparticles, the living

Table 11.1 List of major fungal species utilized in biosynthesis of therapeutically important metallic nanoparticles

Name of the fungus	Nanoparticles	Size (nm)	Medicinal activity	References
Alternaria alternata	Silver	20–60	Antifungal	Gajbhiye et al. (2009)
Alternaria clavatus	Silver	10–25	Antibacterial	Verma et al. (2010)
Aspergillus flavus	Titanium	62–74	Antimicrobial	Rajakumar et al. (2012)
Aspergillus fumigatus	Silver	15–45	Anti-HIV	Alani et al. (2012)
Alternaria niger	Silver	15–20	Antifungal, antibacterial	Kumar et al. (2008a) and Fateixa et al. (2009)
Alternaria terreus	Silver	1–20	Antifungal	Li et al. (2012)
Candida albicans	Gold	60–80	Anti-liver cancer	Chuhan et al. (2011)
Fusarium acuminatum	Silver	5–40	Antibacterial	Ingle et al. (2008)
Fusarium oxysporum	Silver	20–50	Antibacterial	Khosravi and Shojaosadati (2009)
Fusarium vasinfectum	Silver	3–30	Antibacterial	Joshi et al. (2013)
Ganoderma neojaponicum	Silver	5–8	Anticancer	Gurunathan et al. (2013)
Ganoderma spp.	Gold	20	Biocompatibility	Gurunathan et al. (2014)
Helminthosporium solani	Gold	2–70	Anticancer	Kumar et al. (2000b)
Mucor hiemalis	Silver	5–15	Antimicrobial	Aziz et al. (2016)
Penicillium brevicompactum	Gold	10–50	Anticancer	Mishra et al. (2011)
Penicillium purpurogenum	Silver	5–25	Antibacterial	Nayak et al. (2010)
Phoma glomerata	Silver	60–80	Antibiotics	Birla et al. 2009
Pleurotus cornucopiae var. citrinopileatus	Silver	20–30	Anticandidal	Owaid et al. (2015)
Pleurotus djamor var. roseus	Silver	90–370	Anticancer	Raman et al. (2015)
Pleurotus florida	Silver	15–25	Antibacterial	Bhat et al. (2011)
Pleurotus ostreatus	Silver	100	Antibacterial	Mirunalini et al. (2012)
Pleurotus ostreatus	Silver	4–15	Anticandidal, anticancer	Yehia and Al-Sheikh (2014)
Pleurotus sajorcaju	Silver	5–50	Antibacterial	Nithya and Ragunathan (2009)
Trichoderma viride	Silver	5–40	Antibacterial	Fayaz et al. (2010)
Usnea longissima	Usnic acid	50–200	Antifungal	Shahi and Patra (2003)

extracts of fungi, as extracellular or intracellular reductants, have been utilized by the researchers all over the world (Fig. 11.2). Reducing enzymes and the procedure of biomimeting mineralization are the possible mechanisms of nanoparticle biosynthesis using fungi (Boroumand Moghaddam et al. 2015). There is an array of advantage of nanoparticles obtained by fungal species such as gold nanoparticles (AuNPs).

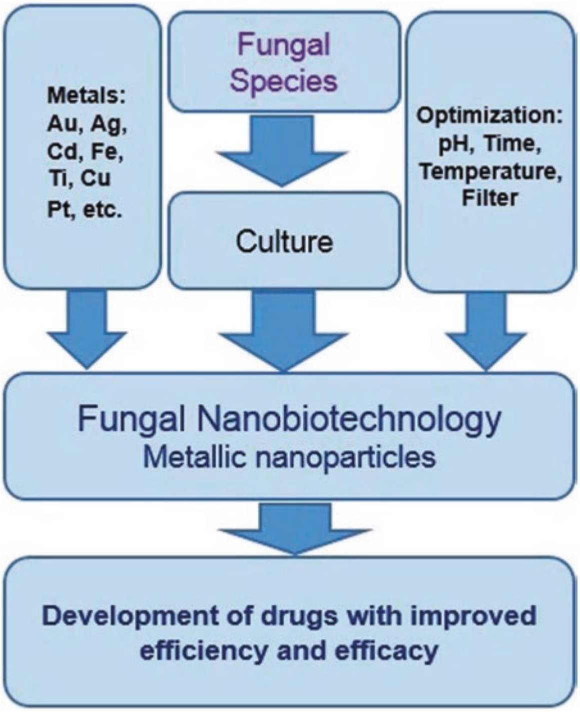

Fig. 11.2 Diagrammatic representation of fungal nanobiotechnology in drug development

AuNPs biosynthesized by utilizing fungi are less invasive and more contrast with nil photo bleaching, and the designed nano capsules help in efficient drug accumulation at the targeted site with sustained drug release even for a week (Ahmad et al. 2003; Duran et al. 2005).

