Chapter 1
Green Synthesized Nanoparticles as a Promising Strategy for Controlling Microbial Biofilm

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Abstract Microbial biofilms are communities of cells adhered to a surface embedded with a matrix of polymeric extracellular substances. The biofilm can present one or more species of microorganisms, depending on its duration and location. It may involve Gram-positive, Gram-negative bacteria and yeast such as *Candida albicans*, Coagulase negative Staphylococcus, *Enterococcus* spp., *Klebsiela pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococccus aureus*. In addition to bacteria, other cellular elements may be aggregated in the biofilm, such as platelets, for example, when the biofilm is installed on a surface bathed in blood. In the health area, there are a variety of possible situations that allow biofilm formation in medical devices directly connected to the patient or indirectly by contamination of the machines or pipes of that environment. Biofilm formation has been linked to 60% of hospital infections. In this way, components and methods that can inhibit the biofilm formation or even dissolve it have been investigated. Nanobiotechnology is an area of nanotechnology related to the creation, use and improvement of nanostructures in biotechnological processes. Among the various research fields in this area is the synthesis, characterization and application of nanoparticles with different sizes, shapes and chemical compositions. The traditional methods used for the synthesis of these nanoparticles are generally chemical methods in which toxic solvents are used and the generation of dangerous by-products can occur and involve high energy consumption. Due to these factors, there is an increasing need to develop non-toxic and environmentally friendly procedures; but with a high yield and low cost. In this context, the routes of synthesis of nanoparticles by biological

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systems, also known as green synthesis or biosynthesis, become quite relevant. This chapter addresses the perspectives by which green synthesis nanoparticles can be integrated as an effective method of control and prevention of microbial biofilms.

Keywords Infection · Prevention · Control · Nanotechnology

1.1 Introduction

Microbial infections are among the main public health concerns, as various bacteria, yeasts, fungi, and other pathogenic microorganisms may be resistant to drugs (Teixeira et al. 2020). Furthermore, the formation of biofilms represents a major challenge in this sense, as it makes the control of these microorganisms even more difficult (Winkelströter et al. 2016; Barzegari et al. 2020).

Thus, the development of new and effective antimicrobial agents is required, especially considering the current scenario. A promising strategy is the application of nanotechnology. The distinctive properties of the nanoscale confer impressive antimicrobial capabilities to nanomaterials which should be further explored (Reshma et al. 2017; Inamuddin et al. 2021).

Nanotechnology can be particularly advantageous in the treatment of bacterial infections. Examples include the use of nanoparticles (NPs) in antibacterial coatings for medical implants and devices to prevent infections and promote wound healing, in antibiotic delivery and bacterial detection systems, and in antibacterial vaccines (Wang et al. 2017).

The "green" synthesis of nanoparticles is based on the use of plant metabolites and natural substances. Its use is particularly rewarding as it is considered a clean, low-cost method, in addition to presenting high safety and stability (Gour and Jain 2019; Prasad 2014; Prasad et al. 2018; Srivastava et al. 2021). However, an important issue associated with the use of nanomaterials is the concern about side effects *in vivo*. Therefore, in-depth knowledge of biocompatible nanostructures intended for antimicrobial therapy is needed (Reshma et al. 2017). This chapter addresses the perspectives by which green synthesis NPs can be integrated as an effective method of control and prevention of microbial biofilms.

1.2 Microbial Biofilms

A biofilm is defined as a group of free microorganisms adhered to a surface and encrusted in a polymeric matrix produced by themselves (Winkelströter et al. 2016; Barzegari et al. 2020). Biofilms can be constituted by microorganisms of a single species or multiple species, with the formation from two or more populations of bacteria and/or fungi, yeasts, and protozoa being more common in nature (Lohse et al. 2018; Boltz et al. 2017).

Among the bacteria most commonly involved in the formation of biofilms are: *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Streptococcus viridans*, *Escherichia coli*, *Proteus mirabilis*, *Methicillin* resistant *staphylococcus aureus* (MRSA), *Streptococcus mutans*, and *Gardnerella vaginalis* (Barzegari et al. 2020; Ghosh et al. 2020). Among the fungi, the following are common; *Aspergillus fumigatus* and *Candida albicans* (Sheppard and Howell 2016; Chevalier et al. 2018; Kean and Ramage 2019).

The presence of the extracellular matrix in the biofilm is a major factor in its structure, in addition to enabling the survival and protection of these microorganisms against various adverse conditions (Limoli et al. 2015; Yan and Bassler 2019). The matrix composed of extracellular polymeric substances (EPS), among which we can mention polysaccharides, proteins, and extracellular DNA (Dragoš and Kovács 2017; Yan and Bassler 2019).

The synthesis of polysaccharides can be influenced by the environment and although there are variations in their composition. Polysaccharides are responsible for the aggregation, protection, nutrition, and architecture of the biofilm (Limoli et al. 2015; Neu and Lawrence 2017).

Extracellular proteins present in biofilms are classified into secreted extracellular proteins, extracellular enzymes, and cell surface adhesins (Neu and Lawrence 2017). An example is the protein associated with biofilm (Bap), an important protein found on the surface of the film and directly related to the role of binding, migration, and formation capacity of biofilms (Colagiorgi et al. 2016; Neu and Lawrence 2017).

Extracellular DNA is produced by active secretion or controlled cell lysis. This is an element of the matrix with a significant role in the maturation of the biofilm, gene transfer, and when together with the other components, enables construction, structural integrity, and protection (Colagiorgi et al. 2016; Neu and Lawrence 2017; Kavanaugh et al. 2019).

The formation of biofilm is carried out in several phases such as initial fixation, irreversible fixation, initial formation of microcolonies, maturation, and dispersion of microorganisms, as shown in Fig. 1.1 (Winkelströter et al. 2016; Barzegari et al. 2020). The cycle of formation of a biofilm begins with the adhesion of single and/or clustered cells to a surface, where the expression of the planktonic state genes changes to the sessile state (Winkelströter et al. 2016; Gordon et al. 2017).

