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Phyto-fabricated Nanoparticles and Their Anti-biofilm Activity: Progress and Current Status

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Biofilm is the self-synthesized, mucus-like extracellular polymeric matrix that acts as a key virulence factor in various pathogenic microorganisms, thereby posing a serious threat to human health. It has been estimated that around 80% of hospital-acquired infections are associated with biofilms which are found to be present on both biotic and abiotic surfaces. Antibiotics, the current mainstream treatment strategy for biofilms are often found to be futile in the eradication of these complex structures, and to date, there is no effective therapeutic strategy established against biofilm infections. In this regard, nanotechnology can provide a potential platform for the alleviation of this problem owing to its unique size-dependent properties. Accordingly, various novel strategies are being developed for the synthesis of different types of nanoparticles. Bio-nanotechnology is a division of nanotechnology which is gaining significant attention due to its ability to synthesize nanoparticles of various compositions and sizes using biotic sources. It utilizes the rich biodiversity of various biological components which are biocompatible for the synthesis of nanoparticles. Additionally, the biogenic nanoparticles are eco-friendly, cost-effective, and relatively less toxic when compared to chemically or physically synthesized alternatives. Biogenic synthesis of nanoparticles is a bottom-top methodology in which the nanoparticles are formed due to the presence of biological components (plant extract and microbial enzymes) which act as stabilizing and reducing agents. These biosynthesized nanoparticles exhibit anti-biofilm activity *via* various mechanisms such as ROS production, inhibiting quorum sensing, inhibiting EPS production, etc. This review will provide an insight into the application of various biogenic sources for nanoparticle synthesis. Furthermore, we have highlighted the potential of phytosynthesized nanoparticles as a promising antibiofilm agent as well as elucidated their antibacterial and antibiofilm mechanism.

Keywords: metal oxide nanoparticles, green synthesis, phyto-synthesis, anti-biofilm activity, biofilm related complications

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INTRODUCTION

The discussion regarding biofilms was first initiated in the 17th century by Antonie Van Leeuwenhoek when he reported the presence of microbial aggregates in the plaque scraped from his teeth (Gebreyohannes et al., 2019). In 1978, Costerton and his fellows coined the term bacterial biofilm and described it as an organized community of microorganisms that remain adhered to a surface and enclosed by an extracellular matrix (Costerton et al., 1978). Numerous bacterial and

fungal species are known to exhibit two modes of development i.e. free-living/planktonic mode and the sessile, surface-adhered mode within biofilms (Oshiro et al., 2019) (Rumbaugh and Sauer, 2020). Biofilm can be defined as "A microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription" (Gebreyohannes et al., 2019). The extracellular polymeric substance (EPS) of biofilm is generally composed of cellulose, proteins, nucleic acids, lipids, extracellular DNA, alginates, poly-N-acetyl glucosamine, polysaccharides, extracellular teichoic acid, and other organic molecules (Costa et al., 2018). EPS has several crucial functions within the biofilm, like developing physical and social interactions, enhancing the rate of gene transfer, and protection from antimicrobials (Flemming et al., 2016). Biofilm is one of the prominent causes of most chronic infections (Lahiri et al., 2021). The microbes present within the biofilm varies from their planktonic equivalents with respect to phenotypic behavior, antimicrobial resistance, and gene regulations. The central role of biofilm is to safeguard the microorganisms present within it from external hostile factors such as temperature, UV, biocides, desiccation, host's immune system, antibiotics, nutrient deficiency, thereby making them resistive to stressful conditions (Yin et al., 2019). Moreover, biofilms form an essential part of the human body, having both constructive and destructive effects on human health depending upon the microbial species and its localization (Macfarlane and Dillon, 2007). Mucosal microflora can exist in both planktonic as well as in sessile forms within biofilms. They play a crucial role in maintaining homeostasis and act as a bacterial reservoir. Various diseases, including inflammatory bowel diseases, are caused by dysregulation or disturbance in the mucosal biofilm of healthy bacteria (IBD) (Xavier and Podolsky, 2007). Further, a microbial biofilm of the gut helps in water retention and prevents any microbial infection (Dunne, 2002) (von Rosenvinge et al., 2013). Moreover, *Lactobacillus* biofilms on vaginal or intestinal epithelia may play an essential role in protecting healthy people from sexually transmitted diseases and intestinal or urinary infections (Watters et al., 2016) (Santos et al., 2016) (Emanuel et al., 2010).

Apart from rendering protection to microbial cells, biofilms can implement various tactics to escape the defense mechanism of the host. Microorganisms within a biofilm can survive in anoxic conditions with limited nutrition due to alteration in metabolism, protein synthesis, and gene expression which lead to reduced metabolic activity and a low rate of cell proliferation (Donlan and Costerton, 2002) (Hall-Stoodley and Stoodley, 2009). Furthermore, these changes make the bacteria more resistant to antimicrobial drugs due to the inactivation of the antimicrobial targets or lowering the cellular function that antimicrobials tend to obstruct. Neither innate nor active immune responses are capable to eradicate the biofilm completely, rather it stimulates the process of the collateral damage of tissue. As a consequence, biofilm facilitates the establishment of chronic infections (Vestby et al., 2020).

According to the reports of the U.S. National Institutes of Health, 80% of all microbial infections within the human body are caused due to biofilms (Khatoon et al., 2018). Microbial biofilms can affect different parts of the body like the respiratory system, reproductive organs, oral cavity, and urinary tract; also, it may develop infections on implanted medical devices (Ramage and Williams, 2013) (Mohammad Reza, 2018). Further, studies have suggested that fungal infections, in particular, caused by the genera *Candida*, *Cryptococcus*, and *Aspergillus* are responsible for more than a million deaths per year (Janbon et al., 2019). With the increased cases of immunocompromised patients and augmented application of medical implants, which forms the potential substrate for biofilm development, people are becoming more susceptible to such infections (Cauda, 2009), (Lebeaux et al., 2014). The bacteria which are commonly associated with biofilm-associated infections include *Pseudomonas fluorescens, Pseudomonas aeruginosa, Vibrio cholera, Escherichia coli* among Gram-negative bacteria. Among Gram-positive, *Staphylococcus aureus, Staphylococcus epidermidis, and enterococci* are the common biofilm producers which are the leading cause of nosocomial infections (Barbosa et al., 2016). Apart from providing resistance against the antibiotic, biofilms play an important role in the pathogenicity of different bacteria. For example, in *P. aeruginosa*, there is upregulation of various virulence factors during biofilm formation (Landini et al., 2010). Apart from the hospital environment, biofilm also affects various other sectors such as water treatment (microbial population of active silt can be destroyed by biofilm), and food manufacturing industries (biofilm formation by spoilage and pathogenic microorganism), and textiles industries (Borzenkov et al., 2020).

Antibiofilm approaches which are currently being applied to combat biofilms are the application of biofilm degrading agents, anti-adhesion compounds, or disruption of biofilm development at initial stages. Typically, infections transmitted *via* medical equipment are cured using traditional antimicrobial agents. These standard antimicrobials are generally susceptible to planktonic cells but often fail to treat sessile counterparts within the biofilm, thereby necessitates surgical elimination of implants (Nadell et al., 2009). Moreover, the application of disinfectants and sanitizers is ineffective against biofilm (Sharahi et al., 2019) (Malhotra et al., 2015). Several approaches, such as maintaining appropriate hygiene and applying antibiotic prophylaxis, are commonly used to manage and prevent biofilm development on medical equipment. Further, incorporation of antimicrobial agents (antiseptics, antibiotics, or metals) on the surface or development of extremely smooth surfaces are some of the techniques to develop biofilm resistive medical equipment (Camargo et al., 2009). Most of them could not fulfill the criteria for long-term application. Also, to prevent biofilm development on catheters, a new approach called the Antimicrobial lock technique (ALT) has been established, in which antibacterial agents are incorporated on the catheter surface profusely. But this technique has certain drawbacks like toxicity and the development of secondary infections which obstruct its effective applications (Banerjee et al., 2020).

Antibiotics are the primary approach to treat a bacterial infection, but due to the rapid increase in bacterial resistance

against antibiotics, the search for new tools has become a hot research topic worldwide. The conventional therapy for treating bacterial biofilm includes the cocktail of different antibiotics which has various killing mechanisms. However, with the increase in resistance against the antibiotic, traditional treatments are collapsing in their efforts to combat biofilm. Likewise, the prime anti-mycotics which are used to treat fungal infections include azoles (e.g., fluconazole), polyenes (e.g., amphotericin B), echinocandins (e.g., caspofungin), allylamines (e.g., terbinafine) (Tits et al., 2020); among these, only liposomal formulations of amphotericin B and echinocandins can be used to treat biofilm-based infections (Kuhn et al., 2002) (Uppuluri et al., 2011). Further, the EPS matrix inhibits the penetration of antibiotics within the biofilm (Pinto et al., 2020). Also, the modifications in the microhabitat within biofilm lead to a change in nutrition supply, development of anoxic conditions, reduced water accessibility, temperature modification. As a result, adaptive stress responses in bacterial cells are enhanced. Consequently, the bacterial cells transform into persisters, which are highly protected spore-like structures, which promotes the emergence of drug resistance (Lahiri et al., 2021).

With the failure of the traditional approach to eliminate biofilm, it is now imperative to explore the possibilities of new drugs and approaches to combat biofilm. The application of nanotechnology in the field of medicine has shown promising results in recent years due to its multidisciplinary approach thereby giving rise to a new arena called "nanomedicine." Lately, The use of various nanoparticles is emerging as a potentially promising alternative to antibiotics for combatting and treating biofilm-producing pathogens, as nanoparticles follow different mechanisms of action to target, against which the bacteria are unable to develop resistance. Nanoparticles impart antibiofilm activity *via* various mechanisms such as generation of ROS, EPS destruction, inhibition of quorum sensing, etc (Baptista et al., 2018). Even though numerous outstanding research has been published in this area, to the best of our knowledge, no comprehensive review of the current developments has been published yet. To this end, this literature reviews the various biogenic approaches employed for the fabrication of nanoparticles. Herein, this review offers an update on the phyto-synthesized nanoparticles and their role in combatting microbial biofilms. This survey might open the way for further progress in this area and we can expect that the application of phyto-synthesized nanomaterials will expand the spectrum of new possibilities for metal oxide nanomaterials and widen the research domains of combating harmful bacteria and biofilms.

DEVELOPMENT OF BIOFILM

The event of biofilm formation is a multistep mechanism involving series of biological, chemical, and physical changes depending upon different external stimuli such as extreme pH, excessive temperature, high pressure, increased salt concentration, desiccation, UV radiation, limited nutrition, and antimicrobial agents (Galié et al., 2018). The formation of biofilm takes place with a reversible adhesion of microbial cells to the substratum, followed by the irreversible attachment, which is facilitated by adhesive components of bacteria and short-range interactions. This process of attachment is progressed further with the secretion of EPS. Subsequently, the bacterial cells develop into a systematized structure enclosed within the EPS matrix. The bacterial cells can leak out from the mature biofilm and get disperse into the environment and colonize new sites. This overall event can be classified into five different phases, viz. *1*) reversible attachment *2*) Irreversible adhesion *3*) microcolonies formation *4*) biofilm maturation, and *5*) dissemination (**Figure 1**; Kirmusaoglu, 2016).

Typically, the reversible attachment is initiated with adherence of microbial cells to the preconditioned substrate in a way that bacteria continue to be in 2D-Brownian motion and can get easily separated from the surface either due to bacterial motion or shearing effects of a fluid flowing over the surface. This initial attachment is aided by various interactions like hydrophobic forces, electrostatic forces, Lifshitz-van der Waals interactions, and microbial cell surface appendages like flagella, fimbriae, pili, and curli-fibers. The second stage is characterized by immobilization and irreversible attachment of microbial cells and thereby monolayer formation of microbial cells due to the involvement of several interactions like hydrophobic interactions, dipole-dipole interactions, hydrogen, covalent and ionic bonding. Subsequently, in the third stage, irreversible adhesion is proceeded by EPSs secretion which forms the vital component of biofilm's extracellular matrix. Further, the development of microcolonies *via* rapid cell proliferation characterizes this phase. EPS plays vital roles in biofilm development, surface attachment, water retention, nutrition entrapment, exchange of genetic material, and protection of microbial cells. As the width of biofilm increases, the fourth stage is reached i.e. maturation which is facilitated by quorum sensing. This stage is characterized by the development of an intricate 3D structure with water-filled channels which circulate nutrients to different cells and remove unwanted waste material. The terminal step of biofilm development is the detachment process or the dispersal process. In this stage, due to the dynamic instability of the biofilm matrix, the microbial cells detach either passively or actively and enter into the surroundings as planktonic cells. These released cells can also propagate to another surface where they may get adsorb and develop new environmental niches. The detachment process is aided by the secretion of numerous saccharolytic enzymes which facilitate the release of microbes from the EPS surface. For example, alginate lyase secreted by *Pseudomonas aeruginosa* and *Pseudomonas fluorescens*, N-acetyl-heparosan lyase secreted by *Escherichia coli,* hyaluronidase secreted by *Streptococcus equi*, causes lysis of EPS and thereby facilitate detachment (Renner and Weibel, 2011) (Ramasamy and Lee, 2016) (Kirmusaoglu, 2016) (Muhammad et al., 2020).

INFECTIONS ASSOCIATED WITH BIOFILM

With the ability to grow on both living and non-living surfaces, biofilm forms one of the primary causes of chronic as well as

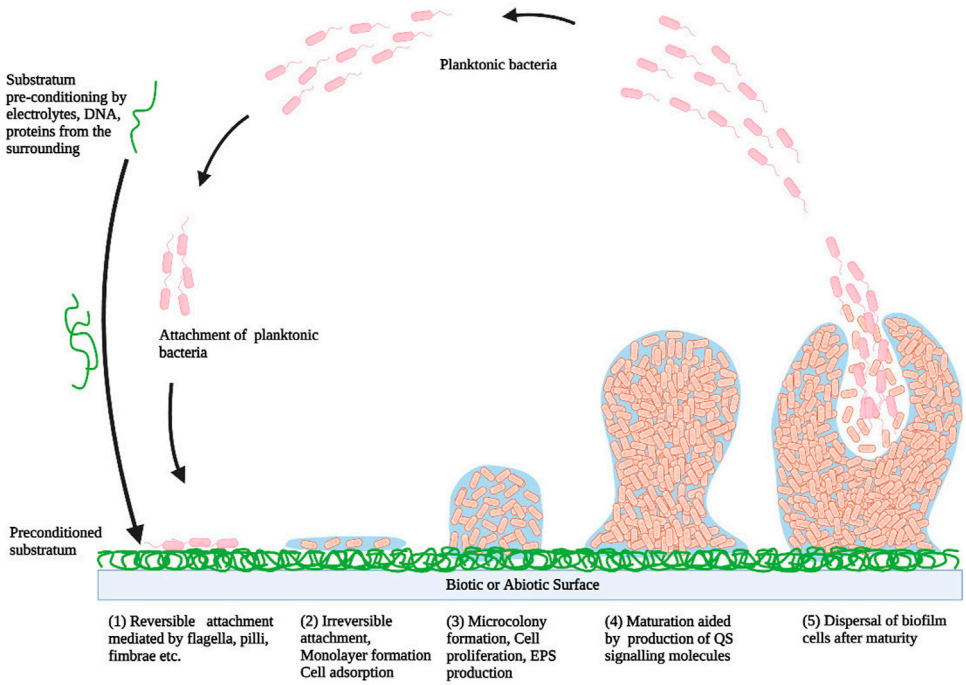

FIGURE 1 | A model showing the typical step-wise development of biofilm (1) Reversible attachment, (2) Irreversible attachment (3) Microcolonies formation (4) Biofilm maturation (5) Dissemination (Kirmusaoglu, 2016).

hospital-acquired infections. These include both, device- and non-device-associated infections (Lewis, 2001).