Delivery of drugs at the targeted place in proper time and amount is a matter of major concern in designing of an effective drug. Many times it has been observed that the synthesized drug is capable enough against a particular disease; however its quick release and/or diminished dose makes them ineffective. Keeping this rationale in mind, achieving a controlled and targeted release of drugs via nano-carriers is attaining a highest impact (Boroumand Moghaddam et al. 2015). The metallic nanoparticles synthesized through FNBT are found to be very appropriate nano-conveyors since they fulfill the prerequisites of an ideal ligand such as passing the blood tissue obstacles and special endocytotic and transcytotic transfer mechanisms across cellular obstacles to reach targeted cells (Hafeli et al. 2009; Fadeel and Garcia-Bennett 2010). AgNPs obtained by utilizing *Aspergillus* and *Fusarium* species are able to pass through blood-brain barrier as most important epithelial joints of the skins due to their nano size. Their precise size also helps in restricting their expose area therefore reducing chances of poisoning. Likewise AuNPs obtained through biological technology by using *Penicillium* species may be another very proper nano-carrier in drug delivery due to their steadiness and tenability role (Giljohann et al. 2010). It has been predicted that nanoparticle-interceded targeted delivery of many drugs especially in cancer therapy may result in improved efficiency and squad toxicities (Alghuthaymi et al. 2015; Boroumand Moghaddam et al. 2015). There are several advantages of fungal nanobiotechnology in drug development: inexpensive and wide spectrum, fewer side effects, easy biomass handling, both extracellular and intracellular biosynthesis of nanoparticles, good metal accumulation, sustainable and environment friendly, high wall-binding capacity, and feasible larger-scale production (Prasad 2016, 2017).

11.3 Applications of FNBT in Effective Drug Development

11.3.1 Anticancer

Development of effective and less toxic drugs with targeted action is the major area where FNBT has shown its significant utilization. Cytotoxicity is vital issue behind the chemosynthetic drugs available in the market for the treatment of various types of cancers. Nanoparticles synthesized by many species of *Penicillium* have shown very effective cure against carcinogenesis. Mishra and colleagues have evaluated the impact of AuNPs biosynthesized by supernatant, live cell filtrate and biomass of *Penicillium brevicompactum* on cancer cells and reported a significant inhibition of cell proliferation via induction of cell death (apoptosis); however the mechanism(s) involved behind this is/are under investigation (Mishra et al. 2011; Jeyaraj et al. 2013).

The study performed by Hsin et al. (2008) on NIH3T3 cells proposed that AgNPs may induce apoptosis in these cells through release of cytochrome c into the cytosol and translocation of Bax, a pro-apoptotic protein. The whole mechanism was mitochondria mediated. Mainly work has been done to study the mechanisms of action of titanium oxide nanoparticles (TiO_2NPs) which can be biosynthesized by using many species of *Aspergillus*. The studies done on human monoblastoid cells and bronchial epithelial cells have described that the anticancer effects of TiO_2NPs were mitochondria-mediated apoptosis and oxidative stress-induced cell death, respectively (Vamanu et al. 2008; Park et al. 2008). Zhao et al. (2009) conducted experiment on mouse JB6 cells (epidermal cells) and reported that TiO_2NPs induce death in cancerous cells via caspase-mediated signaling.

Angiogenesis is one of the key mechanisms involved in growth and development of cancer cells. The growth of new blood vessels from existing vessels is necessary to circulate oxygen and nutrients to the cancerous microenvironment (Nishida et al. 2006). It has been reported that anti-angiogenic therapy is the promising approach to control cell proliferation followed by metastasis (Riechelmann and Grothey 2017). AuNPs which can be biologically synthesized by *Helminthosporium* species have emerged as an effective candidate in therapy of various types of cancers including ovarian and as good nano-conveyors for targeted delivery (Ghosh et al. 2008; Tiwari 2012).