The reversible initial fixation is facilitated by the presence of organic residues on the surface where the biofilm will be installed. This fact is dependent on van der Waal's forces that favor interaction with the EPS. On the other hand, irreversible adhesion occurs through the interaction of extracellular substances in the polymeric matrix when adhering to microcolonies (Winkelströter et al. 2016; van Wolferen et al. 2018).

After adhering to the surface, the microorganisms bind to each other and form a monolayer biofilm composed of single cells or a multilayer biofilm formed by aggregated cells. At this stage of maturation, the structure is developed and characterized by a complex 3D architecture that favors biofilm nutrition (Winkelströter et al. 2016; van Wolferen et al. 2018).

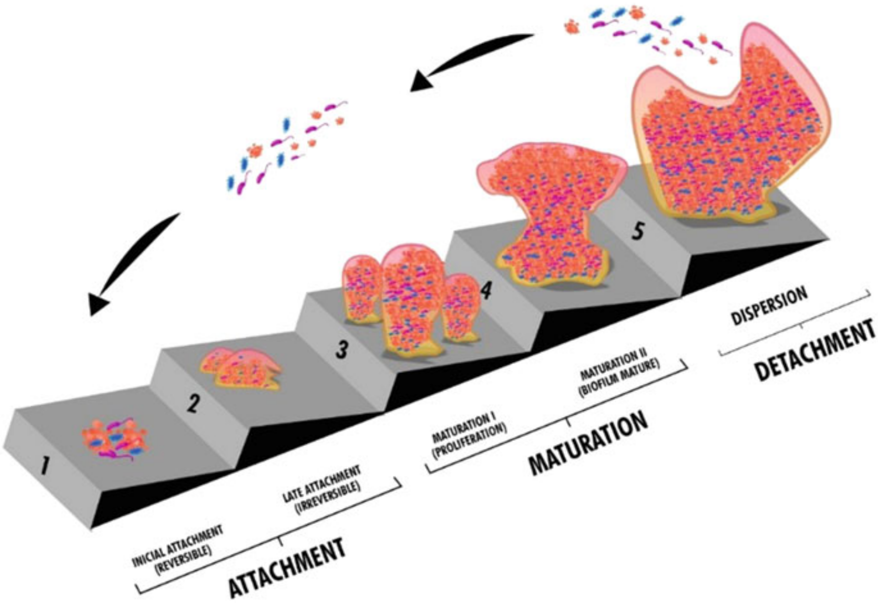

Fig. 1.1 Biofilm formation cycle with the stages of adhesion, maturation, and dispersion

The final stage is characterized by the dispersion process where microbial cells in an isolated or aggregate form detach themselves from the mature biofilm and colonize other sites to form a new biofilm. This process is mainly due to nutrient deprivation, environmental changes, and the *quorum-sensing* (QS) system between bacteria (Gordon et al. 2017; van Wolferen et al. 2018).

Some aspects can influence this process, such as environmental factors, microbial species, temperature, culture medium, the type of adhesion surface, regulation of genes to guarantee the development and maintenance of cells, architecture, and the extracellular matrix. In this way, single methods cannot be used to study biofilms (Winkelströter et al. 2016).

Biofilms can be present in several niches. The presence of microbial biofilms has been observed on biotic surfaces (natural aquatic, plant and mammalian tissues) and abiotic surfaces (artificial devices, implanted hospital devices, and biomaterials) (Boltz et al. 2017; Lohse et al. 2018).

In the clinical context, biofilms are related to contamination and systemic infections, mainly carried by contaminated implants and catheters. According to the National Institutes of Health (NIH), approximately 65% to 80% of cases of bacterial infections in humans may be related to the presence of microbial biofilms (Barzegari et al. 2020; Ghosh et al. 2020). In addition, they are also present as dental plaque, and their pathogenesis can cause cavities and gum disease (Tsui et al. 2016; Boltz et al. 2017; Daubert and Weinstein 2019). In the environment, they can be installed on the internal walls of pipes and tubes, resulting in corrosion and damage, besides generating a bad taste and smell in drinking water (Boltz et al. 2017; Di Pippo et al. 2018).

The presence of biofilms also impacts the food sector, as microbial communities aggregate on surfaces such as plastic, wood, metal, glass, soil fragments, and food products, which motivates contamination of the raw material, economic loss, short validity periods of goods, and transmission of diseases through food (Winkelströter et al. 2014; Winkelströter and Martinis 2015).

Although biofilms are most often considered pathogenic, they can be beneficial. Many of them are part of plant, animal, and human microbiomes, generating benefits in agriculture, and biotechnological applications to be used in industries, contributing to the production of fermented foods and wastewater treatment (Winkelströter et al. 2014; Velmourougane et al. 2019; Yan and Bassler 2019).

In biofilms, mutations in the genes and reduced diffusion of substances can occur, increasing their resistance to antimicrobials and making eradication more difficult (Tsui et al. 2016; Yan and Bassler 2019). Because of this, new alternatives have emerged to combat and prevent biofilms, such as plant extracts, QS inhibitory substances, industrial chemical disinfectants, probiotic products, and nanoparticles (Malafaia et al. 2018; Barzegari et al. 2020).

1.3 Methods to Prevent and Control Biofilms

The damages caused by the presence of biofilms have stimulated the research and development of new methods of elimination and prevention of this active form of life of microorganisms. In order to avoid the formation of biofilms, the following critical points must be taken into account: (1) prevent the initial connection of the microorganisms to the biofilm forming surfaces, (2) interruption of the maturation process, and (3) interference in the microorganism communication system—the QS system (Galié et al. 2018; Subhadra et al. 2018).

Some biofilm control methods act directly on these points, such as: modifications in the surface of biomaterials, such as nanoparticles with different metal oxides, nanocomposites, antimicrobial polymers, hydrogels, or liposomes; inhibition of cell signaling with lactic and citric acids; chemical treatments, such as ozone, quaternary ammonium compounds, NaOCl, and other disinfectants; enzymatic disruption strategies, such as cellulases, proteases, glycosidases, and DNAses; non-thermal plasma treatments; use of thermal processing; use of bacteriophages, such as P100; bacteriocins, such as nisin; biosurfactants, such as lichenisin or surfactin; and essential oils from plants, such as oils containing citral or carvacrol (Zabielska et al. 2016; Galié et al. 2018; Subhadra et al. 2018).