Device-Associated Infections

Biofilms are generally found to be present on or inside indwelling therapeutic devices like mechanical heart valves, central venous catheters, prosthetic joints, peritoneal dialysis catheters, contact lenses, pacemakers, voice prostheses, and urinary catheters (Donlan, 2001). Its microbial composition depends upon the type and the duration of action of residing devices (Donlan, 2002).

Microbial cells tend to adhere to both soft and hard varieties of contact lenses. The extent of adherence depends on various criteria vis. the nature of substrate, electrolyte concentration, water content, bacterial strain involved, and the material used in contact lenses. The microorganism commonly affecting contact lenses includes *E. coli, Staphyloccocus aureus, Pseudomonas aeruginosa, Staphylococcus epidermidis, Proteus, Serratia, Candida species,* and so forth (Donlan and Costerton, 2002). Prosthetic valve endocarditis is another biofilm-related complication in which biofilms are developed on mechanical heart valves and nearby organs (Mrsic et al., 2018). A wide range of microorganisms which include *Staphylococcus epidermidis, Staphylococcus aureus, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Propionibacterium acnes, Enterococcus, Escherichia coli*, *Candida* species, and yeasts, is known to infect different cardiac implants such as pacemakers, defibrillator, prosthetic valves, coronary artery bypass grafts, which gradually forms denser biofilms *in vivo* as compared to *in vitro* (Viola and Darouiche, 2011). These cardiac devices associated with biofilms lowers the rate of blood flow and promote hematogenous spread thereby infecting and developing biofilms in other organs (Bosio et al., 2012). Urinary catheters which are generally constructed of latex or silicone are utilized to accumulate urine during operation, prevent urine retention, and measure urine generation, in ICU. These catheters are generally administered up to the urinary bladder *via* the urethra. Bacterial contamination due to periurethral skin colonization results in bladder migration of the microbial cells thereby leading to biofilms establishment on these catheters (Kokare et al., 2009). *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, Streptococcus epidermidis, Proteus mirabilis,* and other Gram (−ve) bacteria are among the microorganisms that develop biofilms on these devices (Pelling et al., 2019). Further, these microbes develop an alkaline condition by increasing the pH which facilitates the formations of struvite biofilms inside these catheters (Neethirajan et al., 2014). Moreover, Biofilm formation on central venous catheters is quite frequent, although the location and intensity of biofilm formation are both dependent on the duration of action of these catheters. Patients with bone marrow transplants are at higher risk of biofilm infections as they require long-term vascular catheters. The development of the bacterial community depends on the fluid composition which is being administered through these catheters. For instance, gram-positive bacteria like *Staphylococcus epidermidis* and *Staphylococcus aureus*, show poor development in the intravenous fluids, while gram-negative aquatic bacteria, such

as *Klebsiella* sp., *Enterobacter* sp., and *P. aeruginosa,* can grow well in such liquids (Raad et al., 1993) (Jamal et al., 2018). Many research reports have indicated that biofilm infections have been related to aseptic loosening of joint prostheses. Further, infections in prosthetic joints caused by *Propionibacterium acnes* or *Staphylococcus epidermidis* can lead to serious problems and a high death rate, post joint replacement operation (Del Pozo and Patel, 2009). Moreover, numerous studies have reported that microorganisms like *Staphylococcus aureus*, *Bacillus* species, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas* aeruginosa, etc. are found to contaminate and develop biofilms in endotracheal tubes (Vandecandelaere and Coenye, 2015). Also, different bacteria of breast ducts and tissue lead to biofilm development on breast implants (Pajkos et al., 2003).

Non-Device Associated Infections

Most of the chronic infections are related to biofilms, as microbial cells present within the biofilms are resistive to the host defense system, antibiotics, and other therapies. Some of the non-device-related bacterial infections are periodontitis, osteomyelitis, cystic fibrosis, otitis media, and chronic wounds (Vestby et al., 2020).

Periodontitis is the infection of gums, generally caused due to poor oral health. Injury of soft tissues, damage to the bones supporting the teeth, and occasional tooth loss are the common characteristics of this infection (Guiglia et al., 2010). It is caused by biofilm-forming bacteria such as *P. aerobicus* and *Fusobacterium nucleatum* which colonize the teeth surface followed by mucosal cell invasion (Jamal et al., 2018). They may also alter the calcium flow within epithelial cells as well as release toxins. This may lead to the development of plaque within few weeks which can be mineralized with phosphate and calcium ions, thereby leading to the development of calculus or tartar (Overman, 2000). Also, *Candida albicans* are known to form biofilms on the mucosal layer of the oral cavity. And the synergistic relationship between *C. albicans* and *Streptococcus mutans* within the biofilm of oral plaque facilitates bacterial colonization and thereby promotes the formation of dental caries (Ponde et al., 2021). In addition, Osteomyelitis is the disease of bones caused by fungal or bacterial cells. Bacteria invade the bone *via* blood vessels, injury, or prior infections, thereby causing infection in the bone's metaphysis. This leads to infiltration of WBCs at the site of infection which attacks the invading bacteria *via* phagocytosis or secretion of lytic enzymes thereby resulting in the formation of pus and further spread through bone blood vessels. This leads to blockage of proper blood flow and thereby tissue damage in the infected site of the bone (Goodrich, 2019). Cystic fibrosis is one of the most studied biofilm-associated infections which primarily affects the respiratory and the digestive system and is characterized by the generation of viscous mucus and chronic infections (Ciofu et al., 2015). In earlier stages, the airways are primarily colonized by *Staphylococcus aureus* and *Haemophilus influenzae*, while at later stages *Pseudomonas aeruginosa* dominates (Hector et al., 2016). Large numbers of polymorphonuclear leukocytes (PMNs) are being recruited to the infected site in response to the presence of biofilm, thereby causing persistent inflammation, airway blockage, loss of lung function, and tissue damage. Further, the anaerobic condition developed due to the metabolic activity of bacteria facilitates the biofilm mode of *P. aeruginosa* even more (Rada, 2017). Otitis media (OM) is a condition in which the middle ear chamber gets inflamed, commonly affecting pre-school-aged children (DeAntonio et al., 2016). OM can further be classified into chronic supportive OM (CSOM), OM with effusion (OME), and acute OM (AOM) (Schilder et al., 2017). Generally, biofilm develops in the middle-ear mucosa and middle-ear fluid in case of chronic otitis media (COM) patients. The microbial community consisting of *Escherichia coli*, *Haemophilus influenzae, Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Moraxella catarrhalis* as well as other pathogenic bacteria is responsible for the biofilm formation (Homøe et al., 2009). Any damage to living tissue is generally referred to as wounds which can be caused due to various reasons like burns, abrasions, cuts, and surgery or due to other underlying conditions like diabetes (Fijan et al., 2019). Recent studies have indicated that the biofilm mode of bacterial growth is the prime cause of chronic wound infections. Chronic wounds are generally colonized by several bacterial communities among which *Staphylococcus aureus* is found in majority (Brackman et al., 2013). Aerobic bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* are generally isolated from the surface of chronic wounds whereas anaerobic bacteria such as *Bacteroides* sp., *Clostridium* sp., *Peptostreptococcus* sp., and *Fusobacterium* sp. are generally found in deeper tissue (Percival et al., 2012).

DIFFERENT METHODS OF NANOPARTICLES SYNTHESIS

In the last decade, nanoparticle research activities grew dramatically, with a primary focus on the synthesis of nanoparticles. The synthesis of nanoparticles is important to understand the particulate formation process, fine-tune the physicochemical characteristics of the nanoparticles, and enable specific functionalities and applications (Jeevanandam et al., 2016). For the synthesis of nanoparticles, a variety of physical, chemical, and biological techniques are available. These three methods can further be classified into two categories: *1*) the top-bottom approach and *2*) the bottom-top approach (Yadi et al., 2018) (**Figure 2**).

In top-bottom approaches, the bulk counterpart of the compound is broken down systematically thereby leading to the synthesis of fine nanostructures (Dhand et al., 2015). Although this approach is easier to carry out; it is not appropriate to generate informal shaped and very minute particles (Jamkhande et al., 2019). Some of the typically applied top-bottom methods for bulk production of nanoparticles are electron beam lithography, photolithography, thermal/laser ablation, electro explosion, sputtering, anodization, ion and plasma etching, and milling techniques (Ovais et al., 2017). The most significant drawback of the top-bottom method is surface structure imperfections, which impose significant limitations since a material's surface structure has a crucial

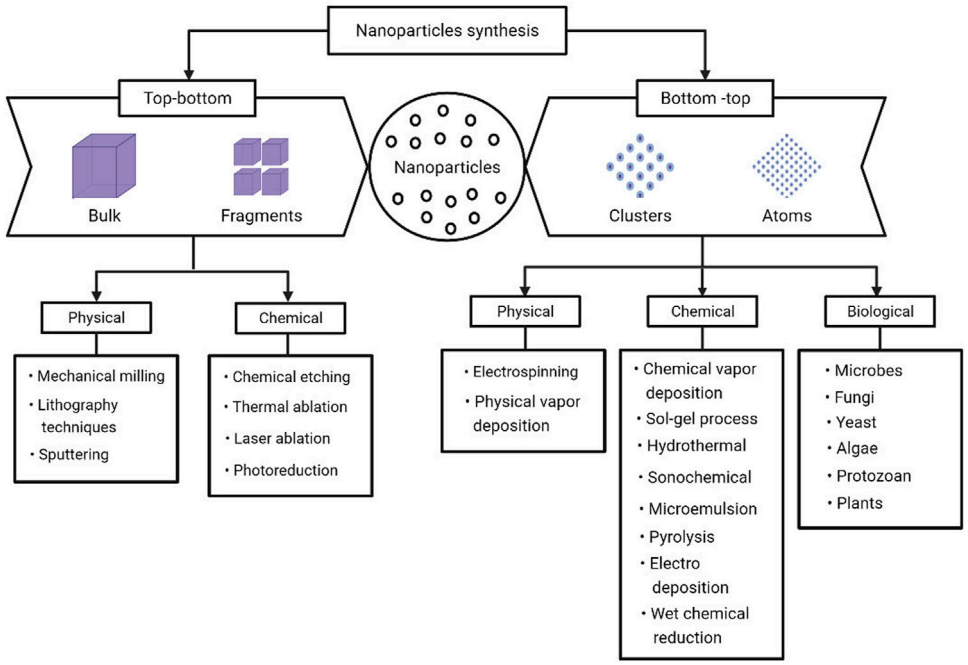

FIGURE 2 | Various approaches available for the synthesis of metal nanoparticles (Patra and Baek, 2014).

role in surface chemistry and the physical characteristics of the material. For example, lithographed nanowires are not necessarily smooth and may have many impurities and structural defects on their surface (Mittal et al., 2013).

The bottom-top approach is an alternative that has the merit to produce less waste and hence is more economical. The synthesis process in bottom-top methods begins with the amalgamation or amassing of atoms and molecules into nuclei, followed by the fabrication of a diverse range of nanoscale particles (Mukherjee et al., 2001). Self-assembly of monomer/polymer molecules, sol-gel processing, chemical vapor deposition (CVD), chemical or electrochemical nanostructural precipitation, laser pyrolysis, plasma or flame spraying synthesis, and biosynthesis are some of the techniques which fall under the bottom-top approach (Daraio and Jin, 2012).

Among the physical, chemical, and biological modes of synthesis, the most effective are the ones that utilize environment-friendly techniques. Even though these nanoparticles have enormous applications in numerous fields, they tend to impart severe toxic effects which nullify the benefits of the material itself. Further, in the field of medicine where sustainability and safety have a vital role to play, the application of green nanotechnology would be more preferred. A green nanotechnology is a multidisciplinary approach that aims to manufacture nanomaterials in an efficient, responsible, and sustainable way thereby holding great potential in biomedicine with special importance on the environment, health, and safety (Kumar et al., 2015). To overcome the issue of toxicity, nanotechnology and green chemistry amalgamate to develop environment-friendly nanoparticles (Lateef et al., 2016). The crucial parameters for the synthesis of nanoparticles are the selection of an eco-friendly solvent, a harmless stabilizing agent, and an effective material for reduction (Jadoun et al., 2021). Biosynthesis is a division of chemistry called "Green Chemistry" which designs and develops chemical components and processes that minimize or exclude the application of hazardous substances (Anastas and Warner, 1998). Biosynthesis fabricates nanoparticles by utilizing the benefits of nature and the environment *via* non-toxic, clean, eco-friendly green chemistry methods which include the use of organisms such as bacteria, plants, fungi (Duan et al., 2015).

Physical Method

Physical methods used for the synthesis of nanoparticles include lithography techniques, mechanical milling, sputtering, electrospinning, physical vapor deposition (PVD), and so on (Khodashenas and Ghorbani, 2014). Although physical techniques are relatively quicker and do not require the use of hazardous chemicals, they have certain major limitations like the requirement of expensive equipment and infrastructure, maintenance of high pressure, and temperature (Thakkar et al., 2010).

Chemical Method

Among chemical methods, the most widely applied methods for nanoparticles synthesis include chemical vapor deposition, sol-gel process, hydrothermal, sonochemical, wet chemical reduction, microemulsion/colloidal, pyrolysis, chemical etching, thermal ablation, laser ablation, photoreduction, and electrodeposition (Nam and Luong, 2019). The composition and the size of the produced nanoparticles depend on the reducing agents

employed, reaction time, temperature, and the length of the surfactant molecule (Simeonidis et al., 2007). The use of inorganic and organic salts as reducing agents is one of the most common methods which is frequently employed due to simple procedures and minimal equipment requirements (Vijayaraghavan and Ashokkumar, 2017). The incorporation of hazardous chemicals in the synthesis, as well as the disposal of these reagents, is a key drawback of chemical techniques (Khodashenas and Ghorbani, 2014).