AgNPs synthesized by *Achillea biebersteinii* have been reported to possess dose-dependent cytotoxic effects on endothelial cells (Baharara et al. 2014). Will et al. (2011) reported the indirect effect of AgNPs on the microcirculation of developing chorioallantoic membrane of chick embryo, an effect associated with the partial preservation of the capillary diameters (Will et al. 2011). Later studies confirmed that AgNPs inhibit vascular endothelial growth factor (VEGF)-mediated formation of new blood microvessels via suppressing VEGF (Gurunathan et al. 2009; Sheikpranbabu et al. 2009). The studies have also reported that AgNPs synthesized by fungal species may also elicit the anticancer effect by inhibiting the vascular permeability in retinal cells (Sheikpranbabu et al. 2009).

11.3.2 Antibacterial

Bacterial infections are one of the most prevailed reasons behind many diseases in humans. In comparison to the numbers of pathogenic bacterial species, with their abilities to resist toward antibiotics and types of life-threating diseases caused by their infections, the available drugs/therapies against these microorganisms are a few and limited. Metallic nanoparticle-based antibiotics/antiseptics against bacterial infections have gain much emphasis in the last few years (Dastjerdi and Montazer 2010; You et al. 2012; Alghuthaymi et al. 2015; Formoso et al. 2016). AgNPs with a size range 5–40 nm, biosynthesized by using *Trichoderma viride*, have exhibited very effective augmentation in antibacterial activities with a variety of antibiotics against both Gram-positive and Gram-negative types of bacteria (Fayaz et al. 2010). A series of frequently used antibiotics including ampicillin, kanamycin, erythromycin, and chloramphenicol were tested for their efficiency after augmentation with AgNPs and found improved potentials against different strains of bacterial species (Dastjerdi and Montazer 2010; Fayaz et al. 2010; You et al. 2012). The researchers have reported that ampicillin exerted maximum augmentation when combined with AgNPs among all the above tested antibiotics (Fayaz et al. 2010). Duran and colleagues have reported that AgNPs biosynthesized by using *Fusarium oxysporum* can avoid or reduce the chance of infections caused by pathogenic bacteria such as *Staphylococcus aureus*, and moreover they can be integrated into textile fabrics (Duran et al. 2007).

Another study performed on an endophytic fungus, *Penicillium* species which was isolated from the leaves of *Curcuma longa* for biosynthesis of AgNPs, reports the successful application of synthesized nanoparticle as a weapon against *Staphylococcus aureus* and *Escherichia coli* in a facial way (Duran et al. 2007; Singh et al. 2014).

11.3.3 Antifungal

It is quite interesting to describe the development of antifungal drugs by using fungal species. Many studies performed in different laboratories in different environmental conditions have claimed that FNBT can be successfully applied in designing the drugs with enhanced effects against many diseases caused by pathogenic fungi (Gajbhiye et al. 2009; Sardi et al. 2013; Poulose et al. 2014). *Aspergillus niger* is the fungal species which is most studied/described for antifungal properties of biosynthesized nanoparticles by them. A vast study performed by Gajbhiye and coworkers in 2009 on antifungal activities of biosynthesized nanoparticles with combination of fluconazole, a widely referred antifungal drug against a series of fungal species including *Phoma glomerata*, *P. herbarum*, *Fusarium semitectum*, and *Trichoderma*, has documented that AgNPs biosynthesized by utilizing *Alternaria alternata* enriched the antifungal activity of fluconazole in most of the tested fungal strains (Gajbhiye et al. 2009).

Dar and Soytong (2014) proposed the ability of electrospinning technique to encapsulate the antifungal compounds. They also encapsulated the effective antifungal agents from *Chaetomium* species (Dar and Soytong 2014). El-Newehy and coworkers (2012) synthesized the nanofibers of polyvinyl alcohol and polyethylene oxide which were quite effective against many pathogenic fungi including *Penicillium* and *Aspergillus* spp. (El-Newehy et al. 2012). In continuation, another study done by Musarrat et al. (2010) to biosynthesize AgNPs by utilizing mycelia-free water extracts of *Amylomyces rouxii* and testing it against microbial infections reported that the biosynthesized AgNPs showed significant antifungal effects against *Candida albicans* and *Fusarium oxysporum* infections (Musarrat et al. 2010). The AuNPs biosynthesized on the fungus surface, *Rhizopus oryzae*, exhibited very strong inhibition of *Saccharomyces cerevisiae* and *Candida albicans* (Das et al. 2009).