A more detailed view of the main methods of control and prevention will be detailed in the following topics:

1.3.1 Chemical Treatments

1.3.1.1 Disinfectants and Sanitizers

These components have a wide spectrum and the most commonly used are hydrogen peroxide, quaternary ammonium compounds, and chlorine-based products. They act both in the matrix and in the microorganisms present in biofilms, acting as important anti-biofilm agents. Although some mechanisms of action are suggested, further investigation is needed on potential toxic effects. Sodium hypochlorite is believed to act directly on the proteins that make up the biofilm matrix and inhibit the main enzymatic functions of microorganisms. Hydrogen peroxide is an oxidizing disinfectant responsible for producing free radicals that come into contact with the biofilm structures. The quaternary ammonium compounds are soluble in water and have a positive charge. Due to these characteristics, they influence the stability of the cell membrane of microorganisms, which can result in lysis (Strempel et al. 2015; Galié et al. 2018; Lineback et al. 2018).

1.3.1.2 Essential Oils

Essential oils (EOs) are volatile substances from plants that may have anti-biofilm, antibacterial, and preservative properties. Studies suggest that the antimicrobial potential of EOs is related to their action on the cell wall of microorganisms. These are a safe option compared to chemical antimicrobial agents. Several substances already have a proven anti-biofilm action against various microorganisms such as monoterpenoids (borneol, camphor, carvacrol, eucalyptol, limonene, pinene, thujone), sesquiterpenoids (caryophyllene, humulene), flavonoids (cinnamaldehyde), and other phenolic compounds. Several EOs are responsible for the regulation of the QS system, which results in the alteration of the expression of various virulence factors, including those related to the maintenance of the biofilm. EOs are recognized for inactivating microorganisms without resistance, in addition to presenting low toxicity and rapid degradation in the environment. A large number of essential oils are available (Galié et al. 2018; Correa et al. 2019; Shahid et al. 2019; Wang et al. 2019).

1.3.1.3 Bacteriocins

Bacteriocins are peptides synthesized by bacterial ribosomes in order to inhibit or eliminate other microorganisms (Strempel et al. 2015).

Bacteriocins have great relevance in the preservation of food and in the fight against pathogenic microorganisms. The bactericidal actions of bacteriocins involve the direct death of bacteria by cell membrane lysis and interruption of cellular processes, such as DNA replication, transcription, protein biosynthesis, and folding or impairment of protein functions and immunomodulatory effects, causing the stimulation of non-inflammatory immune responses in the host. Anti-biofilm effects have also been reported and include the inhibition of bacterial adhesion to surfaces, preventing the formation of new biofilms and the interference of pre-existing biofilms, in addition to great penetration capacity of formed biofilms (Strempel et al. 2015; Mathur et al. 2018; Chikindas et al. 2020).

1.3.1.4 Phagotherapy

Bacteriophages are viruses that infect bacteria. Their composition is formed by a protein capsule that surrounds a DNA genome and their structure contains several devices to contaminate the host cell (Shaffer 2019).

The use of bacteriophages is an alternative to avoid resistance to antimicrobials. The use of phages can control the biofilm EPS matrix and results in the control of biofilm proliferation. Although some bacteriophages produce exopolysaccharide depolymerases, others have low potential for access to the biofilm and demonstrate difficulty reaching bacterial cells within the biofilm (Galié et al. 2018; Shahid et al. 2019).

1.3.1.5 Enzymes

Enzymes are an important tool for biofilm control, since they have low toxicity and are biodegradable. Enzymes are currently used in conjunction with detergents (Galié et al. 2018).

Regarding the composition of the biofilm structure, organic macromolecules (proteins and polysaccharides) characterize the main target components for the action of enzymes. Thus, proteases (serine proteases, proteinase K, pepsin, and trypsin) and glycosides (amylases, dextranase, and pectinase) are the main choices for biofilm removal. Pectin methylesterase is an enzyme that reduces biofilm formation in bioreactors. Other enzymes, such as amylases, cellulases, lyases, glycosides, and DNAses, are used in industrial detergents to remove biofilms (Wang et al. 2016; Galié et al. 2018).

The association of enzymes with different methods, as with other chemical (disinfectant) or physical (ultrasound) treatments, improved the removal of biofilm (Meireles et al. 2016).

1.3.1.6 *Quorum-sensing* Inhibitors (QS)

Multiple signaling pathways are essential for biofilm formation. Among them, QS and cyclic di-GMP (cGMP) signaling are the best defined (Galié et al. 2018; Subhadra et al. 2018; Shahid et al. 2019; Wang et al. 2019).

The biosynthesis of extracellular polymeric substances and reduction in bacterial motility are caused by the high intracellular content of cGMP, favoring the formation of biofilm. Many molecules can disrupt cGMP biosynthesis, such as terpenoid saponin, compounds generated from nitric oxide, azathioprine, or sRNAs (Galié et al. 2018).

Quorum-sensing inhibitors (QSI) have been proposed as a new branch of antimicrobial agents. Several methods are applied to generate interference in bacterial *quorum-sensing* through inhibiting cell-to-cell communication, encompassing the competitive binding of inhibitors to QS receptors, enzymatic degradation of QS signals, post-transcriptional control of QS genes via sRNAs, and inhibition of biosynthesis of the QS signals (Galié et al. 2018; Shahid et al. 2019).

1.3.2 Physical Treatments

1.3.2.1 Heat

Thermal treatment of bacterial biofilm can be applied through heating, representing a non-invasive and non-antibiotic treatment category (Pijls et al. 2020).

Thermal shock is generally used to inactivate bacteria, making it a viable and efficient approach for inhibiting biofilm at accessible temperatures, such as 80 °C. This method can reduce the population density of biofilm by 5 orders of magnitude. The shock significantly inactivates bacteria in biofilms and inhibits the multiplication of microorganisms, in addition to being responsible for damaging bacterial cell membranes, making biofilms more vulnerable and significantly decreasing biomass and biovolume (Pijls et al. 2020).