Biological Method

The biological method employs the use of various biological agents for the synthesis of nanoparticles, such as bacteria, fungus, yeast, virus, protozoan, microalgae, macroalgae, and plant biomass/extract (Shah et al., 2015) (Singh et al., 2016c). Although the biological method takes a longer time to produce nanoparticles compared to chemical and physical methods; the biological synthesis of nanoparticles has the benefits of low toxicity, cost-effectiveness, quick synthesis, ease of scaling up, and simple synthesis procedure (Sharma et al., 2019). One of the prime advantages of plant-mediated biosynthesis is that no hazardous residue products are left on the particles. When people consume them directly, such as through creams or clothing, even minute quantities of hazardous residues can make their safe application unfeasible (Sau and Rogach, 2010) (Fakhari et al., 2019) (Bhattacharya et al., 2019). Also, chemical and physical methods of nanoparticles synthesis are exorbitant due to the fixed price of reagents and apparatus. Moreover, the enormous amount of secondary products produced offers a safe disposal issue (Mirzaei and Darroudi, 2017). Unlike microorganism-assisted nanoparticle synthesis, phyto-synthesis procedures do not involve isolation of microorganisms, identification, optimization of growth conditions, culture preparation, and preservation, which are all complicated and tiresome processes (Patil and Kim, 2017). Rather, plant-assisted green synthesis is quick and straightforward, thereby offers a shorter production time, which indicates potential for scaling-up (Shankar et al., 2004) (Song and Kim, 2009) (Salunke et al., 2014). Due to these advantages, numerous research work has been done to explore the potential of biological materials for the production of metallic nanoparticles. These biologically synthesized nanomaterials have the potential to be applied in various fields like therapeutics, diagnostics, surgical nanodevice development, and commercial product production (Kuppusamy et al., 2015). Among the biological approaches of nanoparticles synthesis, the methods based on plants and microbes have been extensively reported in the literature (Gardea-Torresdey et al., 2003) (Kaler et al., 2011) (Dhillon et al., 2012) (Singh et al., 2016c). Microbial synthesis of nanoparticles is, of course, easily scalable, ecologically friendly, and compatible with the product's usage in medicinal applications, but is often more expensive than nanoparticles synthesis from plant extract (Mittal et al., 2013).

Synthesis of Nanoparticles Using Microorganisms

Although the employment of microorganisms to synthesize nanoparticles is a modern technique; the interaction between metallic ions and microorganisms has been known for years such as the ability of microbial cells to extract and accumulate metals in bioleaching and bioaccumulation procedures (Lombardi and Garcia, 1999). Microorganisms are significant nano factories with enormous potential as they can store and detoxify heavy metals due to a variety of peptides, proteins, organic materials, reducing cofactors, and reductase enzymes that not only convert metallic ions to metal nanoparticles but also provide a natural capping to the synthesized nanoparticles and thereby improving its polydispersity and stability (Singh et al., 2016c). Further, the microorganism-assisted synthesis of nanoparticles is an environment-friendly and cost-effective approach, avoiding the use of harmful, hazardous chemicals as well as the high energy demands of physiochemical synthesis.

Microorganisms can synthesize nanoparticles both intra- and extracellularly *via* various mechanisms (Mandal et al., 2006). The intracellular synthesis of nanoparticles initiates with electrostatic interaction of the positively charged metallic ions with negatively charged cell wall followed by the entry of the metal ion inside the cell *via* a special ion transporter. The ions then undergo enzymatic reduction thereby leading to the formation of nanoparticles, which are then dispersed out through the cell wall (Hulkoti and Taranath, 2014). While the extracellular nanoparticle synthesis involves the accumulation of metallic ions on the cell surface followed by its reduction to nanoparticles in the presence of microbial enzymes. The extracellular synthesis is way more advantageous as compared to intracellular methodologies as it eliminates the downstream processing steps which include multiple centrifugation and washing steps, sonication, and so on which make the intracellular synthesis time-consuming and cumbersome (Zhang et al., 2011).

Bacteria are unicellular living creatures that belong to the prokaryotes family and are found in soil, water, and as symbionts in other species (Lemfack et al., 2020). The following genus includes some of the most significant bacteria investigated for the biosynthesis of nanoparticles: *Bacillus* (Saravanan et al., 2011), *Pseudomonas* (Husseiny et al., 2007), *Klebsiella* (Fesharaki et al., 2010), *Escherichia* (Gurunathan et al., 2009), *Enterobacter* (Karthik and Radha, 2012), *Aeromonas* (Jayaseelan et al., 2013), *Corynebacterium* (Gowramma et al., 2015), *Lactobacillus* (Mohammed et al., 2021), *Weissella* (İspirli et al., 2021), *Rhodobacter* (Bai et al., 2011), *Rhodococcus* (Otari et al., 2012), *Brevibacterium* (Kalishwaralal et al., 2010b), *Bhargavaea* (Singh et al., 2015), *Streptomyces* (Bukhari et al., 2021), *Desulfovibrio* (Gong et al., 2018), *Shewanella* (Kimber et al., 2018), *Rhodopseudomonas* (He et al., 2007), *Pediococcus* (Moodley et al., 2018) and others.

Fungi are easy to culture and pose higher bioaccumulation capability thereby forms an efficient, low-cost with simple downstream processing approach for nanoparticles biosynthesis (Pal et al., 2019). Three probable methods have been proposed to elucidate the mycosynthesis of metal nanostructures i.e. electron shuttle quinones, nitrate reduction action, or both (Gahlawat and Choudhury, 2019). Some of the most important fungi studied for the biosynthesis of nanoparticles belong to the following genera: *Fusarium* (Shafiq et al., 2016), *Aspergillus* (Jain et al., 2011), *Neurospora* (Castro-

Longoria et al., 2011), *Mucor* (Sathishkumar et al., 2015), *Pestalotia* (Raheman et al., 2011), *Hypocrea* (Bhimba et al., 2011), *Trichoderma* (Prameela Devi et al., 2013), *Colletotrichum* (Suryavanshi et al., 2017), *Lecanicillium* (Namasivayam and Chitrakala, 2011), *Rhizopus* (AbdelRahim et al., 2017), and others. Yeast, which belongs to the fungus class *Ascomycetes*, has shown promising potential for the production of nanoparticles. Yeasts, like other microbes, have been extensively studied for large-scale extracellular nanoparticle production with simple downstream processing. *Yarrowia* (Agnihotri et al., 2009), *Rhodosporidium* (Seshadri et al., 2011), *Candida* (Rahimi et al., 2016), *Saccharomyces* (Korbekandi et al., 2016), *Rhodotorula* (Cunha et al., 2018), etc. are the genera that include some of the most studied yeast for nanoparticles biosynthesis.

Further, algae are excellent candidates for nanoparticles production since they can accumulate metals and reduce metal ions. They also offer several benefits, like low-temperature nanoparticles synthesis, ease of handling, and low toxicity (Priyadarshini et al., 2019). Algae can generate nanoparticles from different metal salts by using enzymes and functional groups found in their cell walls; even edible algae can make metallic nanoparticles (H Madkour, 2017). The following genera contain some of the most significant algae investigated for nanoparticle biosyntheses such as *Ulva* (Ishwarya et al., 2018), *Sargassum* (Azizi et al., 2014), *Caulerpa* (Kathiraven et al., 2015), *Spirulina* (Kalabegishvili et al., 2012), *Galaxaura* (Abdel-Raouf et al., 2017), *Sargassum* (Kumar et al., 2012), *Padina* (Bhuyar et al., 2020), *Chlorella* (Arsiya et al., 2017), *Scendesmus* (Aziz et al., 2014), *Chlorococcum* (Jena et al., 2013), *Bifurcaria* (Abboud et al., 2014), *Gracilaria* (de Aragão et al., 2019), *Turbinaria* (Rajeshkumar et al., 2013), and others.

The protozoan-mediated biosynthesis of nanoparticles has been least studied. *Tetrahymena* (Mortimer et al., 2011) and *Leishmania* (Ramezani et al., 2012) are the two genera that have been studied extensively for the biosynthesis of nanoparticles.

Microorganisms mediated synthesis of nanoparticles can occur *via* two methods i.e extracellular or intracellular. In the case of extracellular synthesis, the microbial cells are cultured in a rotating shaker under optimal conditions for 1–2 days, followed by centrifugation for the removal of biomass. The supernatant obtained is then again incubated with a filter-sterilized metal salt solution which leads to the synthesis of nanoparticles which is indicated by a change in color of the reaction mixture. Subsequently, the reaction mixture is centrifuged at high speed, washed thoroughly several times with water or solvent (ethanol/methanol) and the synthesized nanoparticles are collected as a pellet. In the intracellular synthesis, the microbial culture is incubated for an optimum amount of growth period, followed by its centrifugation and washing with sterile water. The microbial mass is again incubated in a water medium along with the filter-sterilized solution of metal salt. Alike extracellular synthesis, the synthesis of nanoparticles is monitored by a change in color of the reaction mixture. Followed by the incubation period, the nanoparticles are obtained by removal of the biomass with the help of repeated ultrasonication, subsequent washing, and centrifugation which promotes cell wall disruption and thereby a collection of the released nanoparticles (Singh et al., 2016c). However, most microorganism-based nanoparticles synthesis is slow and low-productive, and nanoparticle recovery involves tedious downstream processing. Additionally, limitations with microorganism-based nanoparticle production include difficult procedures including microbiological samples isolation, culture, and maintenance.

Synthesis of Nanoparticles Using Plants

Phytonanotechnology, which employs plant-based compounds for the synthesis of nanoparticles, has recently opened up new opportunities in the field of biomedicine, attributed to its superior biocompatibility, scalability, and simple synthesizing method (Noruzi, 2015). Plants can be used either in their live or dead/inactive form for nanoparticle biosynthesis. Different plants are recognized for their ability to collect metals, which are then reduced to nanoparticles within the cell (Kuppusamy et al., 2016). Numerous research work has been done utilizing different parts of plants as a reductant for nanoparticles synthesis such as leaf, stem, fruit, latex, root, flower, seed, and seed coat (Bhati-Kushwaha and Malik, 2013). The reduction of metal ions into nanoparticles is aided by different plant biomolecules that include organic acids, proteins, vitamins, amino acids as well as secondary metabolites like flavones, ketones, alkaloids, terpenoids, phenolics, saponins, aldehydes, tannins, and polysaccharides. As per numerous reports, these plant-derived metabolites can prevent the agglomeration and aggregation of metallic nanoparticles by reducing and stabilizing the reaction in a non-toxic manner (Nath and Banerjee, 2013) (Duan et al., 2015) (Kuppusamy et al., 2016). Numerous studies have shown that polyphenols derived from plants impart a prominent anti-inflammatory response as well as can be used as potential immunonutrient supplements against inflammatory and autoimmune diseases (Campbell et al., 2019). Carbonyl, methoxide, amino, and hydroxyl are some of the prime functional groups which reduce the metal ions into metallic NPs *via* electrostatic interaction (Küünal et al., 2018). Phytosynthesised nanoparticles are diverse in shapes and sizes due to variation in concentration and composition of these bioactive molecules among different plants and their consequent interaction with an aqueous solution of metal ions (Li et al., 2011). Plants have several benefits over other biological systems in terms of nanoparticles synthesis: they facilitate large-scale nanoparticles production, no requirement of culture maintenance, provide natural capping agents, have a wider array of secondary metabolites, safe to handle, are cheap, and readily accessible (Küünal et al., 2018). The actual mechanism and components that cause plant-mediated synthesized nanoparticles are still unknown (Drummer et al., 2021). Popular plant genera studied extensively for the biosynthesis of nanoparticles are *Euphorbia* (Elumalai et al., 2010), *Ginkgo* (Elumalai et al., 2010), *Panax* (Singh et al., 2016b), *Cymbopogon* (Ajayi and Afolayan, 2017), *Azadirachta* (Ahmed et al., 2016), *Nigella* (Amooaghaie et al., 2015), *Cocos* (Roopan et al., 2013), *Catharanthus* (Ahmad et al., 2020), *Pistacia* (Sadeghi et al., 2015), *Nyctanthes* (Sundrarajan and Gowri, 2011), *Anogeissus* (Kora

et al., 2012), *Abutilon* (Mata et al., 2015), *Pinus* (Iravani and Zolfaghari, 2013), *Artocarpus* (Manik et al., 2020), *Citrus* (Sujitha and Kannan, 2013), *Lawsonia* (Naseem and Farrukh, 2015), *Gardenia* (Karade et al., 2019), *Allium* (Velsankar et al., 2020), *Averrhoa* (Isaac et al., 2013), *Sinapis* (Khatami et al., 2015), *Cucurbita* (Hu et al., 2019), *Santalum* (Swamy and Prasad, 2015), *Carissa* (Joshi et al., 2018), *Avena* (Amini et al., 2017), *Piper* (Paulkumar et al., 2014), *Onosma* (Doğan Çalhan and Gündoğan, 2020), and others.

Briefly, phytosynthesis of nanoparticles is initiated by the addition of plant extracts (root, leaf, flower, or seed) to metal salt solutions in specific ratios. To obtain plant extract, the plant part is properly washed using distilled water to make sure there is no dust or other contaminants, it is then followed by drying and cutting them into small pieces. Subsequently, the pieces are converted into a fine paste using a mixer blender. The paste is diluted using Milli-Q water and heated/boiled for a specific period. Alternatively, the same procedure can be followed using plant extract obtained from dried powdered plant parts. The plant extract is then centrifuged and filtered using filter paper to obtain pure supernatant which is then stored in a refrigerator for further experimental use. Various ratios and concentrations of metal salt solution, the plant extract is used for developing nanoparticles. The reaction mixture is incubated for a longer duration of time and the synthesis of nanoparticles is indicated by the color change of the reaction mixture. Following incubation, the reaction mixture is centrifuged, washed, and collected for further characterization (Singh et al., 2016c) (Dwivedy et al., 2018).

The overall bioreduction process of nanoparticles synthesis utilizing plant extract can be categorized into three stages. The process starts with the activation step characterized by nucleation and reduction of the metal ions. This is followed by the growth phase which involves the coalescence of very tiny particles to form large size nanoparticles with enhanced thermodynamic stability. With the progression of the growth phase, nanoparticles accumulate to form a diverse range of morphologies like spheres, cubes, hexagons, triangles, pentagons, wires, rods, and so on. Finally, in the termination phase, the plant extract stabilizes the nanoparticles and determines its most thermodynamically favorable morphology (Akhtar et al., 2013) (Makarov et al., 2014). The characteristics like quality, morphology, size of the fabricated nanoparticles depend on various parameters like concentration of plant extract, reaction mixture pH, reaction time, metal salt concentration, and temperature (Dwivedi and Gopal, 2010) (Mittal et al., 2013).

PLANT SYNTHESIZED NANOPARTICLES AGAINST BIOFILMS

Different plants and their parts have been exploited for the phytogenic synthesis of various metal/metal oxide nanoparticles. These phytofabricated nanoparticles have shown excellent antibacterial properties which have paved the way for future research work assessing its antibiofilm properties. Regarding this, various phytosynthesized nanoparticles (Ag, Au, ZnO, CeO_2, Fe_2O_3, TiO_2, CuO, Pd, Se, NiO) have been evaluated for their antibiofilm potential which is discussed below (**Table 1**). **Table 2** represents the list of microbially synthesized nanoparticles exhibiting anti-biofilm activity for comparative analysis.

Silver Nanoparticles

Silver nanoparticles are the most widely studied nanoparticles for their broad-spectrum antimicrobial properties against a wide variety of pathogens. They are known to impart antibacterial properties *via* several mechanisms such as cell wall and membrane rupture and intracellular biomolecules damage, oxidative stress, etc (Tang and Zheng, 2018). Among various routes employed, plant-mediated synthesis of AgNPs is most preferred due to its several advantages. Numerous research has been carried out using different plants and their parts to study the antibiofilm properties of phytosynthesised AgNPs.