The use of AgNPs as potent antifungal agent is becoming more widespread since technological advances in synthesizing them are being economical day by day. The use of AgNPs biosynthesized by applying FNBT against pathogenic fungi is moderately safer in comparison to synthetic fungicides (Oh et al. 2006). Ag and $AgSiO_2$ nanoparticles synthesized by γ-irradiation, on evaluation of their antibacterial and antifungal efficiencies, showed a strong antifungal effect against *Botrytis cinerea* (Oh et al. 2006). The study conducted by Fateixa and his colleagues (2009) has reported that Ag_2S nano-crystals on amorphous silica particles showed antifungal activity against *Aspergillus niger*. Later studies have also reported that metallic nanoparticles such as ZnO and $ZnTiO_3$ elicit great biocidal effects against *Aspergillus* with different efficiencies (Ruffolo et al. 2010; Jo et al. 2009).

11.3.4 Biosensor and Imagining

The use of biosensors in therapeutic applications is increasing day to day. Nanomaterials biosynthesized by FNBT have been reported as promising tools for development of biosensors with enhanced sensitivity. The optical and electronic properties of nanoparticles make them suitable candidate for their effective utilization in biosensor applications (Gou 2013; Boroumand Moghaddam et al. 2015; Faraz 2018). One of the most significant uses of biosensors is to locate the glucose with accuracy. Zheng et al. (2010) have reported AuNP-based glucose oxidase biosensors on the basis of augmentation of glucose oxidases by gold nanoparticles. Interestingly this AuNP-based biosensor showed a quality response in a range of 20–0.80 mM for glucose with a detection limit of 17 μM. This biosensor may be of important use in determining glucose in various biomedical samples including business glucose injections (Zheng et al. 2010).

In addition to the development of biosensors, the optical features of metallic nanoparticles biosynthesized by fungal species may also be utilized in biomedical techniques. The refractive indicator, photoluminescence, and plasmon resonance features are the characteristics of metallic nanoparticles which are useful in interaction of light of particles (Iskandar 2009; Zhu et al. 2012). AgNPs synthesized by using *Trichoderma viride* emitted photoluminescence in range of 320–520 nm when excited by laser, advocating the suitability of these nanoparticles in imaging techniques (Sarkar et al. 2010; Zhu et al. 2012). The size-based optical features of nanomaterials have been studied by many researchers (Podgaetsky et al. 2004; Sarkar et al. 2010). Studies investigating the cadmium telluride quantum dots (CdTeQDs) fabricated through extracellular synthesis by using yeast and *E. coli* documented that CdTeQD had high solvable ability in water. After spectro-studies it was concluded that CdTe QDs associated with folic acid may be utilized for in vitro imaging of cancer cells. In addition to this, they showed biocompatibility in cytotoxic assays (Bao et al. 2010a, b).

11.3.5 Other Biomedical Applications

Besides mentioned area of medical conditions, there are various fields concerned to human health where FNBT is utilized indirectly for discovery of novel drugs. Many metal nanoparticles biosynthesized by different species of fungi can be used to induce local interaction with tumor cells and thus may help in identification of biomarkers (Gou 2013; De Rosa and Caraglia 2013). Iron nanoparticles are used as one of the most accurate tools for cancer imaging (Toffoli and Rizzolio 2013; De Rosa and Caraglia 2013). Development of nanofiber scaffolds for regenerating central nervous cells, nanospheres as vaccine carriers for nasal vaccination, sequencing of protons and nucleic acids unique to particular pathogenic microorganisms, and detection of various cancers and gene transfections via surface-functionalized nanoparticles are other important areas of medicine where fungal nanobiotechnology is being/may be utilized very successfully (Maite et al. 2000; Rosi and Mirkin 2005; Ellis-Behnke et al. 2006; Gupta et al. 2012; Sardi et al. 2013).

11.4 Conclusion

Development of drugs through nanobiotechnology has raised the expertise and use of various fields of science. Fungal science or mycology has shown an innovative way to develop drugs with enhanced therapeutic index due to its sustained availability, cost-effectiveness, and lowered side effects. Reported success of laboratory as well as community-based studies provides enough reason to believe that in forthcoming years, the benefits of nanodrugs and novel nanodiagnostic tools developed by utilizing fungal nanobiotechnology will provide a considerable impact on human health globally.

Acknowledgment KPB gratefully acknowledges the director of CSIR-CSMCRI, Bhavnagar, for his constant support and encouragement.

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