1.3.2.2 Radiation

In the living organism, ionizing radiation damages the cell's DNA. Cell death is predominantly driven by double-stranded DNA breaks, separated by base pairs that are not repaired by the cell. Regarding biofilm control and prevention, there are several types of radiation, such as ultraviolet rays, gamma radiation, and ultrasound irradiation (Marjani and Khadam 2016). It is suggested that gamma irradiation can weaken the intermolecular interaction of lipopolysaccharide components, disrupt the biofilm structure, leaving it permeable to antimicrobials (Marjani and Khadam 2016).

1.3.3 Genetic Manipulation

Methods with molecular biology tools are becoming increasingly used to control biofilms. CRISPR/Cas9 technology provides modifications in specific locations of selected genes in a main step, leading to deletions, insertions, or transformations in the sequence. Gene inactivation is a powerful method for functional studies. When deletion of genes responsible for structuring the biofilm occurs, the exopolysaccharide matrix exhibits irregular density and discontinuities, demonstrating that the biofilm formation is impaired with modified physical properties (Noirot-Gros et al. 2019; Leonova and Gainetdinov 2020).

Although there are numerous methods for the control and prevention of biofilm, no method can be considered effective for all forms of existing biofilms. In view of this, it is essential that new strategies, such as the use of nanoparticles, be researched. The table below presents the advantages and disadvantages of the main methods of biofilm control and prevention described in the literature (Table 1.1).

1.4 Anti-biofilm Effect of Nanoparticles

Nanoparticles (NPs) are atomic aggregates with a diameter between 1 and 100 nm, a characteristic that guarantees a large surface area and high reactivity. Currently, NPs play an important role in the production of materials from different areas, with emphasis on the pharmaceutical and medical industry (Prasad 2014; Prasad et al. 2016). Their wide application is the result of properties related to their size, which provides a large surface area, favoring their access. Their chemical and physical properties can be improved through combination with biomolecules, a fact that provides greater stability and improves biological properties compared to their native state (Baudrimont et al. 2018; Iriarte-Mesa et al. 2020; Mylona et al. 2020).

Currently, NPs play an important role in the medical field, mainly in oncology. In addition, their potential use in combating microbial infections has been investigated. The antimicrobial effect of NPs and their ability to inhibit the formation of biofilms enables greater therapeutic efficacy, less side effects, and greater adherence to treatment (Meeker et al. 2018; Sengan et al. 2019; de Mélo Silva et al. 2020; Prasad et al. 2020).

1.4.1 Classification of Nanoparticles

NPs can be classified according to their dimensions, shapes, sizes, and the material used in their development. Their dimension is considered to be zero when the length, width, and height are fixed in a single point. They can take on a cylindrical, spherical, tubular, or spiral shape, among others, and may even be irregular. Sizes

Table 1.1 Advantages and disadvantages of the main methods of control and prevention of biofilms

Types of biofilm prevention	Methods of biofilm prevention	Advantages	Disadvantages	References
	Disinfectants	High efficiency in premature biofilms; no side or toxic effects	Resistance, limited effectiveness; high dose	Strempel et al. (2015), Galié et al. (2018) and Lineback et al. (2018)
Chemical treatment	Phagotherapy	One of the most useful anti-biofilm agents; simple and fast isolation; low cost; ecologically friendly; does not disturb the normal microbiota	Low effectiveness; release of a considerable amount of endotoxins; reduced number of phages encoding toxins; insufficient pharmacokinetic data; resistance	Galié et al. (2018), Shaffer (2019) and Shahid et al. (2019)
	Bacteriocins	High efficacy in inhibiting biofilm formation; alternative route to antimicrobials; low toxicity; ease of penetration into the biofilm; more effective than antimicrobials	Reduced efficacy in biofilms already formed; high cost; it can become ineffective as it is of protein nature; lack of information on mechanism of action	Strempel et al. (2015), Mathur et al. (2018) and Chikindas et al. (2020)
	Essential oil	Good efficacy in inhibiting biofilm formation; low cost; low toxicity; rapid degradation in the environment; high availability; low risk of resistance	Little or no ability to inhibit pre-formed biofilm	Galié et al. (2018), Correa et al. (2019), Shahid et al. (2019) and Wang et al. (2019)
	Enzymes	Biodegradable; low toxicity	High cost due to patent protection	Wang et al. (2016), Meireles et al. (2016) and Galié et al. (2018)
	Quorum-sensing inhibitors	No resistance; decreased resistance to multiple drugs; high effectiveness; obtained from natural sources	Varying potential	Galié et al. (2018), Subhadra et al. (2018), Shahid et al. (2019) and Wang et al. (2019)
Physical treatment	Heat	Easy to perform; low cost; does not damage the	Risk of resistance	Pijls et al. (2020)

(continued)

Table 1.1 (continued)

Types of biofilm prevention	Methods of biofilm prevention	Advantages	Disadvantages	References
		environment; high effectiveness; greater vulnerability; non-invasive technique		
	Radiation	Inhibition of biofilm formation; molecule passage facilitated; innovative method	Gene expression does not present a significant decrease; low effectiveness	Marjani and Khadam (2016)
Genetic manipulation	CRISPR Technique	EPS formation drastically affected; structure of the biofilm compromised	A lot of work; limited; high cost	Noirot-Gros et al. (2019) and Leonova and Gainetdinov (2020)

can vary from 1 nm to 100 nm, and the constituent material will determine the characteristic of an inorganic or organic nanoparticle (Ealia and Saravanakumar 2017).

1.4.1.1 Organic Nanoparticles

Organic NPs are biodegradable and non-toxic, and can be composed of biopolymers, liposomes, micelles, chitosan, lignin, among other biocomponents. These nanoparticles are widely used in the biomedical area, mainly in medication administration systems for ensuring their targeted distribution. There is currently a wide variety of edible organic NPs prepared from food-derived ingredients such as polysaccharides, lipids, and proteins (Ealia and Saravanakumar 2017; Azeredo et al. 2019).