Regarding this, Malaikozhundan et al. have synthesized silver nanoparticles using *Momordica charantia* fruit extracts (Mc-AgNPs) and evaluated their antibiofilm efficacy against *Aeromonas hydrophila* and *Enterococcus faecalis*. Light microscopy and CLSM observations revealed that Mc-AgNPs exhibited significant biofilm inhibitory properties (100 μg/ml) against *E. faecalis* when compared to that of *A. hydrophila*. Further, the application of Mc-AgNPs reduced the hydrophobicity index by 76% and 88% in *A. hydrophila* and *E. faecalis* respectively as compared to untreated bacteria (Malaikozhundan et al., 2016).

A similar study done by Arya et al. indicated that AgNPs prepared using aqueous leaf extract of *Acacia nilotica* inhibited biofilm formation by 70% and 53% in *Pseudomonas aeruginosa* and *Staphylococcus aureus* respectively at a concentration of 0.25 μg (Arya et al., 2018).

Accordingly, Choi et al. screened the antibiofilm and antifungal properties of phytofabricated silver nanoparticles (AgNPs) synthesized using *Lycopersicon esculentum* extracts against *Candida species*. SEM analysis revealed the biofilm inhibitory effect of the fabricated AgNPs. They suggested that binding of Ag ions to cell surface resulted in membrane abnormalities, reduced biofilm development, and inhibited growth (Choi et al., 2019). Further, it has been well-established that quorum sensing plays a pivotal role in the development of biofilm. Several studies have reported inhibition of biofilm development *via* anti-QS agents. Regarding this, Ravindran et al. assessed the potential of *Vetiveria zizanioides* root extract-mediated silver nanoparticles (VzAgNPs) as a promising antibiofilm and anti-QS agent against *S. marcescens*. The results revealed that VzAgNPs inhibited the production of various QS-mediated virulence factors such as protease, swarming motility, lipase, prodigiosin, EPS productions, and biofilm formation in *S. marcescens*, thereby reducing its pathogenicity. Further, the genomic studies supported that VzAgNPs target and remarkably inhibit the expression of genes involved in virulence such as flhD, fimC, and bsbB (Ravindran et al., 2018).

Accordingly, Shah et al. evaluated the anti-QS property of *Piper betle* leaf extract (Pb) mediated AgNPs (Pb-AgNPs)

TABLE 1 | List of phytosynthesized nanoparticles exhibiting antibiofilm activity

Nanoparticles	Plants source	Plant tissue	Size (nm)	Concentration for anti-biofilm activity	Biofilm producing microorganisms	References
Ag NPs	*Momordica charantia*	Fruit extracts	16	100 μg/ml	*Enterococcus faecalis* and *Aeromonas hydrophila*	Malaikozhundan et al. (2016)
Ag NPs	*Mimusops elengi*	Fruit extract	10	0.125 mg/ml	*Escherichia coli*	Korkmaz et al. (2020)
GO-Ag NPs	*Lagerstroemia speciosa*	Floral extract	60–100	24 and 12 μg/ml	*Enterobacter cloacae* and *Streptococcus mutans*	Kulshrestha et al. (2017)
Ag NPs	*Punica granatum*	Fruit fleshy pericarp	5–30	-	*P. aeruginosa*	Govindappa et al. (2021)
Ag NPs	*Rhododendron ponticum*	Leaf extracts	12–19	1.0 mg/ml	Biofilm producing bacteria	Nesrin et al. (2020)
Ag NPs	*Carum copticum*	Seed extract	21.48	10, 20, and 30 μg/ml respectively	*C. violaceum, S. marcescens, and P. aeruginosa*	Qais et al. (2020)
Ag NPs	*Mespilus germanica*	Leaf extract	17.60	6.25–100 μg/ml	*Klebsiella pneumoniae*	Foroohimanjili et al. (2020)
Ag NPs	garlic	Clove extract	10–50	100 μg/ml	*Methicillin-resistant S. aureus* and *P. aeruginosa*	Vijayakumar et al. (2019)
Ag NPs	*Acacia nilotica*	Leaf extract	10–20	0.25 μg/ml	*P. aeruginosa* and *S. aureus*	Arya et al. (2018)
Ag NPs	*Moringa oleifera*	Leaf extract	30	50 μg/ml	*P. aeruginosa* and *S. epidermidis*	Gokul Brindha et al. (2020)
Ag NPs	*Prosopis juliflora*	Leaf extract	10–20	-	*Bacillus subtilis* and *Pseudomonas aeruginosa*	Arya et al. (2019)
Ag NPs	*Psidium guajava*	Leaf extract	60	250 mM	*S. aureus, E. coli* and *C. albicans*	Gupta et al. (2014b)
Ag NPs	*Nigella sativa*	Seed extract	55	12.5 μg/ml	*Enterococcus faecalis, E. coli, Klebsiella pneumoniae, Staphylococcus aureus,* and *Pseudomonas aeruginosa*	Almatroudi et al. (2020)
Ag NPs	*Nardostachys jatamansi*	Rhizome extract	10–15	64 μM	*P. aeruginosa* and *S. aureus*	Muthuraman et al. (2019)
Ag NPs	*Semecarpus anacardium, Glochidion lanceolarium,* and *Bridelia retusa*	Leaf extract	62.72, 93.23, and 74.56 respectively	-	*Pseudomonas aeruginosa, Escherichia coli,* and *Staphylococcus aureus*	Mohanta et al. (2020)
Ag NPs	*Cordia dichotoma*	Fruit extract	2–60	100 μg/ml	*S. aureus* and *E. coli*	Bharathi et al. (2018)
Ag NPs	*Citrus macroptera*	Fruit extract	16	260 nM	*Bacillus subtilis* and *Pseudomonas aeruginosa*	Majumdar et al. (2020)
Ag NPs	*Thymus serpyllum*	Leaf extract	25.2	100 μg/ml	*S. aureus*	Erci and Torlak, (2019)
Ag NPs	*Eucalyptus globulus*	Leaf extract	5–25	30 μg/ml	*S. aureus* and *P. aeruginosa*	Ali et al. (2015)
Ag NPs	*Dodonaea viscosa* and *Hyptis suoveolens*	Leaf extract	40–55	10 μg/ml	*Candida* spp.	Muthamil et al. (2018)
Ag NPs	*Azadirachta indica*	Latex	17.4–40.9	4.12–3.25 μg/ml	*Candida tropicalis*	Al Aboody (2019)
Ag NPs	*Rosmarinus officinalis*	Leaf extract	20	-	*Parachlorella kessleri*	Velgosova et al. (2021)
Ag NPs	*Styrax benzoin*	Gum	18.7 ± 1.2	-	*E. coli*	Du et al. (2016)
Ag NPs	*Acorus calamus L*	Plant extracts	20	350 μg/ml	*Helicobacter pylori*	Prasad et al. (2019)
Ag NPs	*Lycopersicon esculentum*	Fruit extracts	108.5	8 μg/ml	*Candida* species	Choi et al. (2019)
Ag NPs	*Vetiveria zizanioides*	Root extract	20–60	2 μg/ml	*Serratia marcescens*	Ravindran et al. (2018)
Ag NPs	*Piper betle*	Leaf extract	-	-	*Chromobacterium violaceum* and *P. aeruginosa*	Shah et al. (2019)
Ag NPs	*Syzygium cumini*	Leaf extract	10–20	250 μg/ml	*P. aeruginosa, S. aureus,* and *C. albicans*	Gupta et al. (2014a)
Ag NPs	*Piper betle*	Leaf extract	156.4	16 and 32 μg/ml	*S. marcescens* and *P. mirabilis*	Srinivasan et al. (2018)
Ag NPs	*Curcuma longa*	Plant extracts	20–40	-	*S. aureus* and *S. pneumoniae*	Kamble and Shinde (2018)
Ag NPs	*Lilium lancifolium*	Leaf extract	*45*	25–50 μl	*S. pneumoniae* and *P.aeruginosa*	Al-Ansari et al. (2019)
Ag NPs	*Ludwigia octovalvis*	Leaf extract	*28–50*	100 μg/ml	*P. aeruginosa* and *S. epidermidis*	Sarathi Kannan et al. (2021)
Ag NPs	*Holarrhena pubescens*	Bark extracts	13.15	20–25 μg/ml	*P. aeruginosa*	Ali et al. (2018)
Ag NPs	*Artemisia scoparia*	Plant extracts	26.68	12.81–8.45 μg/ml	Methylation-dependent restriction system (MDRS) strain	Moulavi et al. (2019)

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TABLE 1 | (*Continued*) List of phytosynthesized nanoparticles exhibiting antibiofilm activity

Nanoparticles	Plants source	Plant tissue	Size (nm)	Concentration for anti-biofilm activity	Biofilm producing microorganisms	References
Ag NPs	*Zataria multiflora*	Aerial parts	25.5	4 μg/ml	*S. aureus*	Barabadi et al. (2021)
Au NPs	*Tinospora cordifolia*	Stem extract	16.1	150 μg/ml	*Pseudomonas aeruginosa* PAO1	Ali et al. (2020)
Au NPs	*Nigella sativa*	Essential oil	-	-	*Staphylococcus aureus* and *Vibrio harveyi*	Manju et al. (2016)
Au NPs	*Musa paradisiaca*	Peel extract	50	100 μg/ml	*Enterococcus faecalis*	Vijayakumar et al. (2017)
Au NPs	*Capsicum annuum*	Fruit extract	19.97	-	*Pseudomonas aeruginosa* and *Serratia marcescens*	Qais et al. (2021)
Au NPs	*Trachyspermum ammi*	Seed extract	16.63	16 and 32 μg/ml	*S. marcescens* and *L. monocytogenes*	Perveen et al. (2021)
ZnO NPs	*Artemisia*	Leaf extract	17	-	*P. aeruginosa*	Galedari and Teimouri (2020)
ZnO NPs	*Plectranthus amboinicus*	Leaf extract	20–50	8–10 μg/ml	Methicillin-resistant *Staphylococcus aureus*	Vijayakumar et al. (2015)
ZnO NPs	*Veronica multifida*	Leaf extract	10–100	10–50 μg/ml	*P. aeruginosa* and *S. aureus*	Doğan and Kocabaş (2020)
ZnO NPs	*Artemisia haussknechtii*	Leaf extract	50–60	100 μg/ml	*S. epidermidis* and *P. aeruginosa*	Alavi et al. (2019)
ZnO NPs	*Costus igneus*	Leaf extract	26.55	75–100 μg/ml	*S. mutans, L. fusiformis*, *P. vulgaris,* and *V. parahaemolyticus*	Vinotha et al. (2019)
ZnO NPs	*Musa balbisiana*	Pseudostem extract	45–65	100 μg/ml	*P. aeruginosa*	Basumatari et al. (2021)
ZnO NPs	*Eucalyptus globulus*	Essential oil	40	100 μg/ml	*S. aureus* and *P. aeruginosa*	Obeizi et al. (2020)
ZnO NPs	*Withania somnifera*	Leaf extract	15.6	100 μg/ml	*E. faecalis* and *S. aureus*	Malaikozhundan et al. (2020)
ZnO NPs	*Myristica fragrans*	Leaf ester	48.32 ± 2.5	-	MDR-*Escherichia coli* (E. coli-336), Methicillin-resistant *Staphylococcus aureus* (MRSA-1)	Cherian et al. (2019)
ZnO NPs	*Ochradenus baccatus*	Leaf extract	50	-	*Chromobacterium violaceum*, *Escherichia coli*, *P. aeruginosa*, *Klebsiella pneumoniae, Serratia marcescens*, and *Listeria monocytogenes*	Al-Shabib et al. (2018)
ZnO NPs	*Nigella sativa*	Seed extract	24	128–512 μg/ml	*L. monocytogenes*, *E. coli, C. violaceum, and P. aeruginosa PAO1*	Al-Shabib et al. (2016)
CuO NPs	*Cassia fistula* and *Meia azedarach*	Leaf extract	-	1 μg/ml	*K. pneumoniae* and *H. pylori*	Naseer et al. (2021)
Cu NPs	Cochlospermum gossypium	*Gum Kondagogu* extract	15	-	*Klebsiella Pneumoniae*	Suresh et al. (2016)
CuO NPs	*Thymbra spicata*	Leaf extract	26.8	100–200 μg/ml	*S.aureus*	Erci et al. (2020)
CuO NPs	*Cymbopogon citratus*	Leaf extract	14.5 ± 2.0	2000 μg/ml	*E. coli-336* and *MRSA-1*	Cherian et al. (2020)
Cu NPs	*Cardiospermum halicacabum*	Leaf extract	30–40	100 μg/ml	*P. aeruginosa, S. aureus, and E. coli*	Punniyakotti et al. (2020)
CuO NPs	*Eucalyptus globulus*	Leaf extract	16.78–22.5	125–2000 μg/ml	*E. coli-336, P. aeruginosa-621* and *MRSA-1*	Ali et al. (2019)
TiO_2	*Withania somnifera*	Root extract	247	-	*P.aeruginosa, E.coli, Listeria monocytogenes, MRSA, serratia marcescens,* and *Candida albicans*	Al-Shabib et al. (2020)
TiO_2	*Ocimum sanctum*	Leaf extract	90–100	250–650 μg/ml	*P. aeruginosa, E. coli, S. aureus* and *C. albicans*	Dan and Khan (2019)
TiO_2	*Rosa davurica*	Leaf extract	146 ± 3	15.62 μg/ml	*S. aureus, B. cereus, S. enterica,* and *E. coli*	Jin et al. (2021)
TiO_2	*Ochradenus arabicus*	Leaf extract	-	-	*P. aeruginosa*	Zubair et al. (2021)
TiO_2	*Aloe barbadensis*	Leaf extract	20	31.25 μg/ml	*P. aeruginosa*	Rajkumari et al. (2019)
TiO_2	*Ficus benghalensis, Azadirachta indica twigs,* and *Syzygium aromaticum*	Twigs and bud extract	10–33	100 μg/ml	*Citrobacter freundii, Streptococcus mutans* and, *Candida albicans*	Achudhan et al. (2020)
Fe_2O_3 NPs	polyherbal ayurvedic drug formulation, Liv 52	Plant extract	-	-	MRSA, MDR *P. aeruginosa* and *C. albicans*	Ansari and Asiri, (2021)

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TABLE 1 | (*Continued*) List of phytosynthesized nanoparticles exhibiting antibiofilm activity

Nanoparticles	Plants source	Plant tissue	Size (nm)	Concentration for anti-biofilm activity	Biofilm producing microorganisms	References
FeO NPs	*Avicennia marina*	Leaf extract	10–25	200 µg/ml	*Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa*	Ramalingam et al. (2019)
FeO NPs	*Thymbra spicata*	Leaf extract	93.9	100 µg/ml	*S. aureus*	Erci and Cakir-Koc, (2020)
CeO_2-NPs	*Acorus calamus*	Plant extract	22.03	-	Biofilm producing bacteria	Altaf et al. (2021)
Sn-CeO_2NPs	*Pometia pinnata*	Leaf extract	15–20	512 µg/ml	*S. aureus* and *Listeria monocytogenes*	Naidi et al. (2021b)
Zr/Sn-CeO_2 NPs	*Pometia pinnata*	Leaf extract	12–17	512 µg/ml	*S. aureus* and *Listeria monocytogenes*	Naidi et al. (2021a)
Ti-CeO_2	*Phoenix dactylifera*	Fruit extract	7–9	1000 µg/ml	*P. aeruginosa*	Ahmed et al. (2020)
Pd NPs	*Orthosiphon stamineus*	Leaf extract	110	15.25 ± 0.012 µg/ml	Methicillin sensitive *staphylococcus aureus* (MSSA) strain	(N et al., 2021)
Se NPs	*Psidium guajava*	Leaf extract	30–50	25 mg/ml	*Enterococcus faecalis*	Miglani and Tani-Ishii (2021)
NiO NPs	*Eucalyptus globulus*	Leaf extract	10–20	0.1–1.6 mg/ml	ESβL (+) *E. coli* and *P. aeruginosa* and methicillin-sensitive and resistant *S. aureus*	Saleem et al. (2017)

TABLE 2 | List of microbially synthesized nanoparticles exhibiting antibiofilm activity.

Nanoparticles	Microbial source	Size (nm)	Concentration for anti-biofilm activity	Biofilm producing microorganisms	References
Ag NPs	*Lactobacillus fermentum*	6	7.8 mg/L	*P. aeruginosa*	Zhang et al. (2014)
Ag NPs	*Escherichia coli*	33.6	10 mM	*E. coli, S. aureus, P. aeruginosa, K. pneumoniae*	Neihaya and Zaman (2018)
Ag NPs	*Klebsiella oxytoca*	-	-	*S. aureus, P. aeruginosa*	Cusimano et al. (2020)
Ag NPs	*Weissella oryzae*	10–30	5–6 µg/ml	*S. aureus and P. aeruginosa*	Singh et al. (2016a)
Ag NPs	*Sporosarcina forensis*	102	3–6.9 µg/ml	*S. aureus, P. aeruginosa, E. coli*	Singh et al. (2016d)
Ag NPs	*Pseudomonas deceptionensis*	10–30	5 µg/L	*S. aureus and P. aeruginosa*	Jo et al. (2016)
Ag NPs	*Streptomyces sp.*	11	3.9–31.25 lg/ml	*P. aeruginosa*	Bakhtiari-Sardari et al. (2020)
Ag NPs	*Pseudomonas sp.*	10–40	10 µg/ml	*S. aureus, P. aeruginosa*	Singh et al. (2018a)
ZnO NPs	*Pseudomonas putida*	25–45	10 µg/ml	*Pseudomonas otitidis, Pseudomonas oleovorans, Acinetobacter baumannii, Bacillus cereus, and Enterococcus faecalis*	Jayabalan et al. (2019)
ZnO NPs	*E. faecalis*	16–96	2–128 µg/ml	*E. coli, K. pneumoniae, P. aeruginosa*	Ashajyothi et al. (2016)
Selenium NPs	*Bacillus sp*	80–220	0–100 µg/ml	*Staphylococcus aureus, Pseudomonas aeruginosa, and Proteus mirabilis*	Shakibaie et al. (2015)
TiO2 NPs	*Bacillus sp.*	10–30	-	Environmental aquatic strains	Dhandapani et al. (2012)
Cu NPs	*E. faecalis*	12–90	2–128 µg/ml	*E. coli, K. pneumoniae, P. aeruginosa, S. flexneri, S. aureus, E. faecalis*	Ashajyothi et al. (2016)
Au NPs	*Caldicellulosiruptor changbaiensis*	1.03, 2.43, and 20	-	*S. aureus, P. aeruginosa*	Bing et al. (2018)
Au NPs	*Acinetobacter baumannii*	15	0.002 mol/L	*P. aeruginosa, V. cholera, Brevibacterium linens*	Rajput and Bankar (2017)

against *Chromobacterium violaceum* and further studied the potential effect of Pb-AgNPs on QS-regulated phenotypes in PAO1 *Pseudomonas aeruginosa*. The data revealed that the phytofabricated Pb-AgNPs remarkably inhibited the QS-mediated virulence factors such as violacein of *C. violaceum*, elastase, and pyocyanin of *P. aeruginosa*. Moreover, these nanostructures imparted significant antibiofilm activity against *P. aeruginosa*, thereby suggesting their potential role in overcoming bacterial resistance against conventional antibiotics (Shah et al., 2019). In a similar study done by Srinivasan et al., the anti-QS and antibiofilm potential of *Piper betle* leaf extract mediated silver nanoparticles (PbAgNPs) against *S. marcescens*

and *P. mirabilis* was evaluated. The data revealed PbAgNPs mediated inhibition of QS-related virulence factors such as protease, prodigiosin, exopolysaccharides, biofilm formation, and hydrophobicity productions in uropathogens. Further, the genomic analysis reported downregulated expression of flhD, flhB, and rsbA genes in *P. mirabilis* and fimC, fimA, flhD, and bsmB genes in *S. marcescens* respectively (Srinivasan et al., 2018).

Ali et al. have developed biogenic silver nanoparticles (AgNPs) employing aqueous leaf extract of *Eucalyptus globulus* (ELE) and evaluated their antibiofilm and antibacterial potential. After 24 h of treatment, biofilms produced by *S. aureus* and *P. aeruginosa* were shown to be inhibited by 82 ± 3% and 81 ± 5%, respectively, at 30 μg/ml (Ali et al., 2015). In 2018, research was done by Muthamil et al., phyto-synthesized silver nanoparticles (AgNPs), prepared using methanolic leaf extracts of *Dodonaea viscosa* and *Hyptis suoveolens* were assessed for their antibiofilm properties against *Candida spp*. AgNPs obtained from both the extract showed significant biofilm inhibitory properties with about 88% of biofilm reduction at a concentration of 10 μg/ml, as evidenced by microscopic analysis and *in vitro* virulence assays (Muthamil et al., 2018).

Sarathi Kannan et al. demonstrated the potential biofilm inhibitory activity of *Ludwigia octovalvis* leaf extracts derived silver nanoparticles (AgNPs) against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. It was noticed that at 100 μg/ml, AgNPs imparted the highest antibiofilm activity of 62.42 and 50.62% against *S. epidermidis* and *P. aeruginosa* respectively (Sarathi Kannan et al., 2021). Moreover, Ali et al. biofabricated silver nanoparticles using bark extract of medicinal plant *Holarrhena pubescens* (HP-AgNPs) and screened their antibacterial and antibiofilm activity against imipenem-resistant *Pseudomonas aeruginosa* clinical isolates. The HP-AgNPs exhibited antibacterial and antibiofilm activity in a dose-dependent fashion as confirmed by the confocal laser scanning microscopy (Ali et al., 2018).

Also, Vijayakumar et al. prepared silver nanoparticles using garlic clove extract (G-AgNPs) and evaluated its broad-spectrum therapeutic activity including antibiofilm properties. They demonstrated that G-AgNPs (100 μg/ml) imparted significant antibacterial as well as anti-biofilm activity against clinically relevant pathogens like methicillin-resistant *S. aureus* and *Pseudomonas aeruginosa* (Vijayakumar et al., 2019). Arya et al. fabricated bio-inspired AgNPs utilizing aqueous leaf extract of *Prosopis juliflora* and evaluated its biofilm inhibitory properties. The data obtained from congo red agar (CRA) plate assay showed the synthesized AgNPs exhibited significant antibiofilm activity against *Bacillus subtilis* and *Pseudomonas aeruginosa* (Arya et al., 2019).

Moreover, Bharathi and her coworkers reported that silver nanoparticles synthesized using fruit extract of *Cordia dichotoma* (Cd-AgNPs) lead to a significant reduction in *S.aureus* and *E.coli* biofilms by 92 percent and 95 percent, respectively, at100 μg/ml concentration (Bharathi et al., 2018). Also, Majumdar et al. developed silver nanoparticles (CM-AgNPs) using fruit extract of *Citrus macroptera* (CM) and explored their antibiofilm potential. The biosynthesized CMAgNPs efficiently inhibited the development of biofilm in a dose-dependent manner with 70 and 80 percent of biofilm inhibition in *Bacillus subtilis* and *Pseudomonas aeruginosa* respectively, at the highest concentration (260 nM) (Majumdar et al., 2020). Interestingly, Eric and Torlak synthesized Ag nanoparticles (AgNPs) by using the aqueous leaf extract of *Thymus serpyllum*. The antibiofilm data revealed that AgNPs (100 μg/ml) inhibited the biofilm formation by 73% in *S. aureus* (Erci and Torlak, 2019).

Juan et al. synthesized silver nanoparticles by using extract of benzoin gum as bioreductant and capping agent and studied their antibiofilm activity against biofilm-producing *E. coli* strain. At 1, 2, 5, and 10 μg/ml concentrations, treatment for 24 h resulted in a reduction in biofilm development of about 10.9, 44.1, 54.0, and 65.5 percent, respectively thereby indicating that the AgNPs were capable to inhibit the biofilm development in *E. coli* (Du et al., 2016). Further, Prasad and his coworkers reported phytogenic synthesis of silver nano bactericides by utilizing *Acorus calamus L.* extracts. The biofilm inhibitory activity was evaluated against *Helicobacter pylori* clinical isolates. The synthesized NPs exhibited significant antibiofilm activity at concentration 350 μg/ml, as evidenced by crystal violet and ruthenium red assays (Prasad et al., 2019).

Interestingly, Gupta and his coworkers showed silver nanoparticles synthesized using methanolic leaf extract of *Syzygium cumini* have the potential to impede biofilm development of *P. aeruginosa, S. aureus,* and *C. albicans* in a concentration-dependent manner. At 250 μg/ml, AgNPs inhibited more than 90% biofilm formation, while at 125 μg/ml concentration, 85% biofilm inhibition was recorded (Gupta et al., 2014a). Moreover, Al-Ansari et al. reported the antibiofilm and antibacterial activity of *Lilium lancifolium* leaf extract mediated silver nanoparticles against *Streptococcus pneumonia* and *Pseudomonas aeruginosa*. Treatment with 25 μl of AgNPs imparted antibacterial activity while treatment with 50 μl showed significant antibiofilm properties, as evident from crystal violet assay and confocal micrographic images (Al-Ansari et al., 2019).

Interestingly, Barbadi et al. compared the antibiofilm activity of *Zataria multiflora* aerial extract-mediated silver nanoparticles (P-AgNPs) and commercial silver nanoparticles (C-AgNPs) against *Staphylococcus aureus* ATCC 25923 bacteria. The data showed dose-dependent biofilm inhibitory activity, with excellent inhibition at concentration ≥8 μg/ml for both P-AgNPs and C-AgNPs. Further, they showed that plant-derived AgNPs (P-AgNPs) imparted higher biofilm inhibitory properties at lower concentrations as compared to C-AgNPs (Barabadi et al., 2021). Similarly, Moulavi et al. stated that phytofabricated AgNPs using *Artemisia scoparia* as bioreductant imparted relatively more antibiofilm activity as compared to commercial AgNPs against methylation-dependent restriction system (MDRS) strains. The mean MIC value for the commercial and biosynthetic AgNPs was found to be 12.81 and 8.45 μg/ml respectively, on MDRS isolates. Also, the biofabricated AgNPs exhibited superior antibiofilm activity against MDRS *via* unknown mechanisms (Moulavi et al., 2019).

Further, Gupta et al. showed that silver nanoparticles (AgNPs) obtained *via* green synthesis using leaf biomass of *Psidium guajava* have a remarkable ability to inhibit biofilm development of *S. aureus, E. coli,* and *C. albicans* by 96, 90,

and 75% respectively, as evident from crystal violet assay (Gupta et al., 2014b). Recently, Almatroudi et al. assessed the antibiofilm activity of silver nanoparticles (Ns-AgNPs) biosynthesized using seed extract of *Nigella sativa*. They showed that at concentration 12.5 μg/ml, Ns-AgNPs limited the biofilm development by 84.92% for *E. coli,* 88.42% for *Enterococcus faecalis*, 81.86% for *Klebsiella pneumonia*, 82.84% for *Staphylococcus aureus*, and 49.9% for *Pseudomonas aeruginosa*, respectively (Almatroudi et al., 2020).

Interestingly, Kulshrestha et al. developed a bioinspired graphene oxide-silver nanocomposite (GO-Ag) by employing an eco-friendly route using *Lagerstroemia speciosa (L.) Pers* floral extract. It was observed that at concentrations 24 and 12 μg/ml, GO-Ag resulted in 90 and 49% biofilm reduction respectively, in *Enterobacter cloacae.* Similarly, 89 and 34% biofilm declination was observed in *Streptococcus mutans* when exposed to 47 and 24 μg/ml of GO-Ag respectively (Kulshrestha et al., 2017). Accordingly, Korkmaz et al. have synthesized silver nanoparticles (AgNPs) with the help of *Mimusops elengi* liquid fruit extract. According to their results, AgNPs (1250 μg/ml) inhibited 86.36% of the biofilm formation in *Escherichia coli* (Korkmaz et al., 2020).

In a recent study, Nersin et al. evaluated the antibiofilm activity of biosynthesized AgNPs prepared using aqueous leaf extracts of *Rhododendron ponticum*. They found that almost at each concentration AgNPs imparted biofilm inhibitory activity in a dose-dependent manner. The highest concentration of AgNPs which showed maximum antibiofilm activity was 1.0 mg/ml (Nesrin et al., 2020).

Accordingly, biogenic silver nanoparticles (Ag@CC-NPs) were fabricated using aqueous extract of *Carum copticum* seed by Qais et al. The synthesized Ag@CC-NPs imparted biofilm inhibitory activity with 86.3%, 77.6%, and 75.1% biofilm inhibition of *S. marcescens, P. aeruginosa, and C. violaceum* respectively. Further at sub-MIC, Ag@CC-NPs inhibited the production of virulence factors such as pyoverdin, pyocyanin, swimming motility, elastase activity, exoprotease activity, and rhamnolipid in *P. aeruginosa* by 49.0, 76.9, 89.5, 53.3, 71.1, and 60.0% respectively. Moreover, virulence factors of *S. marcescens* viz. swarming motility, exoprotease activity, and prodigiosin production was reduced by 90.7, 67.8, and 78.4% respectively. Further, the SEM and CLSM observations showed a remarkable reduction in biofilm development on glass coverslip (Qais et al., 2020). Further, Foroohimanjili et al. investigated the antibiofilm, antibacterial, and anti quorum sensing properties of phytosynthesized silver nanoparticles (AgNPs) prepared using leaf extract of *Mespilus germanica* against multidrug-resistant *Klebsiella pneumoniae* strains. Their work revealed that at sub-MIC, AgNPs prominently inhibited the establishment of biofilm in all the biofilm-producing strains (Foroohimanjili et al., 2020).

In another study silver nanoparticles, synthesized employing aqueous leaf extracts of *Moringa oleifera Lam* imparted excellent biofilm eradication potential (78%) for *P. aeruginosa* whereas only 43% for *S. epidermidis,* as reported by Gokul Brindha (Gokul Brindha et al., 2020).