1.4.1.2 Inorganic Nanoparticles

Inorganic NPs are made up of metals or metal oxides such as gold (Au), silver (Ag), copper (Cu), and zinc (Zn). All metallic components can be used to form a nanoparticle, using destructive or constructive methods. Therefore, metallic NPs can have different properties in relation to their size, high surface to volume ratio, and shape that varies from spherical to cylindrical. Metal oxide nanoparticles demonstrate greater reactivity and efficiency when compared to metallic nanoparticles, with aluminum oxide (Al_2O_3), iron oxide (Fe_2O_3), titanium oxide (TiO_2), and zinc (ZnO) being the most commonly used (Ealia and Saravanakumar 2017; Kumari et al. 2020).

Silver Nanoparticles

Silver nanoparticles (AgNPs) are the most commonly applied; it is estimated that their global production is greater than 500 t. They have wide applications, ranging from electronic food products to health-related products. However, the fact that they can be released into the environment and the possibility of having a great impact on ecosystems and especially on human health are some of their disadvantages. Silver can induce fibrosis of the bronchial epithelial cells in addition to resulting in disorders of the intestinal microbiota (Azeredo et al. 2019; Liang et al. 2020; Mylona et al. 2020).

The Ag + ions present in nanoparticles larger than 10 nm have an antimicrobial function through electrostatic interaction with negatively charged bacterial membranes. However, those smaller than 10 nm, demonstrate activity through their internalization by bacterial cells resulting in the oxidation of Ag to Ag+. It is also believed that AgNPs lead to gene expression disorders, damage to mitochondrial function, destabilization of the bacterial cell membrane, and formation of reactive oxygen species. In biofilms, the inhibition is due to its high penetrating power, however, some elements of this structure such as genetic elements, membrane proteins, and an efflux pump are able to confer resistance to silver, resulting in inhibition failure (Gholamrezazadeh et al. 2018; Azeredo et al. 2019; Meza-Villezcas et al. 2019; Meier et al. 2020; Zou et al. 2020).

Copper Nanoparticles

Copper nanoparticles (CuNPs) are used in several applications such as household, medical, industrial, and environmental products (Yadav et al. 2017). Copper is widely used in the synthesis of nanoparticles due to its natural abundance and free elemental form. CuNPs are more potent than other metal oxide nanoparticles as they induce greater cytotoxicity resulting from DNA damage. The antimicrobial activity of CuNPs is also related to the damage to the bacterial cell wall, which generates high Cu++ efflux and creates a localized ionic effect (Sengan et al. 2019; Padmavathi et al. 2020). However, its synthesis is more complex, since copper is prone to rapid oxidation, a fact that reduces the effectiveness of its production (Lotha et al. 2019; Miao et al. 2019; Sengan et al. 2019).

Regarding the anti-biofilm activity, studies suggest that copper nanoparticles have the ability to remove established biofilms through the interaction of electrical charges with the exopolysaccharide matrix. Anti-biofilm activity may also be related to inhibition of QS and genes involved in biofilm formation as seen for the species *Methyl bacterium* spp. (Seo et al. 2018).

Gold Nanoparticles

Gold nanoparticles (AuNPs) have widespread use due to their optical-electronic properties, bio-stability, and catalytic and antimicrobial activity. This nanomaterial provides a versatile surface and can easily function as a binder for the surface receptors of target cells. It can also act in biomarking, nano diagnosis, vectorization of drug molecules, radiotherapy, and transmission electron microscopy (Boda et al. 2015; Ahmed et al. 2016; Feurtet-Mazel et al. 2016; Baudrimont et al. 2018; Khan et al. 2019).

Compared to other nanomaterials, AuNPs are highly inert, being considered non-toxic due to their low chemical reactivity. However, their toxicity may change according to their oxidation state, the composition of the nanomaterial, as well as the location or type of cell exposed to AuNPs (Boda et al. 2015).

The anti-biofilm effect of AuNPs is related to strong electrostatic interactions with negatively charged bacterial membranes and by the photothermal action, capable of inhibiting the proliferation and formation of biofilms. In addition, AuNPs have a low propensity to develop microbial resistance compared to antibiotics (Ahmed et al. 2016; Habimana et al. 2018; Lu et al. 2018).

Zinc Nanoparticles

Zinc nanoparticles (ZnONPs), have low synthesis cost, excellent biocompatibility, robustness, and resistance to both corrosion and oxidation, allowing wide use in products. Although, in low concentrations, ZnONPs have no toxicity to eukaryotic cells, in the environment their interaction with natural organic materials can alter their toxicity, stabilization, agglomeration, and dissolution (Vijayakumar et al. 2015; Al-Shabib et al. 2016; Khan et al. 2016; Ouyang et al. 2017).

ZnONPs exhibit strong protein adsorption properties, which modulate cytotoxicity, metabolism, and cellular responses. Thus, this nanocomponent has a potential inhibitory effect on cancer cells and Gram-positive bacteria and fungi (Al-Shabib et al. 2016; Mehta et al. 2019).

The antimicrobial effects of ZnONPs are associated with the size of the nanoparticle, since smaller ones can more easily penetrate the cell membrane and have a large surface area, increasing the degree of antimicrobial activity. Studies suggest that upon entering the cell, ZnONPs generate reactive oxygen species, inducing apoptosis through lipid peroxidation, in addition to deactivating proteins and causing structural changes in membranes and nucleic acids (Bhuyan et al. 2015). Their anti-biofilm potential is limited when faced with mature biofilms, being potentially insufficient to eradicate them (Abdulkareem et al. 2015; Gong et al. 2019; Lim et al. 2018; Mehta et al. 2019).

1.4.1.3 Carbon-based Nanoparticles

Carbon-based nanoparticles are used in various applications in everyday life, in industry, and in technologies with multiple-walled or single-walled nanotubes, being advantageous mainly in the electronic and optical areas. Fluorescent carbon nanoparticles are used as carbonaceous emitters with superior photoluminescence properties, and have been applied in areas such as bioimaging (Gorrochategui et al. 2017; Hu et al. 2020).