Interestingly, Muthuraman et al. employed a green route for the synthesis of silver nanoparticles (AgNPs) using medicinally relevant *Nardostachys jatamansi* rhizome extract. They showed that AgNPs (64 μM) prepared using heated plant extract exhibited superior antibiofilm activity against *P. aeruginosa* and *S. aureus.* Whereas AgNPs prepared using stirred plant extract required a relatively higher dose (500 μM) to impart their anti-biofilm effect (Muthuraman et al., 2019). In another study, Mohanta and colleagues developed biocompatible silver nanoparticles (AgNPs) utilizing foliage extracts of three different plants namely *Glochidion lanceolarium, Semecarpus anacardium,* and *Bridelia retusa*. The phytosynthesized AgNPs were screened for antibacterial and anti-biofilm activity against *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Escherichia coli*; their data indicated promising results (Mohanta et al., 2020).

Further, Govindappa et al. assessed the antibiofilm activity of silver nanoparticles synthesized using fleshy pericarp of *Punica granatum* (Pfp-AgNPs). The Pfp-AgNPs were investigated for the antibiofilm effectiveness against *Pseudomonas aeruginosa*. The outcome revealed that the nanoformulations significantly increased the toxicity level in *P. aeruginosa* in a concentration-dependent fashion and led to potassium leakage, cellular damage, and biofilm inhibitory activity (Govindappa et al., 2021).

Interestingly, Al Aboody et al. synthesized silver nanoparticles (AgNP) using latex of *Azadirachta indica*. They demonstrated the antibiofilm activity of AgNPs against Fluconazole resistant clinical isolate of *Candida tropicalis* and concluded that at concentrations of 4.12 and 3.25 μg/ml, AgNPs inhibited the biofilms of fluconazole-resistant and fluconazole-susceptible *C. tropicalis*, respectively (Al Aboody, 2019). Velgosova et al. evaluated AgNPs and nanocomposites doped with AgNPs against biofilm development. For this, they synthesized AgNPs *via* green route using leaf extract of *Rosmarinus officinalis.* And further, doped Polyvinyl alcohol (PVA) matrix with green synthesized AgNPs to obtain polymer matrix composite (PMC) microfibers. The antibiofilm efficacy was screened against biofilm-producing one-cell green algae *Parachlorella kessleri*. The results revealed that there was no antibiofilm effect of pure PVA matrix whereas AgNPs and PMC (PVA-AgNP composites) microfibers showed significant antibiofilm activity (Velgosova et al., 2021).

Gold Nanoparticles

Gold nanoparticles (AuNPs) are one of the most extensively exploited metal nanoparticles (NPs) paving their way in various fields of science and industry. Due to its various therapeutic properties like antibacterial, anticancer, antimalarial, and antibiofilm, there is a surge in their demand. To fulfill such demands, rigorous research is required to optimize its synthesizing approaches. Among various methods employed for the synthesis of AuNPs, a biogenic approach using plant extract is simple, effective, cheap, and eco-friendly (Ali et al., 2020). In this regard, Ali et al. developed gold nanoparticles utilizing *Tinospora cordifolia* plant stem (Ayurvedic medicinal plant) and assessed its biofilm inhibitory properties against *Pseudomonas aeruginosa* PAO1 biofilm. The SEM and crystal violet assay data revealed that the sub-MIC value of AuNPs significantly reduced the biofilm-producing capability of *P. aeruginosa* in a concentration-dependent manner. Their data

showed that biofilm formation was inhibited up to 59.9, 36.6, 27.1% at 150, 100, and 50 μg/ml concentrations of AuNPs respectively. The CLSM analysis further indicated that the structure of the biofilm in the sub-MIC of AuNPs had abnormalities. Also, treatment of PAO1 with AuNPs at 150 μg/ml displayed internalization of the nanoparticles (Ali et al., 2020). Similarly, Manju et al., showed that gold nanoparticles biosynthesized applying essential oil of *Nigella sativa* (NsEO-AuNPs), efficiently inhibited the biofilm establishment of *Staphylococcus aureus* and *Vibrio harveyi* by reducing the hydrophobicity index (78 and 46% respectively) (Manju et al., 2016).

In another study, Vijayakumar et al. developed AuNPs using *Musa paradisiaca* peel extract (MPPE-AuNPs) and studied its biofilm inhibitory properties in multiple antibiotic-resistant *Enterococcus faecalis*. Confocal light microscopic observations demonstrated that the MPPE-AuNPs meritoriously repressed the biofilm formed by *E. faecalis* at concentration 100 μg/ml (Vijayakumar et al., 2017). Interestingly, Qais et al. biosynthesized gold nanoparticles by employing an aqueous fruit extract of *Capsicum annuum* (AuNPs-CA) and assessed its efficacy against the QS-regulated virulence factors and biofilms of *Serratia marcescens* and *Pseudomonas aeruginosa*. The result showed a significant reduction of QS-mediated virulent traits of *P. aeruginosa* PAO1 such as pyoverdin, elastase activity, exoprotease activity, pyocyanin, swimming motility, and rhamnolipids production by 72.16, 65.72, 81.12, 91.94, 46.09, 46.66%, respectively. Further, microscopic studies showed that the growth and synthesis of exopolysaccharides have been suppressed due to reduced bacterial adhesion and colonization on a solid substrate (Qais et al., 2021).

Accordingly, Perveen and colleagues fabricated biogenic gold nanoparticles by utilizing the seed extract of *Trachyspermum ammi* (TA-AuNPs), followed by assessing its effectiveness against biofilms of *Serratia marcescens* and *Listeria monocytogenes*. It was demonstrated that there was substantial anti-biofilm activity against both *S. marcescens* (81%) and *L. monocytogenes* (73%). Moreover, the key factors of biofilm development and maintenance such as cell surface hydrophobicity, exopolysaccharide, and motility were considerably inhibited at sub-MICs. Also, the NPs efficiently eradicated preformed established biofilms of *L. monocytogenes* and *S. marcescens* by 58 and 64%, respectively (Perveen et al., 2021).

Zinc Oxide Nanoparticles

Among several metallic nanoparticles, zinc oxide nanoparticles have held the attention of several researchers owing to their multifunctional properties and versatility. The antibacterial efficacy of zinc oxide nanoparticles has been well established against both gram-negative and gram-positive bacteria as well as against fungi. It has already been reported that ZnO NPs are nontoxic to human cells while imparting antibacterial properties via several mechanisms like the generation of ROS, the release of metal ions, etc (Gudkov et al., 2021). Further, green synthesized zinc oxide nanoparticles have been known to impart superior properties due to their eco-friendly characteristics. Regarding this several plant-based syntheses of ZnO NPs have been carried and their antibacterial and antibiofilm efficacies have been evaluated.

Interestingly, Vijayakumar et al. biologically developed *Plectranthus amboinicus* mediated zinc oxide nanoparticles (Pam-ZnO NPs). Their data showed that the synthesized nanoparticles exhibited antibiofilm activity at concentrations range 8–10 μg/ml against the biofilms of methicillin-resistant *Staphylococcus aureus*. Further, Confocal laser scanning microscopy analysis suggested that the biofilm-forming ability of *S. aureus* is intensely inhibited by Pam-ZnO NPs (Vijayakumar et al., 2015).

Similarly, in their other study, they reported the QS inhibitory property of zinc oxide nanoparticles synthesized using seed extract of *Nigella sativa* (NS-ZnNPs). Their fabricated nanoparticles inhibited QS-mediated functions of *C. violaceum* and inhibited the production of pyocyanin, alginate, protease, and elastase in *P. aeruginosa* PAO1 evidently. Also, at sub-MICs, NS-ZnNPs prevented the biofilm development as well as eradicated pre-formed biofilms of food-borne bacteria viz. *C. violaceum* 12472, PAO1, *L. monocytogenes*, *E. coli*. Preformed biofilms were eradicated by 66, 78, 68, and 72% in *E. coli, P. aeruginosa, C. violaceum, and*, *L. monocytogenes* respectively as observed by CV assay. Further, CLSM also confirmed the antibiofilm property of NS-ZnNPs (Al-Shabib et al., 2016).

Further, Al-Shabib et al. investigated the protein-binding and antibiofilm activity of zinc oxide nanoparticles synthesized from *Ochradenus baccatus* leaf extract (OB-ZnNPs). The synthesized OB-ZnNPs imparted considerable antibiofilm properties against human and foodborne pathogens (*Listeria monocytogenes Chromobacterium violaceum*, *Serratia marcescens*, *P. aeruginosa*, *Klebsiella pneumoniae,* and *Escherichia coli*) at sub-MICs. Further, the NPs significantly impaired swarming motility and EPS production which aids in biofilm development. Their data showed the highest inhibition of biofilm in *P. aeruginosa* by 84%; in *E. coli* by 67%; in *L. monocytogenes* by 78%; in *K. pneumonia* by 70%; in *S. marcescens* by 80%; and, in *C. violaceum* by 64% (Al-Shabib et al., 2018).

Accordingly, Dogan and Kocabas synthesized zinc oxide (ZnO) nanoparticles (NPs) using foliage extracts of *Veronica multifida* under various physical conditions. The antibiofilm activity of the prepared NPs was evaluated against *S. aureus and P. aeruginosa*. The results revealed that in *S. aureus*, 10 μg/ml of ZnO NPs at pH 7 inhibited 88% of biofilm development, and 50 μg/ml ZnO NPs at pH 12 inhibited 87% of the biofilm development. While in *P. aeruginosa,* at both pH 7 and pH 12, the maximum biofilm inhibitory activity was observed at a concentration of 50 μg/ml (Doğan and Kocabaş, 2020). Further, Alavi et al. demonstrated the antibiofilm efficacy of zinc oxide NPs synthesized using *Artemisia haussknechtii* leaves extract. Their crystal violet (CV) assay analysis revealed a significant reduction in biofilm formation for *S. epidermidis* with 63.43% (0.562 ± 0.015) and *P. aeruginosa* with 62.88% (0.582 ± 0.025) at 100 μg/ml ZnO NPs. Further, Light microscopic observations showed there was a significant reduction of biofilm formation with the increase in ZnO NPs concentration (Alavi et al., 2019).

Interestingly, Vinotha et al. reported a novel fabrication of ZnO nanoparticles by utilizing foliage extract of *Costus igneus* (Ci-ZnO NPs). Their prepared Ci-ZnO NPs displayed encouraging antibiofilm and antibacterial activities against *L. fusiformis, S. mutans*, *V. parahaemolyticus,* and *P. vulgaris* bacteria at concentrations 75 and 100 μg/ml. Further, the light microscopy and CLSM analysis revealed disintegration and reduced growth of biofilm in a concentration-dependent fashion. Also, they suggested that the biofilm inhibitory activity of ZnO NPs was due to the generation of ROS and the action of surface ions released from the nanoparticles (Vinotha et al., 2019).

Similarly, Malaikozhundan et al. synthesized *Withania somnifera* leaf extract-assisted ZnO NPs (Ws-ZnO NPs) and evaluated its antibiofilm efficacy against *S. aureus and E. faecalis.* They showed that at concentration 100 μg/ml, the Ws-ZnO NPs imparted significant biofilm inhibitory activity. Further, Ws-ZnO NP's surface activity resulted in disruption of the bacterial cell wall and biofilm inhibition. Also, excessive generation of ROS leads to enhanced antibacterial properties (Malaikozhundan et al., 2020). Accordingly, Cherian et al. developed bio-inspired zinc oxide nanoparticles (MFLE-ZnONPs) fabricated by using *Myristica fragrans* leaf ester (MFLE) and assessed its antibiofilm activity against methicillin-resistant *Staphylococcus aureus* and multi-drug resistant *Escherichia coli* clinical isolates. It was found that the synthesized nanoparticles showed dose-dependent declination of biofilm development in both the tested bacterial strain (Cherian et al., 2019).

Employing the alcoholic extract of *Artemisia*, Galederi and Teimouri fabricated ZnO-NPs and studied its inhibitory effects on biofilm development by *P. aeruginosa* strains. The outcomes suggested that ZnO-NPs were effective on the isolates at the minimum and maximum viscosities of 3.125 and 100 mg/ml, respectively. (Galedari and Teimouri, 2020).

Moreover, Obeizi et al. reported the antibiofilm efficacy of biogenic zinc oxide nanoparticles prepared by using *Eucalyptus globulus* essential oil. Their results revealed that ZnO NPs effectively inhibited biofilm development in *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 in a dose-dependent manner. The percentage of biofilm inhibition at 100 μg/ml ZnO NPs was observed to be 97 and 85% against *P. aeruginosa* biofilm and *S. aureus*, respectively (Obeizi et al., 2020).

Accordingly, Basumatari et al. fabricated zinc oxide nanoparticles (ZnONPs) by utilizing an aqueous pseudostem extract of *Musa balbisiana* Colla ash (AEPA), a plant biowaste, and evaluated its efficacy as an antibiofilm and antibacterial agent. The AEPA mediated ZnO NPs exhibited note-worthy antibiofilm activity against *P. aeruginosa*, as revealed by 96-microtitre well plate and Congo red agar method. At a dosage of 100 μg/ml, the percent inhibition for *P. aeruginosa* was 95.13%, indicating an enhanced inhibitory impact on bacterial biofilm breakdown (Basumatari et al., 2021).

Copper and Copper Oxide Nanoparticles

The U.S. Environmental Protection Agency (USEPA) has designated elemental copper and its compounds as antibacterial materials. Nanoformulations of Copper oxide exhibit enhanced antimicrobial activity towards pathogenic microorganisms. Further, numerous reports have also discussed the antibiofilm activity of copper oxide nanoparticles (Mahmoodi et al., 2018). Green synthesized CuO nanoparticles have been known to impart superior properties due to their less toxic nature.

Regarding this, Naseer et al. demonstrated the antibiofilm efficacy of biogenic copper oxide nanoparticles (CuO NPs) prepared by utilizing *Melia azedarach* and *Cassia fist*ula leaf extracts. The results revealed that at concentration 1 μg/ml the *M. azadarech* derived NPs the prevented biofilm development of *H. pylori* and *K. pneumoniae* by 99.5 and 92.5% respectively. While, at the same concentration, the *C. fistula*-derived NPs inhibited biofilm inhibition by 100 and 99.8% for *H. pylori* and *K. pneumoniae*, respectively (Naseer et al., 2021). In another report, Suresh et al., synthesized CuNPs applying a two-stage chemical reduction method, where Hydrazine Hydrate (HH) was used as a reducing agent and *Gum kondagogu* extracts were used as a stabilizing agent. The SEM results revealed complete destruction of biofilm with destabilized cell masses in *Klebsiella pneumoniae* clinical isolates (ATCC 27736) treated with *Gum kondagogu* extract mediated CuNPs (Suresh et al., 2016).

Similarly, Punniyakotti et al., prepared copper nanoparticles (Cu NPs) using leaf extracts of *Cardiospermum halicacabum* and evaluated their antibiofilm efficacy against three clinical strains of *S. aureus, E. coli,* and *P. aeruginosa*. They demonstrated that at 100 μg/ml, Cu NPs exhibited maximum antibiofilm activity with 79, 78, and 72% of biofilm inhibition in *P. aeruginosa, E. coli*, and *S. aureus* respectively (Punniyakotti et al., 2020). Similarly, Ali and his coworkers biosynthesized terpenoids entrapped copper oxide nanoparticles (ELE-CuONPs) prepared using *Eucalyptus globulus* (ELE) leaf extract. The results revealed that application of ELE-CuONPs in a dose ranging from 125 to 2000 μg/ml, prevents biofilm development by 19.03 ± 9% to 60.93 ± 8%, 44.41 ± 7% to 70.75 ± 8%, and 34.41 ± 7% to 62.29 ± 8% in *P. aeruginosa-621, E. coli-336, and MRSA-1*, respectively, hence suggesting the promising potential of ELE-CuONPs as an anti-biofilm therapeutic (Ali et al., 2019).

Interestingly, Erci and colleagues synthesized CuONPs by using various concentrations of aqueous leaf extract of *Thymbra spicata* to obtain Ts1CuONPs (40 ml plant extract) and Ts2CuONPs (80 ml plant extract). Their data showed, at a dosage of 100 μg/ml, the biofilm inhibition value for *S.aureus* was found to be 57.6 ± 1.03% and 49.1 ± 4.0% for Ts2CuONPs, Ts1CuONPs respectively (Erci et al., 2020). Accordingly, Cherian et al. manufactured CuONP *via* the one-pot green method by employing *Cymbopogon citratus* (CLE) leaf extract. The results revealed that the biofilm growth in MRSA-1 and *E.coli* was decreased to 49.0 ± 3.1% and 33.0 ± 3.2%, respectively on exposure to CLE-CuONPs (2000 μg/ml). Further, CLSM data suggested superior antibiofilm properties against *E.coli* followed by *S. aureus* owing to the variation in their cell wall compositions (Cherian et al., 2020).

Titanium Dioxide Nanoparticles

Titanium oxide nanoparticles have a broad spectrum of applications like antibacterial, cosmetics, photocatalyst,

wastewater treatment, and other medical fields. In fact, they are among the most extensively utilized nanoparticles attributed to their superior properties like non-toxic, stable, safe, and having surface activity (Al-Shabib et al., 2020). For instance, a study done by Narayanan et al. showed that TiO_2 NPs prevented the growth of bacterial pathogens *via* the generation of ROS, DNA, and cell membrane damage (Narayanan et al., 2021).

Accordingly, Al-Shabib and his colleagues fabricated TiO_2 NPs using root extract of *Withania somnifera* and evaluated its antibiofilm efficacy. Their results showed that at a concentration below MIC (0.5×MIC), TiO_2 NPs exhibited a significant inhibitory effect on biofilm development (43–71%) and mature biofilms (24–64%) in pathogens like *P. aeruginosa, E. coli, Listeria monocytogenes, MRSA, Serratia marcescens,* and *Candida albicans*. Consequently, they inferred that excessive ROS generation followed by cell death could be the possible cause for the compromised biofilm development in TiO_2 NP-treated pathogens (Al-Shabib et al., 2020).

Rajkumari and coworkers fabricated titanium dioxide nanoparticles (TiO_2 NPs) employing *Aloe barbadensis* leaf extract. Their results showed treatment of *P. aeruginosa* in biofilm mode with TiO_2 NPS leads to a significant reduction in cell viability by 30.76 ± 3.96%. Further, the MIC value of TiO_2 NPs imparted prominent antibiofilm activity against *P. aeruginosa* by hindering the adhesion of planktonic cells to the substratum (Rajkumari et al., 2019). Similarly, Achudhan and colleagues fabricated TiO_2 NPs using twigs and bud extract of *Ficus benghalensis*, *Azadirachta indica* twigs, and *Syzygium aromaticum* and evaluated their antibacterial and antibiofilm efficacy against bacteria (*Citrobacter freundii* and *Streptococcus mutans*) and fungi (*Candida albicans*). The green synthesized TiO_2 NPs inhibited biofilms of both the pathogens at a concentration of 100 μg/ml (Achudhan et al., 2020).

Interestingly, Dan et al., studied the antibiofilm activity of green synthesized titanium oxide using the leaf extract of *Ocimum sanctum* against *P. aeruginosa*, *E. coli, S. aureus,* and *C. albicans*. Their results showed the effective range of these NPs was between 250 and 650 μg/ml with a minimum effective dosage of 450 μg/ml against *E. coli* while for the remaining microbes 250 μg/ml was sufficient (Dan and Khan, 2019). Further, Jin et al. synthesized titanium dioxide nanostructures with the help of *Rosa davurica* leaf extract (RDL-TiO_2NPs) and evaluated its antibiofilm potential against different biofilm-producing bacteria. The minimum inhibitory concentration (MIC) of RDL-TiO_2NPs was 15.62 μg/ml for *S. aureus* and *B. cereus*, 62.5 μg/ml for *S. enterica,* and 31.25 μg/ml for *E. coli*. Also, the IC50 value for *S. enterica* and *S. aureus* were 158.75 and 76.84 μg/ml respectively. Further, the TEM and CV assay results indicated that RDL-TiONPs prevented bacterial biofilm *via* cell wall and membrane rupture (Jin et al., 2021).

Zubair et al. evaluated the efficacy of green synthesized TiO_2 NPs using leaf extract of *Ochradenus arabicus* to repress biofilm development and associated pathways in MRSA and MDR strains of *P. aeruginosa* isolated from foot ulcers. They studied that the constructed NPs reduced the biofilm formation by 22–70%, inhibited EPS production and cell surface hydrophobicity at sub-MICs. Further, severe impairment of motility and a prominent decrease in alginate production was also observed in *P. aeruginosa*. Also, significant damage (51–63 percent) to the preformed biofilms of all tested strains was observed. Moreover, the treatment of bacterial cells with TiO_2 NPs leads to increased ROS production which could be the possible reason for biofilm inhibition (Zubair et al., 2021).

Iron Oxide Nanoparticles

Recently, iron oxide nanoparticles (IONPs) have grabbed the limelight owing to their distinctive properties like higher surface area, superparamagnetism, surface-to-volume ratio, and simple separation procedure (Ali et al., 2016). These magnetic nanoparticles are known to impart antibacterial as well as antibiofilm properties *via* various mechanisms such as generation of ROS, electrostatic interaction with the cell membrane and its proteins, leading to physical damage and ultimately microbial death (Thukkaram et al., 2014). Further, the use of green materials for the synthesis of IONPs offers several advantages of low toxicity, biocompatibility for medical application, and eco-friendliness (Kanagasubbulakshmi and Kadirvelu, 2017).

In this regard, Ramalingam et al., constructed plant-assisted iron oxide nanoparticles utilizing leaf extract of grey mangrove *Avicennia marina* and studied its antibiofilm efficacy against marine pathogenic biofilm-forming bacteria. The designed NPs restricted the initial attachment and development of biofilm in biofilm-producing bacteria like *Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa.* Their results showed that nearly, 72% of quorum sensing factors of *Pseudomonas aeruginosa*, 63% of *S. aureus,* and about 46% of *E.coli* were inhibited by 200 μg/ml of FeO-NPs. Moreover, the FeO-NPs reduced the hydrophobicity index of *P. aeruginosa*, *S. aureus,* and *E. coli*, from 19, 15, 16% to 11, 11, and 9% respectively. Also, the designed FeO-NPs prevented the formation of EPS in *P. aeruginosa*, *S. aureus,* and *E. coli* from 92, 86, 90%, to 65, 60, and 69% respectively. Hence, they concluded that their designed biogenic FeO-NPs have the promising potential to be employed as an antibiofilm drug against pathogenic biofilm-producing microbes (Ramalingam et al., 2019).

Interestingly, the iron oxide nanoparticles synthesized using *Thymbra spicata* leaf extract imparted remarkable antibacterial properties against *Salmonella typhimurium* at a concentration of 100 μg/ml, as studied by Erci et al. Further, the NPs inhibited the growth of *S. aureus* growth and inhibited biofilm growth by 25.9 ± 3.36% at a concentration of 6.25 μg/ml. Therefore, they concluded that green synthesized FeONPs using *T. spicata* could serve as a potential antibacterial and antibiofilm therapeutic candidate (Erci and Cakir-Koc, 2020).

Accordingly, Ansari and his coworkers have used an extract of a polyherbal ayurvedic drug formulation, Liv 52 for the synthesis of superparamagnetic maghemite nanoparticles (L52E-γ-Fe_2O_3 NPs). Their formulated NPs imparted superior antibacterial, antifungal as well as antibiofilm properties against MRSA, MDR *P. aeruginosa,* and *C. albicans*. Further, there was significant damage in the biofilm structure of *C. albicans* majorly due to intense cell wall damage and inhibited hyphal growth, as observed by scanning electron microscopy. Also, the molecular docking reports showed that there was an effective

interaction between Fe_2O_3 NPs and cell wall peptidoglycan and mannoprotein which may lead to the cell wall and membrane damage (Ansari and Asiri, 2021).

Cerium Oxide Nanoparticles

Cerium oxide is a cubic-fluorite type of oxide which is regarded as the most prime among the rare earth oxides. Lately, CeO_2 nanoparticles have been widely studied for a wide array of prospective applications in various fields including nanomedicine. Although, their antioxidant property has been well studied, but their antimicrobial and antibiofilm studies are still at it infancy with very limited studies (Kannan and Sundrarajan, 2014). Even though phytosynthesised CeO_2 nanoparticles have shown promising antibiofilm potential, very little research work has been done.

In this regard, Ahmed and his coworkers employed fruit extract of *Phoenix dactylifera* for CeO_2 and Ti-decorated CeO_2 nanoparticles synthesis. They evaluated the antibiofilm efficacy of undoped and Ti-doped CeO_2 NPs against the *P. aeruginosa* developed biofilm. Their result revealed that undoped CeO_2 nanoparticles prevented biofilm development by 11.0, 18.7, 31.3, and 54.5% at a concentration of 125, 250, 500, and 1000 μg/ml respectively. Similarly, 5% Ti-doped CeO_2 nanoparticles inhibited biofilm formation by 10.9, 25.0, 34.2, and 57.4% at a concentrations of 125, 250, 500, 1000 μg/ml respectively. Also, similar trends were observed with 10, 15, and 20% Ti-CeO_2 nanoparticles, with about 75% biofilm inhibition by 1000 μg/ml of 20% Ti-CeO_2 nanoparticles. Hence, their data indicated increasing the titanium doping concentration in CeO_2 nanoparticles, enhances the antibiofilm activity, possibly because of the increased titanium ions release from the formulated nanocomposite (Ahmed et al., 2020).

Accordingly, Altaf et al. found that biosynthesized cerium oxide nanoparticles (CeO_2-NPs) prepared using *Acorus calamus* extract prevented the growth of bacterial biofilms by more than 75 percent. The confocal and electron microscopic data revealed that the application of CeO_2-NPs prevented the development and colonization of the bacteria on solid surfaces. Moreover, dose-dependent inhibition of preformed biofilms was also observed. There was a significant reduction in the exopolysaccharides (EPS) formation by test bacteria grown in CeO_2-NPs supplemented culture media (Altaf et al., 2021).

Interestingly, Naidi et al., applied a green chemistry route for the synthesis of cerium oxide (S-CeO_2) and 1, 5, and 10% tin-doped cerium oxide nanoparticles (Sn-doped CeO_2NPs) using aqueous foliage extract of *Pometia pinnata* as reductant. The fabricated nanoparticles imparted substantial antibiofilm properties against *S. aureus* and *Listeria monocytogenes* at a concentration of 512 μg/ml. The 1% Sn-doped CeO_2 NPs did not exhibit any antibiofilm activity while there was a significant antibiofilm activity imparted by the 10% Sn-doped CeO_2 at a concentration of 512 μg/ml nearly similar to that of S-CeO_2 NPs (Naidi et al., 2021b). Similarly, in their other research work, they synthesized zirconium/tin-coated nanoparticles (Zr/Sn-CeO_2 NPs) using *Pometia pinnata* aqueous plant extract. All Zr/Sn-doped CeO_2 NPs (1, 5, and 10%) exhibited a concentration-dependent biofilm inhibition of *L. monocytogenes*, and only 10% Zr/Sn-dual doped-CeO_2 NPs were found to impart antibiofilm activity against *S. aureus* at higher concentrations. The maximum biofilm inhibition was obtained at a concentration of 512 μg/ml for all of the synthesized nanoparticles i.e. S-CeO_2 NPs, and Zr/Sn-dual doped CeO_2 NPs (Naidi et al., 2021a).

Other Photosynthesized Nanoparticles

Apart from the above-mentioned nanoparticles, few other phytosynthesized nanoparticles have also been remotely evaluated for their anti-biofilm properties. Regarding this, Saleem et al. employed a green route method for the synthesis of nickel oxide nanoparticles (NiO-NPs) by utilizing *Eucalyptus globulus* leaf extract as a bioreductant. They prominently established the antibiofilm and antibacterial efficacy of the synthesized NPs against ESβL (+) *E. coli*, *P.aeruginosa,* and *S.aureus*. Further, the SEM images of NiO-NPs treated with microbial cells revealed irregular shrinkage and distortion with prominent depression/indentations with the cells. Hence, their work indicated substantial antibiofilm and antibacterial activity of plant synthesized NiO-NPs (Saleem et al., 2017).

Similarly, Prakashkumar and his coworkers fabricated biocompatible palladium nanoparticles (NG@Pd NPs) using leaf extract of *Orthosiphon stamineus* and evaluated its antibiofilm and antibacterial properties. The results showed enhanced bactericidal activity of NG@Pd NPs against *E. coli*, *S. aureus,* and extended-spectrum beta-lactamase strain relative to the PdNPs alone. Moreover, the antibiofilm study demonstrated inhibition of biofilm development in a concentration-dependent manner in methicillin-sensitive *Staphylococcus aureus* strain with the IC50 value of 15.25 ± 0.012 μg/ml, whereas the Pd NPs exhibited reduced inhibitory effect (N et al., 2021). Accordingly, Miglani and Tani-Ishii et al., constructed a biogenic selenium nanoparticle (SeNPs) using leaf extract of *Psidium guajava* with an aim to study its antimicrobial and antibiofilm properties against *Enterococcus faecalis.* Consequently, they evaluated the relative antibiofilm efficacy of five test groups namely distilled water (control), SeNPs (1 mg/ml), Calcium hydroxide (1 mg/ml), 5.25% Sodium hypochlorite, and 2% Chlorhexidine gluconate. The result revealed that SeNPs were the most efficacious among others against the biofilm of *E. faecalis* (Miglani and Tani-Ishii, 2021).