These NPs have the ability to interact with cell membranes, being able to penetrate them and thus interact with the internal components of the cell. Carbon nanotubes present properties that favor the antimicrobial effect, related to the ability to generate reactive oxygen species (Li et al. 2016; Gorrochategui et al. 2017; Seo et al. 2018).

1.4.2 Methods to Synthesize Nanoparticles

1.4.2.1 Conventional

NPs synthesized conventionally come from physical and chemical methods that involve chemical reduction, electrochemistry, laser waves, and lithography, responsible for generating monodisperse particles of homogeneous composition and morphology. Conventional syntheses require several preparation steps that interfere with large-scale production, requiring the use, in most cases, of potentially hazardous materials that may remain on the surface of the nanoparticle even after its purification process (Starsich et al. 2019; Foroohimanjili et al. 2020).

For conventional synthesis of metallic NPs, for example, chemical reducing agents such as sodium hydrochloride and hydrazine are used, which have the ability to reduce metal ions. Conventional synthesis of gold nanoparticles can be performed using the Turkevich or Brust-Schifrin method. In the Turkevich technique, AuNPs are obtained by reducing hydrogen tetrachloroaurate ($HAuCl_4$) by the agent trisodium citrate, generating nanoparticles that vary between 10 and 150 nm. In the Brust-Schifrin method, particles smaller than 10 nm are obtained, using sodium borohydride ($NaHB_4$) as the reducing agent and tetraoctylammonium bromide (TOAB) as a catalyst phase transfer, thus, the anion of the gold complex ($AuCl_{4-}$) is transferred from the aqueous to organic phase through electrostatic interactions with the positively charged TOAB (Iriarte-Mesa et al. 2020).

With the progressive influence of nanoparticles in the most diverse fields of application, they began to be produced on a large scale, thus, the production method became the focus of attention. Conventional synthesis techniques are no longer widely used owing to their high cost, use of toxic substances, and that large-scale production is impaired by the low stability and monodispersion of the produced nanoparticles (Ali et al. 2019; Yew et al. 2020).

1.4.2.2 Green Synthesis of Nanoparticles Using Plants, Microorganisms, and Biopolymers

The "green" synthesis of nanoparticles is an alternative method to conventional chemical and physical methods and is based on the use of biological systems, plant extracts, and biomass. Green synthesis does not require elaborate processes for ion reduction, as occurs, for example, in the development of silver and gold nanoparticles, since in this type of synthesis biomolecules are used. The biological components that line the surface of NPs during their green synthesis, act as ecologically correct precursors for their formation, this being an important differential for their application (Islam et al. 2019).

Biological methods for synthesis of NPs provide several benefits, since they are clean, low cost methods, in addition to presenting high safety, stability, and speed during the synthesis process. In this way, there is a reduction in the potential risks for both human health and the environment, in addition to presenting better properties in terms of size, shape, biocompatibility, and stability of the nano material (Al-Shabib et al. 2016; Khan et al. 2019; Mellinas et al. 2019).

There are several biological systems for "green" synthesis of NPs such as the use of biomolecules: enzymes, amino acids, vitamins, proteins, phenolic compounds, and alkaloids (Al-Shabib et al. 2016).

Plant extracts, rich in biomolecules, can be used for the development of metallic NPs, and act as reducing and stabilizing agents during the process (Prasad 2014, 2019a, b; Prasad et al. 2018). Bacteria can also be involved in biological synthesis, such as *Pseudomonas* spp. which allows the preparation of colloidal silver (Foroohimanjili et al. 2020; Iriarte-Mesa et al. 2020; Silveira et al. 2020). Biopolymers such as Levan have promising properties due to their ability to form nanostructures in water through self-assembly, resulting in a biodegradable polymeric micelle with high biocompatibility (González-Garcinuño et al. 2019).

The great challenge in the application of this nanomaterial in *in vivo* systems is related to the concentration of administered NPs. The large volume of blood reduces the concentration of nanoparticles and disintegrates their chains, releasing the encapsulated drug in an uncontrolled manner (González-Garcinuño et al. 2019).

1.4.3 Characterization Techniques and Properties

After the synthesis of the NPs, characterization aims to verify their morphology, surface area, size, distribution, and other important parameters of nanomaterial compliance. Knowledge of these characteristics is essential for the application of the nanoparticle, in addition to ensuring better efficiency in its synthesis. Some techniques can be used for this purpose such as: UV absorption spectroscopy (UV-vis), powder X-ray diffraction (XRD), dynamic light scattering (DLS), Fourier infrared transmission spectroscopy (FTIR), dispersive energy x-ray examination

(EDAX), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) (Khade et al. 2015; Muthukrishnan et al. 2015; Chaudhuri and Malodia 2017).

Spectroscopic and diffractographic techniques are indirect methods used to analyze the composition, structure, and crystalline phase of NPs. UV-vis enables the study of the arrangement of NPs by measuring optical absorption, transmittance, and reflectance, which assist in calculating band intervals and determining the photoactivity and conductance of the material. The FTIR technique identifies functional or metabolic groups present on the surface of the NPs, responsible for their reduction and stabilization. DLS analysis can estimate the size distribution in addition to quantifying the surface loads of the nanoparticles. The purity, crystalline size, geometry, and phase orientation are determined by the XRD technique with the use of diffraction patterns present in crystallographic databases. The EDX technique separates characteristic x-rays from different elements in a given energy spectrum, being used to identify the elemental composition of, for example, metallic NPs (Santhoshkumar et al. 2017; Gour and Jain 2019; Khanna et al. 2019).

To determine the size, morphological characteristics, and topography of the NPs surface, advanced electron microscopy techniques are used. The SEM technique provides three-dimensional information for direct visualization of the product, with spatial resolution of 10 to 5 nm. In this technique, the sample is digitized by electron beams and its surface characteristics are obtained from secondary electrons, thus allowing data to be obtained regarding the surface morphology as well as the dispersion of the NPs in the mass or matrix. On the other hand, the TEM technique presents a two-dimensional image resulting from the interaction of an electron beam with the sample, with a resolution higher than SEM. Thus, this technique is widely used in determining the size, shape, and number of layers. The possible combination of the SEM technique with EDX enables important elementary analysis of the nanoparticle, this being important to provide information about the metals present (Yedurkar et al. 2016; Khanna et al. 2019).

1.4.4 Application of Green Synthesis of Nanoparticles in Microbial Biofilm

Several studies have reported the use of NPs produced by biological synthesis as an alternative for the control of biofilms, due not only to their ability to eliminate microorganisms present in the structure, but also to promote the inhibition of EPS secretion by biofilm-forming bacteria (Rajkumari et al. 2017; Hasan et al. 2019; Shanmuganathan et al. 2019).

It is believed that the use of biosynthesized NPs facilitates electrostatic interactions that result in the structural rupture of the biofilm matrix. Their reduced size allows penetration into microbial cell walls leading to loss of cell viability and alteration in the biofilm cell physiology. The use of NPs also ensures controlled

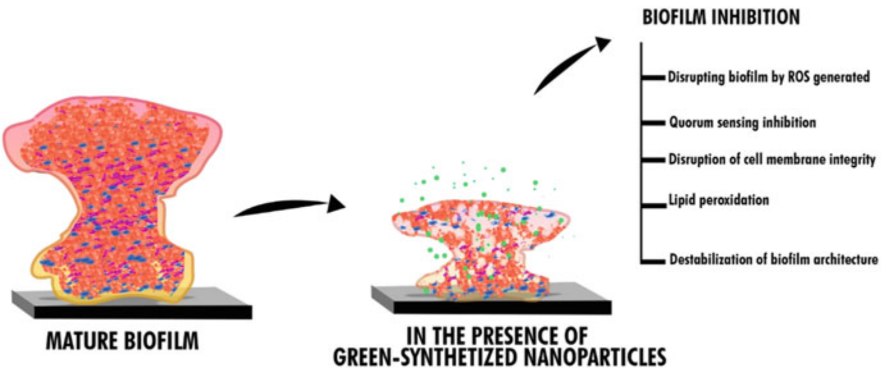

Fig. 1.2 Effects of the application of green synthesis of nanoparticles on microbial biofilms

release of the antimicrobial agent, presenting reduced toxicity and greater stability, thus also providing greater antimicrobial effects on the biofilm (Fig. 1.2) (Habimana et al. 2018; Singh et al. 2018a; Banerjee et al. 2019; Prasad et al. 2020).

The possibility of using medicinal plants and phytochemicals with antimicrobial effects on the synthesis of NPs contributes to the biofilm eradication. Many phytochemicals have the ability to alter the cell membrane and compromise the respiratory activity of cells, in addition to causing lipid peroxidation and the production of free radicals that cause deleterious effects on biofilms (Rajkumari et al. 2017; Rodríguez-Serrano et al. 2020; Ruddaraju et al. 2020).

Nanoparticles biosynthesized with polystyrene interact with polysaccharides from the biofilm matrix and through hydrophobic complexation lead to the rupture of the biofilm. Nanoparticles of biodegradable hydrogels are capable of reducing cell viability and act in the elimination of biomass, removing planktonic and sessile forms. NPs synthesized with biopolymers also act effectively in the eradication of biofilms since their polycationic groups have the ability to interact and break with the bacterial membrane resulting in the inhibition of biofilm formation. The mature biofilm can also undergo alterations caused by nanoparticles due to their elevated degree of penetration and high relationship between surface and volume (Liu et al. 2017; Banerjee et al. 2019).

In the studies of Rajkumari et al. (2017), dextrin was used for biological synthesis of silver particles, demonstrating a remarkable reduction of approximately 70% in the formation of biofilms by the pathogens *K. pneumoniae*, *P. aeruginosa*, *C. albicans,* and *S. aureus MRSA*. The study also evaluated a positive effect on the inhibition of EPS secretion, guaranteeing an important role of biosynthesized NPs in the face of infection by multi-resistant microorganisms that form biofilms. Ramalingam et al. (2019) used *avicennia marina* for biosynthesis of Fe_2O_3NPs, obtaining a percentage of 65% in the inhibition of biofilm formation at a concentration of 2 ppm for species of *P. aeruginosa* and 5 ppm for the pathogen *S. aureus*, while complete anti-biofilm activity was achieved in doses of 28 μg/mL for *E. coli* and 52 μg/mL for *P. aeruginosa*.

The great demand for innovative strategies to control and prevent the formation of biofilms has stimulated studies regarding the application of nanoparticles. The effective action of nanocomponents is remarkable due to their physical and chemical characteristics. However, improvement in some techniques is necessary, mainly in relation to large-scale production and knowledge of their mechanism of action (Zacchino et al. 2017; Wolferen et al. 2018; Shanmuganathan et al. 2019).

1.5 Other Applications of Green Synthesis of Nanoparticles

In addition to the application as an antimicrobial and anti-biofilm agent, the "green" synthesis of NPs has been directed to other applications, such as antioxidant, anti-cancer, and anticoagulant, among others (Qais et al. 2020). Rehman et al. (2020) performed the synthesis of AgNPs and titanium oxide (TiO_2) from fungi of the species *Fomes fomentarius*, and observed good antibacterial action against *S. aureus* and *E. coli*, in addition to verifying the anti-cancer activity of these particles. In human colorectal carcinoma cells, strong cytotoxic effects and cell death were observed after treatment with concentrations below 0.5 μg/mL of both studied nanoparticles, with no damage observed to the control cells. Although the mechanism that induces the apoptosis of cancer cells by these NPs is not well understood, it is suggested that AgNPs activate the apoptotic pathway with the production of oxygen free radicals, which results in anti-tumor and anti-proliferative effects (Barabadi et al. 2017; Aziz et al. 2019).