THE MECHANISM OF NANOPARTICLES EFFICACY AGAINST BIOFILM

There are several studies done that support the superior efficacy of nanoparticles against biofilm-forming microorganisms. Due to their unique characteristics and small size, nanoparticles form a potential alternative to conventional antibiotics to treat biofilm-related complications. Also, due to their higher surface area, they act as a suitable drug carrier by immobilizing drugs onto its surface thereby increasing its solubility and targeted delivery (Wang et al., 2017). There are numerous mechanisms *via* which nanoparticles impart their antimicrobial activity against these biofilm-forming pathogens which can be summarised under three categories i.e. *1*) ROS (Reactive oxygen species)

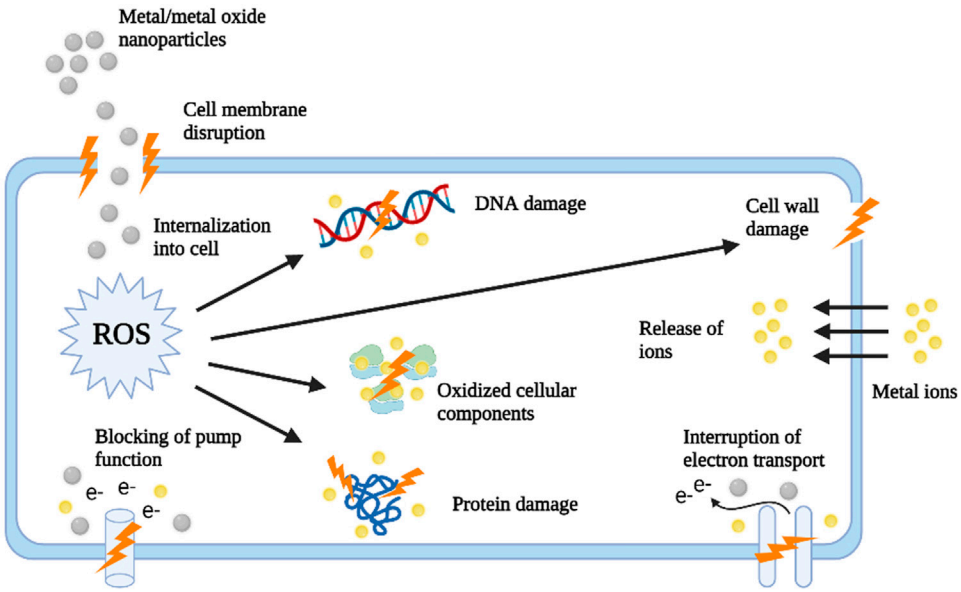

FIGURE 3 | Diagrammatic illustration representing of effects of various metal/metal oxide nanoparticles on a bacterial cell (Baptista et al., 2018).

induced oxidative stress, *2*) release of metal ion thereby leading to alteration in enzyme activity, disruption of cell structures and protein denaturation, and *3*) mechanical destruction of cell wall due to electrostatic interaction (Shkodenko et al., 2020) (**Figure 3**) (Baptista et al., 2018).

One of the prime antibacterial mechanisms of NPs includes induction of oxidative stress due to the production of ROS *via* electromagnetic irradiation of NPs (Dwivedi et al., 2014). Generally, ROS is formed due to aerobic respiration in bacteria which has an important role in cell death and survival modulation, cell signaling, and differentiation (Schieber and Chandel, 2014). But the extreme generation of ROS *via* NPs leads to imbalanced redox homeostasis thereby inducing oxidative stress which in turn affects the membrane lipids, proteins, and DNA structure. Various nanoparticles produce different ROS viz. hydrogen peroxide (H_2O_2), superoxide (O_2^-), and hydroxyl radical (. OH) which is dependent on the chemical nature of the nanoparticles themselves (Dayem et al., 2017). It has been studied that while the endogenous antioxidants can neutralize the effects of superoxide (O_2^-) and peroxide (H_2O_2) radicals; the singlet oxygen and hydroxyl (. OH) are fatal to bacterial cells causing acute death. Further, the production of ROS is directly proportional to the surface-to-volume ratio of the nanoparticles (L. Vega-Jiménez et al., 2019).

The metal ions of the metal oxide nanoparticles which are absorbed by the bacterial cell, can disturb the structure of the cell, alter the normal physiological functions and modify the activity of various proteins and enzymes *via* their interaction with functional groups of various intracellular nucleic acid and proteins such as sulfhydryl (-SH), amino (-NH), and carboxyl (-COOH) groups. Metal ions also interact with DNA and modify its helical structure *via* cross-linking between as well as within DNA strands (Wang et al., 2017).

Non-oxidative mechanisms involve the interaction of the nanoparticles with the cell wall and cell membrane. The cell walls and membrane of bacteria function as protective shields against environmental damages. Cell membrane components provide various adsorption routes for the nanoparticles (Lesniak et al., 2013). The negatively charged bacterial cell wall interacts with the positively charged surface of NPs, *via* electrostatic interaction and Van der Waals interactions, this, in turn, causes alteration of cell membrane structure and permeability due to the accumulation of the nanoparticles onto the cell surface (Baptista et al., 2018).

Various research studies have indicated that NPs can obstruct biofilm formation *via* cell membrane disruption, thereby promoting bacterial death. Evidence from earlier reports showed that by interacting with EPS, eDNA, proteins, bacterial communication-quorum sensing (QS), and lipids of biofilm, NPs can disrupt biofilm stability (Qayyum and Khan, 2016). The surface chemistry and size of NPs play a central role in their antibiofilm activity as size regulates its effective penetration within the EPS matrix and surface chemistry guides the amount of interaction between NPs and EPS matrix. The strategies against biofilm inhibitions majorly aim to interfere with QS molecules. QS plays a vital role in bacterial pathogenesis including biofilm formation (Paluch et al., 2020). Therefore, the foundation for potential next-generation antivirulence treatments to be developed is the targeting and disruption of QS signaling systems and, as a result, biofilm formation.

Moreover, numerous nature-derived compounds are known to impart excellent antibiofilm activity but their clinical application is restricted due to their poor solubility and stability. Also, the free antibiotic fails to penetrate within these biofilms due to the EPS matrix. Further, the hydrophilic nature of commonly used antibiotics makes their cell penetration difficult.

In this regard, NPs are known to function as an efficient delivery vehicle for the effective delivery of antibiotics/drugs within biofilm as well as within bacterial cells and thus increasing the efficacy of these drugs synergistically. Hence, in this way, NPs may be used to target bacterial biofilms in a variety of ways, including antibiotic-free and antibiotic-coated methods (Dos Santos Ramos et al., 2018).

POTENTIAL ADVERSE EFFECTS OF METAL OXIDE NANOPARTICLES

Despite displaying an array of significant applications in the field of medicine, nanoparticles can cause several prominent adverse effects on human health and the environment (Lanone and Boczkowski, 2006). Nanotoxicology is a sub-discipline of nanotechnology which encompasses the study of the toxicity of nanomaterials and evaluation of potential health risks associated with its application. The biomedical application of NPs for treating various diseases is a "double-edged sword," as the properties (small size, high reactivity, large surface area) which favor the beneficial application of nanoparticles, are also known to cause significant toxic effects (Donaldson et al., 2004). Other physicochemical properties like crystallinity, elemental composition, solubility, shape, charge, and surface derivatives may also affect the toxic potential of the nanoparticles (Dreher, 2004) (Nel et al., 2006). Moreover, agglomeration is one of the major obstructions in converting nanomaterials into medicine attributing to its potential toxic effects on various organs and organ systems (Andleeb et al., 2021). The small size makes the penetration of nanoparticles within minute capillaries feasible. Further, it has been reported that NPs with a size below 100 nm can penetrate cells, while sizes less than 40 nm can enter the nucleus, and sizes below 35 nm can cross the blood-brain barrier and enter the brain thereby may cause cellular damage. Further, studies have shown that these nanoparticles may exert cytotoxic effects in a cell type-, treatment time-, and dose-dependent manner (Brooking et al., 2001) (Arora et al., 2012).

When living organisms are exposed to different nanoparticles, it induces several toxic characteristics such as cytotoxicity, genotoxicity, and epigeneticity (Schrand et al., 2010) (Jennifer and Maciej, 2013). Further, The cyto-physiology of the cell may get affected by nanoparticles at various levels like genetic, organelle, or cellular levels which thereby add to the cytotoxicity, tumor development, and other side effects (Arora et al., 2012). Also, the application of NPs has made humans more prone to diseases like cancer, diabetes, allergies, bronchial asthma, inflammation, etc. Nanoparticles may impart their toxic effects on different cell structures *via* direct or indirect interactions with organic molecules of cells. Generation of excessive ROS and thereby disruption of intracellular redox homeostasis is considered to be one of the major mechanisms associated with NPs mediated macromolecule toxicity which leads to oxidative damage of macromolecules such as lipids, proteins, and nucleic acids (Radu et al., 2010) (De Planque et al., 2011). The oxidative DNA damage therefore may alter the interaction of DNA and methyltransferases thereby leading to DNA hypomethylation. In addition, nanoparticles may enhance the expression of different pro-inflammatory genes like TNF-α, IL-1, IL-8, IL-6 *via* activation of the NF-κB signaling pathway. Consequently, these molecular and cellular alterations lead to oxidative stress, followed by intense genotoxicity and subsequent programmed cell death (Luo et al., 2015). The alterations in hematological, oxidative enzymes, biochemical, and other histopathological criteria are regarded as the possible biomarkers for assessing the toxicity of nanoparticles in different living organisms (Kanwal et al., 2019).

Further, the enormous discharge of NPs as industrial nano-waste into the surrounding environment is proving to cause ecosystem imbalance and is hazardous to the indigenous living organisms. Also, the massive generation of NPs is distressing the food web of the ecosystem. NPs released in the atmosphere can gain excess into the plant *via* the stomatal openings of leaves whereas the NPs occurring in water or soil can selectively gain access *via* roots of the plants (Wang et al., 2013) (Tripathi et al., 2017). NPs may exert their toxicity on plants *via* excessive ROS production, DNA damage, a decline in plant biomass, reducing photosynthetic pigments and protein content, etc.; thereby impeding the growth and development of the plants (Zhu et al., 2019).

Also, due to their non-specific antimicrobial nature, the NPs not only kill pathogenic micro-organisms but also targets the symbiotic microbial population (Qayyum and Khan, 2016). Further, if the concentration of nanoparticles is not enough to eradicate biofilms but enough to cause mutation, then the nanoparticles can lead to the development of "super mutant" variants of bacteria (Shkodenko et al., 2020). The occurrence of NPs mutagenicity in bacterial biofilms plays an important role. The genetic material of lysed bacterial cells gets accumulated within the EPM, thereby leading to enhanced gene transfer frequency among bacterial cells (Kalishwaralal et al., 2010a). The genetic components like plasmid may contain genes for antibiotic resistance, therefore it can be assumed that nanoparticles may add to the development of antibiotic resistance bacteria (Durmus et al., 2013)

Since conventional chemical synthesis utilizes several hazardous compounds for nanoparticle synthesis, the developed nanoparticles tend to show undesirable side effects. An alternative to overcome this problem is to adopt eco-friendly methods to synthesis less toxic NPs i.e. biosynthesis of NPs. The utilization of the biological approach for the synthesis of NPs can also reduce the toxicity of nanoparticles. Studies have reported the biocompatible nature of several phyto-constituents (Singh J. et al., 2018). The toxic properties of the nanoparticles can also be regulated by incorporating free functional groups onto their surface. Moreover, toxicity can also be reduced by controlling the particle size of the designed metal nanoparticles (Singh and Lillard, 2009).

CONCLUSION AND FUTURE PERSPECTIVE

Biofilms being the most predominant mode of bacterial growth presents a significant challenge which is not been effectively

encountered by traditional antimicrobial therapeutics. Further, its spatial and temporal diversity, both in terms of chemical and microbial structure, has added a degree of complexity to eradication methods. It has raised concerns that the usage of long-term antibiotics may lead to the occurrence of multidrug-resistant strains. Biofilm infections are extremely resilient to present antimicrobial therapy and thereby is a severe matter of concern for the healthcare sector. As a consequence, the development of efficacious approaches to combat biofilms needs a multidisciplinary strategy to overcome various challenges offered by biofilms. Some of the pioneering and potential antibiofilm strategies include disruption of matured biofilms, isolation of quorum quenching compounds, an amalgamation of quorum quenching compounds with antibiotics, or a mixture of these mentioned techniques, which are still under investigation and did not reach clinical trial. Recently, the potential of nanoparticles as a promising anti-biofilm agent has taken hold, attributed to its unique properties like small size, superior surface-area-to-volume ratio, and others. Among various routes employed for nanoparticles synthesis, the application of the green chemistry route has gained significant attention due to its several merits like eco-friendly, cost-effectiveness, low toxicity.

Even though the biological mode of synthesis has the advantages of green chemistry as mentioned in this literature, there are certain unsettled issues associated with it like, reproducibility of the synthesis process, consistency in particles shape and size, and the exact mechanism involved in the biosynthesis of nanoparticles. In the case of phytosynthesis, the mechanism of nanoparticles formation varies with different plant species. Further, the compositions of identical plants cultivated in various geographical locations or harvested in different climates might show variations in their active components. This, in turn, would influence the morphology of the synthesized nanoparticles as the shape and size of nanoparticles are majorly determined by the different compositions of bioactive molecules with predefined molecule sizes. This would lead to a fall in their commercial value and thereby make the marketing of phyto-synthesized nanoparticles more challenging. In the case of chemical synthesis, they have the advantage of regulated size and shape and which is why it is more preferred. Nonetheless, the beneficial facets outweigh the bad, which also pushes researchers to upgrade the ways of plant-mediated synthesis. Therefore, there is a need for a thorough understanding and evaluation of the plant-assisted synthesis mechanisms. This is a poorly explored area and requires serious attention to fully explore and use the benefits of green synthesized metallic nanoparticles.

Various green synthesized metal/metal oxide nanoparticles such as Ag, Au, ZnO, CeO_2, Fe_2O_3, CuO, TiO_2, Pd, Se, NiO, have been assessed for their antibiofilm properties, among which phytosynthesized AgNPs are the most studied nanoparticles against biofilms. Yet, further research should be promoted to detect the activity of nanoparticles in industrial settings and their impact on the environment. Phytosynthesised nanoparticles have a promising future and can be applied in different biomedical fields involving nanoparticles like targeted drug delivery, fluorescent labeling in immunoassays, as antibacterial agents in bandages, and in destroying tumors *via* heating (hyperthermia). Even though there is increasing evidence regarding the promising potential of these green nanoparticles, it is obligatory to establish procedures to ensure their benign application to convert these preparations into reality as anti-biofilm therapeutics. It may be stated that, despite significant studies on nanoparticles across the world, many topics still need to be investigated further. Without them, the clinical introduction of these nano drugs can prove to be havoc for both mankind and the microbial community. A more structured and explicit study regarding NP's mechanism of action on planktonic cells, biofilms, mutagenicity, and genotoxicity may permit more targeted application thereby enhancing their effectiveness. Further, it is equally crucial to study the systemic *in vivo* effectiveness of these upcoming methodologies from the biomedical perspective. Specificity being the crucial factor for clinical applications, it is extremely important to differentiate between commensal and pathogenic bacteria and host tissue. Another key factor to be considered for investigation is how the nanoparticles are adapted in the biological setting, such as blood, and how these modifications will influence their effectiveness. Moreover, prospective directions should emphasize on the complete removal of biofilm by targeting the EPS matrix and the microbial cells simultaneously, thereby enhancing the therapeutic efficacy, while minimalizing toxic effects and development of resistance.

AUTHOR CONTRIBUTIONS

PD and SG are the first authors and they have contributed equally towards the literature survey and writing of the whole manuscript. BN is the corresponding author. She developed the concept, evaluated and verified the entire process from beginning to end, and corrected the final manuscript.

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