Hosseinzadeh et al. (2020), synthesized AuNPs from essential oil of *ferula persica*, which showed greater cytotoxic, apoptotic, and antiproliferative effects in colon cancer CT26 cells when compared to *Vero* cells. The morphological difference between cancerous and normal cell membranes, in terms of pore size, can result in a noticeable difference in the toxicity of NPs in cancer and normal cells, underscoring the importance of studying NPs in anti-cancer applications (Basavaraja et al. 2008).

AuNPs and AgNPs from *Olax nana* extract also presented anti-cancer activity, and the authors emphasize that the use of these same nanoparticles in imaging is promising, as it allows better visualization and outlining of the tumor design (Ovais et al. 2018). Nanoparticles can be phagocyted by cells of the liver, spleen, lungs, and bone marrow, in addition to being detected in the blood or lymphatic circulation, which can improve the diagnosis of the tumor (Brigger et al. 2012).

The NPs obtained by Ovais et al. (2018) also presented significant antibacterial and anti-leishmania activity, by presenting inhibition of amastigotes and promastigotes of *Leishmania tropica*. The use of nanotechnology in patients with leishmaniasis is promising, both in treatment and in prevention with the use of vaccines.

In addition to the antiparasitic action, the insecticidal potential of nanoparticles has also been studied (Kumar et al. 2020; Bhattacharyya et al. 2016). Chitra et al. (2015) used AgNPs synthesized from leaf extracts of *Mukia maderaspatana* and verified effective larvicidal activity against *Aedes aegypti* and *Culex* *quinquefasciatus* (Buhroo et al. 2017). Hajra et al. (2016) found a high mortality rate of *Aedes albopictus* when subjected to concentrations of cadmium NPs (CdNPs) synthesized from clove petal extract. A study developed by Arokiyaraj et al. (2015) presented insecticidal potential against *A. albopictusde* AgNPs obtained from *Chryasanthemum indicum* L. extract, emphasizing the importance of nanoparticles in the elimination of mosquitoes that are vectors of viruses and parasites that cause diseases in humans.

The catalytic properties of NPs are currently well described (Wang et al. 2020; Kumar et al. 2020). 4-Nitrophenol and its derivatives are considered compounds of great risk to the environment, since their use in the production of herbicides, insecticides, and synthetic dyes can harm the ecosystem as a wastewater pollutant, so that a reduction is necessary (Singh et al. 2018b). Knowing that sodium borohydride ($NaBH_4$) is used as a reducer of 4-Nitrophenol to 4-Aminophenol, Nayan et al. (2018) demonstrated a high catalytic capacity of these substances using AuNPs synthesized from *Mangifera indica*.

Another industrial pollutant of great importance is methylene blue dye, since, if ingested it can restrict oxidase enzymes, leading to central nervous system toxicity, gastrointestinal infections, and discoloration of the brain parenchyma (Kumar et al. 2020). Varadavenkatesan et al. (2019) verified the catalytic activity of AgNPs synthesized from *Ipomoea digitata* flower extract in reducing methylene blue dye, using $NaBH_4$ as a reducing agent. The results confirmed the catalytic activity of the nanoparticles, with a reduction of methylene blue in 15 minutes, indicating good perspectives of AgNPs for environmental remediation (Kumar et al. 2020).

The green synthesis of NPs is also being studied for application in food preservation. Lignocellulose is one of the most commonly used materials for packaging food products and beverages and many studies aim to modify the surface of this material for better food preservation. In studies by Bumbudsanpharoke and Ko (2018), the unbleached "kraft" (UBK) pulp of lignin and hemicellulose was used for the "green" synthesis of AuNPs, which were deposited on the surface of the UBK fiber, promoting the elimination of radicals and an antioxidant effect.

Other models of "green" nanoparticle synthesis and their applications are shown in Table 1.2. Given the various applications of NPs, the green synthesis approach opens alternative paths to the use of chemicals that are toxic to man and harmful to the environment, representing a field of study that has been extensively explored in the last decade and with a promising future.

1.6 Conclusion

The "green" synthesis of nanoparticles has been a highly attractive area of research for the past decade. Nanoparticles have been applied extensively in important areas, such as the pharmaceutical, food, and cosmetic industries. In this chapter, several applications were demonstrated, including as antimicrobial and anti-biofilm agents. However, research should be encouraged in order to observe the action of

Table 1.2 Nanoparticles obtained from green synthesis and their applications

NPs	Source	Activity	References
Ag	*Allamanda cathartica*	Antioxidant and antibacterial	Karunakaran et al. (2016)
	Tagetes erecta	Antibacterial	Padalia et al. (2015)
	Chrysanthemum indicum L.	Larvicidal and pupicidal	Arokiyaraj et al. (2015)
	Heracleum persicum	catalytic	Mohammadi et al. (2020)
	Atropa acuminata	Antioxidant, anti-inflammatory, anti-cancer, and Larvicidal	Rajput et al. (2020)
	Carum copticum	*Quorum-sensing* inhibition and bacterial biofilm	Qais et al. (2020)
Au	*Gnidia glauca*	Chemocatalytic	Ghosh et al. (2012)
	Tussilago farfara	Antibacterial and anti-cancer	Lee et al. (2019)
Cu	*Mimusops elengi*	Antibacterial; antifungal; antioxidant; thrombolytic; larvicidal; cytotoxic; heavy metal removal	Kumar et al. (2020)
	Cymbopogon Citratus	Antibacterial and anti-biofilm	Cherian et al. (2020)
Fe	*Piliostigma thonningii*	Antibacterial	Bibi et al. (2019)
Zn	*Nyctanthes arbor-tristis*	Antifungal	Jamdagni et al. (2018)
Cd	*Tagetes* sp.	Larvicidal	Hajra et al. (2016)
Ti	*Calotropis gigantean*	Acaricide	Marimuthu et al. (2013)
Mg	*Rosmarinus o_cinalis L.*	Antibacterial	Abdallah et al. (2019)

nanoparticles on an industrial scale and their effects on the environment. Concerns have also been raised about their safety and side effects for humans during therapy. Although the promising results of research in this area are increasing, it is necessary to establish guidelines to ensure the safe use of green synthesized nanomaterials to turn these new formulations into reality as anti-biofilm agents.

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